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Continuous glucose monitoring: beyond diabetes management

Edited by
Ma Jianhua, Gang Hu and Jianzhong Xiao

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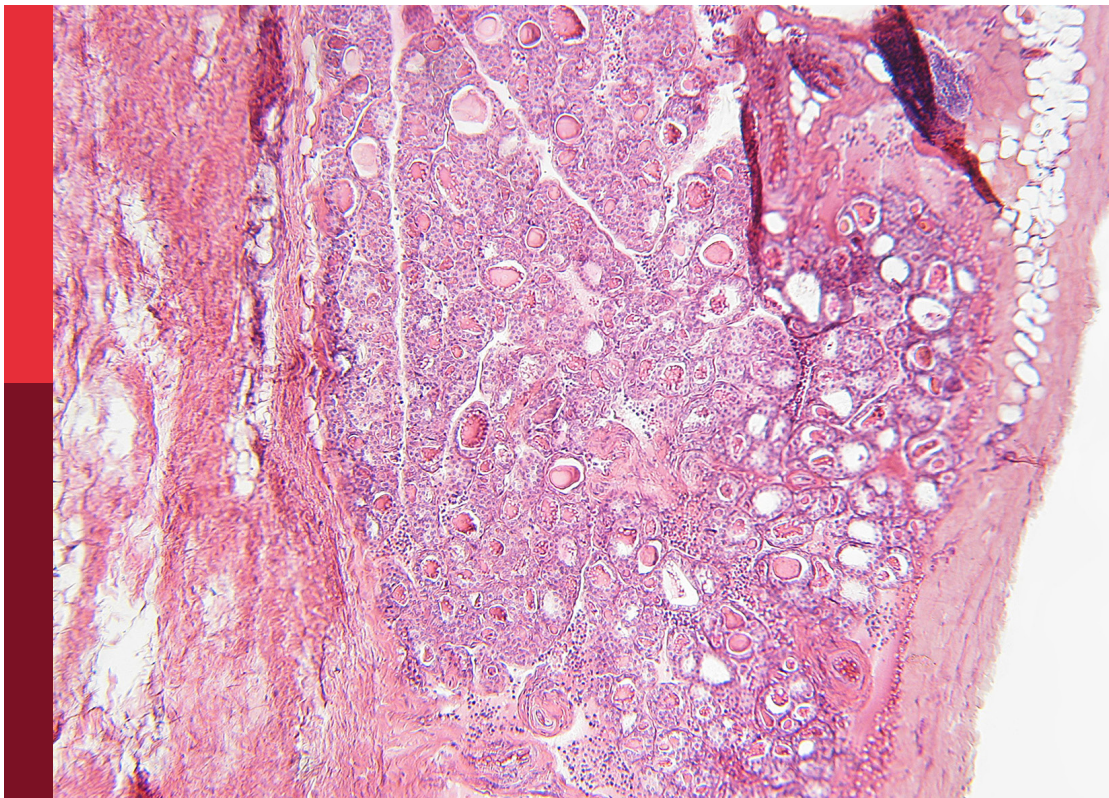

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Continuous glucose monitoring: beyond diabetes management

Topic editors

Ma Jianhua — Nanjing Medical University, China

Gang Hu — Pennington Biomedical Research Center, United States

Jianzhong Xiao — Beijing Tsinghua Changgung Hospital, China

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Åke Sjöholm,
Gävle Hospital, Sweden

*CORRESPONDENCE
Jianzhong Xiao
xjza01150@btch.edu.cn

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Editorial: Continuous glucose monitoring: beyond diabetes management

Jianzhong Xiao*

Department of Endocrinology and Metabolism, Beijing Tsinghua Changgung Hospital, Tsinghua University Clinical Medical School, Tsinghua University, Beijing, China

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Editorial on the Research Topic
Continuous glucose monitoring: beyond diabetes management

Since the establishment of the causal relationship between blood glucose levels and diabetes complications, glycemic control has become a cornerstone of diabetes metabolic management (1). In recent years, continuous glucose monitoring (CGM) systems have emerged as transformative tools for diabetes care (2). By measuring glucose levels in interstitial fluid, CGMs provide near-continuous real-time glucose readings and comprehensive ambulatory glucose profiles (AGP) (3). These capabilities are critical for optimizing insulin dosing, dietary planning, and physical activity management (4–6). The real-time visualization of glycemic variability has not only revolutionized diabetes treatment but also significantly enhanced patients' quality of life (7). Moreover, CGM-derived metrics such as Time in Range (TIR), Time Below Range (TBR), and Time Above Range (TAR) have introduced new paradigms in glycemic assessment (3). Notably, the application of CGM is expanding beyond traditional diabetes management, opening new frontiers in personalized health optimization. This article reviews current evidence including articles in this Research Topic, to discuss the potential applications, limitations, and prospects of CGM technology.

Beyond diabetes management: expanding applications of CGM

We know that glucose is a major substrate of energy metabolism and a core player in overall metabolic health, energy regulation, and cellular function. Fluctuations, even within physiologically "normal" ranges - can profoundly influence wellbeing and performance (8). This understanding has driven growing interest in CGM applications among non-diabetic populations:

1. Optimize metabolic health & prevent diabetes:

CGM provides immediate, personalized feedback on how specific foods and dietary components (carbohydrate type/fiber/fat/protein ratio, serving size, order) affect blood glucose (9). One person's "healthy" meal can cause another person's blood sugar to spike dramatically (10). CGM provides support for truly personalized dietary choices to minimize harmful blood sugar spikes and promote metabolic stability.

2. Early identification and prevention of dysglycemia: CGM can reveal abnormal blood glucose fluctuations long before standard fasting blood glucose or HbA1c tests show abnormalities (11). Users seeing frequent or prolonged postprandial spikes can be a powerful motivator for lifestyle interventions to prevent the progression to type 2 diabetes (12).

3. Athlete nutrition management and training intensity monitoring (13).

Athletes rely heavily on glycogen stores. CGM helps them understand how different fuel strategies affect glucose availability and stability during training and competition. At the same time, glycemic patterns after exercise can provide clues about recovery status and the effectiveness of energy replenishment. A stable blood glucose overnight after strenuous activity indicates adequate nutrition, while an unstable blood sugar may indicate inadequate intake or constant stress. CGM can sometimes show how different training loads or types affect glucose regulation, potentially marking over-training states.

4. Weight Management and Body Composition Goals:

The "calorie intake, calorie burn" model is increasingly seen as oversimplifying. A spike in blood sugar triggers the release of insulin, a hormone that promotes fat storage and can inhibit fat burning (14). To identify foods that cause significant spikes and to choose dietary variety (i.e. low carbohydrate high protein) promoting more stable glucose and insulin levels, potentially create a more favorable hormonal environment for fat loss and muscle gain (15). Furthermore, large blood glucose spikes are often accompanied by rapid drops, which can trigger hunger, fatigue, and cravings – especially for more carbohydrates or sugar (16). Minimizing these spikes through dietary modification probably supports adherence to healthy eating patterns.

5. Understand energy, mood, and nerve function:

Many people with diabetes experience depression. CGM can directly link these subjective feelings to blood sugar levels (17). Minimizing extreme blood sugar fluctuations by taking a CGM may help some people improve the nerve response to hypoglycemia (18).

6. Women's Health and Hormonal Fluctuations:

Hormones such as estrogen and progesterone significantly affect insulin sensitivity. In most of the study population, glucose levels rose linearly throughout the menstrual cycle, reaching a maximum in the late luteal phase. A sharp decrease was seen in women at the beginning of menstrual bleeding (19). Polycystic ovary syndrome (PCOS) is often associated with insulin resistance. CGM can be a valuable tool for managing blood glucose levels in women with PCOS.

7. Longevity and diets intervention:

Some researchers hypothesize that minimizing high blood sugar spikes and excessive variability (even within normal limits) may reduce oxidative stress and inflammation, potentially slowing the aging process (20). CGM provides data to proactively manage this variability. Biohackers used CGM to test the effects of various interventions—specific diets (ketosis, intermittent fasting), supplements, sleep patterns, stress reduction techniques—on their blood glucose profile, seeking optimal metabolic function (21).

8. Enhancing Quality of Life in Special Diabetic Populations.

Type 1 diabetes management faces unique challenges during Ramadan, where patients experience dawn phenomenon before Suhoor meals, post-Iftar hyperglycemia, and nocturnal hypoglycemia risks. (Alguwaihes et al.) Similarly, pregnant women with diabetes endure significant psychological burdens from stringent glycemic targets. Liu et al. found CGM improved self-rating anxiety, pregnancy-related anxiety, and diabetes specific quality of life. While advanced technologies like sensor-augmented pumps with automated insulin suspension theoretically alleviate hypoglycemia fear syndrome (HFS), current evidence indicates limited improvement regardless of SmartGuard™ or CGM implementation—potentially due to insufficient usage duration. (Schierloh et al.) Notably, CGM offers unique advantages for evaluating novel hypoglycemic agents through comprehensive pharmacodynamic profiling of glucose excursions, surpassing traditional spot-check measurements (Wei et al.).

Technical limitations and future trajectory

Despite promising applications, CGM technology faces inherent physiological constraints. Accuracy needs next generation technology or systemic calibration. (Wu et al.) The 5–15 minute physiological lag between interstitial fluid and blood glucose measurements becomes particularly problematic during rapid glycemic fluctuation (22). Accuracy challenges persist during intense physical activity and other metabolic stressors (Maytham et al.). Implementation barriers include clinical data overload ("glucose fatigue"), reimbursement limitations for non-diabetic applications, and privacy concerns regarding cloud-stored health data (23). Future developments will likely focus on multimodal biometric integration, machine learning-enhanced predictive alert systems, and closed-loop systems for health optimization. These innovations may ultimately transform CGM from a monitoring tool into integrated health management platforms (24).

Author contributions

JX: Writing – original draft, Writing – review & editing. ZL: Writing – review & editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. (1998) 352:837–53. doi: 10.1016/S0140-6736(98)07019-6

2. Uhl S, Choure A, Rouse B, Loblack A, Reaven P. Effectiveness of continuous glucose monitoring on metrics of glycemic control in type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. (2024) 109:1119–31. doi: 10.1210/clinem/dgad652

3. Nguyen M, Han J, Spanakis EK, Kovatchev BP, Klonoff DC. A review of continuous glucose monitoring-based composite metrics for glycemic control. *Diabetes Technol Ther*. (2020) 22:613–22. doi: 10.1089/dia.2019.0434

4. Nwokolo M, Hovorka R. The artificial pancreas and type 1 diabetes. *J Clin Endocrinol Metab*. (2023) 108:1614–23. doi: 10.1210/clinem/dgad068

5. Song J, Oh TJ, Song Y. Individual postprandial glycemic responses to meal types by different carbohydrate levels and their associations with glycemic variability using continuous glucose monitoring. *Nutrients*. (2023) 15:3571. doi: 10.3390/nu15163571

6. Moser O, Zaharieva DP, Adolfsson P, Battelino T, Bracken RM, Buckingham BA, et al. The use of automated insulin delivery around physical activity and exercise in type 1 diabetes: a position statement of the European Association for the Study of Diabetes (EASD) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). *Diabetologia*. (2025) 68:255–80. doi: 10.1007/s00125-024-06308-z

7. Polonsky WH, Fortmann AL. Impact of real-time CGM data sharing on quality of life in the caregivers of adults and children with type 1 diabetes. *J Diabetes Sci Technol*. (2022) 16:97–105. doi: 10.1177/1932296820978423

8. Ku CW, Zheng RT, Tan HY, Lim JYQ, Chen LW, Cheung YB, et al. Early continuous glucose monitoring-derived glycemic patterns are associated with subsequent insulin resistance and gestational diabetes mellitus development during pregnancy. *Diabetol Metab Syndr*. (2024) 16:271. doi: 10.1186/s13098-024-01508-4

9. Zheng Y, Campbell Rice B, Melkus GD, Sun M, Zweig S, Jia W, et al. Dietary self-management using mobile health technology for adults with type 2 diabetes: A scoping review. *J Diabetes Sci Technol*. (2023) 17:1212–25. doi: 10.1177/19322968231174038

10. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. *Cell*. (2015) 163:1079–94. doi: 10.1016/j.cell.2015.11.001

11. Gottfried S, Pontiggia L, Newberg A, Laynor G, Monti D. Continuous glucose monitoring metrics for earlier identification of pre-diabetes: protocol for a systematic review and meta-analysis. *BMJ Open*. (2022) 12:e061756. doi: 10.1136/bmjopen-2022-061756

12. Ehrhardt N, Al Zaghal E. Behavior modification in prediabetes and diabetes: potential use of real-time continuous glucose monitoring. *J Diabetes Sci Technol*. (2019) 13:271–5. doi: 10.1177/1932296818790994

13. Flockhart M, Larsen FJ. Continuous glucose monitoring in endurance athletes: interpretation and relevance of measurements for improving performance and health. *Sports Med*. (2024) 54:247–55. doi: 10.1007/s40279-023-01910-4

14. Dimova R, Chakarova N, Daniele G, Bianchi C, Dardano A, Del Prato S, et al. Insulin secretion and action affect glucose variability in the early stages of glucose intolerance. *Diabetes Metab Res Rev*. (2022) 38:e3531. doi: 10.1002/dmrr.3531

15. Beaudry KM, Devries MC. Nutritional strategies to combat type 2 diabetes in aging adults: the importance of protein. *Front Nutr*. (2019) 6:138. doi: 10.3389/fnut.2019.00138

16. Karakas SE. Reactive hypoglycemia: A trigger for nutrient-induced endocrine and metabolic responses in polycystic ovary syndrome. *J Clin Med*. (2023) 12:7252. doi: 10.3390/jcm12237252

17. Hermanns N, Ehrmann D, Kulzer B, Klinker L, Haak T, Schmitt A. Somatic and mental symptoms associated with dysglycaemia, diabetes-related complications and mental conditions in people with diabetes: Assessments in daily life using continuous glucose monitoring and ecological momentary assessment. *Diabetes Obes Metab*. (2025) 27:61–70. doi: 10.1111/dom.15983

18. Ly TT, Hewitt J, Davey RJ, Lim EM, Davis EA, Jones TW. Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes. *Diabetes Care*. (2011) 34:50–2. doi: 10.2337/dc10-1042

19. Tatulashvili S, Baptiste Julla J, Sritharan N, Rezgani I, Levy V, Bihan H, et al. Ambulatory glucose profile according to different phases of the menstrual cycle in women living with type 1 diabetes. *J Clin Endocrinol Metab*. (2022) 107:2793–800. doi: 10.1210/clinem/dgac443

20. Ji SH, Dong C, Chen R, Shen CC, Xiao J, Gu YJ, et al. Effects of variability in glycemic indices on longevity in chinese centenarians. *Front Nutr*. (2022) 9:955101. doi: 10.3389/fnut.2022.955101

21. Basiri R, Cheskin LJ. Personalized nutrition therapy without weight loss counseling produces weight loss in individuals with prediabetes who are overweight/obese: A randomized controlled trial. *Nutrients*. (2024) 16:2218. doi: 10.3390/nu16142218

22. Zaharieva DP, Turksoy K, McGaugh SM, Pooni R, Vienneau T, Ly T, et al. Lag time remains with newer real-time continuous glucose monitoring technology during aerobic exercise in adults living with type 1 diabetes. *Diabetes Technol Ther*. (2019) 21:313–21. doi: 10.1089/dia.2018.0364

23. Randine P, Pocs M, Cooper JG, Tsolovos D, Muzny M, Besters R, et al. Privacy concerns related to data sharing for european diabetes devices. *J Diabetes Sci Technol*. (2025) 19:611–9. doi: 10.1177/19322968231210548

24. Shamanna P, Joshi S, Thajudeen M, Shah L, Poon T, Mohamed M, et al. Personalized nutrition in type 2 diabetes remission: application of digital twin technology for predictive glycemic control. *Front Endocrinol (Lausanne)*. (2024) 15:1485464. doi: 10.3389/fendo.2024.1485464

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EDITED BY
Jianzhong Xiao,
Tsinghua University, China

REVIEWED BY
Parag Garhyan,
Eli Lilly, United States
Davide Tinti,
University of Turin, Italy

*CORRESPONDENCE
Andreas Andersen
andreas.andersen.04@regionh.dk
Per G. Hagelqvist
per.gustav.hagelqvist.01@regionh.dk

†These authors share first authorship

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Accuracy of continuous glucose monitoring during exercise-related hypoglycemia in individuals with type 1 diabetes

Kaisar Maytham[1,2†], Per G. Hagelqvist[1,2*†], Susanne Engberg[1], Julie L. Forman[3], Ulrik Pedersen-Bjergaard[4,5], Filip K. Knop[1,2,4], Tina Vilsbøll[1,2,4] and Andreas Andersen[1,2*]

[1]Clinical Research, Copenhagen University Hospital – Steno Diabetes Center Copenhagen, Herlev, Copenhagen, Denmark, [2]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, [3]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark, [4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [5]Department of Endocrinology and Nephrology, Nordsjællands Hospital Hillerød, University of Copenhagen, Hillerød, Denmark

Background: Hypoglycemia is common in individuals with type 1 diabetes, especially during exercise. We investigated the accuracy of two different continuous glucose monitoring systems during exercise-related hypoglycemia in an experimental setting.

Materials and methods: Fifteen individuals with type 1 diabetes participated in two separate euglycemic-hypoglycemic clamp days (Clamp-exercise and Clamp-rest) including five phases: 1) baseline euglycemia, 2) plasma glucose (PG) decline ± exercise, 3) 15-minute hypoglycemia ± exercise, 4) 45-minute hypoglycemia, and 5) recovery euglycemia. Interstitial PG levels were measured every five minutes, using Dexcom G6 (DG6) and FreeStyle Libre 1 (FSL1). Yellow Springs Instruments 2900 was used as PG reference method, enabling mean absolute relative difference (MARD) assessment for each phase and Clarke error grid analysis for each day.

Results: Exercise had a negative effect on FSL1 accuracy in phase 2 and 3 compared to rest (ΔMARD = +5.3 percentage points [(95% CI): 1.6, 9.1] and +13.5 percentage points [6.4, 20.5], respectively). In contrast, exercise had a positive effect on DG6 accuracy during phase 2 and 4 compared to rest (ΔMARD = -6.2 percentage points [-11.2, -1.2] and -8.4 percentage points [-12.4, -4.3], respectively). Clarke error grid analysis showed a decrease in clinically acceptable treatment decisions during Clamp-exercise for FSL1 while a contrary increase was observed for DG6.

Conclusion: Physical exercise had clinically relevant impact on the accuracy of the investigated continuous glucose monitoring systems and their ability to accurately detect hypoglycemia.

KEYWORDS

accuracy, continuous glucose monitoring, exercise, hypoglycemia, mean absolute relative difference, type 1 diabetes

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1 Introduction

Exogenous insulin replacement to obtain glycemic control is a hallmark for type 1 diabetes (T1D) treatment (1). The American Diabetes Association (ADA) recommends physical activity for individuals with type 1 diabetes as it improves glycemic control, decreases insulin requirements, and reduces cardiovascular complications in individuals with type 1 diabetes (2–5). However, exercise in these individuals is associated with hypoglycemia, which may be a barrier for obtaining glycemic control, and as a result many individuals with type 1 diabetes avoid engaging in regular physical activity (6, 7). Individuals with type 1 diabetes may need to consume considerable amounts of carbohydrates prior to physical activity in order to avoid exercise-induced hypoglycemia, which may reduce the potential benefits of vascular health and glycemic control that physical activity brings (8, 9). Continuous glucose monitoring (CGM) systems offer a way to frequently monitor glycemic changes throughout the day and particularly during exercise (10, 11). This provides individuals with type 1 diabetes a level of detail that cannot be achieved using capillary glucose meters, thus assisting in reduction of unnecessary glycemic fluctuations and episodes of hypoglycemia (12, 13).

Studies have indicated reduced accuracy of several CGM sensors during rapid glucose changes and low blood glucose levels, both commonly observed in individuals with type 1 diabetes and especially during exercise (14). CGM performance is clinically important since low sensor precision may lead to undetected events of hypoglycemia or unnecessary meal intake ensuing hyperglycemia. Here, we investigated the performance of two commonly used CGM systems, Dexcom G6 (DG6) and FreeStyle Libre 1 (FSL1), during plasma glucose (PG) decline and hypoglycemia, induced with or without exercise in individuals with type 1 diabetes.

2 Materials and methods

2.1 Approvals and registrations

CGM data presented in this study was obtained from a clinical trial investigating cardiovascular effects of exercise-related hypoglycemia in individuals with type 1 diabetes (registration with ClinicalTrials.gov, NCT04650646) (15). The trial was performed at Steno Diabetes Center Copenhagen and Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark from September 2020 to June 2021. The study was conducted following the Helsinki Declaration and was approved by the Scientific Ethical Committee of the Capital Region of Denmark (ID No. H-20023688) and the Danish Data Protection Agency (ID No. P-2020-434). Written consent was obtained from all participants before being included in the study.

Abbreviations: ADA, American Diabetes Association; CGM, Continuous glucose monitoring; MARD, Mean absolute relative difference; PG, Plasma glucose; T1D, Type 1 diabetes; YSI, Yellow Springs Instrument.

2.2 Study design

Fifteen men diagnosed with type 1 diabetes participated in a randomized crossover study including two separate euglycemic-hypoglycemic clamp days. One clamp day included a bout of moderate-intensity cycling exercise performed during declining plasma glucose and hypoglycemia (Clamp-exercise). In the other clamp day, hypoglycemia was induced at rest (Clamp-rest). The participants were recruited from the outpatient clinic at Steno Diabetes Center Copenhagen, Herlev, Denmark. Data reported are a pre-planned secondary analysis from a previously published study. Hence, the sample size was calculated based of the primary aim of that study and has been reported elsewhere (15). The study design is illustrated in Figure 1. The two clamp days were separated

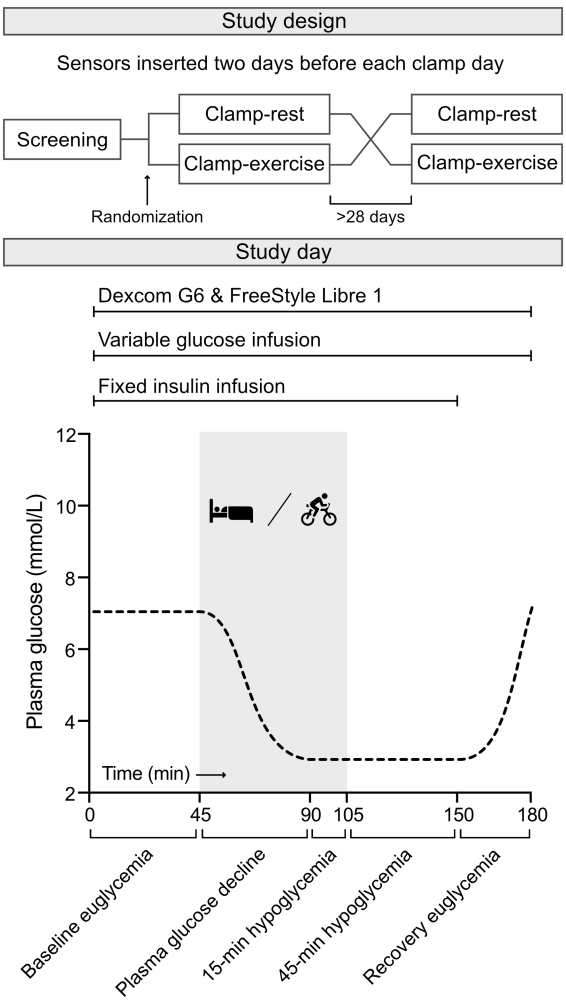

FIGURE 1
Study design. A randomized crossover euglycemic-hypoglycemic clamp study including Clamp-rest and Clamp-exercise. During Clamp-rest, participants were at bed rest during all phases. Clamp-exercise had an exercise element during plasma glucose decline phase and 15-minute hypoglycemic phase marked with gray (time 45 to 105 minute). Each clamp day was divided into five phases. Two continuous glucose monitoring systems, Dexcom G6 and FreeStyle Libre 1, were active throughout the clamp days. Further details and illustrations on the study design has been reported before (15).

by at least four weeks to rule out possible carry-over effects. Inclusion criteria were age ≥18 years, type 1 diabetes diagnosis according to World Health Organization (WHO) classification, C-peptide levels <200 pmol/L, insulin treatment for at least 1 year, and informed and written consent. Further details of inclusion and exclusion criteria have previously been reported (15).

2.3 Clamp procedure

Participants were supplied with and instructed to insert two CGM systems in parallel, Dexcom G6® (Dexcom, Inc., San Diego, CA, USA) and FreeStyle Libre 1® (Abbott Laboratories, Ltd., Alameda, CA, USA). The systems were inserted two days before the clamp days to reduce sensor inaccuracies (16). The participants were admitted in the morning after an overnight 10 hour fast including medicine fasting. Participants receiving insulin pen treatment were instructed to continue their usual basal insulin treatment, regardless of dosing time. Likewise, participants using insulin pump treatment were instructed to solely continue with the basal rate infusion throughout the test days. Sensors were not user-calibrated but relied on the factory calibrations as instructed in the devices' user guide (17, 18). A peripheral intravenous catheter was inserted in the antecubital fossa of each forearm. One arm was heated throughout the clamp to obtain arterialized blood while the contralateral arm was used for isotonic saline (0.9% NaCl, Fresenius Kabi, Bad Homburg, Germany), insulin (Actrapid®; Novo Nordisk, Bagsværd, Denmark), and glucose (20% solution; Fresenius Kabi, Bad Homburg, Germany) infusion. The isotonic saline solution was administered at a constant infusion rate throughout the clamp to avoid volume depletion due to blood draw and to keep the intravenous cannula working properly. The hyperinsulinemic-euglycemic clamp was initiated at time 0 minutes when the target PG between 5.0 and 8.0 mmol/L was reached. A combination of a fixed insulin infusion rate at 80 mU/m2/min and a variable 200 mg/ml (20%) glucose infusion was initiated to clamp PG. Both clamp days (Clamp-exercise and Clamp-rest) contained the following phases: 1) a baseline euglycemic phase, 2) a PG decline phase induced at bed rest or during exercise, 3) a 15-minute hypoglycemic phase at bed rest or during exercise, continued by 4) a 45-minute hypoglycemic phase at bed rest and finally 5) recovery euglycemia. Exercise was performed at a moderate intensity defined as 64% to 76% of maximum heart rate calculated using the formula [207-(Age) × (0.7)] (19). The participants exercised on a Monark Ergomedic 839E (Monark Exercise AB, Vansbro, Sweden) for a total period of 60 minutes. Target heart rate was reached by adjusting the resistance of the cycle ergometer throughout the exercise period. The participants were instructed to begin exercise at a low-level intensity and gradually increase the intensity until reached target level. The target level of PG during the phases of hypoglycemia was <3.0 mmol/L, representing level 2 hypoglycemia (20). Glucose concentrations were determined every five minutes throughout the clamp days using DG6 and FSL1 in parallel. FSL1 was manually scanned during the clamp days whereas DG6 automatically stored the glucose values. Yellow Springs Instrument (YSI) 2900 biochemistry analyzer (Xylem, Inc., Rye Brook, NY, USA) was used to carry out the clamps as a PG reference method by sampling arterialized venous blood in 0.2 mL NaF tubes centrifuged at 7,400 g for 30 seconds and then analyzed.

2.4 Data and statistical analysis

For each sensor reading, the absolute relative difference was computed as the absolute difference between the reading and reference PG value divided by reference PG multiplied by 100 (21). For descriptive statistics, the absolute relative differences were summarized as mean ± standard error and plotted against clamp-time in figures. To compare the accuracy of each sensor between Clamp-exercise and Clamp-rest, we applied a linear mixed model with clamp time and clamp day and the interaction between them as fixed effect and with a heterogeneous compound symmetry covariance pattern to account for repeated measurements on each study participant. Results were reported as difference in mean absolute relative difference (ΔMARD) with 95% confidence interval for each clamp phase. Finally, a Clarke error grid analysis was performed for each clamp day to quantify the clinical significance of sensor inaccuracies (22). Paired sensor readings and reference PG values are depicted on a plot with five zones corresponding to varying clinical consequences. $P < 0.05$ was considered statistically significant. SAS Studio version 3.8 (SAS Institute, Inc., Cary, NC, USA) was used to perform the linear mixed model analysis. The Clarke error grid plot was made with ega-package version 2.0.0 in R Statistical software version 4.2.1.

3 Results

All 15 participants (Table 1) completed both clamp days yielding 551 and 543 DG6 sensor-PG pairs for Clamp-rest and Clamp-exercise, respectively, as well as 491 and 512 FSL1 sensor-PG pairs for Clamp-rest and Clamp-exercise, respectively. All participants placed the sensors according to specified guidelines except one who placed FSL1 on the upper thigh. For both clamp days, mean PG was kept at 6-7 mmol/L during the baseline-euglycemic phase although slightly decreasing towards the decline phase (Figure 2). Target hypoglycemia was reached after 90-minutes and followed by steady-state hypoglycemia of <3.0 mmol/L. Overall, PG levels for both clamp days were comparable.

3.1 Comparison of accuracy between clamp days

When comparing the clamp days (Table 2), FSL1 had a comparable MARD during phase 1 indicating similar baseline accuracies (Figure 3). Compared to rest, exercise increased MARD during phase 2 which continued during phase 3. There was a comparable MARD during phase 4 post exercise and during phase 5 recovery. DG6 had a comparable MARD between clamp days during phase 1, although this was surprisingly high compared to the expected (Figure 3). Compared to rest, exercise decreased

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TABLE 1 Baseline characteristics of the study participants.

	Mean (SD) or N (%)
Males	15 (100%)
Age (years)	29.4 (8.1)
Body mass index (kg/m^2)	23.7 (2.0)
Duration of type 1 diabetes (years)	13.1 (6.3)
HbA1c (mmol/mol)	51.0 (5.5)
HbA1c (%)	6.8 (0.5)
Fasting plasma glucose (mmol/L)	9.7 (2.1)
Heart rate (bpm)	64.8 (10.7)
Physical activity levels	
Low activity	3 (20%)
Moderate activity	3 (20%)
High activity	9 (60%)

Categorical data are presented as N (%), and continuous variables are presented as mean (SD). Further details on the participants have been reported before (15). bpm, beats per minute; HbA1c, glycated hemoglobin A1c; mmHg, millimeter of mercury; SD, standard deviation.

MARD during phase 2 and phase 3, although not significantly. During phase 4, MARD was lower post-exercise, while a comparable MARD was observed between clamp days during phase 5.

3.2 Clarke error grid analysis of DG6 and FSL1

Assessing the clinical performance according to Clarke error grid analysis showed a difference between clamp days (Figure 4). FSL1 performance decreased during Clamp-exercise where data points in the combined zones A+B decreased compared to Clamp-rest and accordingly increased in the clinically unacceptable estimates zone D. DG6 performance increased during Clamp-exercise where data points in zones A+B increased indicating an increase in sensor estimates to more clinical acceptable accuracies. No data points were observed in zones C and E for all error grid analyses.

4 Discussion

We report that exercise can affect the sensor accuracy of the investigated CGM systems by either a decrease in sensor accuracy and the ability to detect hypoglycemia as seen with DG6, or contrary by an increase in sensor accuracy as seen for FSL1 which may be of clinical relevance for physically active individuals with type 1 diabetes when choosing between CGM systems.

The overall MARD of DG6 obtained in this study under baseline euglycemia was substantially higher compared to previous studies (23–25). Shah et al. compared DG6 sensor readings with YSI glucose values in 62 participants and demonstrated a general overall MARD of 9% (23). Generally, the design in the studies were similar e.g., utilizing a YSI analyzer, obtaining arterialized venous blood, and relying on the factory calibration. Furthermore, we followed the manufacturer's specified guidelines for inserting and initializing the sensor and doing so two days before the clamp days to avoid possible inaccuracy during the sensor warm-up time. Since the overall FSL1 MARD of our study was more comparable with previous studies (26–29), and since our study followed the same principles as previous studies, the deviating MARD values obtained from DG6 may not be explained by the design of our study. The deviation may rather be related to the applied sensors. As the higher-than-expected MARD of DG6 was observed at baseline for both test days, and that they were comparable to each other, the comparison outcomes between clamp days were considered valid.

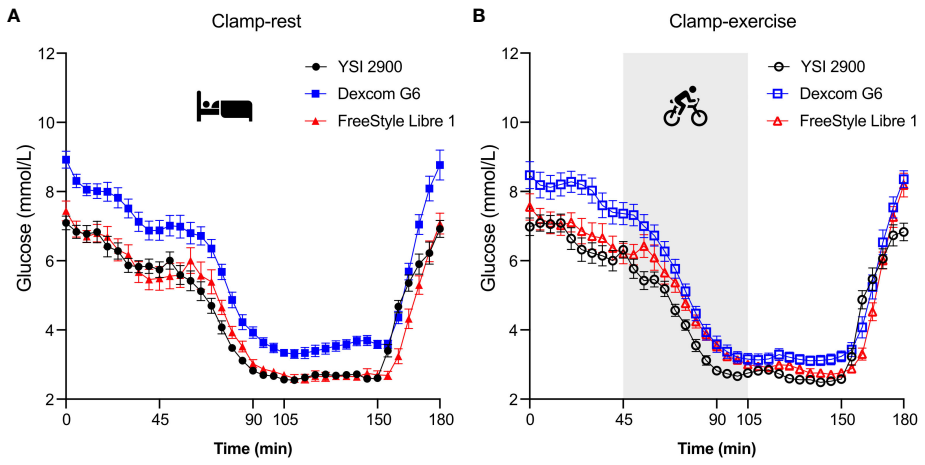

FIGURE 2
Glucose readings represented as mean ± SE. The clamp period totals 180 minutes and consists of 37 data points (data collected every five minutes). Clamp-rest **(A)** was at bed rest throughout the clamp period. Clamp-exercise **(B)** contained an exercise element on a cycle ergometer during plasma glucose decline phase and 15-minute hypoglycemic phase (time 45 to 105 minute). YSI, Yellow Springs Instrument.

TABLE 2 Comparison of Clamp-exercise and Clamp-rest throughout clamp phases.

Clamp phase	Sensor	ΔMARD %	Δ95% CI	*P*
Baseline euglycemia	DG6	-0.2	-4.3; 3.9	0.9227
	FSL1	0.0	-2.3; 2.4	0.9929
Plasma glucose decline (+/-exercise)	DG6	-6.2	-11.2; -1.2	0.0161
	FSL1	5.3	1.6; 9.1	0.0057
15-min hypoglycemia (+/- exercise)	DG6	-8.1	-16.3; 0.0	0.0505
	FSL1	13.5	6.4; 20.5	0.0005
45-min hypoglycemia	DG6	-8.4	-12.4; -4.3	<.0001
	FSL1	-0.5	-3.6; 2.6	0.7298
Recovery euglycemia	DG6	-2.8	-7.3; 1.6	0.2078
	FSL1	1.8	-3.0; 6.6	0.4680

Hypoglycemia was defined as plasma glucose <3.0 mmol/L, representing level 2 hypoglycemia. CI, confidence interval. ΔMARD%, mean absolute relative difference of Clamp-exercise – Clamp-rest in percentages.

Our results suggest that exercise has a negative effect on FSL1 performance without affecting the post-exercise sensor performance. Contrary, DG6 had an improvement in performance during exercise which persisted post-exercise. We hypothesize that the exercise-related performance increase of DG6 is caused by increased blood circulation and production of heat during exercise resulting in a subsequent increase in skin blood flow (30). This could potentially lead to a higher interstitial space fluid turnover rate and better equilibrium between plasma and interstitial space fluid, thus more accurate estimates of glucose (31). Conversely, a worsening in performance was seen for FSL1 during exercise. This may be explained by the placement of the sensor in an area of high movement and mechanical activity during exercise as opposed to the abdomen as seen for DG6 (32). Thus, the continual mechanical movement of the sensor may have outweighed the possible performance increase from increased skin blood flow.

Few studies have assessed the sensors' performance during exercise (33–37), although they mostly relied on capillary blood glucose as a reference method. Guillot et al. showed no notable changes in DG6 sensor accuracy during exercise while wearing the sensors on the abdomen (33). Dyess et al. showed an overall decrease in DG6 sensor performance during exercise, however apart from the abdomen, the participant had the option to wear the sensor on the upper arms, buttocks, and thighs (34). When sub-analyzing for the abdomen only, Dyess et al. found an increase in sensor performance which is in accordance with our study and supports our hypothesis about the role of placement of sensors.

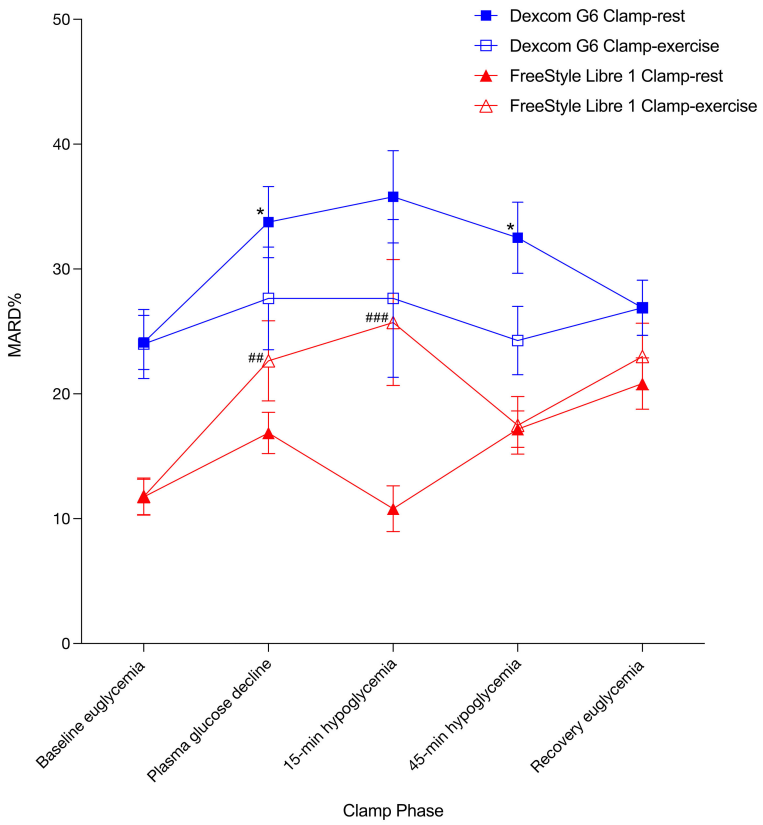

FIGURE 3
MARD% ± SE. * indicates significant difference between Dexcom G6 Clamp-exercise vs Dexcom G6 Clamp-rest. # indicates significant difference between FreeStyle Libre 1 Clamp-exercise vs FreeStyle Libre 1 Clamp-rest. Results at $P < 0.05$ was considered statistically significant and are shown with a single symbol. Results at $P < 0.01$ and $P < 0.001$ are shown with double and triple symbols, respectively. MARD%, mean absolute relative difference in percentages.

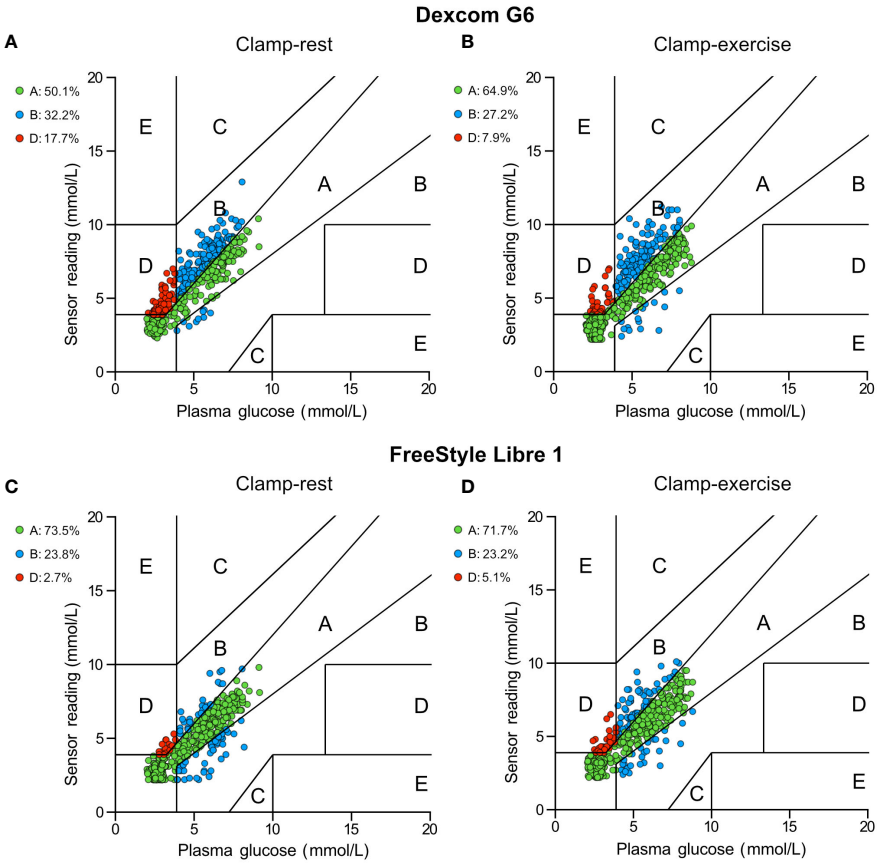

FIGURE 4
Clarke error grid analysis of Dexcom G6 and FreeStyle Libre 1. **(A)** Dexcom G6 for Clamp-rest. **(B)** Dexcom G6 for Clamp-exercise. **(C)** FreeStyle Libre 1 for Clamp-rest. **(D)** FreeStyle Libre 1 for Clamp-exercise. Each dot represents a glucose sensor reading paired with corresponding reference plasma glucose. Pairings in zone A and B are defined as clinically acceptable sensor estimates whereas pairings in zones C, D, and E are defined as clinically unacceptable and could lead to errors in diabetes treatment.

For FSL1, Moser et al. showed higher MARD during exercise in 19 individuals with type 1 diabetes compared to capillary blood glucose (35). Likewise, Fokkert et al. showed an increase in MARD for FSL1 during exercise in 23 individuals with type 1 diabetes compared to capillary blood glucose (36). However, Giani et al. showed no performance difference between rest and exercise in 17 young individuals with type 1 diabetes (37). As FSL1 is placed on the upper arm, an area of high activity during exercise, the decrease in sensor performance may be of this reason. We can only speculate if the performance of FSL1 would remain unchanged or increase if placed on the abdomen during exercise compared to rest. However, Charleer et al. showed a worsening in FSL1 performance when placed on the abdomen (38). Although sensor placement may have a notable role, factors such as varying populations included, different exercise forms and intensities employed, different extent of glycemic excursions and varying PG reference methods utilized may contribute to differing results.

According to Clarke error grid analysis, most of the data points in our study were in the clinically safe zones A+B for both sensors regardless of the clamp day, although the percentage of data points in the upper zone D was surprisingly high for DG6 during Clamp-rest. During Clamp-exercise, DG6 had a shift in data points from the clinically unacceptable zones (solely located in the upper D zone) to the clinically acceptable zones with an increase in zones A +B by almost 10 percentage points compared to Clamp-rest. This indicates that exercise potentially improves sensor accuracy and/or sensor lag time during rapid PG decline and hypoglycemia. In contrast, FSL1 showed a slight decrease of data points in the clinically acceptable zones during Clamp-exercise compared to Clamp-rest. FSL1 had almost a doubling of data points in zone D for Clamp-exercise indicating exercise having a clinically relevant negative effect. Thus, Clarke error grid analysis is consistent with the MARD results and could be explained in the same manner.

The previously mentioned studies also evaluated the clinical safety of DG6 and FSL1 using Clarke Error grid analysis. Guillot et al. showed good clinical reliability for DG6 during exercise with 99% of all values located in the clinically safe zones A+B (33). Dyess et al. found that individuals who wore DG6 on their buttocks during exercise had an increase of values in zone D while an increase of values in zones A+B was seen when wearing the sensor on the abdomen (34). For FSL1, Giani found 97% of sensor readings fell in zones A+B during rest and 98% during exercise indicating a marginal difference between the two settings (37). Moser et al. found 91% of sensor values were in zones A+B during rest while

78% for FSL1 during exercise indicating a decrease in the clinical accuracy of the sensor during exercise (35). Throughout all the studies where exercise negatively impacted the sensor performance, sensor values specifically increased in the upper zone D similarly to our study indicating an increase in failure to detect hypoglycemia.

The strengths of the present study include the cross-over design, the direct comparison of exercise versus rest and the conduction in a controlled clinical research facility. Sensors were initialized two days prior to the clamp day to prevent possible sensor inaccuracies. Unlike other studies that used capillary blood glucose, our study utilized PG measured by YSI 2900 as a glucose reference method which is often cited as the gold standard (39). Furthermore, the sensors were not user-calibrated but relied on the factory calibration mimicking a real-life setting with individuals doing the same.

A limitation to our study is the small number of participants and that the study only included male adults thus limiting the generalizability to females and other age groups. One participant had their FSL1 placed on the upper thigh which could potentially influence on the results, although Charleer et al. showed a minimal difference between the placement of FSL1 on the upper thigh and the upper arm (38). Another limitation is the rather high MARD observed for Dexcom G6 which could influence the results and that MARD does not take sensor errors into account (e.g., consistent higher glucose estimates). To overcome this, an adjunctive analysis called precision absolute relative deviation, which requires the insertion of an identical parallel sensor, could potentially have added value to our study (40). A limitation of Clarke Error grid analysis is the rather stringent limits between the zones which newer error grids seek to mitigate (41). Finally, the physiological effect of physical activity on glucose levels is rather complex and different at differing exercise types, intensities, and durations. Thus, the observed performance of the sensors cannot be generalized to other exercise intensities or durations.

In conclusion, the two commonly used sensors DG6 and FSL1 showed different responses to exercise in relation to PG decline and hypoglycemia in individuals with type 1 diabetes. Exercise negatively impacted FSL1 sensor performance during both declining PG and hypoglycemia, whereas DG6 had more accurate sensor readings during exercise and post-exercise. Individuals with type 1 diabetes and healthcare practitioners should be aware of the potentially negative or positive impacts of exercise on CGM sensor accuracy in detecting clinically relevant episodes of hypoglycemia.

Author's note

Parts of the following study were presented as an oral presentation at the European Association of the Study of Diabetes (EASD) 58th annual meeting in Stockholm, Sweden, September 2022

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Scientific Ethical Committee of the Capital Region of Denmark. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KM: Data curation, Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Investigation, Formal analysis. PH: Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. SE: Writing – review & editing, Validation, Resources, Methodology. JF: Formal analysis, Software, Supervision, Validation, Writing – review & editing. UP-b: Writing – review & editing, Methodology, Validation, Supervision, Conceptualization. FK: Conceptualization, Methodology, Resources, Supervision, Validation, Writing – review & editing. TV: Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. AA: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

SE is currently employed by Novo Nordisk and holds stock in Novo Nordisk. UP-b has served on advisory boards for and/or received lecture fees from Novo Nordisk and Sanofi. FK has served on advisory panels at, been part of speaker's bureaus for, served as a consultant to, and/or received research support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gubra, MSD/Merck, Novo Nordisk, Sanofi, ShouTi, Zealand Pharma and Zucara. TV has served on scientific advisory panels at, been part of speaker's

bureaus for, served as a consultant to, and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, Mundipharma, MSD/Merck, Novo Nordisk, Sanofi, and Sun Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Chiang JL, Maahs DM, Garvey KC, Hood KK, Laffel LM, Weinzimer SA, et al. Type 1 diabetes in children and adolescents: A position statement by the American diabetes association. *Diabetes Care*. (2018) 41:2026–44. doi: 10.2337/dci18-0023

2. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American diabetes association. *Diabetes Care*. (2016) 39:2065–79. doi: 10.2337/dc16-1728

3. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol*. (2017) 5:377–90. doi: 10.1016/S2213-8587(17)30014-1

4. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 5. Facilitating positive health behaviors and well-being to improve health outcomes: Standards of care in diabetes—2023. *Diabetes Care*. (2023) 46:S68–96. doi: 10.2337/dc23-S005

5. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia*. (2012) 55:542–51. doi: 10.1007/s00125-011-2403-2

6. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. (2008) 31:2108–9. doi: 10.2337/dc08-0720

7. Finn M, Sherlock M, Feehan S, Guinan EM, Moore KB. Adherence to physical activity recommendations and barriers to physical activity participation among adults with type 1 diabetes. *Ir J Med Sci*. (2022) 191(4):1639–46. doi: 10.1007/s11845-021-02741-w

8. Dubé MC, Prud'homme D, Lemieux S, Lavoie C, Weisnagel SJ. Relation between energy intake and glycemic control in physically active young adults with type 1 diabetes. *J Sci Med Sport*. (2014) 17:47–50. doi: 10.1016/j.jsams.2013.01.009

9. Yardley J, Mollard R, MacIntosh A, MacMillan F, Wicklow B, Berard L, et al. Vigorous intensity exercise for glycemic control in patients with type 1 diabetes. *Can J Diabetes*. (2013) 37:427–32. doi: 10.1016/j.jcjd.2013.08.269

10. Lin R, Brown F, James S, Jones J, Ekinci E. Continuous glucose monitoring: A review of the evidence in type 1 and 2 diabetes mellitus. *Diabetes Med J Br Diabetes Assoc*. (2021) 38:e14528. doi: 10.1111/dme.14528

11. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). *Diabetologia*. (2020) 63:2501–20. doi: 10.1007/s00125-020-05263-9

12. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: An observational field study. *Diabetes Technol Ther*. (2011) 13:819–25. doi: 10.1089/dia.2011.0052

13. Burckhardt MA, Chetty T, Smith GJ, Adolfsson P, de Bock M, Jones TW, et al. Use of continuous glucose monitoring trends to facilitate exercise in children with type 1 diabetes. *Diabetes Technol Ther*. (2019) 21:51–5. doi: 10.1089/dia.2018.0292

14. Stone JY, Bailey TS. Benefits and limitations of continuous glucose monitoring in type 1 diabetes. *Expert Rev Endocrinol Metab*. (2020) 15:41–9. doi: 10.1080/17446651.2020.1706482

15. Hagelqvist PG, Andersen A, Maytham KB, Andreasen CR, Engberg S, Lindhardt TB, et al. Exercise-related hypoglycaemia induces QTC -interval prolongation in individuals with type 1 diabetes. *Diabetes Obes Metab*. (2023) 25(5):1186–95. doi: 10.1111/dom.14964

16. Tsoukas M, Rutkowski J, El-Fathi A, Yale JF, Bernier-Twardy S, Bossy A, et al. Accuracy of freeStyle libre in adults with type 1 diabetes: the effect of sensor age. *Diabetes Technol Ther*. (2020) 22:203–7. doi: 10.1089/dia.2019.0262

17. Dexcom, Inc. Dexcom G6 Continuous Glucose Monitoring Systems User Guide. San Diego, CA: Dexcom, Inc. Available online at: https://s3-us-west-2.amazonaws.com/dexcompdf/G6-CGM-Users-Guide.pdfhttps://dexcompdf.s3.us-west-2.amazonaws.com/en-us/G6-CGM-Users-Guide-new.pdf (Accessed August 27, 2023).

18. Abbott Laboratories, Ltd. FreeStyle Libre Flash Glucose Monitoring System User's Manual. Alameda, CA: Abbott Laboratories, Ltd. Available online at: https://freestyleserver.com/Payloads/IFU/2023/q1/ART40989-201_rev-A-WEB.pdfhttps://freestyleserver.com/Payloads/IFU/2023/q1/ART40989-201_rev-A-WEB.pdf (Accessed August 27, 2023).

19. Canning KL, Brown RE, Jamnik VK, Salmon A, Ardern CI, Kuk JL. Individuals underestimate moderate and vigorous intensity physical activity. *PLoS One*. (2014) 9:e97927. doi: 10.1371/journal.pone.0097927

20. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. (2017) 40:155–7. doi: 10.2337/dc16-2215

21. Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, Hinzmann R, Kassab A, Freckmann G, et al. Benefits and limitations of MARD as a performance parameter for continuous glucose monitoring in the interstitial space. *J Diabetes Sci Technol*. (2020) 14:135–50. doi: 10.1177/1932296819855670

22. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care*. (1987) 10:622–8. doi: 10.2337/diacare.10.5.622

23. Shah VN, Laffel LM, Wadwa RP, Garg SK. Performance of a factory-calibrated real-time continuous glucose monitoring system utilizing an automated sensor applicator. *Diabetes Technol Ther*. (2018) 20:428–33. doi: 10.1089/dia.2018.0143

24. Castorino K, Polsky S, O'Malley G, Levister C, Nelson K, Farfan C, et al. Performance of the dexcom G6 continuous glucose monitoring system in pregnant women with diabetes. *Diabetes Technol Ther*. (2020) 22:943–7. doi: 10.1089/dia.2020.0085

25. Davis GM, Spanakis EK, Migdal AL, Singh LG, Albury B, Urrutia MA, et al. Accuracy of dexcom G6 continuous glucose monitoring in non–critically ill hospitalized patients with diabetes. *Diabetes Care*. (2021) 44:1641–6. doi: 10.2337/dc20-2856

26. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technol Ther*. (2015) 17:787–94. doi: 10.1089/dia.2014.0378

27. Welsh JB, Zhang X, Puhr SA, Johnson TK, Walker TC, Balo AK, et al. Performance of a factory-calibrated, real-time continuous glucose monitoring system in pediatric participants with type 1 diabetes. *J Diabetes Sci Technol*. (2019) 13:254–8. doi: 10.1177/1932296818798816

28. Ólafsdóttir AF, Attvall S, Sandgren U, Dahlqvist S, Pivodic A, Skrtic S, et al. A clinical trial of the accuracy and treatment experience of the flash glucose monitor freeStyle libre in adults with type 1 diabetes. *Diabetes Technol Ther*. (2017) 19:164–72. doi: 10.1089/dia.2016.0392

29. Nagl K, Berger G, Aberer F, Ziko H, Weimann K, Bozic I, et al. Performance of three different continuous glucose monitoring systems in children with type 1 diabetes during a diabetes summer camp. *Pediatr Diabetes*. (2021) 22:271–8. doi: 10.1111/pedi.13160

30. González-Alonso J. Human thermoregulation and the cardiovascular system: Tissue blood flow and temperature regulation. *Exp Physiol*. (2012) 97:340–6. doi: 10.1113/expphysiol.2011.058701

31. Moser O, Yardley J, Bracken R. Interstitial glucose and physical exercise in type 1 diabetes: Integrative physiology, technology, and the gap in-between. *Nutrients*. (2018) 10:93. doi: 10.3390/nu10010093

32. Coates AM, Cohen JN, Burr JF. Investigating sensor location on the effectiveness of continuous glucose monitoring during exercise in a non-diabetic population. *Eur J Sport Sci*. (2023) 23:2109–17. doi: 10.1080/17461391.2023.2174452

33. Guillot FH, Jacobs PG, Wilson LM, Youssef JE, Gabo VB, Branigan DL, et al. Accuracy of the dexcom G6 glucose sensor during aerobic, resistance, and interval exercise in adults with type 1 diabetes. *Biosensors*. (2020) 10:138. doi: 10.3390/bios10100138

34. Dyess RJ, McKay T, Feygin Y, Wintergerst K, Thrasher BJ. Factory-calibrated continuous glucose monitoring system accuracy during exercise in adolescents with

type 1 diabetes mellitus. *J Diabetes Sci Technol*. (2022) 0(0). doi: 10.1177/19322968221120433

35. Moser O, Eckstein ML, McCarthy O, Deere R, Pitt J, Williams DM, et al. Performance of the Freestyle Libre flash glucose monitoring (flash GM) system in individuals with type 1 diabetes: A secondary outcome analysis of a randomized crossover trial. *Diabetes Obes Metab*. (2019) 21:2505–12. doi: 10.1111/dom.13835

36. Fokkert M, van Dijk PR, Edens MA, Díez Hernández A, Slingerland R, Gans R, et al. Performance of the Eversense versus the Free Style Libre Flash glucose monitor during exercise and normal daily activities in subjects with type 1 diabetes mellitus. *BMJ Open Diabetes Res Care*. (2020) 8:e001193. doi: 10.1136/bmjdrc-2020-001193

37. Giani E, Macedoni M, Barilli A, Petitti A, Mameli C, Bosetti A, et al. Performance of the Flash Glucose Monitoring System during exercise in youth with Type 1 diabetes. *Diabetes Res Clin Pract*. (2018) 146:321–9. doi: 10.1016/j.diabres.2018.10.001

38. Charleer S, Mathieu C, Nobels F, Gillard P. Accuracy and precision of flash glucose monitoring sensors inserted into the abdomen and upper thigh compared with the upper arm. *Diabetes Obes Metab*. (2018) 20:1503–7. doi: 10.1111/dom.13239

39. Han J, Nichols JH, Rice M, Klonoff DC. The end of the road for the YSI 2300 analyzer: where do we go now? *J Diabetes Sci Technol*. (2020) 14:595–600. doi: 10.1177/1932296819886603

40. Obermaier K, Schmelzeisen-Redeker G, Schoemaker M, Klötzer HM, Kirchsteiger H, Eikmeier H, et al. Performance evaluations of continuous glucose monitoring systems: precision absolute relative deviation is part of the assessment. *J Diabetes Sci Technol*. (2013) 7:824–32. doi: 10.1177/193229681300700404

41. Klonoff DC, Lias C, Vigersky R, Clarke W, Parkes JL, Sacks DB, et al. The surveillance error grid. *J Diabetes Sci Technol*. (2014) 8(4):658–72. doi: 10.1177/1932296814539589

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EDITED BY
Stefano Passanisi,
University of Messina, Italy

REVIEWED BY
Benli Su,
Second Hospital of Dalian Medical University, China
Sergio Di Molfetta,
University of Bari Aldo Moro, Italy

*CORRESPONDENCE
Jianhua Ma
majianhua196503@126.com
Jindan Wu
wujindandan@sina.com

†These authors have contributed equally to this work and share first authorship

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Ultra rapid lispro improves postprandial glucose control versus lispro in combination with basal insulin: a study based on CGM in type 2 diabetes in China

Lu Yuan†, Yi Luo†, Yong Luo, Bo Ding, Peng Zhang, Jianhua Ma* and Jindan Wu*

Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China

Aim: To evaluate the efficacy and safety of URLi (ultra rapid lispro insulin) compared to insulin lispro as bolus insulin with basal insulin using CGM in the individuals with type 2 diabetes(T2D) in China.

Methods: This was a double-blind, randomized, parallel, prospective, phase 3 study. Subjects with uncontrolled T2D were recruited and randomized 1:2 into the insulin lispro and URLi groups. Subjects received a consistent basal insulin regimen during the study and self-administered insulin lispro or URLi before each meal throughout the treatment period. Subjects underwent a 3-day continuous glucose monitoring (CGM) at the baseline and endpoint respectively, and then CGM data were analyzed. The primary endpoint was to compare the difference in postprandial glucose (PPG) control using CGM between the two groups.

Results: A total of 57 subjects with T2D completed the study. Our CGM data showed that postprandial glucose excursions after breakfast (BPPGE) in the URLi group was lower than that in the insulin lispro group (1.59 $\pm$ 1.57 mmol/L vs 2.51 $\pm$ 1.73 mmol/L, p = 0.046). 1-hour PPG was observed to decrease more in the URLi group than that in the insulin lispro group (-1.37 $\pm$ 3.28 mmol/L vs 0.24 $\pm$ 2.58 mmol/L, p = 0.047). 2-hour PPG was observed to decrease more in the URLi group than that in the insulin lispro group (-1.12 $\pm$ 4.00 mmol/L vs 1.22 $\pm$ 2.90 mmol/L, p = 0.021). The mean HbA1c level decreased by 1.1% in the URLi group and 0.99% in the insulin lispro group, with no treatment difference (p = 0.642). In the CGM profile, TBR was not significantly different between the two groups (p = 0.743). The weight gain also did not differ between the two groups (p = 0.303).

Conclusion: URLi can control breakfast PPG better than insulin lispro in adults with T2D in China, while it is non-inferior in improving HbA1c. The incidence of hypoglycemic and weight gain were similar between the two groups.

KEYWORDS

ultra rapid lispro insulin, postprandial glucose, postprandial glucose excursions, continuous glucose monitoring, HbA1c

1 Introduction

Diabetes mellitus (DM) has become one of the most common chronic diseases in the world. The global prevalence of diabetes was estimated to be 10.5% in 2021, with China having the largest number of people with diabetes, with more than 140 million, and more than 174 million by 2045 (1). According to statistics, about 95% of Chinese people with diabetes are type 2 diabetes mellitus (T2D) (2). Compared with the Western population, the age of onset of diabetes in Asian patients was generally younger, early β-cell dysfunction was also more obvious in the setting of insulin resistance because there appears to be a predisposition to impaired insulin secretion among East Asian population (3), and polished rice and refined wheat form the basis of most Asian diets with high glycemic index and high glycemic load values (4), postprandial glucose(PPG) fluctuates obviously (5). In the Asian population, postprandial blood glucose levels tend to be higher than in the Caucasian population, even after eating the same foods (6–8). A study conducted in China found that nearly 70% of Chinese T2D patients received insulin therapy, but less than 20% of them reached the glycated hemoglobin A1c (HbA1c) target (HbA1c<7.0) (9).

The HbA1c value is one of the main indicators reflecting long-term glycemic control (10, 11). In order to achieve the HbA1c target value, both fasting plasma glucose(FPG) and PPG should be monitored (12, 13). As HbA1c decreased, PPG had a greater impact on HbA1c than FPG, and PPG accounted approximately 80% of HbA1c when HbA1c was <6.2% and only about 40% when HbA1c was above 9.0% (14). A study in China showed that PPG contributed more than FPG in individuals with HbA1c < 8.5%, whereas FPG became the predominant contributor in the poorly controlled individuals with HbA1c ≥ 8.5% (15). Control of PPG is essential for achieving recommended HbA1c targets. A survey in China showed that the number of participants with isolated fasting hyperglycemia (IFH), isolated postprandial hyperglycemia (IPH) and combined hyperglycemia (CH) were 18.5%, 43.1% and 38.4%, respectively (16). People with diabetes with the IPH phenotype showed increased risks of diabetic microvascular complications compared to participants with the IFH phenotype (16). Clinical studies have demonstrated that targeting PPG can effectively improve glycemic control and long-term results in persons with T2D (17).

However, HbA1c does not necessarily refer daily glucose variability (GV), because the previous studies found that individuals with similar HbA1c may have different GV (18–20). GV is associated with oxidative stress, chronic inflammation and endothelial dysfunction, which contribute to vascular endothelial cell damage (21). Importantly, studies have already demonstrated the positive association between GV and macro/microvascular complications of diabetes (22, 23). Therefore, both HbA1c and GV should be taken into account to reduce the incidence of diabetic complications (20). Continuous glucose monitoring (CGM) continuously provides the glucose readings every 5 minutes for several consecutive days, which may be a potential tool to assess GV in subjects with T2D (24–26).

Reducing postprandial glucose excursions(PPGE), defined as the difference between peak PPG and FPG, is a valuable strategy for reducing GV in the individuals with diabetes (27). Furthermore, the data suggest that PPGE may be a particularly important therapeutic target in person with diabetes. Compared to long-term, sustained hyperglycemia, BG variety postprandially or during glucose 'swings' have a more specific triggering effect on oxidative stress, a factor that plays a pivotal role in the development of various diabetic complications (28). There is also evidence that postprandial hyperglycemia is a greater predictor of cardiovascular disease than elevated FPG levels (29).

Besides HbA1c and GV, the scientific community has recently focused on the importance of time in tight range 3.9-10.0 mmol/L (TITR) as a glucose control indicator, correlating with both average glucose levels and GV. TITR is important because it better reflects near-normal, or healthy, glucose physiology than TIR. Low PPGE contributes to achieving tight glycemic control. So the highest TITR may be associated with the lowest PPGE (30–32).

Postprandial glucose can be control with bolus insulin therapy (33, 34). However, the action of many bolus insulins is not sufficiently rapid to match carbohydrate absorption, limiting their efficacy and dosing flexibility (35). Ultra rapid insulins can better match carbohydrate absorption through faster absorption, more rapid onset, and shorter duration of action is highly desired for optimizing PPG control (35).

The active substance of ultra rapid insulin lispro (URLi) is insulin lispro. The excipients contain treprostinil and citrate, which can improve vascular permeability, cause local vasodilation, increase blood flow at the injection site and accelerate the entry of insulin-dependent proline into the vascular circulation to achieve a faster onset of action, shorter duration of action and more effective control of PPG levels (36). Studies have shown that URLi is superior to insulin lispro in controlling PPG levels and has also been shown to be non-inferior in improving HbA1c levels in adults with T2D (37). To date, there has been no study using continuous glucose monitoring systems (CGMS) to evaluate the efficacy and safety of URLi in the treatment of T2D in the Chinese population. Therefore, the aim of this study was to evaluate the efficacy and safety of URLi compared to insulin lispro as bolus insulin (administered 0 to 2 minutes before meal) with basal insulin using CGM in T2D in China.

2 Materials and methods

This was a double-blind, randomized, prospective, phase 3 study. The study was conducted in accordance with the ethical standards of institutional and/or national research committees and following the principles of the 1964 Declaration of Helsinki and later amendments. The study protocol and informed consent documents were approved by the Institutional Ethics Committee of Nanjing First Hospital. Written informed consent was obtained from all patients. The trial was registered with ClinicalTrials.gov (NCT03952143).

Abbreviations: URLi, ultra rapid lispro insulin; PPG, postprandial glucose; PPGE, postprandial glucose excursions.

2.1 Participants

From May 2019 to April 2020, T2D individuals in outpatient who presented with poorly controlled blood glucose for at least 90 d were enrolled in the Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, China. Our site was one of the centers. Data sourced from our center.

The inclusion criteria were as follows: 1) age: above 18 years, 2) T2D duration: at least one year, 3) HbA1c: 7.0% to 11.0% at screening, 4) body mass index (BMI): ≤35.0 kg/m^2, 5) basal insulin combined with ≥1 prandial insulin or premixed insulin with ≥2 injections daily for ≥90 d prior to screening, 6) combined oral anti-diabetic medication (OAM): no more than three types.

Key exclusion criteria were as follows: 1) any episode of severe hypoglycemia within 6 months prior to screening, 2) one or more episodes of acute complications of diabetes within 6 months prior to screening.

2.2 Randomization

Following an eight-week lead-in period, subjects were randomized to receive either URLi or insulin lispro in a 2:1 ratio.

2.3 Study design

2.3.1 Insulin titration

The study included a one-week screening period and an 8-week lead-in period, followed by a 26-week treatment period, and a 4-week safety follow-up (Supplementary Figure S1). During the 8-week lead-in study period, all the individuals switch from premixed insulin or basal-bolus insulin to basal-bolus insulin. Initial insulin dose allocation: basal insulin accounted for 40-60% of the baseline total daily dose, and meal insulin accounted for another 40-60%. The unit of each meal was assigned by the researchers according to the subjects' eating patterns. The subjects received a uniform basal insulin regimen during this period: insulin glargine U-100 once daily or insulin degludec U-100 once daily (all the subjects in our site received insulin glargine U-100). The basal insulin dose was titrated according to the median of the last three FBG during the 8-week lead-in period at least once a week, the titration algorithm was in Supplementary Table S1. All subjects self-administered insulin lispro before each meal during the lead-in period, and the dose was adjusted under the guidance of the investigator. During the first 12 weeks after randomization (the intensive titration period), the insulin dose at breakfast was adjusted according to the median of the last three self-monitoring of blood glucose (SMBG) before lunch, the insulin dose at lunch was adjusted according to the median of the last three SMBG before dinner and the insulin dose at dinner was adjusted according to the median of the last three SMBG before bedtime at least once a week (Supplementary Table S2). During 12 to 26 weeks (the maintenance period), neither prandial nor basal insulin were allowed to be adjusted, except for safety reasons such as hypoglycemia or unacceptable hyperglycemia. From the beginning of the 8-week lead-in period and during the 26-week treatment period, only stable dosing of metformin and/or sodium glucose cotransporter-2 inhibitors (SGLT2is) were continued, and other OAMs were discontinued. The investigator gave the subjects dietary guidance about the meal composition and size.

2.3.2 MMTT

A 4-hour mixed glucose tolerance test (MMTT) was determined for all the subjects at baseline (visit 8) and at the end of the primary treatment period (visit 18), where MMTT at V8 had to be performed before randomization. MMTT required the subjects to be on an empty stomach for at least 8 hours, and patients had to have a FBG range of 3.9-10.0 mmol/L before starting MMTT. The standard meal for MMTT was a liquid nutrient mixture, with individualized insulin doses at mealtime, injected within 0-2 minutes before mealtime, and the subjects completed their meal within 15 minutes, with 0 being the time at which the subject began eating. Venous blood was collected 15 minutes before the meal and 0,15,30,60,120,180 and 240 minutes after the start of the meal (8 times).

2.3.3 CGM

All recruited subjects were subjected to a two-time, 3-day, retrospective CGM (Sof-sensor, CGMS-Gold, Medtronic Incorporated, Northridge, USA) at 3 days before Visits 8 and 18, as described previously (38). During the two-time CGM period, subjects were instructed to maintain moderate physical activity and have breakfast, lunch, and dinner at 07:00, 11:00, and 17:00, respectively, with a total daily caloric intake of 25kcal/kg/day. The percentages of carbohydrates, proteins, and fats were 55%, 17%, and 28%, respectively. After the CGM data collection, glucose indicators, such as the 24hr mean glucose concentration (MBG), 24hr standard deviation of the MG (SD), coefficient of variation (CV), TIR (time in range), TAR (time above range), TBR (time below range), TITR (time in tight range), and postprandial glucose excursions (PPGE) were recorded.

2.4 Endpoints

The primary endpoint was to compare the difference of PPGE between the two groups used CGM. The secondary endpoint included HbA1c, other CGM data, hypoglycemia and weight gain.

2.5 Statistical analysis

The sample size required was calculated using PASS 15.0. The level of significance, α, was set as 0.05, and the desired power of the study ($1 - \beta$) was 90%. Assuming that the mean of PPGE was 2.2 and 2.9 for the URLi and insulin lispro groups, the hypothesized standard deviation (SD) was 0.7 and 0.75 in each group. The minimum number of subjects required was 56 and assuming a

20% drop out rate over 26 weeks. It was estimated that we need enrolled at least 70 subjects.

Data are presented as mean ± SD, median (interquartile range), or percentage as appropriate. Standard t test was used to compare normally distributed data, and the Wilcoxon test was used for asymmetrically distributed data. The categorical data were examined with chi-square test. All statistical analyses were performed using SPSS version 22.0 software (IBM Corp., USA). A p value < 0.05 was considered statistically significant.

3 Results

3.1 Demographic characteristics

Overall, 75 participants with T2D were assessed for eligibility, 18 participants did not meet the inclusion criteria. Thus, the CGM data of 57 participants were collected and analyzed at the endpoint (insulin lispro, n = 21; URLi, n = 36).

There were no differences in the demographic characteristics of participants between the two groups (Table 1).

TABLE 1 The baseline characteristics of subjects of the two groups.

	Insulin lispro	URLi	p value
Gender (M/F)	12/9	20/17	0.820
Age (year)	62.00 ± 6.94	64.70 ± 9.49	0.490
Weight (kg)	65.45 ± 10.40	69.00 ± 9.05	0.180
BMI (kg/m^2)	24.47 ± 2.38	25.52 ± 2.69	0.144
ALT (U/L)	20.76 ± 9.26	23.68 ± 14.80	0.419
AST (U/L)	19.62 ± 5.27	20.73 ± 9.82	0.633
Cr (mmol/L)	90.40 ± 30.83	78.05 ± 20.89	0.078
HbA1c (%)	8.71 ± 1.00	8.89 ± 1.14	0.549
FPG (mmol/L)	12.05 ± 4.43	12.40 ± 4.52	0.779
Insulin used at study entry (Basal-bolus insulin/Pre-mix insulin)	7/14	12/24	0.611
Time of Pre-mix insulin			0.264
2	12	23	
3	2	1	
Time of Bolus insulin			0.253
2	0	2	
3	7	10	
Insulin dose at study entry (U/d)	42.19 ± 15.07	39.47 ± 15.76	0.522
OAMs used at baseline			
SGLT-2 inhibitors (n)	0	0	/
Metformin (n)	2	8	0.224

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Cr, creatinine; FPG, fasting plasma glucose; HbA1C, Hemoglobin A1c; OAM, oral anti-diabetic medication.

3.2 HbA1c

After 26 weeks of treatment, the HbA1c levels in the two groups significantly decreased (Table 2). Also in Table 2, we showed that there were no differences in the HbA1c levels between the two groups at different stages of treatment. URLi was non-inferior to insulin lispro in terms of the changes in the HbA1c levels from baseline to week 26. The mean HbA1c level decreased by 1.1% in the URLi group and 0.99% in the insulin lispro group with no treatment difference (p = 0.642) (Table 2).

3.3 MMTT

The superiority of URLi over insulin lispro in controlling 1-and 2-h PPG was demonstrated during the MMTT. Notably, 1-hour PPG was observed to decrease more in the URLi group than that in the insulin lispro group (-1.37 ± 3.28 mmol/L vs 0.24 ± 2.58mmol/L, p = 0.047). Also 2-hour PPG was observed to decrease more in the URLi group than that in the insulin lispro group (-1.12 ± 4.00 mmol/L vs 1.22 ± 2.90 mmol/L, p = 0.021) (Table 3).

3.4 CGM profile

Notably, MBG, SD, CV, TIR, TITR and TAR showed no significant differences between the two groups (p = 0.873, 0.582, 0.152, 0.465 and 0.542, respectively) (Table 4).

PPGE was calculated as the peak value of glucose after meals minus the glucose level at the beginning of each meal. The BPPGE (PPGE of breakfast) in the URLi group was lower than that in the insulin lispro group (1.59 ± 1.57 mmol/L vs 2.51 ± 1.73 mmol/L, p =0.046). The LPPGE (PPGE of lunch) and DPPGE (PPGE of dinner) did not differ between the two groups (p = 0.759 and 0.262, respectively) (Table 5). The time to achieve the peak value of glucose after each meal had no difference between the two groups (Table 5). TIR and TAR after each meals also showed no significant differences between the two groups (Table 6).

Although the CGM data showed that individuals in the two groups had similar hourly blood glucose concentrations per hour at the baseline, except at 12:00, the hourly MBG concentration at 12:00 in the URLi group was significantly higher than it in the insulin lispro group (Figure 1A). At the endpoint, the hourly MBG concentrations at 9:00, 10:00, 11:00, 12:00 in the URLi group were significantly lower than those in the insulin lispro group (Figure 1B).

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TABLE 2 Different stages of treatment of HbA1c in the two groups.

	V1	V8	V18	Δ	p value 1	p value 2
Insulin lispro	8.71 ± 1.00	7.78 ± 0.90	6.80 ± 0.75	-0.99 ± 0.80	0.000	0.000
URLi	8.89 ± 1.14	7.88 ± 1.00	6.77 ± 0.73	-1.10 ± 0.94	0.000	0.000
p value	0.549	0.723	0.913	0.642		

P value 1: V18 vs. V1; P value 2: V18 vs. V8.
Δ: the change of HbA1c from V8 to V18 (V18-V8).

3.5 Safety and weight gain

We also compared the risk of severe hypoglycemia (glucose <3.9 mmol/L) between the two groups. Subjects in the URLi group did not show an increased number of hypoglycemic episodes compared with those in the insulin lispro group.

TBR was not significantly different between the two groups (p = 0.743) in the CGM profile (Table 4).

The body weight at baseline and endpoint both did not differ between the two groups. The weight gain in the URLi group did not significantly differ from that in the insulin lispro group (2.74 ± 2.36 kg vs 2.95 ± 2.81 kg, p = 0.303).

TABLE 3 The MMTT profile of the two groups.

Time	Insulin lispro	URLi	p value
Δ-15min	0.22 ± 1.71	-0.12 ± 2.29	0.532
Δ0min	0.37 ± 1.71	-0.16 ± 2.15	0.318
Δ15min	-0.05 ± 2.27	-0.54 ± 2.55	0.463
Δ30min	0.22 ± 3.00	-1.05 ± 2.87	0.128
Δ60min	0.24 ± 2.58	-1.37 ± 3.28	0.047
Δ120min	1.22 ± 2.90	-1.12 ± 4.00	0.021
Δ180min	1.51 ± 2.70	-0.45 ± 4.93	0.060
Δ240min	1.17 ± 3.20	0.04 ± 3.92	0.246

Δ: V18-V8.

TABLE 4 The CGM profile of the two groups at the endpoint.

Parameter	Insulin lispro	URLi	p value
24 h MBG (mmol/L)	7.80 ± 1.31	7.73 ± 1.54	0.873
SD (mmol/L)	1.90 ± 0.87	2.05 ± 0.92	0.582
CV (%)	22.46 ± 6.71	25.74 ± 9.32	0.152
TIR (%)	84.42 ± 15.86	80.89 ± 17.34	0.465
TITR (%)	69.26 ± 19.72	65.87 ± 22.15	0.581
TAR (%)	0.00 (0.00, 0.18)	0.00 (0.00, 6.51)	0.196
TBR (%)	7.29 (0.00, 19.88)	8.33 (0.00, 17.53)	0.969

CV, coefficient of variation (%); MBG, mean glucose concentration (mmol/L); SD, the standard deviation of the MBG (mmol/L); TAR, time above range (> 10.0 mmol/L) (%); TBR, time below range (< 3.9 mmol/L) (%); TIR, time in range (3.9 - 10 mmol/L) (%); TITR (%): time in tight range (3.9 – 7.8 mmol/L) (%).

TABLE 5 The difference of the PPGE before and after treatment between the two groups.

	Insulin lispro	URLi	p value
BPPGE (mmol/L)			
Baseline	2.99 ± 2.31	3.95 ± 2.93	0.314
Endpoint	2.51 ± 1.73	1.59 ± 1.57	0.046
peak time after breakfast(min)			
Baseline	98.53 ± 52.70	95.54 ± 51.23	0.778
Endpoint	88.23 ± 50.25	77.94 ± 43.87	0.423
LPPGE (mmol/L)			
Baseline	4.07 ± 4.36	3.04 ± 2.42	0.750
Endpoint	2.27 ± 1.81	2.24 ± 1.86	0.759
peak time after lunch(min)			
Baseline	85.67 ± 66.70	65.71 ± 42.60	0.444
Endpoint	64.21 ± 28.25	67.18 ± 40.05	0.824
DPPGE (mmol/L)			
Baseline	3.93 ± 4.30	2.91 ± 2.31	0.731
Endpoint	1.99 ± 1.56	2.60 ± 1.88	0.262
peak time after dinner(min)			
Baseline	87.67 ± 77.04	77.50 ± 48.81	0.888
Endpoint	73.16 ± 55.13	77.21 ± 50.78	0.689

BPPGE, postprandial glucose excursions of breakfast (mmol/L); DPPGE, postprandial glucose excursions of dinner (mmol/L); LPPGE, postprandial glucose excursions of lunch (mmol/L).

TABLE 6 The difference of the postprandial 2h and 4h TIR/TAR before and after treatment between the two groups.

	Insulin lispro	URLi	p value
TIR-2hB (%)			
Baseline	82.02 ± 31.95	73.28 ± 33.76	0.362
Endpoint	83.33 ± 29.22	85.05 ± 23.91	0.821
TIR-2hL (%)			
Baseline	62.50 (20.83, 95.83)	66.67 (9.38, 100.00)	0.873

(Continued)

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TABLE 6 Continued

	Insulin lispro	URLi	p value
TIR-2hL (%)			
Endpoint	90.28 ± 20.56	86.76 ± 28.36	0.645
TIR-2hD (%)			
Baseline	70.83 (20.83, 100.00)	66.67 (3.13, 100.00)	0.679
Endpoint	82.41 ± 29.17	89.22 ± 25.89	0.392
TAR-2hB (%)			
Baseline	0.00 (0.00, 33.33)	0.00 (0.00, 42.71)	0.211
Endpoint	0.00 (0.00, 19.79)	0.00 (0.00, 14.58)	0.424
TAR-2hL (%)			
Baseline	16.67 (0.00, 66.67)	33.33 (0.00, 90.63)	0.438
Endpoint	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.793
TAR-2hD (%)			
Baseline	29.17 (0.00, 79.17)	33.33 (0.00, 96.88)	0.808
Endpoint	0.00 (0.00, 39.58)	0.00 (0.00, 0.00)	0.206
TIR-4hB (%)			
Baseline	78.95 ± 28.43	64.15 ± 35.77	0.148
Endpoint	79.51 ± 28.50	83.27 ± 20.67	0.588
TIR-4hL (%)			
Baseline	47.92 (18.75, 89.58)	50.00 (20.83, 90.63)	0.838
Endpoint	85.76 ± 23.29	85.60 ± 28.32	0.983
TIR-4hD (%)			
Baseline	68.75 (14.58, 100.00)	45.83 (8.33, 81.77)	0.524
Endpoint	83.10 ± 25.31	84.99 ± 26.61	0. 806
TAR-4hB (%)			
Baseline	8.33 (0.00, 37.50)	21.88 (0.00, 60.94)	0.150
Endpoint	0.00 (0.00, 43.75)	0.00 (0.00, 25.52)	0.856
TAR-4hL (%)			
Baseline	39.58 (0.00, 81.25)	44.79 (9.38, 79.17)	0.716
Endpoint	0.00 (0.00, 12.50)	0.00 (0.00, 0.00)	0.463
TAR-4hD (%)			
Baseline	31.25 (0.00, 81.25)	46.88 (0.00, 91.67)	0.977
Endpoint	0.00 (0.00, 24.48)	0.00 (0.00, 21.35)	0.338

TAR-2hB: time above range (> 10 mmol/L) from 0 to 120 minutes after the start of the breakfast; TAR-2hD, TAR from 0 to 120 minutes after the start of the dinner; TAR-2hL, TAR from 0 to 120 minutes after the start of the lunch; TAR-4hB, TAR from 0 to 240 minutes after the start of the breakfast; TAR-4hD, TAR from 0 to 240 minutes after the start of the dinner; TAR-4hL, TAR from 0 to 240 minutes after the start of the lunch; TIR-2hB, time in range (3.9 - 10 mmol/L) from 0 to 120 minutes after the start of the breakfast; TIR-2hD, TIR from 0 to 120 minutes after the start of the dinner; TIR-2hL, TIR from 0 to 120 minutes after the start of the lunch; TIR-4hB, TIR from 0 to 240 minutes after the start of the breakfast; TIR-4hD, TIR from 0 to 240 minutes after the start of the dinner; TIR-4hL, TIR from 0 to 240 minutes after the start of the lunch.

At the endpoint, the basal insulin dose did not differ between the two groups, and the bolus insulin dose also did not differ between the two groups (Figure 2).

4 Discussion

This prospective study showed that individuals with T2D who received URLi with basal insulin had better postprandial glycemic control than those who received lispro with basal insulin.

Overall, the results of this study suggest that URLi may provide a glycemic control comparable to lispro insulin in individuals with T2D who have significantly elevated PPG. In individuals with T2D, PPG levels typically peak about 2 hours after a meal (39). The increase in PPG is due to loss of insulin secretion in the first phase, decreased insulin sensitivity in peripheral tissues, and decreased suppression of hepatic glucose production after meals (40). Bolus pre-meal insulin treatment reduces PPGE in T2D (41) The first generation of fast acting insulin analogs has shown better PPGE regulation than standard human insulin. However, there is still an unmet need for insulin analogs with faster onset and a shorter duration of action that could potentially contribute to better PPG control than the rapid-acting insulin analogs (42, 43).

Although there was no clinically significant difference in HbA1c reduction between the URLi groups and the lispro insulin group in the study. It is known that HbA1c measurements can be influenced by factors other than glucose levels (44), such as hemoglobinopathies, red blood cell survival, and metabolic factors that influence the glycation response. Information about glycemic variability or the distinction between fasting, preprandial and PPG is not accurately reflected by the HbA1c value (45). It is therefore not surprising that the HbA1c value may not accurately reflect the improvement in average daily blood glucose levels, particularly the reduction in PPGE in individuals treated with URLi. A 1-h plasma glucose cut off of 155 mg/dL post oral glucose tolerance test (OGTT) is an important predictor of developing T2D (46, 47). PPGE is also associated with inflammation, thrombosis, endothelial dysfunction and the development of oxidative stress, all of which may contribute to the pathogenesis of cardiovascular disease (48, 49). Elevated 2-hour PPG levels are associated with an increased risk of cardiovascular events and mortality (50).The MMTT assessment (at breakfast) showed that URLi lowered 1-hour and 2-hour PPG levels and excursions as effectively or in some cases (in the early post-meal phase), even more effectively than pre-meal insulin lispro.

Similarly, CGM profile results at baseline and after 26 weeks of treatment showed that URLi was more effective than insulin lispro in lowering PPG levels and PPGE after breakfast. The effect of URLi was greatest during breakfast. The most important finding of this study is that URLi works particularly well at breakfast, a meal with a high physiological demand for insulin.

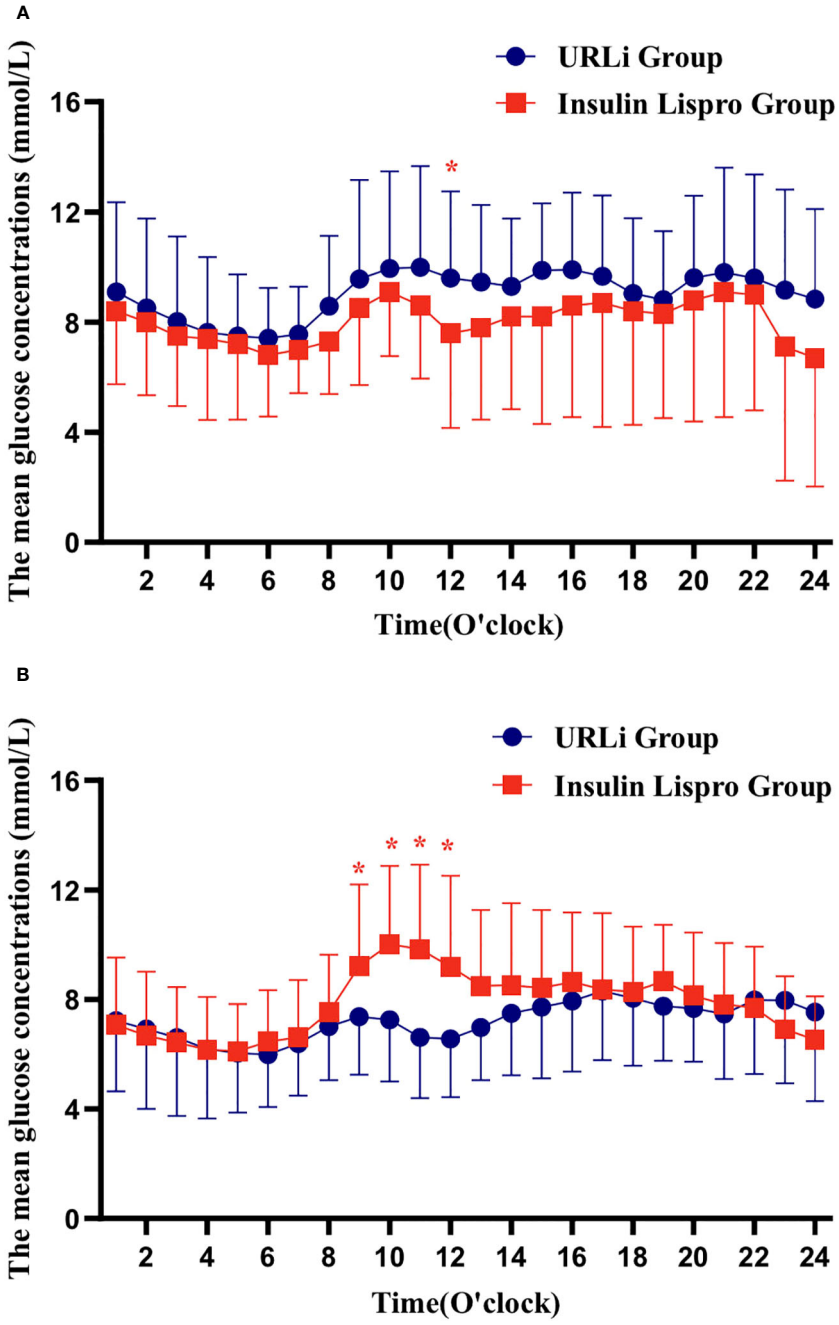

FIGURE 1
hourly blood glucose concentrations per hour in 24h (**A**: at the baseline; **B**: at the endpoint). *: $p < 0.05$.

The BPPGE in the URLi group was lower than it in the insulin lispro group, the URLi can improve the PPGE of breakfast. The peak PPG after breakfast was relatively the highest and reached the peak value the fastest, indicating severe acute postprandial hyperglycemia. In addition to the influence of dietary habits, this was also related to the peak effect of glucose- increasing hormones such as cortisol during this period.

Our results showed a similar safety profile for URLi and insulin lispro. Importantly, the improvement in PPG control with URLi was not associated with an increase in hypoglycemic events.

There was no previous study investigating the efficacy and safety of URLi in the treatment of T2D with CGM. This study has highlighted that URLi can improve PPG more than insulin lispro. One strength of the study is the use of CGM, which can capture more detailed information about blood glucose levels than SMBG and HbA1c, such as PPGE, SD, TIR, TAR and TBR. One limitation of the study is that it did not assess β-cell function in those with

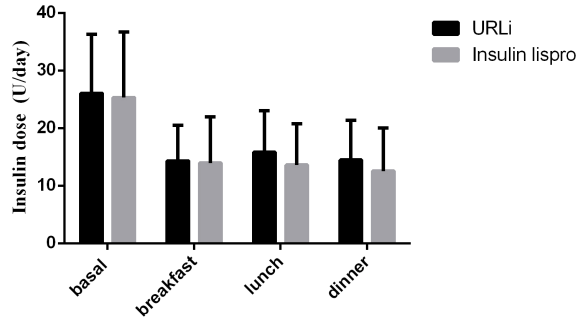

FIGURE 2
insulin dose between the two groups at the endpoint.

T2D. Thus, the result did not account for differences in the efficacy of URLi in individuals with different islet function.

5 Conclusion

In conclusion, this study shows that URLi can control breakfast PPG better than insulin lispro in adults with T2D in China, while being non-inferior in improving HbA1c. The incidence of hypoglycemic and weight gain were similar in both groups.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Institutional Ethics Committee of Nanjing First Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LY: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. YiL: Writing – original draft. YoL: Writing – original draft, Investigation. BD: Writing – original draft, Investigation. PZ: Writing – original draft, Investigation. JM: Writing – review & editing, Project administration, Investigation, Funding acquisition. JW: Writing – review & editing, Investigation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1364585/full#supplementary-material

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

2. Hu C, Jia W. Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication. *Diabetes*. (2018) 67:3–11. doi: 10.2337/dbi17-0013

3. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann New York Acad Sci*. (2013) 1281:64–91. doi: 10.1111/nyas.12098

4. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *Jama*. (2002) 287:2414–23. doi: 10.1001/jama.287.18.2414

5. Sacks FM, Carey VJ, Anderson CA, Miller ER, Copeland T, Charleston J, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *Jama*. (2014) 312:2531–41. doi: 10.1001/jama.2014.16658

6. Dickinson S, Colagiuri S, Faramus E, Petocz P, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. *J Nutr*. (2002) 132:2574–9. doi: 10.1093/jn/132.9.2574

7. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet*. (2017) 390:2050–62. doi: 10.1016/S0140-6736(17)32252-3

8. Wang X, Xie C, Marathe CS, Malbert C, Horowitz M, Jones KL, et al. Disparities in gastric emptying and postprandial glycaemia between Han Chinese and Caucasians with type 2 diabetes. *Diabetes Res Clin Pract*. (2020) 159:107951. doi: 10.1016/j.diabres.2019.107951

9. Dong Q, Huang J, Liu S, Yang L, Li J, Li B, et al. A survey on glycemic control rate of type 2 diabetes mellitus with different therapies and patients' satisfaction in China. *Patient preference adherence*. (2019) 13:1303–10. doi: 10.2147/PPA.S198908

10. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *New Engl J Med*. (2000) 342:381–9. doi: 10.1056/NEJM200002103420603

11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. (1998) 352:837–53. doi: 10.1016/S0140-6736(98)07019-6

12. Umpierrez G, Pantalone KM, Atisso CM, Landó LF, Patel H. Relative contribution of basal and postprandial hyperglycaemia stratified by HbA1c categories before and after treatment intensification with dulaglutide. *Diabetes Obes Metab*. (2019) 21:1365–72. doi: 10.1111/dom.13662

13. Saisho Y. Importance of beta cell function for the treatment of type 2 diabetes. *J Clin Med*. (2014) 3:923–43. doi: 10.3390/jcm3030923

14. Woerle HJ, Neumann C, Zschau S, Tenner S, Irsigler A, Schirra J, et al. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes Importance of postprandial glycemia to achieve target HbA1c levels. *Diabetes Res Clin Pract*. (2007) 77:280–5. doi: 10.1016/j.diabres.2006.11.011

15. Yan R, Hu Y, Li F, Jiang L, Xu X, Wang J, et al. Contributions of fasting and postprandial glucose concentrations to haemoglobin A1c in drug-naïve mal-glucose metabolism in chinese population using continuous glucose monitoring system. *Int J Endocrinol*. (2019) 2019:1267475. doi: 10.1155/2019/1267475

16. Liu G, Dou J, Zheng D, Zhang J, Wang M, Li W, et al. Association between abnormal glycemic phenotypes and microvascular complications of type 2 diabetes mellitus outpatients in China. *Diabetes Metab syndrome obesity: Targets Ther*. (2020) 13:4651–9. doi: 10.2147/DMSO.S242148

17. Lu J, He J, Li M, Tang X, Hu R, Shi L, et al. Predictive value of fasting glucose, postload glucose, and hemoglobin A(1c) on risk of diabetes and complications in chinese adults. *Diabetes Care*. (2019) 42:1539–48. doi: 10.2337/dc18-1390

18. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. (2008) 31:1473–8. doi: 10.2337/dc08-0545

19. Zhou J, Mo Y, Li H, Ran X, Yang W, Li Q, et al. Relationship between HbA1c and continuous glucose monitoring in Chinese population: a multicenter study. *PloS One*. (2013) 8:e83827. doi: 10.1371/journal.pone.0083827

20. Del Prato S. In search of normoglycaemia in diabetes: controlling postprandial glucose. *Int J Obes related Metab disorders: J Int Assoc Study Obes*. (2002) 26:S9–17. doi: 10.1038/sj.ijo.0802172

21. Cha JJ, Min HS, Kim K, Lee MJ, Lee MH, Kim JE, et al. Long-term study of the association of adipokines and glucose variability with diabetic complications. *Korean J Internal Med*. (2018) 33:367–82. doi: 10.3904/kjim.2016.114

22. Johnson EL. Glycemic variability in type 2 diabetes mellitus: oxidative stress and macrovascular complications. *Adv Exp Med Biol*. (2012) 771:139–54. doi: 10.1007/978-1-4614-5441-0_13

23. Prázný M, Škrha J, Šoupal J, Škrha J Jr. [Short-term and long-term glycemic variability and its relationship to microvascular complications of diabetes]. *Vnitrni lekarstvi*. (2016) 62:S85–93.

24. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. (2017) 40:1631–40. doi: 10.2337/dc17-1600

25. Petrie JR, Peters AL, Bergenstal RM, Holl RW, Fleming GA, Heinemann L. Improving the clinical value and utility of CGM systems: issues and recommendations: A joint statement of the European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group. *Diabetologia*. (2017) 60:2319–28. doi: 10.1007/s00125-017-4463-4

26. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19-0028

27. Monnier L, Colette C. Glycemic variability: should we and can we prevent it? *Diabetes Care*. (2008) 31:S150–154. doi: 10.2337/dc08-s241

28. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Jama*. (2006) 295:1681–7. doi: 10.1001/jama.295.14.1681

29. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. (2003) 26:881–5. doi: 10.2337/diacare.26.3.881

30. Dunn TC, Ajjan RA, Bergenstal RM, Xu Y. It time to move beyond TIR to TITR? Real-world data from over 20,000 users of continuous glucose monitoring in patients with type 1 and type 2 diabetes. *Diabetes Technol Ther*. (2024) 26:203–10. doi: 10.1089/dia.2023.0565

31. Beck RW, Raghinaru D, Calhoun P, Bergenstal RM. A comparison of continuous glucose monitoring-measured time-in-range 70-180 mg/dL versus time-in-tight-range 70-140 mg/dL. *Diabetes Technol Ther*. (2024) 26:151–5. doi: 10.1089/dia.2023.0380

32. Passanisi S, Piona C, Salzano G, Marigliano M, Bombaci B, Morandi A, et al. Aiming for the best glycemic control beyond time in range: time in tight range as a new continuous glucose monitoring metric in children and adolescents with type 1 diabetes using different treatment modalities. *Diabetes Technol Ther*. (2024) 26:161–6. doi: 10.1089/dia.2023.0373

33. Jia W, Weng J, Zhu D, Ji L, Lu J, Zhou Z, et al. Standards of medical care for type 2 diabetes in China 2019. *Diabetes/metabolism Res Rev*. (2019) 35:e3158. doi: 10.1002/dmrr.3158

34. American Diabetes Association Professional Practice Committee. 9.Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024. *Diabetes Care*. (2024) 47:S158–s178. doi: 10.2337/dc24-S009

35. Wong EY, Kroon L. Ultra-rapid-acting insulins: how fast is really needed? *Clin diabetes: Publ Am Diabetes Assoc*. (2021) 39:415–23. doi: 10.2337/cd20-0119

36. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care*. (2020) 43:2991–8. doi: 10.2337/dc19-2550

37. Zhou J, Chen S, Cheng J, Zhu J, Lou Y, Bao Y, et al. Ultra rapid lispro improves postprandial glucose control versus lispro in combination with insulin glargine/degludec in adults with type 2 diabetes: a prospective, randomized, double-blind, phase 3 trial. *Sci Bull*. (2022) 67:1785–91. doi: 10.1016/j.scib.2022.08.002

38. Li FF, Fu LY, Zhang WL, Su SF, Wu JD, Sun J, et al. Blood glucose fluctuations in type 2 diabetes patients treated with multiple daily injections. *J Diabetes Res*. (2016) 2016:1028945. doi: 10.1155/2016/1028945

39. American Diabetes Association. Postprandial blood glucose. American Diabetes Association. *Diabetes Care*. (2001) 24:775–8. doi: 10.2337/diacare.24.4.775

40. Erlinger TP, Brancati FL. Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. *Diabetes Care*. (2001) 24:1734–8. doi: 10.2337/diacare.24.10.1734

41. Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough–what next? *Diabetes/metabolism Res Rev*. (2007) 23:257–64. doi: 10.1002/dmrr.733

42. Heinemann L, Muchmore DB. Ultrafast-acting insulins: state of the art. *J Diabetes Sci Technol*. (2012) 6:728–42. doi: 10.1177/193229681200600402

43. Home PD. Plasma insulin profiles after subcutaneous injection: how close can we get to physiology in people with diabetes? *Diabetes Obes Metab*. (2015) 17:1011–20. doi: 10.1111/dom.12501

44. Nitin S. HbA1c and factors other than diabetes mellitus affecting it. *Singapore Med J*. (2010) 51:616–22.

45. Lu J, Wang C, Cai J, Shen Y, Chen L, Zhang L, et al. Association of HbA1c with all-cause mortality across varying degrees of glycemic variability in type 2 diabetes. *J Clin Endocrinol Metab*. (2021) 106:3160–7. doi: 10.1210/clinem/dgab532

46. Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. *Diabetes Care*. (2009) 32:281–6. doi: 10.2337/dc08-1264

47. Jagannathan R, Buysschaert M, Medina JL, Katz K, Musleh S, Dorcely B, et al. The 1-h post-load plasma glucose as a novel biomarker for diagnosing dysglycemia. *Acta diabetologica*. (2018) 55:519–29. doi: 10.1007/s00592-018-1105-3

48. Jiang J, Zhao L, Lin L, Gui M, Aleteng Q, Wu B, et al. Postprandial blood glucose outweighs fasting blood glucose and HbA1c in screening coronary heart disease. *Sci Rep*. (2017) 7:14212. doi: 10.1038/s41598-017-14152-y

49. Cavalot F, Pagliarino A, Valle M, Martino LD, Bonomo K, Massucco P, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care*. (2011) 34:2237–43. doi: 10.2337/dc10-2414

50. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia*. (1996) 39:1577–83. doi: 10.1007/s001250050617

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EDITED BY
Lingling Xu,
Peking Union Medical College Hospital (CAMS), China

REVIEWED BY
Yaru Zhou,
The Third hospital of Hebei University, China
Artur Rydosz,
AGH University of Science and Technology, Poland
Eduardo Gutiérrez-Abejón,
Universidad de Valladolid, Spain

*CORRESPONDENCE
Jianhua Ma
majianhua196503@126.com
Dafa Ding
dingdafa@njmu.edu.cn

†These authors share first authorship

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Accuracy of a novel real-time continuous glucose monitoring system: a prospective self-controlled study in thirty hospitalized patients with type 2 diabetes

Shenghui Ge[1†], Hui Zhang[2†], Jun Wang[3†], Huiqin Li[1], Xiaofei Su[1], Dafa Ding[4*] and Jianhua Ma[1*]

[1]Department of Endocrinology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China, [2]Department of Endocrinology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China, [3]Department of Health Management Center, Nanjing First Hospital, Nanjing Medical University, Nanjing, China, [4]Department of Endocrinology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China

Aims: The present study aimed to investigate the accuracy of the Glunovo® real-time continuous glucose monitoring system (rtCGMS).

Methods: We conducted a 14-day interstitial glucose level monitoring using Glunovo® rtCGMS on thirty hospitalized patients with type 2 diabetes. The flash glucose monitoring (FGM) was used as a self-control. Consistency tests, error grid analysis, and calculation of the mean absolute relative difference (MARD) were performed using R software to assess the accuracy of Glunovo® rtCGMS.

Results: Glunovo® exhibited an overall MARD value of 8.89% during hospitalization, compared to 10.42% for FGM. The overall percentages of glucose values within ±10%/10, ± 15%/15, ± 20%/20, ± 30%/30, and ±40%/40 of the venous blood glucose reference value were 63.34%, 81.31%, 90.50%, 97.29%, and 99.36% for Glunovo®, respectively, compared with 61.58%, 79.63%, 88.31%, 96.22% and 99.23% for FGM. The Clarke Error Grid Analysis showed that 99.61% of Glunovo® glucose pairs and 100.00% of FGM glucose pairs within zones A and B.

Conclusion: Our study confirms the superior accuracy of Glunovo® in monitoring blood glucose levels among hospitalized patients with type 2 diabetes.

KEYWORDS

Glunovo®, rtCGMS, type 2 diabetes, flash glucose monitoring, venous blood glucose

Introduction

Diabetes and its complications impose a heavy burden on patients. It is estimated that the global diabetes prevalence among individuals aged 20–79 will increase to 12.2% (783.2 million) (1). Effective management of blood glucose levels is paramount for individuals with diabetes, as abnormal levels can cause irreversible damage to the cardiovascular and nervous systems (2, 3). Traditional self-monitoring of blood glucose (SMBG) often poses challenges due to its painful and inconvenient nature, hindering standardized blood glucose management. Moreover, while HbA1c provides an average of long-term blood glucose levels, it fails to capture short-term fluctuations (4). Continuous glucose monitoring systems (CGMS) have emerged as a solution to address these limitations. CGM measures glucose concentration in the interstitial fluid rather than blood, and its values are determined by the rate of glucose diffusion from plasma to interstitial fluid and the rate at which subcutaneous tissue cells take up glucose (5). Currently, two types of CGMS are available: flash glucose monitoring (FGM) or intermittently scanned CGMS (isCGMS), and real-time CGMS (rtCGMS) (6).

Glunovo® is an rtCGMS consisting of a sensor, transmitter, and a mobile application for data analysis. The sensor, designed for subcutaneous installation, has a 14-day lifespan. It generates electrical signals, which are transmitted to the mobile application for display of blood glucose readings. While previous studies have indicated the stability and repeatability of Glunovo®, there remains a lack of head-to-head research to evaluate its accuracy (7). To address this gap, we conducted a head-to-head study to assess the accuracy of Glunovo®.

Methods

Study design and study population

Patients with type 2 diabetes who underwent standardized treatment at the Nanjing First Hospital from March 2019 to October 2019 were enrolled in this study.

Inclusion criteria

(1) Age: 18–70 years.

(2) Confirmed diagnosis of type 2 diabetes with a duration of at least 3 months.

(3) No participation in other clinical studies in the past 3 months.

Exclusion criteria

(1) Pregnancy or breastfeeding.

(2) History of adhesive tape allergy.

(3) Acute diabetes complications (e.g., diabetic ketoacidosis and hyperglycemic hyperosmolar coma).

(4) Severe immunosuppressive disorders or systemic neurological diseases.

Data collection

(1) General clinical data, including name, age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), hemoglobin A1c (HbA1c), triglyceride (TG), creatinine and duration of diabetes.

(2) Blood glucose values recorded from two groups of CGM devices at three stages: initial (1st or 2nd day), intermediate (7 ± 1 days), and final (14th day), along with paired venous blood glucose measurements.

Details of Glunovo®

The Glunovo® device featured a 14-day real-time glucose oxidase electrochemical sensor with a flexible sensor probe. Glucose and oxygen from tissue fluid permeate the probe, triggering an electrochemical reaction that generates an electrical signal. This signal, emitted every 3 minutes, was processed by a transmitter (7 mm thick, with a lifespan of 3 years), an applicator for the transmitter applied by a simple click, and software for processing and sharing data. The applicator, designed for ease of use, included a button to position the sensor and retract the insertion needle upon pressing.

The processed signals from the transmitter were converted into blood glucose readings, transmitted via Bluetooth to a mobile application. The application provided real-time display of blood glucose readings, reflected glucose fluctuation trends through trend curves, and enabled exportation of historical data. The analysis software could analyze exported data from the application and conduct statistical analyses for a deeper understanding of the titration of anti-diabetic drugs. All sensors were clinically implanted using an automatic abdominal sensor applicator, with each participant receiving two sensors for improved performance. Paired sensors values were calculated using pairwise average absolute difference and matched to corresponding venous blood glucose levels. In case of sensor failure, the replacement sensor would match the venous blood glucose value.

Procedures

All participants underwent a 14-day adaptation period using the CGMS. Following the sensor's recommendations, the device calibrated twice daily using SMBG measurements every 24 hours.

After the 14-day adaptation period, paired continuous glucose values and venous blood glucose values were collected for each participant, with a minimum of 24 readings collected within different time periods over 7 hours. The collection of paired continuous glucose and venous blood glucose readings was randomized, assigning each participant a random collection period divided into three stages: initial, middle, and final. FGM was performed as a matched control during this period.

Real-time blood glucose values measured by Glunovo® were compared with venous blood glucose values measured by hospital nurses using the EKF Fast Blood Glucose Analyzer (Biosen-C-Line, EKF Diagnostics, Cardiff, UK). The measurement range of Glunovo® was approximately 2.2–22.2 mmol/L; values outside this range were not included in the analysis. The study was conducted in accordance with the Helsinki Declaration of 1964 and its subsequent amendments and received ethical approval from the Ethics Committee of Nanjing First Hospital (Approval Number: ChiCTR2100045233).

Statistical analysis

For continuous variables, Shapiro-Wilk test was used to assess normality. Normally distributed data were presented as mean ± SD, and non-normally distributed data as median (interquartile range). Categorical variables were presented as count (percentage). Mean absolute relative difference (MARD) was determined as the average relative difference between the CGMS and venous blood glucose pairs and expressed as a percentage. CGM performance evaluation followed statistical recommendations from Clarke and Kovatchev (8). The numbers of glucose pairs in various risk zones of error grid analyses were determined with the R package "ega," which is designed for Clarke or Parkes error grid analysis (https://cran.r-project.org/web/packages/ega/ega.pdf). A p-value less than 0.05 was considered statistically significant. All statistical calculations were performed using R software (version 4.3.1).

Results

Baseline characteristics and venous blood glucose

A total of 31 patients were enrolled, with one participant dropping out midway, resulting in the final collection of data from 30 patients. The patients' characteristics were presented in Table 1, including 18 females and 12 males, with a median age of 56.00 years and an average BMI of 24.55 kg/m^2. The median duration of diabetes was 9.00 years, with average SBP and DBP of 123.60 mmHg and 75.07 mmHg, respectively. Blood indicators, including HbA1c, TG, and creatinine, were 7.81%, 1.41 mmol/L, and 64.31 μmol/L, respectively. A total of 2,327 pairs of matched glucose data were available for evaluation. Venous blood glucose levels were categorized as <3.9 mmol/L (6 pairs), 3.9–10.0 mmol/L (1,422 pairs), and ≥10.0 mmol/L (899 pairs).

CGM performance and error grid analysis

MARD values were shown in Table 2. Overall, the MARD for Glunovo® was 8.89%, and for FGM, it was 10.42%. The data were further categorized into rate of change in venous blood glucose groups defined by intervals: <-0.11, (-0.11, -0.06], (-0.06, 0], (0, 0.06], (0.06, 0.11], >0.11 mmol/L/min. The Glunovo® exhibited MARD values of 10.09%, 7.44%, 7.93%, 9.41%, 12.70%, and 17.11% for these respective intervals, whereas the FGM demonstrated MARD values of 10.73%, 9.81%, 10.12%, 10.19%, 11.25%, and 21.30%. For venous blood glucose categorizations: < 3.90, [3.90, 10.00), ≥ 10.00 mmol/L, Glunovo® exhibited MARD values of 8.65%, 8.09%, and 10.58%, respectively, while FGM demonstrates MARD values of 15.21%, 9.60%, and 8.57%. In the initial, middle, and final stages of data collection, MARD values were 8.65%, 8.09%, and 10.58% for Glunovo®, while 15.21%, 9.60%, and 8.57% for FGM.

Agreement analyses were presented in Table 3. The overall percentages of glucose values within ±10%/10 mmol/L, ± 15%/15 mmol/L, ± 20%/20 mmol/L, ± 30%/30 mmol/L, and ±40%/40 mmol/L of the venous blood glucose reference value were 63.34%, 81.31%, 90.50%, 97.29%, and 99.36% for Glunovo®, respectively, compared with 61.58%, 79.63%, 88.31%, 96.22% and 99.23% for FGM.

As shown in Figure 1, Clarke Error Grid Analysis demonstrated acceptable clinical accuracy. For Glunovo®, 99.61% of glucose values fell within zones A (93.64%, n = 2,179) and B (5.97%, n = 139). In comparison, for FGM, 100.0% of glucose values were within zones A (90.29%, n = 2,101) and B (9.71%, n = 226). As

TABLE 1 Baseline patient characteristics.

Subject	Data
Total	30
Gender (N, %)	
Male	12 (40.00%)
Female	18 (60.00%)
Age (years)	56.00 (51.25 - 61.00)
BMI (kg/m^2)	24.55 ± 2.78
HbA1c (%)	7.81 ± 1.52
SBP (mmHg)	123.60 ± 13.97
DBP (mmHg)	75.07 ± 9.74
TG (mmol/L)	1.41 (0.89 - 2.09)
Creatinine (μmol/L)	64.31 ± 12.42
Duration of diabetes (years)	9.00 (6.25 - 12.00)

BMI, body mass index; HbA1c, glycosylated Hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride.

TABLE 2 Comparison of MARD values between Glunovo® and FGM.

Group	FGM (%)	Glunovo® (%)
Total	10.42	8.89
Venous blood glucose (mmol/L)		
< 3.90*	13.12	25.16
[3.90, 10.00)	11.53	7.93
≥ 10.00	8.64	10.29
ROC (mmol/L/min)		
< -0.11	10.73	10.09
[-0.11, -0.06)	9.81	7.44
[-0.06, 0)	10.12	7.93
[0, 0.06)	10.19	9.41
[0.06, 0.11)	11.25	12.70
≥ 0.11	21.30	17.11
Period of data collection		
Initial stage	10.59	8.83
Intermediate stage	7.51	9.03
Final stage	13.03	8.90

*There were only six paired matched glucose values for glucose readings 3.90 mmol/L. MARD, mean absolute relative difference; FGM, flash glucose monitoring; ROC, rate of change in venous blood glucose.

shown in Figure 2, Parkes Error Grid Analysis demonstrated acceptable clinical accuracy. For Glunovo®, 100.0% of glucose values fell within zones A (92.52%, n = 2,153) and B (7.48%, n = 174). In comparison, for FGM, 100.0% of glucose values were within zones A (90.29%, n = 2,101) and B (9.71%, n = 226).

Discussion

Our findings demonstrated that the Glunovo® exhibited high accuracy, with an overall MARD of 8.89%. In the initial, middle, and final stages of data collection, Glunovo® consistently exhibited excellent performance. The 2013 CGM Roundtable emphasized that MARD values below 14% are desirable, while values exceeding 18% indicate poor accuracy (9). In comparison, the FGM system exhibited a slightly higher MARD value of 10.42%. A study of 72 diabetic patients evaluated a Dexcom G4 Platinum CGMS with a MARD value of 13% (10). The study on Dexcom G5 Platinum CGMS indicated a MARD value of 9.5% (11). In addition, a separate study of Dexcom G6 Platinum CGMS showed a MARD value of 9.0% (12). The Guardian Connect CGMS had a MARD value of 9.7% (13). Notably, due to limited available data within the hypoglycemic range, the accuracy of the sensors in the low blood glucose range (< 3.9 mmol/L) could not be effectively assessed. Previous studies have indicated that MARD values during hypoglycemia were significantly higher than those within the normal glucose range (14). Therefore, the focus of rtCGM in predicting hypoglycemia should be increased in the future.

The accuracy of Glunovo® was impaired during rapid changes in blood glucose, especially when the blood glucose change rate surpasses 0.11 mmol/L/min. Similarly, in a study of CGM in patients with type 1 diabetes, overall MARD during acute exercise was 29.8% (15). Since CGM does not directly measure glucose concentration in the veins, its values are determined by the rate of glucose diffusion from the plasma to the interstitial fluid and the rate of glucose uptake by cells in subcutaneous tissue (5). The rate of change in glucose concentration in interstitial fluid within tissues is typically slower than that in plasma, often resulting in a delay (16). When blood glucose undergoes rapid fluctuations, this delay was amplified, which could compromise the accuracy of CGM.

The Clarke Error Grid Analysis estimated high clinical performance, with 99.61% of samples in the clinically acceptable error zones A and B. In a multicenter study focusing on the Eversense implantable CGM sensor, the results showed that 99.2% of samples were within the clinically acceptable error zones A (84.3%) and B (14.9%) (17). Moreover, real-time continuous glucose monitoring (rtCGM) has shown promising results in monitoring diabetes for peritoneal dialysis patients, with 99.9% of data points falling within zones A and B (18). The evidence mentioned above strongly supports the implementation of rtCGM, providing patients with viable monitoring options.

Several limitations should be considered. First, as subjects received standardized hospital treatment, results may not apply to home care. Second, the potential impact of confounding factors, such as patient medication profiles and the severity of diabetes, may not have been comprehensively addressed. Third, limited hypoglycemia data may impact the assessment of monitoring effectiveness in low glucose conditions. Future studies should aim

TABLE 3 Agreement analysis between Glunovo® and FGM.

Category	± 10/10%	± 15/15%	± 20/20%	± 30/30%	± 40/40%
FGM	61.58	79.63	88.31	96.22	99.23
(95% CI)	(61.56, 61.60)	(79.61, 79.65)	(88.3, 88.32)	(96.21, 96.23)	(99.22, 99.23)
Glunovo®	63.34	81.31	90.50	97.29	99.36
(95% CI)	(63.32, 63.36)	(81.29, 81.32)	(90.49, 90.51)	(97.29, 97.30)	(99.35, 99.36)

FGM, flash glucose monitoring.

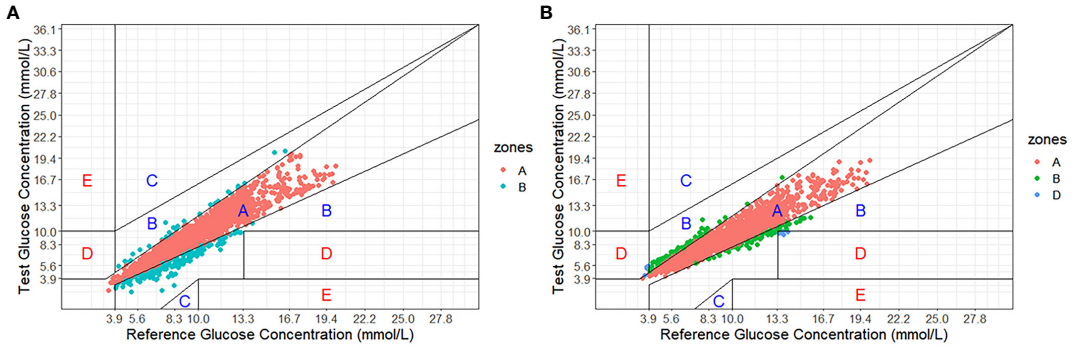

FIGURE 1
Clarke error grid analysis. **(A)** flash glucose monitoring; **(B)** Glunovo®. The percentage of measuring points falling in A + B zones was 100.00% for flash glucose monitoring and 99.61% for Glunovo®. Zone A, clinically accurate; Zone B, benign errors; Zone C, overcorrection errors; Zone D, failure to treat errors; and Zone E, erroneous treatment errors.

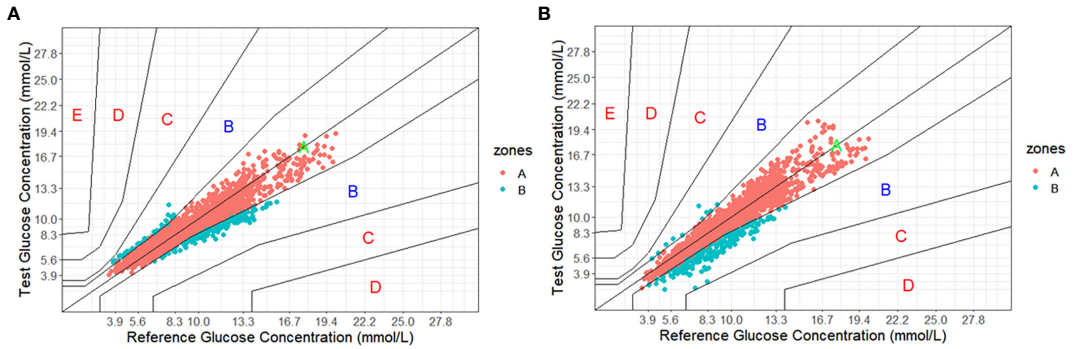

FIGURE 2
Parkes error grid analysis. **(A)** flash glucose monitoring; **(B)** Glunovo®. The percentage of measuring points falling in A + B zones was 100.00% for flash glucose monitoring and 100.00% for Glunovo®. Zone A, clinically accurate; Zone B, benign errors; Zone C, overcorrection errors; Zone D, failure to treat errors; and Zone E, erroneous treatment errors.

for larger sample sizes to detect differences in the low blood glucose range, thereby providing more insights for physicians.

Conclusion

In conclusion, our study highlights the enhanced accuracy of Glunovo® in blood glucose monitoring for hospitalized patients, providing an alternative for diabetes assessment and management. Nevertheless, the reliability of Glunovo® in low blood glucose monitoring requires verification. Further research is warranted to provide insights for the utilization of Glunovo® in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of Nanjing First Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was obtained from the participants or the participants' legal guardians/next of kin.

Author contributions

SG: Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. HZ: Writing – review & editing, Investigation, Software, Validation. JW: Investigation, Software, Validation, Writing – review & editing. HL: Data curation, Investigation, Writing – review & editing. XS: Data curation, Investigation, Writing – review & editing. DD:

Project administration, Supervision, Writing – review & editing. JM: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

2. Malone JI. Diabetic central neuropathy: CNS damage related to hyperglycemia. *Diabetes*. (2016) 65:355–7. doi: 10.2337/dbi15–0034

3. Snell-Bergeon JK, Wadwa RP. Hypoglycemia, diabetes, and cardiovascular disease. *Diabetes Technol Ther*. (2012) 14 Suppl 1:S51–58. doi: 10.1089/dia.2012.0031

4. Chehregosha H, Khamseh ME, Malek M, Hosseinpanah F, Ismail-Beigi F. A view beyond hbA1c: role of continuous glucose monitoring. *Diabetes Ther*. (2019) 10:853–63. doi: 10.1007/s13300–019-0619–1

5. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol Ther*. (2009) 11:S–11-S-16. doi: 10.1089/dia.2009.0002

6. Bruttomesso D, Laviola L, Avogaro A, Bonora E, Del Prato S, Frontoni S, et al. The use of real time continuous glucose monitoring or flash glucose monitoring in the management of diabetes: A consensus view of Italian diabetes experts using the Delphi method. *Nutr Metab Cardiovasc Dis*. (2019) 29:421–31. doi: 10.1016/j.numecd.2019.01.018

7. Meng R, Gu T, Yang F, Liu J, Sun Q, Zhu D. Performance evaluation of the glunovo® Continuous blood glucose monitoring system in chinese participants with diabetes: A multicenter, self-controlled trial. *Diabetes Ther*. (2021) 12:3153–65. doi: 10.1007/s13300–021-01171–2

8. Clarke W, Kovatchev B. Statistical tools to analyze continuous glucose monitor data. *Diabetes Technol Ther*. (2009) 11 Suppl 1:S45–54. doi: 10.1089/dia.2008.0138

9. Wernerman J, Desaive T, Finfer S, Foubert L, Furnary A, Holzinger U, et al. Continuous glucose control in the ICU: report of a 2013 round table meeting. *Crit Care*. (2014) 18:226. doi: 10.1186/cc13921

10. Nakamura K, Balo A. The accuracy and efficacy of the dexcom G4 platinum continuous glucose monitoring system. *J Diabetes Sci Technol*. (2015) 9:1021–6. doi: 10.1177/1932296815577812

11. Link M, Kamecke U, Waldenmaier D, Pleus S, Garcia A, Haug C, et al. Comparative accuracy analysis of a real-time and an intermittent-scanning continuous glucose monitoring system. *J Diabetes Sci Technol*. (2021) 15:287–93. doi: 10.1177/1932296819895022

12. Shah VN, Laffel LM, Wadwa RP, Garg SK. Performance of a factory-calibrated real-time continuous glucose monitoring system utilizing an automated sensor applicator. *Diabetes Technol Ther*. (2018) 20:428–33. doi: 10.1089/dia.2018.0143

13. Yeoh E, Png D, Khoo J, Chee YJ, Sharda P, Low S, et al. A head-to-head comparison between Guardian Connect and FreeStyle Libre systems and an evaluation of user acceptability of sensors in patients with type 1 diabetes. *Diabetes Metab Res Rev*. (2022) 38:e3560. doi: 10.1002/dmrr.3560

14. Jin Z, Thackray AE, King JA, Deighton K, Davies MJ, Stensel DJ. Analytical performance of the factory-calibrated flash glucose monitoring system freeStyle libre2 (TM) in healthy women. *Sensors (Basel)*. (2023) 23:402–4. doi: 10.3390/s23177417

15. Moser O, Eckstein ML, McCarthy O, Deere R, Pitt J, Williams DM, et al. Performance of the Freestyle Libre flash glucose monitoring (flash GM) system in individuals with type 1 diabetes: A secondary outcome analysis of a randomized crossover trial. *Diabetes Obes Metab*. (2019) 21:2505–12. doi: 10.1111/dom.13835

16. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes*. (2003) 52:2790–4. doi: 10.2337/diabetes.52.11.2790

17. Kropff J, Choudhary P, Neupane S, Barnard K, Bain SC, Kapitza C, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, multicenter, pivotal trial. *Diabetes Care*. (2017) 40:63–8. doi: 10.2337/dc16–1525

18. Ng JKC, Ling J, Luk AOY, Lau ESH, Ma RCW, Li PKT, et al. Evaluation of a fourth-generation subcutaneous real-time continuous glucose monitor (CGM) in individuals with diabetes on peritoneal dialysis. *Diabetes Care*. (2023) 46:1191–5. doi: 10.2337/dc22–2348

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EDITED BY
Jianzhong Xiao,
Tsinghua University, China

REVIEWED BY
Yan Bi,
Nanjing Drum Tower Hospital, China
Tanja Milicic,
University of Belgrade, Serbia

*CORRESPONDENCE
Kuanxiao Tang
tangkx_ql@hotmail.com

†These authors have contributed equally to this work and share first authorship

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A moderately higher time-in-range threshold improves the prognosis of type 2 diabetes patients complicated with COVID-19

Riping Cong[1†], Jianbo Zhang[1,2†], Lujia Xu[1†], Yujian Zhang[1], Hao Wang[3], Jing Wang[3], Wei Wang[1], Yingli Diao[1], Haijiao Liu[4], Jing Zhang[5] and Kuanxiao Tang[1*]

[1]Department of General Practice, Qilu Hospital of Shandong University, Jinan, Shandong, China, [2]Department of Emergency and Chest Pain Center, Qilu Hospital of Shandong University, Jinan, Shandong, China, [3]Department of Pulmonary and Critical Care Medicine, Qilu Hospital of Shandong University, Jinan, Shandong, China, [4]Department of Internal Medicine, Jinan Hospital, Jinan, Shandong, China, [5]Department of Endocrinology, Lanling County Traditional Chinese Medicine Hospital, Linyi, Shandong, China

Objective: After fully lifting coronavirus disease 2019 (COVID-19) pandemic control measures in mainland China in 12/2022, the incidence of COVID-19 has increased markedly, making it difficult to meet the general time-in-range (TIR) requirement. We investigated a more clinically practical TIR threshold and examined its association with the prognosis of COVID-19 patients with type 2 diabetes(T2D).

Research design and methods: 63 T2D patients complicated with COVID-19 were evaluated. Patients were divided into favorable outcome group and adverse outcome group according to whether achieving composite endpoint (a >20-day length of stay, intensive care unit admission, mechanical ventilation use, or death). TIR, the time-below-range (TBR) and the time-above-range (TAR) were calculated from intermittently scanned continuous glucose monitoring. Logistic regression analysis and other statistical methods were used to analyze the correlation between glucose variability and prognosis to establish the appropriate reference range of TIR.

Results: TIR with thresholds of 80 to 190 mg/dL was significantly associated with favorable outcomes. An increase of 1% in TIR is connected with a reduction of 3.70% in the risk of adverse outcomes. The Youden index was highest when the TIR was 54.73%, and the sensitivity and specificity were 58.30% and 77.80%, respectively. After accounting for confounding variables, our analysis revealed that threshold target ranges (TARs) ranging from 200 mg/dL to 230 mg/dL significantly augmented the likelihood of adverse outcomes.

Conclusion: The TIR threshold of 80 to 190 mg/dL has a comparatively high predictive value of the prognosis of COVID-19. TIR >54.73% was associated with a decreased risk of adverse outcomes. These findings provide clinically critical insights into possible avenues to improve outcomes for COVID-19 patients with T2D.

KEYWORDS

type 2 diabetes, COVID-19, time-in-range, continuous glucose monitoring, glucose variability

1 Introduction

The Chinese Center for Disease Control and Prevention had reported that since the pandemic control measures of coronavirus disease 2019 (COVID-19) were fully lifted in mainland China in 12/2022, the peak number of COVID-19 nucleic acid-positive cases had reached 6.94 million, admissions to hospitals had reached a peak of 1.625 million, of which the highest number of severe cases had reached 128 thousand, and the cumulative number of deaths had reached 4273 by January 2023.

Diabetes has already become the second most common comorbidity of COVID-19 due to the coinciding of two global pandemics (1, 2). A meta-analysis including 7 studies with 1,576 patients showed the prevalence of diabetes of approximately 9.7% (95% CI: 7.2–12.2%) (3). Another meta-analysis was a comprehensive systematic search including data from 76,993 patients (4). According to this study, the prevalence of diabetes was estimated to be 7.87% (95% CI: 6.57–9.28%). Poor glycemic control increased the risk of mortality, morbidity, and secondary infections (5, 6).

These associations between diabetes and worse outcomes in COVID-19 patients were incontrovertible, as blood glucose fluctuation was not conducive to the improvement of disease, and inflammation caused by hyperglycemia led to increased mortality (7, 8). However, excessively tight glycemic control may increase the risk of hypoglycemia, which also increased mortality (9).The impact of COVID-19 on the patients and the use of glucocorticoids and nutritional support during the treatment increased blood glucose fluctuations, which had adverse effects on the prognosis (10). The UK Diabetes guidelines recommend a blood glucose target of 110 to 180mg/dL for diabetes patients with COVID-19, and a blood glucose level of less than 220mg/dL for patients with hypoglycemia and high risk factors (including the elderly, patients with low body weight, patients with severe COVID-19 and/or renal impairment) (11). American Diabetes Association guidelines recommend targeting blood glucose < 180 mg/dL in critically ill patients (12). Clinicians face a significant challenge in improving outcomes for individuals with COVID-19 and type 2 diabetes(T2D) due to uncertainty surrounding the optimal degree of glycemic management and its potential impact on treatment benefits and risks. The definition of optimal blood glucose control remains controversial (13). The wide application of hormonal and nutritional support treatment has led to significant fluctuations in blood glucose levels in clinical practice, making it challenging to maintain the general range. Consequently, our study aimed to analyze glycemic profiles using intermittently scanned continuous glucose monitoring (isCGM) to determine a more clinically practical threshold for TIR and investigate its correlation with prognosis.

2 Materials and methods

In our observational study, data of patients admitted to Qilu Hospital of Shandong University (public tertiary care) from Dec 2022 to Apr 2023 were analyzed. The patients all had moderate or severe cases and were diagnosed according to the guidelines issued by the World Health Organization (WHO) (14), meeting at least the following criteria: positive COVID-19 RNA PCR and characteristic imaging manifestations of novel coronavirus pneumonia. Additionally, eligible patients were those with T2D that had been diagnosed before admission or with newly diagnosed T2D after admission. All patients met the diagnostic criteria of T2D: typical diabetes symptoms plus random blood glucose ≥11.1 mmol/L or plus fasting plasma glucose(FPG)≥7.0 mmol/L or OGTT 2h blood glucose≥11.1 mmol/L. Exclusion criteria included patients who were intubated on admission and those younger than 18 years of age. The study was approved by the Ethics Committees of Qilu Hospital of Shandong University (KYLL-202307–047). Trial Registration: clinicaltrials.gov Identifier: NCT06156137 (Registered November 24, 2023).

Patient information that we collected through electronic medical records include gender, age, vital signs, symptoms on admission, duration of diabetes, comorbidities, FPG, hemoglobin A_{1c} (HbA_{1c}), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), total cholesterol (TC), triglycerides (TG), serum creatinine, uric acid, estimated glomerular filtration rate (eGFR), inflammatory biomarkers, brain natriuretic peptide (BNP), CK-MB and medication, including oral hypoglycemic agent (OHA), insulin, anticoagulant drugs and

glucocorticoids. CGM was initiated on admission. Diabetic meals were ordered for all patients during hospitalization.

All patients were equipped with isCGM sensors (FreeStyle Libre Flash glucose monitoring system; Abbott Diabetes Care Ltd, UK) on admission, and the nurse retrieved the probe when the patient was discharged or when the composite endpoint was reached. The routine protocol for glucose monitoring during hospitalization was fixed at four swipes daily (fasting, premeal and bedtime). In addition, scans can be performed when the patient encounters symptoms of hypoglycemia or any other discomfort. Measures of glycemic variability, such as time-in-range (TIR), time-below-range (TBR) and time-above-range (TAR), mean sensor glucose level and coefficient of variation (CV) of glucose levels, were calculated from isCGM records. TIR was defined as the percentage of time within the following ranges: 70–180 mg/dL, 80–190 mg/dL, 90–200 mg/dL, 100–210 mg/dL, 110–220 mg/dL, and 120–230 mg/dL.

A composite adverse outcome included a hospital stay of more than 20 days, admission to the intensive care unit, the need for mechanical ventilation, and death.

2.1 Statistical analysis

All data were analyzed using the SPSS software v.25(IBM Corporation, Armonk, NY). The normal distribution of continuous variables was checked by the Shapiro-Wilk test. Nonnormally distributed variables are presented as the median (IQR), and the Mann-Whitney U test and Kruskal-Wallis ANOVA were used for comparisons between groups. Categorical variables were expressed as numbers (percentages) and were compared using the χ^2 test or Fisher's exact test. To identify the covariates for inclusion in the multivariate analysis, a univariate logistic regression was initially performed. Candidate covariates were selected based on a significance level of $P < 0.05$ in the univariate analysis. Subsequently, multivariable-adjusted logistic regression models were employed to evaluate the association between TIR using isCGM and composite adverse outcomes. All analyses were adjusted for age, sex, CK-MB, symptoms on admission, LDH, use of OHA and anticoagulant. A receiver-operating characteristic (ROC) curve was constructed with TIR as the independent variable and prognosis as the dependent variable, and the diagnostic value of TIR was assessed based on the area under the curve (AUC). The optimal cutoff value was determined using the Youden index. All statistical tests were two-sided, and a significance level of $P < 0.05$ was considered statistically significant. Odds ratios (ORs) with 95% CIs are presented.

3 Results

3.1 Clinical characteristics of patients with COVID-19 and T2D upon admission

This study included a total of 63 patients who met the inclusion criteria (Figure 1). Among them, the mean age was 71.59 ± 12.24 years, including 42.90% female and 57.10% male. 27 of the 63 patients experienced composite adverse outcomes. The characteristics of these patients are presented in Table 1. Patients with adverse composite outcome had obvious cardiac damage on admission, and the myocardial injury markers LDH (280 [234,342.75] U/L vs. 242[194.25,286] U/L) and CK-MB (2.20 [1.30,4.20] ng/mL vs. 1.50[0.78,2.10] ng/mL) were significantly increased ($P<0.05$). Additionally, patients in the adverse outcome group appeared to be older(75 vs. 72 years), accompanied by comorbidities(hypertension:70% vs. 67%; coronary heart disease: 70% vs. 56%) and higher levels of CRP(67.29[20.84,127.00] mg/L vs. 41.72 [7.51,95.99]mg/L), D-dimmer(1.76 [0.96,2.85] μg/mL vs. 0.97 [0.56,1.81]μg/mL) on admission but there was no significant difference between the two groups.

3.2 Clinical treatment of patients with COVID-19 and T2D

The treatment of hospitalized patients with T2D and COVID-19 mainly includes anti-inflammatory therapy, hypoglycemic therapeutics and other nutritional support therapy. More than 70% of the 63 patients were treated with glucocorticoids therapy, 75% of the patients were treated with nutritional support, 52.4% of the patients were treated with anticoagulant therapy and 66.7% of

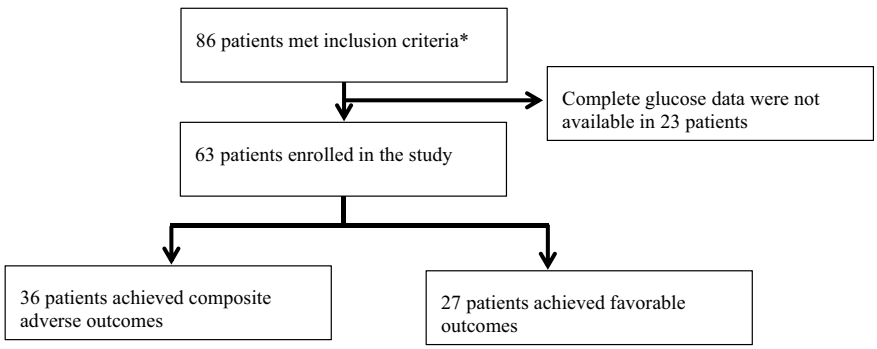

FIGURE 1
Trial profile. *Meeting the following criteria: 1. Inpatients; 2. Patients diagnosed with T2D; 3. Patients receiving CGM during hospitalization; 4. Positive COVID-19 RNA PCR and characteristic imaging manifestations of novel coronavirus pneumonia.

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TABLE 1 Characteristics and isCGM data of patients with COVID-19 and T2D.

Parameters	Presence of the composite adverse outcome	
	No (n = 36)	Yes (n = 27)
Clinical Characteristics on Admission		
Age (years)	72 (62, 82)	75 (65,80)
Male gender	21 (58.30)	15 (55.56)
Heart rate (bpm)	80 (71,72)	84 (80,99)
Respiratory rate (bpm)	18 (18,20)	20 (18,21)
SBP (mmHg)	130 (118,142)	133 (120,147)
DBP (mmHg)	76 (68,80)	77 (70,81)
Fatigue	18 (50)	13 (48)
Dyspnea	20 (56)	14 (52)
Comorbidities on Admission		
Hypertension	24 (67)	19 (70)
Coronary heart disease	20 (56)	12 (70)
Chronic renal diseases	8 (22)	5 (19)
Laboratory Examination on Admission		
Leukocyte count (10^9/L)	7.37 (5.68,10.05)	7.54 (5.84,10.19)
Neutrophil count (10^9/L)	5.63 (3.54,8.51)	6.60 (4.60,8.05)
Lymphocyte count (10^9/L)	1.27 (0.73,1.54)	0.84 (0.57,1.30)
C-reactive protein (mg/L)	41.72 (7.51,95.99)	67.29 (20.84,127.00)
Procalcitonin level (ng/mL)	0.12 (0.07,0.32)	0.28 (0.14,0.94)
ALT (U/L)	18 (10,25)	16 (13,30)
AST (U/L)	20 (15,28)	26 (16,33)
Creatinine (μmol/L)	68.50 (53.25,103)	91 (55,144)
eGFR (mL/min/1.73 m^2)	86.69 (57.76,100.65)	55.40 (36.83,98.58)
CK (U/L)	44.00 (25.50,67)	65.00 (26.5,121.25)
CK-MB (ng/mL)	1.50 (0.78,2.10)*	2.20 (1.30,4.20)*
LDH (U/L)	242(194.25,286)*	280(234,342.75)*
Triglycerides (mmol/L)	1.35 (0.96,1.64)	1.43 (0.94,1.9)
LDL cholesterol (mmol/L)	2.25 (1.67,3.28)	1.95 (1.55,2.51)
HDL cholesterol (mmol/L)	1.08 (0.83,1.33)*	0.94 (0.72,1.09)*
D-dimer (μg/mL)	0.97 (0.56,1.81)	1.76 (0.96,2.85)
FPG (mg/dL)	7.53 (6.54,16.15)	13.07 (9.43,16.46)
HbA_{1c} (%)	7.6 (6.8,9.33)	8.15 (6.78,10.13)
Sensor glucose (mg/dL)	177.84 (153.70,217.95)*	222.84 (183.33,283.49)*
Coefficient of variation (%)	32.95 (28.95,37.15)	34.35 (27.23,37.93)
Treatment		
Antibiotic therapy	35 (97)	25 (93)
Glucocorticoids	24 (67)	23 (85)
Anticoagulant Therapy	14 (39)*	19 (70)*
Non-insulin Hypoglycemic Agents	25 (69)*	12 (44)*
insulin Hypoglycemic Agents	21 (58)	21 (78)

(Continued)

TABLE 1 Continued

Data were presented as n (%) or median (IQR). *P < 0.05
ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; CK, creatine kinase; CK-MB, creatine kinase-myocardial isoenzyme.

the patients were treated with insulin. Compared with the improved discharge group, more patients in the poor outcome group used anticoagulant therapy (70% vs. 39%, $P<0.05$). There was no significant difference in the use of antibiotics (93% vs. 97%), glucocorticoids (85% vs. 67%) and insulin (78% vs. 58%) between the two groups ($P>0.05$).

3.3 Comparison of TIR between the adverse and favorable outcome groups

In the study, the mean TIR (70–180mg/dl) of patients was 48.57%, the mean sensor glucose level was 203.57 (162.7–235.88) mg/dl, and the mean CV was 33.29% (27.88 – 37.62). The proportion of patients with TIR (70–180mg/dL)>70% during hospitalization was 26.9%. Patients with composite adverse outcomes exhibited significantly lower TIR values compared to those with favorable outcomes ($P < 0.05$) (Figure 2). Univariate and multivariable logistic regression models were used to analyze data from all 63 patients. Univariate regression analysis showed that TIR variables (0.977 [0.957–0.996], 0.968 [0.947–0.990], 0.960 [0.935–0.985], 0.957 [0.930–0.984], 0.958 [0.931–0.986], 0.963 [0.936–0.991]) were associated with a decreased risk of the composite outcome (Figure 3). Univariate logistic regression analysis of composite outcomes is shown in Table 2. After adjustment for multiple covariates (age, sex, CK-MB, symptoms on admission, LDH, use of OHA and anticoagulant), TIRs (0.975 [0.948–1.002], 0.963 [0.932–0.995], 0.951 [0.916–0.988], 0.950 [0.914–0.987], 0.960 [0.926–0.995], 0.967 [0.934–1.001]) exhibited a significant association with reduced odds of composite adverse outcomes (Table 3). Thus, a TIR of 80–190 mg/dL was significantly associated with favorable outcomes.

3.4 TIR predicted the prognosis of T2D patients with COVID-19

The multivariate logistic regression analysis revealed that the TIRs of 80–190, 90–200, and 100–210 mg/dL remained as independent predictors of composite adverse outcomes even after

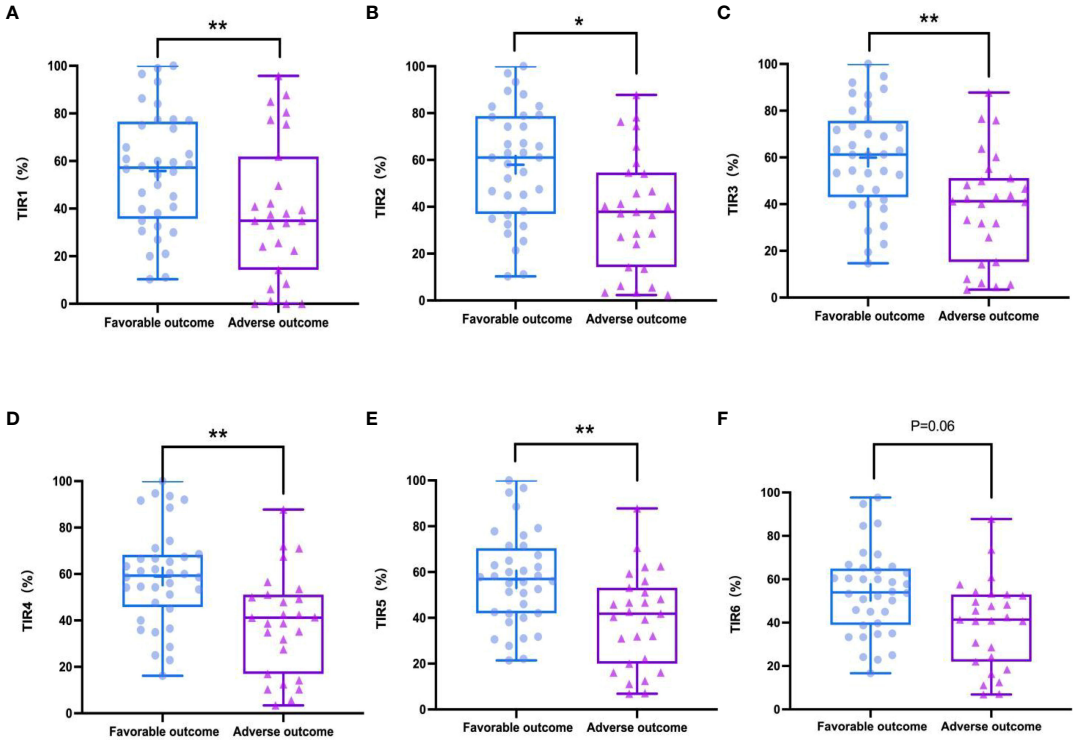

FIGURE 2
TIRs in favorable outcomes and adverse outcomes groups during hospitalization. Adverse outcomes showed significantly lower TIR1 (70-180 mg/dL) than favorable outcomes **(A)**, TIR2 (80-190 mg/dL) **(B)**, TIR3 (90-200 mg/dL) **(C)**, TIR4 (100-210 mg/dL) **(D)**, TIR5 (110-220 mg/dL) **(E)** but TIR6 (120-230 mg/dL) had a weakly negative correlation with the outcomes **(F)**. *$P < 0.05$, **$P < 0.01$.

adjusting the multiple covariates. ROC analysis was employed to evaluate the prognostic value of TIR for COVID-19 patients with T2D. The test variables were defined as TIRs within the ranges of 80–190, 90–200, and 100–210mg/dL while the state variable was represented by composite adverse outcomes in patients (Figure 4A). The area under the ROC curve was 0.713 (95% CI: 0.585–0.841, $P = 0.004$), 0.739 (95% CI: 0.614–0.863, $P = 0.0013$), and 0.748 (95% CI: 0.624–0.872, $P < 0.001$). The area under the curve is maximized when TIR exhibits high predictive value for COVID-19 patient prognosis. Although the TIR (100–210 mg/dL) had the largest area under the ROC curve, it was not significantly different from the other two ROC curves. This does not indicate that the TIR (100–210 mg/dL) has higher prognostic value than the TIR (80–190 mg/dL) and the TIR (90–200 mg/dL). In this study, the average TIR (80–

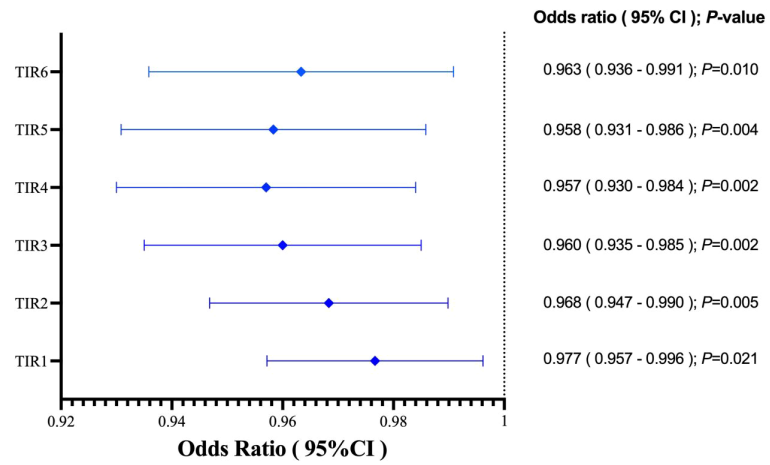

FIGURE 3
TIRs variables was associated with decreased risk of the adverse outcome. TIR1:70-180 mg/dL; TIR2:80-190 mg/dL; TIR3:90-200 mg/dL; TIR4:100-210 mg/dL; TIR5:110-220 mg/dL; TIR6:120-230 mg/dL.

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TABLE 2 Univariate logistic regression analysis of composite outcomes of COVID-19.

	Odds ratios (95% confidence interval)	P
Clinical Characteristics on Admission		
Age (years)	1.015(0.973,1.058)	0.489
Male gender	1.120(0.409,3.068)	0.826
Heart rate (bpm)	1.014(0.850,1.045)	0.345
Respiratory rate (bpm)	0.998(0.944,1.033)	0.584
SBP(mmHg)	1.009(0.988,1.031)	0.410
DBP(mmHg)	1.005(0.969,1.041)	0.803
Fatigue	0.929(0.342,2.520)	0.929
Dyspnea	0.862(0.317,2.344)	0.770
Gastrointestinal symptoms	2.125(0.33,13.704)	0.428
Comorbidities on Admission		
Hypertension	1.187(0.404,3.490)	0.755
Coronary heart disease	0.640(0.234,1.747)	0.640
Chronic renal diseases	0.795(0.228,2.774)	0.720
Laboratory Examination on Admission		
Leukocyte count (10^9/L)	1.073(0.958,1.203)	0.224
Neutrophil count (10^9/L)	1.107(0.973,1.260)	0.123
Lymphocyte count (10^9/L)	0.617(0.257,1.480)	0.279
C-reactive protein (mg/L)	1.006(0.998,1.015)	0.122
Procalcitonin level (ng/mL)	0.950(0.831,1.085)	0.447
ALT (U/L)	1.004(0.962,1.049)	0.844
AST (U/L)	1.038(0.985,1.095)	0.160
Creatinine (μmol/L)	0.999(0.996,1.003)	0.801
eGFR (mL/min/1.73 m^2)	0.991(0.976,1.006)	0.244
CK (U/L)	1.004(0.998,1.010)	0.175
CK-MB (ng/ml)	1.543(1.070,2.224)	0.020
LDH(U/L)	1.009(1.001,1.017)	0.021
Triglycerides (mmol/L)	1.299(0.775,2.180)	0.321
LDL cholesterol (mmol/L)	0.593(0.322,1.094)	0.094
HDL cholesterol (mmol/L)	0.184(0.032,1.040)	0.055
D-dimer (μg/mL)	1.129(0.966,1.319)	0.128
FPG (mg/dL)	1.000(0.965,1.037)	0.986
HbA_{1c} (%)	1.129(0.900,1.578)	0.221
Sensor glucose (mg/dL)	1.010(1.001,1.019)	0.031
Coefficient of variation (%)	1.007(0.945,1.073)	0.831
Treatment		
Antibiotic therapy	0.357(0.031,4.158)	0.411
Glucocorticoids	0.348(0.098,1.236)	0.103
Anticoagulant Therapy	3.732(1.288,10.812)	0.015
Non-insulin Hypoglycemic Agents	0.352(0.125,0.995)	0.049
Insulin Hypoglycemic Agents	2.500(0.813,7.689)	0.110

190mg/dl) of patients with adverse composite outcome was significantly lower than that of the favorable outcome group (38.29 ± 24.94% vs. 57.94 ± 24.42%, $P<0.05$), while TAR was significantly higher (55.59 ± 31.35% vs. 39.82 ± 25.47%, $P<0.05$). Therefore, glycemic control between 80 and 190mg/dl can improve the prognosis. In all patients, the TIR of 80–190 mg/dL corresponds to 54.73% and maximizes the Youden index, with a sensitivity and specificity of 58.3% and 77.8%, respectively (Figure 4B).

4 Discussion

Data from this cross-sectional study showed that optimal glycemic control during hospitalization was associated with a lower risk of severe illness and death in patients with COVID-19. After adjusting for covariates, maintaining TIR within the thresholds of 80 to 190 mg/dL significantly relates to favorable outcomes.

In our study, the patient population was divided into two cohorts based on the occurrence of composite adverse events. The proportion of severe COVID-19 cases at admission was higher in the population with composite adverse events than in the second cohort (63% vs. 33.3%, $P = 0.002$). Although patients with composite adverse outcomes were more likely to be male and older than 65 years with comorbidities and higher levels of inflammatory, endothelial, and coagulopathy markers on admission, there was no significant difference between the two groups. Patients achieving composite adverse outcomes had significantly higher CK-MB and LDH levels on admission. When analyzing TIR as a factor influencing outcome, all of the above confounding variables were adjusted for to reach the following conclusion: TIR values with thresholds of 80 to 190 mg/dL were significantly associated with a lower risk of the composite adverse outcomes.

Previous studies have shown that variability is a potential risk predictor of death and other complications (4, 15). The presence of COVID-19 has been shown to play a significant role in impairing blood glucose control within the range of 70–150 mg/dL (13). A study of 548 patients with COVID-19 and T2D has confirmed that the parameters such as mean glucose, peak glucose, and the

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TABLE 3 Multivariate analysis for predicting composite adverse outcomes by glycemic metrics derived from isCGM.

	Odds ratios (95% confidence interval)
Sensor glucose levels (mg/dL)	
TIR	
TIR1(70-180)	0.975 (0.948-1.002)
TIR2(80-190)	0.963 (0.932-0.995)
TIR3(90-200)	0.951 (0.916-0.988)
TIR4(100-210)	0.950 (0.914-0.987)
TIR5(110-220)	0.960 (0.926-0.995)
TIR6(120-230)	0.967 (0.934-1.001)

Data are adjusted for age, sex, CK-MB, symptoms on admission, LDH, Use of OHA and anticoagulant.

magnitude of glycemic fluctuations in the early stage of hospitalization are significantly correlated with adverse outcomes, and are closely related to increased hospitalization expenses, prolonged hospitalization time, and increased risk of all-cause death (16). A small-sample study (17) suggested that maintaining TIR (70–160 mg/dL) >70% could improve outcomes. In clinical practice, we found that only 15.87% of patients achieved that target, and the average TIR in our study was 39.36% during the pandemic. Inpatient medication (corticosteroids) and enteral and parenteral nutrition contribute to hyperglycemia (18). The widespread use of glucocorticoids caused patients to experience wide fluctuations in blood glucose levels, which may have more adverse effects than sustained hyperglycemia. In our study, more than 70% of the patients were received glucocorticoids therapy, and 75% were treated with enteral or parenteral nutrition, which resulted in a high mean sensor glucose level [203.57 mg/dL (162.7–235.88)] and a wide CV of glucose values [33.29% (27.88 to 37.62)]. This also explained why the TIR threshold of COVID-19 patients with T2D was higher.

Moreover, the elevation of cortisol levels resulting from COVID-19 infection, stress, and similar factors can contribute to excessive hepatic gluconeogenesis, impaired glucose utilization, and insulin deficiency (19–21). There is a suggested direct impact of SARS-CoV-2 on pancreatic β-cell function and survival, exacerbating rapid and severe metabolic deterioration in individuals with preexisting diabetes (22, 23). Angiotensin-converting enzyme 2 (ACE 2) potentially serves as a crucial molecular link between COVID-19 severity and insulin resistance (23–25). Our findings supported this hypothesis, as the patients who achieved the composite adverse outcomes had a significantly lower TIR (80–190 mg/dL) and a higher TAR >190 mg/dL. Furthermore, they used a higher maximum insulin dose during hospitalization [34(18–47) vs. 19(0–40), P = 0.046]. In this study, we found that poor glycemic control was associated with a worse outcome that included a higher need for medical intervention, hospitalization, and mortality. The insights gained here provide direct suggestions for the clinical management of T2D during the COVID-19 pandemic.

Excessive glycemic control leading to severe hypoglycemia has been associated with increased mortality rates (9). The international consensus on TIR (26) indicated that although evidence regarding TIR for older or high-risk individuals is limited, several studies have demonstrated an elevated risk for hypoglycemia. Therefore, they reduced the TIR target from 70% to 50%. In our study, the age of enrolled patients was relatively high, the mean age was 71.59 ± 12.24 years old, and the TIR (80 to 190 mg/dL) corresponded to 54.73% and had a maximum Youden index. This cutoff value had good clinical significance.

The major advantage of our study lies in the utilization of the isCGM system for T2D patients complicated with COVID-19, enabling comprehensive assessment of hyperglycemia, hypoglycemia, and glycemic variability. Our study has presented the appropriate threshold and cutoff point for TIR in patients with COVID-19 and T2D, which is more relevant to clinical practice. However, several limitations need to be acknowledged. Firstly, it was a retrospective study, which may introduce patient selection bias. Secondly, the sample size was relatively modest and might not

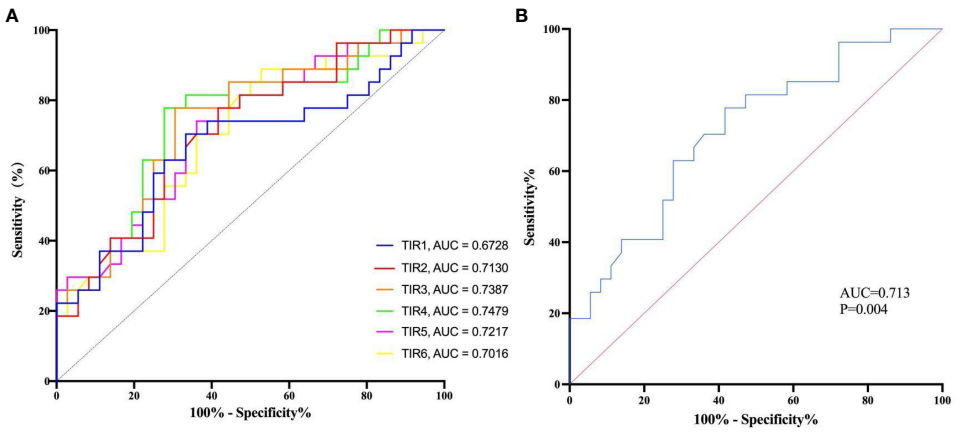

FIGURE 4
The diagnostic value of TIR was evaluated by the receiver operating characteristic (ROC) analysis. **(A)** The receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic value of TIRs. TIR1:70-180 mg/dL; TIR2:80-190 mg/dL; TIR3:90-200 mg/dL; TIR4:100-210 mg/dL; TIR5:110-220 mg/dL; TIR6:120-230 mg/dL; AUC, area under curve. **(B)** The receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic value of TIR of 80-190 mg/dL and estimate the optimal cutoff value.

fully capture the complexity of the general population. Therefore, large-scale prospective cohort studies involving ethnically diverse cohorts from different geographical regions are warranted to gain a better understanding of the association between glycemic control and COVID-19 progression. Finally, it should be noted that our analysis excluded individuals with type 1 diabetes, but glycemic control could also influence their outcomes.

5 Conclusions

In conclusion, maintaining a TIR (80–190 mg/dL) above 54.73% independently correlates with a significant reduction in composite adverse outcomes associated with COVID-19 infection among patients with T2D. These findings provide valuable insights into the clinical characteristics of glycemic variability in individuals affected by both COVID-19 and T2D while offering potential avenues for improving disease outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committees of Qilu Hospital of Shandong University. The studies were conducted in accordance with the local legislation and institutional requirements. The medical records or biological specimens used in this study are obtained from previous clinical treatment, and the risk to the subjects is not greater than the minimum risk, and the exemption from informed consent will not adversely affect the rights and health of the subjects. Subjects' privacy and personally identifiable information will be protected by the researchers. The project leader solemnly promises not to use the medical records and specimens that patients have explicitly refused to use before. This research project does not involve personal privacy and commercial interests, and the samples and related information are only used for this research project.

Author contributions

KT: Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing. RC: Methodology, Formal analysis, Writing – original draft. JBZ: Methodology, Formal analysis, Supervision, Writing – review & editing. LX: Formal analysis, Writing – original draft. YZ: Data curation, Writing – review & editing. HW: Data curation, Writing – original draft. JW: Data curation, Writing – original draft. WW: Data curation, Writing – original draft. YD: Data curation, Writing – original draft. HL: Data curation, Writing – original draft. JZ: Data curation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3

2. Papazafiropoulou AK, Antonopoulos S. The COVID-19 pandemic and diabetes mellitus. *Arch Med Science. Atherosclerotic Dis*. (2020) 5:200–5. doi: 10.5114/amsad.2020.97435

3. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. (2020) 94:91–5. doi: 10.1016/j.ijid.2020.03.017

4. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Arch Acad Emerg Med*. (2020) 8:e35. doi: 10.1016/j.jcv.2020.104371

5. Sun L, Yang X, Cao B, Su X, Wang J, Xu C. Retrospective study of the impact of diabetes on the severity and prognosis of COVID−19. *Exp Ther Med*. (2024) 27:194. doi: 10.3892/etm.2024.12482

6. Katulanda P, Dissanayake HA, Ranathunga I, Ratnasamy V, Wijewickrama PSA, Yogendranathan N, et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. *Diabetologia*. (2020) 63:1440–52. doi: 10.1007/s00125-020-05164-x

7. Tan JK, Lim GH, Mohamed Salim NN, Chia SY, Thumboo J, Bee YM. Associations between mean HbA1c, HbA1c variability, and both mortality and macrovascular complications in patients with diabetes mellitus: A registry-based cohort study. *Clin Epidemiol*. (2023) 15:137–49. doi: 10.2147/CLEP.S391749

8. Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab*. (2020) 31:1068–1077.e3. doi: 10.1016/j.cmet.2020.04.021

9. Charu V, Liang JW, Chertow GM, Li J, Montez-Rath ME, Geldsetzer P, et al. Heterogeneous treatment effects of intensive glycemic control on kidney microvascular outcomes and mortality in ACCORD. *J Am Soc Nephrol*. (2024) 35:216–28. doi: 10.1681/ASN.0000000000000272

10. Nixon A, Butler S, Clark A, Nordbeck S, Ang L. 392: glycemic control in critically ill adult patients with regular insulin added to parenteral nutrition. *Crit Care Med*. (2024) 52:pS170. doi: 10.1097/01.ccm.0000999748.80470.22

11. Rayman G, Lumb A, Kennon B, Cottrell C, Nagi D, Page E, et al. Guidelines for the management of diabetes services and patients during the COVID-19 pandemic. *Diabetes Med*. (2020) 37:1087–9. doi: 10.1111/dme.14316

12. American Diabetes Association Professional Practice Committee. 16. Diabetes care in the hospital: standards of medical care in diabetes-2022. *Diabetes Care*. (2022) 45:S244–53. doi: 10.2337/dc22-S016

13. Kapoor R, Timsina LR, Gupta N, Kaur H, Vidger AJ, Pollander AM, et al. Maintaining blood glucose levels in range (70-150 mg/dl) is difficult in COVID-19 compared to Non-COVID-19 ICU patients-A retrospective analysis. *J Clin Med*. (2022) 9:3635. doi: 10.3390/jcm9113635

14. Agarwal A, Hunt B, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. A living WHO guideline on drugs for covid-19. *BMJ*. (2020) 370:m3379. doi: 10.1136/bmj.m3379

15. Jindal R, Gupta M, Khan FR, Chaudhry G. Prevalence of co-morbidities and its association with mortality in Indian patients with COVID-19: A meta-analysis. *Indian J Anaesth*. (2022) 66:399–418. doi: 10.4103/ija.ija_845_21

16. Chen L, Sun W, Liu Y, Zhang L, Lv Y, Wang Q, et al. Association of early-phase in-hospital glycemic fluctuation with mortality in adult patients with coronavirus disease 2019. *Diabetes Care*. (2021) 44:865–73. doi: 10.2337/dc20-0780

17. Shen Y, Fan X, Zhang L, Wang Y, Li C, Lu J, et al. Thresholds of Glycemia and the Outcomes of COVID-19 Complicated with Diabetes: A retrospective exploratory study using continuous glucose monitoring. *Diabetes Care*. (2021) 44:976–82. doi: 10.2337/dc20-1448

18. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect*. (2020) 81:e13–20. doi: 10.1016/j.jinf.2020.03.062

19. He X, Liu C, Peng J, Li Z, Li F, Wang J, et al. COVID-19 induces new-onset insulin resistance and lipid metabolic dysregulation *via* regulation of secreted metabolic factors. *Signal Transduct Target Ther*. (2021) 6:427. doi: 10.1038/s41392-021-00822-x

20. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol*. (2022) 8:782–92. doi: 10.1016/S2213-8587(20)30238-2

21. Drucker DJ. Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. *Cell Metab*. (2021) 33:479–98. doi: 10.1016/j.cmet.2021.01.016

22. Brufsky A. Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic. *J Med Virol*. (2020) 92:770–5. doi: 10.1002/jmv.25887

23. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. (2020) 181:271–80. doi: 10.1016/j.cell.2020.02.052

24. Sankrityayan H, Kale A, Sharma N, Anders HJ, Gaikwad AB. Evidence for use or disuse of renin-angiotensin system modulators in patients having COVID-19 with an underlying cardiorenal disorder. *J Cardiovasc Pharmacol Ther*. (2020) 25:299–306. doi: 10.1177/1074248420921720

25. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol*. (2020) 17:11–30. doi: 10.1038/s41574-020-00435-4

26. Bellido V, Aguilera E, Cardona-Hernandez R, Diaz-Soto G, González Pérez de Villar N, Picón-César MJ, et al. Expert recommendations for using time-in-range and other continuous glucose monitoring metrics to achieve patient-centered glycemic control in people with diabetes. *J Diabetes Sci Technol*. (2023) 17:1326–36. doi: 10.1177/19322968221088601

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EDITED BY
Jianzhong Xiao,
Tsinghua University, China

REVIEWED BY
Sueziani Binte Zainudin,
Sengkang General Hospital, Singapore
Aminu Mohammed,
Ahmadu Bello University, Nigeria

*CORRESPONDENCE
Mingzhe Li
lnsnfm@126.com

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A real-world observational study on the effect of Qingre Lishi decoction on glycemic profile using continuous glucose monitoring in obese type 2 diabetes adults

Bingchen Wei[1], Tianshu Gao[2], Mingzhe Li[3]*, Xiaojun Tian[4] and Jinxi Wang[5]

[1]The First Clinical College, Liaoning University of Traditional Chinese Medicine, Shenyang, China, [2]Endocrinology Department, the First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang, China, [3]Internal Medicine Department, the Third Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang, China, [4]The Fourth Encephalopathy Department, Shenyang Second Hospital of Traditional Chinese Medicine, Shenyang, China, [5]Teaching Laboratory Center, Liaoning University of Traditional Chinese Medicine, Shenyang, China

Objective: To observe the clinical efficacy and safety of the Qingre Lishi decoction in treating of newly diagnosed overweight and obese patients with type 2 diabetes mellitus (T2DM) from an evidence-based medical perspective.

Methods: 70 cases of overweight and obese patients with newly diagnosed T2DM treated in the outpatient clinic of the Department of Endocrinology of the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine from December 2021 to November 2022 were selected, of which 35 cases were in the observation group and 35 cases were in the control group. The observation group was treated with the Qingre Lishi decoction add lifestyle intervention, and the control group was treated with lifestyle intervention only. We compared and analyzed the fasting blood glucose (FPG), 2-hour postprandial glucose (2hPG), the occurrence of adverse reactions, and the related indexes provided by wearing the CGM device during the observation period of the patients in the two groups.

Results: 53 participants completed the clinical trial. In relation of glycemic control, a decreasing trend has shown in both groups, with the decreases in FPG, 2hPG, eHbA1c, and MG in the observation group being higher than those in the control group ($P<0.05$). In regard to blood glucose attainment, at the 28d, the attainment rate of patients in the observation group with TIR>80% was 87.10%, and the magnitude of changes in the rise of TIR and the fall of TAR was significantly better than that in the control group ($P<0.01$). In terms of blood glucose fluctuation, CV and SD of the patients in the observation group decreased compared with the 0d; the magnitude of daytime blood glucose fluctuation was significantly alleviated compared with that of the control group. The degree of decrease in LAGE, MAGE, and MODD was significantly lower than that of the control group ($P<0.01$).

Conclusion: The Qingre Lishi decoction can effectively improve the hyperglycemic condition of overweight and obese patients with newly diagnosed T2DM. It can reduce blood glucose, alleviate blood glucose fluctuations, reduce the incidence of hypoglycemia, and improve patients' adherence and self-confidence in controlling blood glucose.

Clinical Trial Registration: https://itmctr.ccebtcm.org.cn/, identifier ITMCTR2024000006.

KEYWORDS

newly diagnosed type 2 diabetes mellitus, type of damp-heat trapped spleen, Qingre Lishi decoction, CGM, blood glucose fluctuation

1 Introduction

The number of newly diagnosed type 2 diabetes (T2DM) patients in the world is increasing year by year and growing faster than before, of which the proportion of overweight people has reached 41.0%, while the proportion of obese people is 24.3% (1). Additionally, only 30.2% of those with a body mass index (BMI) over 28 have achieved glycated hemoglobin (HbA1c) control (2, 3). In 2021, the definition and criteria for alleviating T2DM were clearly stated at the American Diabetes Association (ADA) (4). Subsequently, the *Consensus of Chinese Experts on the Remission of Type 2 Diabetes Mellitus* was officially promulgated, re-emphasizing the importance of alleviating T2DM (5). Varies of domestic and international studies have confirmed that early intensive lifestyle intervention and medication for overweight and obese T2DM patients can substantially improve their hyperglycemic state and delay the progression of T2DM (6–8). Therefore, we have committed to alleviating T2DM as the ultimate goal of treating patients with newly diagnosed T2DM.

Nowadays, an increasing number of patients with newly diagnosed T2DM in China are opting to use Chinese herbs to manage their blood glucose levels. The *Guideline for the Prevention and Treatment of Type 2 diabetes mellitus in China* (2020 edition), along with several meta-analyses and randomized controlled studies, confirm that early herbal treatment for newly diagnosed T2DM can reduce patients' symptoms, effectively regulate their blood glucose. In addition to this, herbal medicine can improve the β-cell functional index and insulin sensitivity post-treatment while restoring their own pancreatic islet function (9–16). For instance, Chinese herbal ginseng and astragalus compounds can rectify the instability of the internal environment caused by pathogenic factors and relieve inflammation, subsequently reducing blood glucose and improving the patients' quality of life.

After years of clinical experience, our research team has concluded that the pathogenic perspective of Damp-heat induced Wasting-thirst (17, 18). We believe that most newly diagnosed T2DM are overweight, and mainly belongs to the type of Damp-heat trapped spleen, with severe insulin resistance and pancreatic islets β-cells damage. From multiple perspectives, including animal experiments and clinical evidence-based researches, we found that in overweight or obese T2DM individuals, those belonging to the type of Damp-heat trapped spleen showed significantly elevated levels of clear IL-6 and PRA, Ang II, and ALD of the RASS system (19–21). In this way, it was confirmed that impaired glucose regulation mechanisms contribute to the exacerbation of oxidative stress in vascular endothelium. Combined with the contemporary high-sugar and high-fat dietary pattern, we also found that pancreatic β-cells in individuals with T2DM often experience overload, resulting in repetitive stimulation of the vascular endothelium and subsequent development of oxidative stress, which then leads to persistent fluctuations in blood glucose (22–24). Similarly, an increasing number of experimental studies focusing on glucose-lipid metabolism, intestinal flora, and other aspects of overweight/obesity T2DM have shown common characteristics related to Damp-heat trapping the spleen. These studies have also revealed a disordered inflammatory regulatory mechanism in the body, dysfunction in adipokines and intestinal flora, as well as damaged or dysfunctional pancreatic islet β-cells (25–30). Although numerous evidence-based studies have been conducted to showcase the efficacy of Chinese herbal medicines in reducing and controlling blood glucose, the majority of these studies have combined with treatment of both traditional Chinese medicine and Western medicine.

However, this approach fails to provide a comprehensive evaluation of the actual effectiveness of Chinese herbal medicines alone. In a word, the principle of blood glucose lowered by traditional Chinese medicine still lacks the basis of clinical observation. Therefore, from the perspective of evidence-based medicine, our team treated newly diagnosed overweight and obese T2DM patients with the addition and subtraction of the Qingre Lishi decoction and evaluated its clinical efficacy and safety. Additionally, we integrated a continuous glucose monitoring system and a mobile application device to evaluate the impacts of treatment with the addition and subtraction of the Qingre Lishi decoction on blood glucose fluctuations.

2 Methods

2.1 Study design and participants

In this trial, 70 overweight and obese patients with newly diagnosed T2DM in the Department of Endocrinology of the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine between December 2021 and November 2022 were selected. All participants were included according to the T2DM criteria defined in the ADA *Guidelines for the Diagnosis and Treatment of Diabetes* (2021 edition) and *Guideline for the Prevention and Treatment of Type 2 diabetes mellitus in China* (2020 edition). This research was approved by Ethics Committee of the First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine [Y2023109CS(KT)-109-01]. And it was also registered with the code of ITMCTR2024000006 (Registration date: 15/01/2024) in the International Traditional Medicine Clinical Trial Registry.

2.1.1 Specific inclusion criteria

a. newly diagnosed T2DM, with no comorbidities or complications of diabetes; b. the course of the disease is within 12 months (including 12 months); c. the age of patients were between 18 and 65, regardless of gender; d. overweight and obese, BMI ≥ 24kg/m^2, defined by Chinese criteria (30); e. no COVID-19 infections in the last 6 months, 48 hours negative for novel coronavirus-N gene test and negative for novel coronavirus-ORF1ab gene test.

2.1.2 The exclusion criteria

a. failure to meet the new diagnosis of T2DM; b. women who are pregnant or breastfeeding; c. those with severe heart, lung, brain, liver and kidney diseases; d. combination of any diabetic comorbidities and complications of diabetes mellitus; e. allergy or intolerance to therapeutic drugs; f. severe mental disorders, functional neurologic disorders and inability to communicate properly; g. other diseases that may have an effect on glucose metabolism; h. experience of a critical illness or other stressful situation within the last month; i. participation in other studies within the last 3 months; j. COVID-19 infection in the last 6 months, or 48 hours positive for novel coronavirus-N gene and positive for novel coronavirus-ORF1ab gene. Termination criteria: Newly diagnosed overweight and obese T2DM remained HbA1c/eHbA1c > 7.5% after 1 month of treatment with the addition and subtraction of the Qingre Lishi decoction.

2.1.3 Procedure

All 70 eligible participants underwent an OGTT test upon enrollment and wore ambulatory glucose monitoring. At the same time, the attending physician provided them with training and guidance on the application of CGM and APP software, and conducted follow-up visits at the 14d and 28d after enrollment. Each participant was required to wear the CGM throughout the observation period, including during showering and sleeping. The participants were provided with dietary instructions for managing diabetes, specifying a consumption of 30 kcal/(kg·d), distributed across three meals, with 50% from carbohydrates, 15% from protein and 35% from fat (9). The exercise instruction requires each patient to walk slowly for 30 minutes each morning. Smoking, alcoholic beverages, or drinks containing alcohol are not allowed during the observation period.

The observation group was given Traditional Chinese Medicine, the Qingre Lishi decoction. Essential medicine composition: radix bupleuri (Chai Hu, 柴胡) 15g, rhizoma pinellinae praeparata (Fa Banxia, 法半夏) 15g, scutellaria baicalensis (Huang Qin, 黄芩) 15g, wine-treated rhubarb (Jiu Dahuang, 酒大黄) 15g, sinocalamus affinis (Zhu Ru, 竹茹) 15g, fructus aurantii immaturus rhizome (Zhi Shi, 枳实) 10g, anemarrhenae (Zhi Mu, 知母) 10g, raw gypsum (Sheng Shigao, 生石膏) 15g, coptis chinensis (Huang Lian, 黄连) 15g, cassia twig (Gui Zhi, 桂枝) 10g, rhizoma zingiberis (Gan Jiang, 干姜) 10g, dark plum (Wu Mei, 乌梅) 5g, schisandra chinensis (Wu Weizi, 五味子) 5g. Method of administration: prepare 300 mL of the above Chinese medicine after decocting it in water, and take 100 mL of it warm during the three meals in a day, analyze the pattern of disease in combination with the participants, and adjust the treatment accordingly. All participants in the control group expressed a voluntary preference for lifestyle interventions over medication. At the same time, they were willing to receive CGM to better understand their glycemic changes. Apart from that the control group remained consistent with the observation group in meeting all other requirements.

2.2 Outcomes and measures

2.2.1 Primary outcome

The primary was the change from baseline levels in relevant glycemic indicators at the 14d and 28d. Indicators include fasting blood glucose (FPG, mmol/L) and 2-hour postprandial blood glucose (2hPG, mmol/L) obtained after the OGTT test; estimated HbA1c (eHbA1c, %), standard deviation (SD, mmol/L), mean amplitude of glycemic excursions (MAGE, mmol/L), large amplitude of glycemic excursions (LAGE, mmol/L), mean of daily differences (MODD, mmol/L), coefficient of variation (CV, %), time in range (TIR, %): percentage of time with blood glucose between 3.9 and 10.0 mmol/L, time above range (TAR, %): percentage of time with blood glucose ≥10.0 mmol/L, time below range (TBR, %), mean blood glucose (MG, mmol/L) in CGM reports.

2.2.2 Secondary outcomes

Included BMI, triglyceride (TG, mmol/L), low density lipoprotein (LDL-C, mmol/L), alanine aminotransferase (ALT, U/L), aspartate aminotransferase (AST, U/L), γ-glutamyl transpeptidase (GGT, U/L), serum creatinine (Scr, μmol/L), urea nitrogen (UREA, mmol/L).

2.2.3 Laboratory data measures

In this study, FPG, TG, LDL-C, ALT, AST, GGT, Scr, and UREA were measured with a fully automated biochemical analyzer (HITACHI Model 7600-020; Hitachi, Japan; Immunoturbidimetric method). Normal reference range for monitoring biochemical indicators: FPG: 3.9 ~ 6.1mmol/L, TG: 0.7 ~ 1.7mmol/L, LDL-C: ≤ 3.62mmol/L, ALT: 5 ~ 40U/L, AST: 8 ~ 40U/L, GGT: 11 ~ 50U/L, Scr: 59 ~ 104μmol/L, UREA: 2.9 ~ 8.2mmol/L. Detection of HbA1c and FCP by fully automated electrochemiluminescence immunoassay

analyzer (Cobas Model e601; Roche, Germany; immunoluminescent method). Normal reference range for monitoring biochemical indicators: HbA1c: 4.0% ~ 6.0%, FCP: 1.1 ~ 4.4ng/mL. The ATTD International Consensus recommends a TIR attainment cutoff of 70 percent. Considering that this study is on newly diagnosed T2DM, the higher the percentage of TIR attainment, the more it contributes to their T2DM remission, so 80% was chosen as the cut-off point for TIR attainment in this study (31).

2.2.4 Glucose measures

The CGM monitor was used in this study to monitor patients' daily blood glucose in real time. The continuous glucose monitoring system (model: GS1, Registration Certificate No.: National Equipment Standard 20213070871) produced by Shenzhen Silicon-Based Sensing Technology Co., Ltd. is selected for blood glucose monitoring, including the sensor package and the mobile phone Silicon-based Dynamic APP software (version: 01.11.00.00). The sensor package includes the sensor electrode assembly and guide pin, while the applicator includes the transmitter and transmitter back glue. The effective range of the blood glucose test for this instrument is 2.2 ~ 25 mmol/L.

The sensing probe is inserted into the subcutaneous tissue of the inner side of the participant's upper arm. It receives an electrical signal each minute, storing and recording a factual blood glucose value each 5 minutes. This amounts to 288 values per day, providing continuous monitoring of the participant's blood glucose for 14 days, resulting in a total of 4021 blood glucose values. If the participant's blood glucose value exceeds the effective range, the mobile app will display an alert message stating very low blood glucose or very high blood glucose accompanied by an alarm sound. After wearing the device for 14 days, the APP system automatically generates an AGP map based on the recorded values.

2.3 Statistical analysis

Data processing was performed with SPSS 25.0 statistical software. All measures conforming to a normal distribution expressed by means ± standard deviation (SD), and non-normally distributed measures were expressed by medians (interquartile range), except for separate labeling. Independent *t* test and paired *t* test were used to analyze and compare between and within groups for data conforming to normal distribution, respectively, while non-normally distributed data were compared between and paired within groups using non-parametric rank sum test and Friedman test. $P< 0.05$ was considered a statistically significant difference, and $P< 0.01$ was considered a statistically significant difference.

3 Results

A total of 53 patients finally completed the observation. Among the dropouts, there were 4 cases in the observation group where 2 cases refused to continue with the original medication or clinical regimen, and 2 cases exhibited poor adherence during the wearing process. In the control group, there were 13 dropouts where 5 cases could not be revisited for various reasons, 2 cases showed poor adherence during the wearing process, and 6 cases refused to continue with the original medication or the clinical treatment regimen, and asked to withdraw from the study (Figure 1). There were 26 males and 27 females, with an average age of (47.36 ± 11.71) years, BMI (27.17 ± 2.39) kg/m^2, and FPG (venous blood) 9.42 ± 2.44 mmol/L. During the observation process, the differences in age, disease duration, BMI and blood glucose indexes between the two groups were not statistically significant ($P > 0.05$) (Tables 1, 2).

3.1 Comparison of changes in blood glucose control indexes before and after observation

Throughout the trial, we noticed a decrease in FPG, 2hPG, and eHbA1c levels in newly diagnosed overweight and obese T2DM patients when compared to the 0d. However, the observed change was statistically significant ($P< 0.05$) only within the observation group, both in comparison to the 0d and in comparison to the

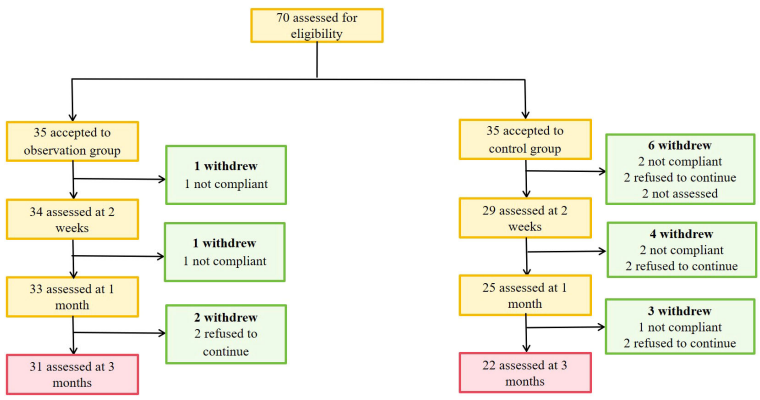

FIGURE 1
Progress of the research.

TABLE 1 Comparison of baseline characteristics between the observation and control groups [$\overline{X}$ ± s or M (Ql, Qu)].

Parameters	Observation group	Control group	*P* value
Gender (*n*)			
Male	16	10	0.659
Female	15	12	
Age (years)	45.77 ± 11.36	49.59 ± 12.09	0.246
Course of disease (months)	1.50 (0.50,12.00)	1.00 (0.50,4.00)	0.439
BMI (kg/m^2)	27.00 ± 2.34	27.40 ± 2.49	0.549
Education (0~12years/>13years)			
0~12	12	13	0.143
>13	19	9	
Physical activity intensity (*n*)			
Low	14	12	0.822
Moderate	12	7	
High	4	3	
Smoking (*n*)			
Yes	7	2	0.197
No	24	20	
Drinking (*n*)			
Yes	9	6	0.889
No	22	14	
Family history of diabetes Genetic history (*n*)			
Yes	8	8	0.409
No	23	14	

Body mass index (BMI).

TABLE 2 Comparison of basic biochemical indexes between observation and control groups [$\overline{X}$ ± s or M (Ql, Qu)].

Parameters	Observation group	Control group	*P* value
C peptide (ng/mL)	3.20 (2.33,4.98)	2.91 (1.97,3.29)	0.159
LDL-C (mmol/L)	2.83 ± 1.32	2.91 ± 0.99	0.805
TG (mmol/L)	1.92 (1.25,3.25)	1.94 (1.07,2.68)	0.718
ALT (U/L)	27.74 ± 13.21	29.86 ± 13.89	0.579
AST (U/L)	25.06 ± 11.33	32.18 ± 11.92	0.034
GGT (U/L)	24.84 ± 9.75	35.55 ± 11.99	0.001
Scr (μmol/L)	61.71 ± 13.49	58.77 ± 12.85	0.426
UREA (mmol/L)	5.60 (3.80,7.30)	5.79 ± 1.28	0.752

Low density lipoprotein (LDL-C), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), serum creatinine (Scr), urea nitrogen (UREA).

control group. Furthermore, this difference was found to be statistically significant when comparing the two groups ($P< 0.01$) (Table 3).

3.2 Comparison of changes in CGM monitoring indicators before and after observation

3.2.1 Changes in blood glucose fluctuations index

The results indicated that after the 28d of treatment with the Qingre Lishi decoction, the SD, CV, LAGE, MAGE, and MODD of patients in the observation group exhibited a decreasing trend (Figure 2). The differences in LAGE, MAGE, and MODD were statistically significant ($P< 0.01$) when compared to both the 0d and the control group (Table 4).

In pairwise analysis within the observation group, it was observed that compared to the 14d, the amplitude of blood glucose fluctuation was significantly improved after the patients were treated with Qingre Lishi decoction. And the changes in LAGE, MAGE, and MODD were statistically significant ($P< 0.05$). However, in the control group, which underwent only lifestyle intervention, it was found that changes in LAGE, MAGE, and MODD were not significant, and the changes in SD and CV exhibited an increasing trend. Additionally, the upward change in SD was statistically significant compared to the 0d ($P< 0.05$). This indicates that patients who only underwent lifestyle interventions had greater fluctuations in their own blood glucose (Table 4).

3.2.2 Changes in blood glucose compliance index

Paired analyses showed statistically significant differences in TIR, TAR, and TBR compared to the 0d among patients in the observation group ($P< 0.05$). Furthermore, when comparing the 28d to the 14d with the Qingre Lishi decoction, significant differences in TIR and TAR were observed ($P< 0.01$). Meanwhile, we noted slight improvements in TIR and MG through lifestyle intervention alone, but after the 28d of intervention, we observed a rebound trend in TIR, TAR, TBR, and MG among the patients (Table 4).

In conclusion, using TIR > 80% as the measure of success, the TIR attainment rate in the observation group significantly improved to 87.10% after the 28d of treatment with the Qingre Lishi decoction. This indicates a notable upward trend in TIR and significant relief in blood glucose levels among the patients. On the other hand, the TIR attainment rate in the control group was only 22.73%. Moreover, as time progressed, the changes in TIR, TAR, TBR, and MG were not evident and even exhibited a rebound effect (Table 5; Figure 3).

3.2.3 Changes in AGP mapping

The 1d, 14d, and 28d after wearing CGM were chosen as observation points. The matplotlib library for Python used to visualize AGP in both groups of patients. The results showed that before the 0d, the majority of newly diagnosed T2DM patients in the group had high blood sugar levels and experienced significant fluctuations. Their hyperglycemic condition improved after lifestyle

TABLE 3 Comparison of changes in blood glucose-related indexes before and after observation between the observation group and the control group ($\overline{X}$ ± s).

Parameters	Observation time point (d)	Observation group	Control group	*t*	*P* value
FPG (mmol/L)	0	8.96 ± 1.91	10.08 ± 2.96	1.691	0.097
	14	7.25 ± 1.05*†	7.92 ± 1.67*	1.794	0.079
	28	5.99 ± 0.74*†	7.98 ± 1.64*	5.972	0.000#
2hPG (mmol/L)	0	13.10 ± 2.83	13.12 ± 4.44	0.026	0.980
	14	10.05 ± 1.97*†	10.46 ± 2.32*	0.699	0.488
	28	7.69 ± 1.30*†	10.37 ± 2.11*	5.710	0.000#
eHbA1c (%)	0	8.79 ± 1.82	9.31 ± 2.10	0.943	0.350
	14	6.65 ± 0.96*†	8.01 ± 1.76*	3.616	0.001#
	28	6.02 ± 0.60*†	8.49 ± 1.96	6.616	0.000#

*P< 0.05 compared with the 0d of own group.
†P< 0.05 compared with the 14d of own group.
#P< 0.05 compared the observation group with the control group at the 0d, 14d, 28d.
Fasting blood glucose (FPG), 2-hour postprandial blood glucose (2hPG), estimated glycated hemoglobin (eHbA1c).

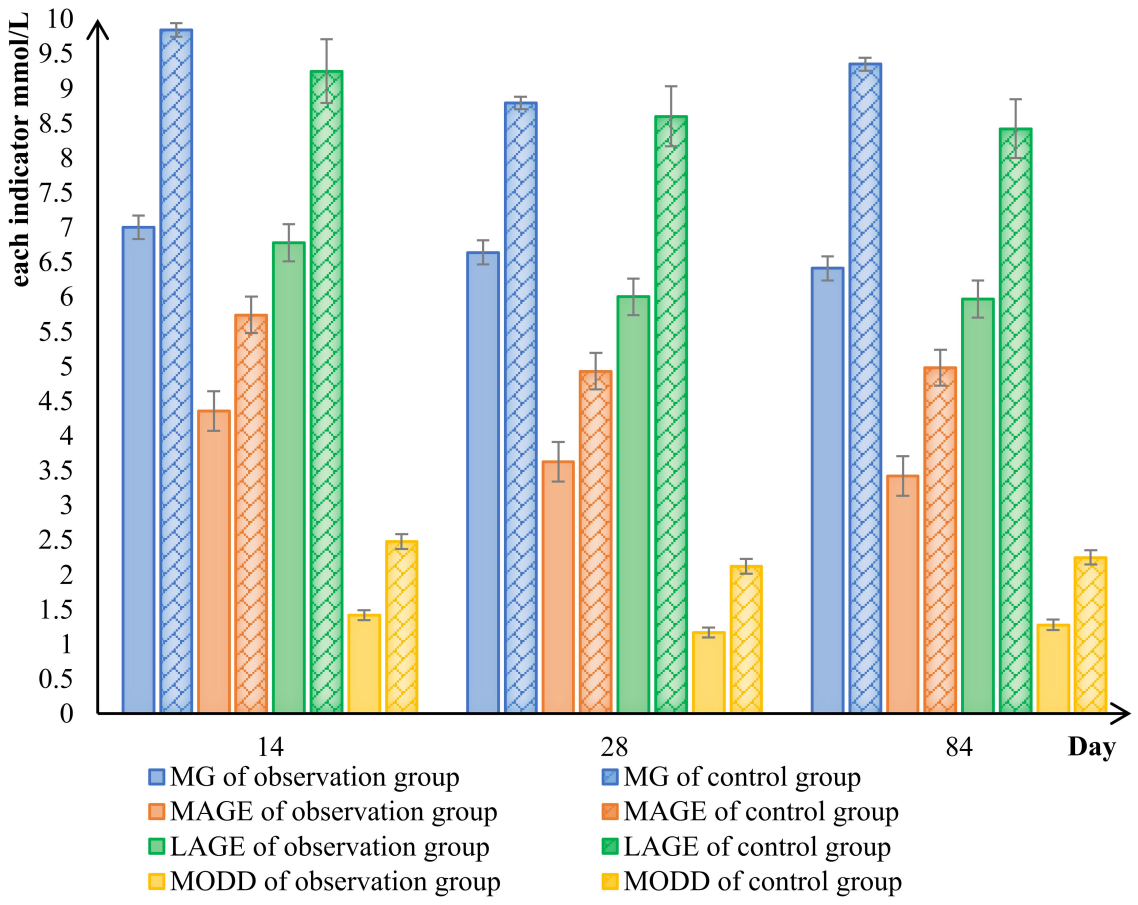

FIGURE 2
Comparison of changes in blood glucose fluctuation indicators between the observed and control groups. mean blood glucose (MG), large amplitude of glycemic excursions (LAGE), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD).

TABLE 4 Comparison of changes in CGM indexes before and after observation between the observation group and the control group [$\overline{X}$ ± s or M (Ql, Qu)].

Parameters	Observation time point (d)	Observation group	*P* value	Control group	*P* value	*t*/*Z*	*P* value
TIR (%)	1	76.60 (69.90,87.40)		76.85 (66.00,85.25)		-0.036	0.971
	14	91.80 (85.30,96.80)	0.000	77.35 (66.00,83.35)	0.249	-4.008	0.000#
	28	94.60 (88.70,99.00)	0.001*	66.95 (41.48,79.35)	0.020†	-5.335	0.000#
TAR (%)	1	19.20 (10.30,25.30)		21.55 (10.75,23.45)		-0.081	0.935
	14	8.00 (2.10,12.90)	0.000	21.55 (14.40,23.68)	0.400	-4.026	0.000#
	28	4.10 (0.90,10.00)	0.003*	32.70 (20.50,58.38)	0.007†	-5.335	0.000#
TBR (%)	1	2.70 (0.40,4.90)		1.60 (0.25,4.08)		-0.859	0.416
	14	1.20 (0.20,1.80)	0.003*	1.45 (0.10,3.68)	0.917	-1.647	0.390
	28	0.70 (0.10,1.80)	0.191	0.30 (0.00,1.43)	0.032†	-0.826	0.409
MG (mmol/L)	1	7.35 ± 1.68		7.71 ± 1.74		-0.762	0.449
	14	7.00 ± 1.36	0.074	7.66 ± 1.52	0.593	-1.653	0.104
	28	6.64 ± 1.00	0.000*	8.79 ± 1.79	0.013†	-5.230	0.000#
CV (%)	1	24.72 (21.75,27.11)		22.39 (20.67,25.86)		-0.993	0.321
	14	23.24 (21.23,27.19)	0.737	27.30 (22.99,28.49)	1.000	-0.478	0.632
	28	21.67 (19.16,24.78)	0.063	24.41 (21.41,31.18)	0.355	-2.175	0.030#
LAGE (mmol/L)	1	7.11 ± 1.53		6.97 ± 1.71		0.308	0.760
	14	6.78 ± 1.07	0.265	7.08 ± 1.66	0.113	-0.798	0.429
	28	6.00 ± 1.51	0.000*	8.60 ± 2.11	0.245	-5.230	0.000#
MAGE (mmol/L)	1	4.13 ± 1.02		3.99 ± 1.10		0.449	0.655
	14	4.36 ± 1.18	0.276	4.00 ± 1.11	0.476	-3.691	0.152
	28	3.63 ± 1.02	0.001*	4.93 ± 1.65	0.035†	-3.533	0.001#
MODD (mmol/L)	1	1.56 (1.28,2.11)		1.66 ± 0.66		-0.045	0.964
	14	1.42 (1.27,1.55)	0.134	1.67 ± 0.65	0.198	-5.411	0.299
	28	1.17 (0.97,1.49)	0.007*	2.12 ± 0.65	0.112	-5.814	0.000#

*P< 0.05 compared with the 0d of own group.
†P< 0.05 compared with the 14d of own group.
#P< 0.05 compared the observation group with the control group at the 0d, 14d, 28d.
Time in range (TIR), time above range (TAR), time below range (TBR), mean blood glucose (MG), coefficient of variation (CV), large amplitude of glycemic excursions (LAGE), mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD).

TABLE 5 Comparison of TIR attainment at each observation stage between the observation group and the control group.

Parameters	Observation time point (d)	Observation group	Control group
TIR ≤ 80%	14	5 (16.12)	18 (81.82)
	28	4 (12.90)	17 (77.27)
80%< TIR ≤ 90%	14	10 (32.26)	3 (13.64)
	28	7 (22.58)	4 (18.19)
TIR > 90%	14	16 (51.62)	1 (4.54)
	28	20 (64.52)	1 (4.54)

Time in range (TIR).

intervention or treatment with the addition of the Qingre Lishi decoction (Figure 4).

At the 14d of observation, there were already noticeable differences in AGP maps between the two groups of patients. At the 28d of observation, the patients in the observation group exhibited more stable AGP maps and experienced less fluctuation in blood glucose levels compared to the control group. The observation group showed improvements in hyperglycemia, with reduced and stabilized fluctuations in the blood glucose change curve compared to the previous one. After 28d of clinical treatment, the blood glucose change curve in the observation group became smoother, with smaller fluctuation amplitudes, which was significantly improved compared with the 0d (Figure 4).

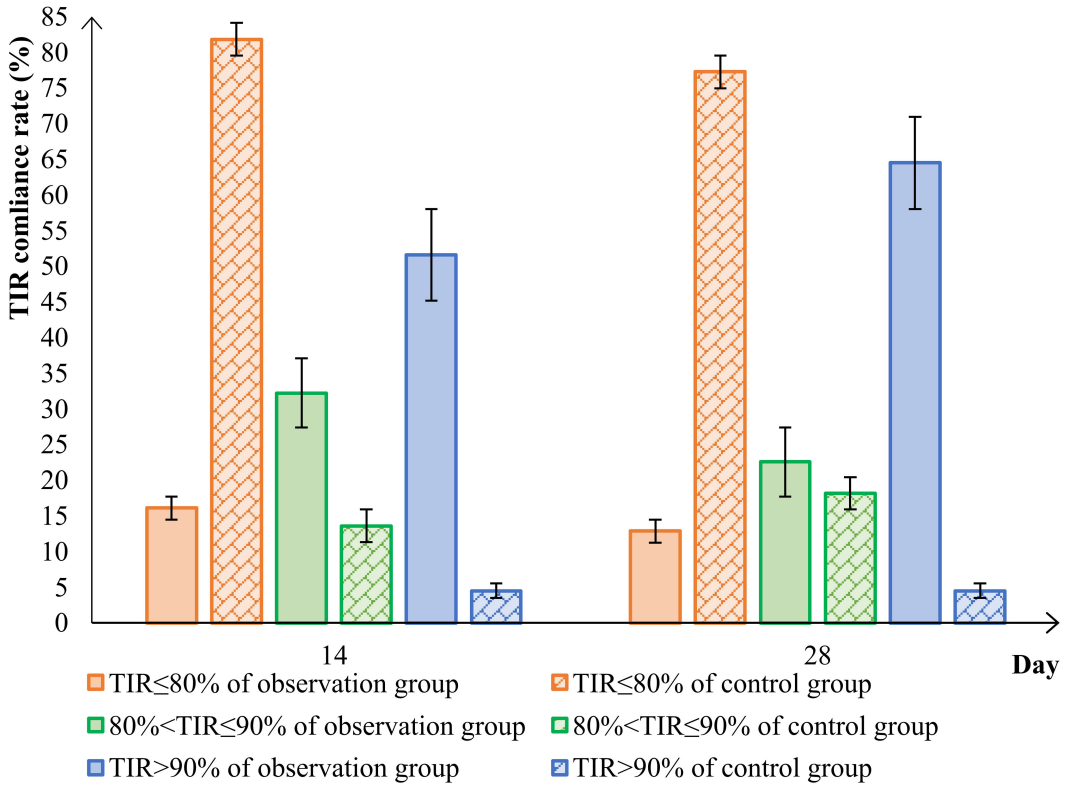

FIGURE 3
Comparison of TIR attainment in the observation group and control group. time in range (TIR).

3.3 Adverse reactions

We observed that in the observation group, all newly diagnosed overweight and obese T2DM patients did not exhibit significant abnormalities in ALT, AST, GGT, UREN, and Scr after treatment with the Qingre Lishi decoction. The differences in the changes were not statistically significant ($P > 0.05$). It means that the Qingre Lishi decoction will not affect liver and kidney functions in humans. In terms of hypoglycemic events, there were 2 cases of hypoglycemia in the observation group and 6 cases of hypoglycemia in the control group, the incidence of hypoglycemia in the two groups was 6.45% and 27.27% respectively, demonstrating a statistically significant difference in the occurrence of hypoglycemia according to the chi-square test ($P< 0.05$) (Table 6).

4 Discussion

The results of this study suggested that treatment with the Qingre Lishi decoction could significantly relieve blood glucose levels in overweight and obese patients with newly diagnosed T2DM. It was found that from the 14th day of observation, the changes in eHbA1c of the patients in the observation group were statistically significant when compared with the control group. At the 28d, the changes in FPG and 2hPG of the patients in the observation group started to show statistical differences. We believe that this may be related to the fact that Chinese herbal tonics require a certain amount of time to accumulate efficacy in controlling blood glucose and regulating the patient's internal environment stability. This finding was also consistent with the results described in a previous study by Liying Zhang (32). Comparison within the group revealed that in those who adhered to the Qingre Lishi decoction for 28 days, the patients' FPG, 2hPG and eHbA1c were significantly relieved, and their quality of life was improved. It also provided a good foundation for remission of newly diagnosed T2DM. This was consistent with the findings of the latest real-world study by Prof. Guoming Pang's team (33, 34).

Another strength of our study was the use of a continuous glucose monitoring system in order to demonstrate that the Qingre Lishi decoction reduces glycemic fluctuations and enhances glycemic stability in newly diagnosed overweight and obese T2DM patients, with a low incidence of hypoglycemia and a safety profile. Glycemic fluctuations have now been shown to increase vascular endothelial oxidative stress, thus becoming an independent risk factor for vascular complications in diabetes. Our team's previous study has also demonstrated that IL-6 levels are significantly elevated in newly diagnosed T2DM patients of the type of dampness heat trapped spleen, and that oxidative stress damage to the vascular endothelium is more severe (18). Meanwhile, it has also been shown in a large number of studies that beneficial genera such as rumenococci and Bradyrhizobium spp are diminished in the intestinal flora of obese T2DM patients. This reduction weakens

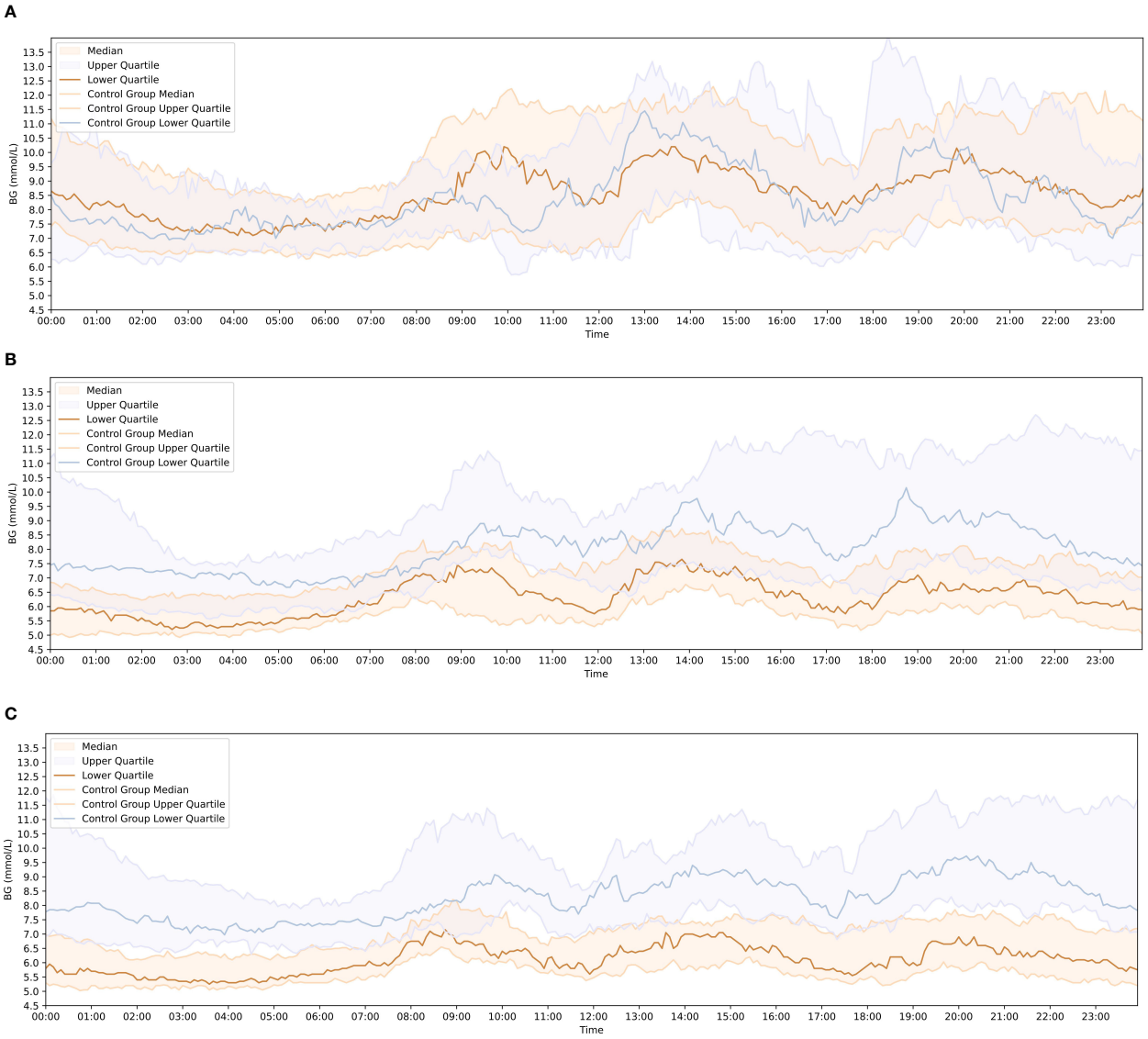

FIGURE 4
Comparison of blood glucose change curves between the observation and control groups at each observation time point. **(A)** Blood glucose fluctuation profiles of patients in the observation group and control group on the 1 day of wearing CGM. **(B)** Blood glucose fluctuation profiles of patients in the observation group and control group on the 14 day of wearing CGM. **(C)** Blood glucose fluctuation profiles of patients in the observation group and control group on the 28 day of wearing CGM.

bile acid metabolism, resulting in glucose metabolism disorders, decreased insulin sensitivity, and significant fluctuations in blood glucose levels (21, 22, 35, 36). Therefore, the focus of clinicians has shifted towards achieving a more precise and effective reduction in blood glucose levels while also minimizing fluctuations.

In recent years, there has been an increasing number of studies using CGM to evaluate TIR in patients with T2DM. Moreover, TIR has been proposed as a valuable addition to the glycemic control targets (9). After evaluating CGM data, we observed that as the duration of the treatment with the Qingre Lishi decoction increased, patients achieved higher rates of TIR. Additionally, TAR decreased significantly, while the change in TBR was not conspicuous. After the 28d of treatment with the formula, patients exhibited smoother blood glucose change patterns within a 24-hour period, and the amplitude of blood glucose fluctuation was significantly reduced. To assess blood glucose variability, we used SD and CV, and then, we found that after treatment with the Qingre Lishi decoction, the patients' blood glucose fluctuations decreased compared to the 0d. On the other hand, relying solely on lifestyle interventions did not relieve blood glucose fluctuations and, in fact, tended to exacerbate their intensity. This further suggests that the administration of the Qingre Lishi decoction can effectively decrease blood glucose

TABLE 6 Comparison of the incidence of hypoglycemia between the observation group and the control group.

Parameters	Observation group	Control group	χ^2	*P* value
Hypoglycemia [*n* (%)]	2 (6.45)	6 (27.27)	4.353	0.037

fluctuations and strengthen blood glucose regulation. This study also discovered that in the short term, lifestyle interventions alone could partially manage blood glucose, though to a limited extent. However, in the long run, the majority of patients struggle to maintain a consistent and appropriate diet and exercise routine. As a consequence, glycemic control rates diminish, blood glucose experiences significant fluctuations, and then, in some cases, a rebound effect may manifest.

The incidence of newly diagnosed T2DM in China is gradually rising. It is marked by a substantial number of individuals being overweight or obese, low adherence to glycemic control, and insufficient patient awareness. However, TCM treatment for T2DM possesses distinct advantages and has garnered increasing recognition. In recent years, large-scale clinical trials have confirmed that TCM has made good achieved positive outcomes in regulating overall metabolic functions and managing blood glucose levels (13, 37, 38). These findings open up new possibilities for TCM to effectively manage blood glucose levels in newly diagnosed T2DM patients, aiming for stable blood sugar levels and achieving remission of newly diagnosed T2DM. However, it is important to note that there is limited research on the use of herbal formulas alone as interventions for controlling blood glucose in newly diagnosed T2DM patients. Therefore, we combined the CGM technique to confirm the effectiveness and safety of herbal formula in mitigating and stabilizing blood glucose in newly diagnosed T2DM patients from the perspective of clinical medical research.

In this study, the selected drugs were based on Da Chai Hu Decoction as the fundamental formula. Modern pharmacological studies have confirmed that the active ingredients in the drugs of the formula possess anti-inflammatory properties, prevent vascular endothelial oxidation, lower blood glucose levels, and improve insulin resistance. For example, the Chaihu polysaccharides and Chaihu saponins in radix bupleuri (Chai Hu, 柴胡) can increase the sensitivity to inhibit inflammatory signaling pathways, such as the HMGB1-TLR4 signaling pathway, inhibit oxidative stress, and activate the 5-HT2C receptor that suppresses appetite in humans. Thus they play a crucial role in preventing inflammation, inhibiting the oxidation of the vascular endothelium, and preventing weight gain (39–41). Scutellaria baicalensis (Huang Qin, 黄芩) decoction regulates the metabolism of substances in the body thereby reducing blood lipids and treating obesity; it inhibits NO production, exerts anti-inflammatory effects, and is closely related to diseases such as edema, hypertension and heart disease (42, 43). The organic acids and polysaccharides contained in dark plum (Wu Mei, 乌梅) can exhibit antioxidant activity, protect pancreatic β-cells, and improve insulin resistance, thereby reducing blood glucose levels. The organic acids present in dark plum (Wu Mei, 乌梅) can also reduce oxidative stress and inflammation by modulating the Nrf2/ARE signaling pathway and inhibiting ROS overproduction (44, 45). Additionally, a large number of animal experiments have also confirmed the effectiveness of the drugs in the formula (46, 47). For instance, rhizoma zingiberis (Gan Jiang, 干姜) decoction can resist vascular oxidation, inhibit platelet aggregation, improve lipid metabolism, and also improve cardiac function by modulating Ang II, TNF-α, MDA, and NO (48–50). In both *in vivo* and *in vitro* studies, cinnamaldehyde in cassia twig (Gui Zhi, 桂枝) has been shown to be the component most closely associated with reducing blood glucose levels (51–53). The team from Iran even demonstrated that aqueous extract of rhubarb (Da Huang, 大黄) had a positive effect on insulin resistance and lipoproteins in T2DM patients (54).

As far as we know, the strength of this study lies in its clinical approach, combining CGM monitoring techniques with the use of herbal formulas to control glycemia in newly diagnosed overweight and obese T2DM. However, there are some limitations and shortcomings in this study. Firstly, it is limited by a small sample size and a short follow-up period. Secondly, when it comes to acquiring observational metrics, we only compared the differences between pre- and post-observations of eHbA1c in the enrolled patients, disregarding the differences in HbA1c itself. Additionally, we only collected the fasting C-peptide values at the time of enrollment and did not collect their fasting insulin values, which prevented us from calculating the HOMA-β and Matsuda index to assess the effect of the Qingre Lishi decoction on the improvement of insulin resistance and insulin secretion/sensitivity in the patients. Thirdly, although each patient received formal diabetic diet and exercise instructions, their related behaviors were not meticulously recorded, which could also have an impact on blood glucose indicators.

In the future, we plan to conduct a large-sample, multi-center randomized controlled trial to validate the effectiveness of the Qingre Lishi decoction in managing blood glucose, improving insulin resistance and alleviating blood glucose fluctuations among individuals newly diagnosed with T2DM from multiple perspectives.

5 Conclusion

The Qingre Lishi decoction can effectively improve the hyperglycemic condition of overweight and obese patients with newly diagnosed T2DM. It can reduce blood glucose, alleviate blood glucose fluctuations, reduce the incidence of hypoglycemia, and improve patients' adherence and self-confidence in controlling their own blood glucose.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Hospital of Liaoning University of Traditional Chinese Medicine Liaoning University of Traditional Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed

consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BW: Writing – original draft, Writing – review & editing. TG: Project administration, Writing – review & editing. ML: Funding acquisition, Supervision, Writing – review & editing. XT: Data curation, Writing – review & editing. JW: Data curation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hou X, Lu J, Weng J, Ji L, Shan Z, Liu J, et al. Impact of waist circumference and body mass index on risk of cardiometabolic disorder and cardiovascular disease in Chinese adults: a national diabetes and metabolic disorders survey. *PloS One*. (2013) 8: e57319. doi: 10.1371/journal.pone.0057319

2. Gao LL, Ji LN, Lu JM. Current status of blood glucose control and treatment of type 2 diabetes in China 2009–2012. *Chin J Diabetes*. (2014) 22:594–8. doi: 10.3969/j.issn.1006-6187.2014.07.005

3. Rong C, Linong J, Liming C. Glycemic control rate of T2DM outpatients in China: a multi-center survey. *MSM*. (2015) 21:1440–6. doi: 10.12659/MSM.892246

4. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care*. (2021) 44:2438–44. doi: 10.2337/dci21-0034

5. Zou DJ, Zhang Z, Ji LN. Consensus of Chinese experts on the remission of type 2 diabetes mellitus. *Chin Gen Pract*. (2021) 24:4037–48. doi: 10.12114/j.issn.1007-9572.2021.01.105

6. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. *Lancet*. (2018) 391:541–51. doi: 10.1016/S0140-6736(17)33102-1

7. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. (2013) 369:145–54. doi: 10.1056/NEJMoa1212914

8. Wei J, Chen J, Wei X, Xiang X, Cheng Q, Xu J, et al. Long-term remission of type 2 diabetes after very-low-calorie restriction and related predictors. *Front Endocrinol (Lausanne)*. (2022) 13:968239. doi: 10.3389/fendo.2022.968239

9. Chinese Medical Association Diabetes. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). *Chin J Diabetes Mellitus*. (2021) 13:315–409. doi: 10.3760/cma.j.cn311282-20210304-00142

10. Yu WR. Clinical observation and analysis of the efficacy of traditional Chinese medicine symptoms in newly diagnosed type 2 diabetes mellitus patients treated with tianmai thirst-quenching tablets combined with metformin. *World Latest Med Inf*. (2019) 19:124+127. doi: 10.19613/j.cnki.1671-3141.2019.13.086

11. Gu Y, Xu X, Wang Z, Xu Y, Liu X, Cao L, et al. Chromium-containing traditional Chinese medicine, Tianmai Xiaoke Tablet, for newly diagnosed type 2 diabetes mellitus: a Meta-analysis and systematic review of randomized clinical trials. *Evid Based Complement Alternat Med*. (2018) 2018:3708637. doi: 10.1155/2018/3708637

12. Lian F, Tian J, Chen X, Li Z, Piao C, Guo J, et al. The efficacy and safety of Chinese Herbal medicine Jinlida as add-on medication in type 2 diabetes patients ineffectively managed by metformin monotherapy: a double-blind, randomized, placebo-controlled,multicenter trial. *PloS One*. (2015) 10:e0130550. doi: 10.1371/journal.pone.0130550

13. Lian F, Jin D, Bao Q, Zhao Y, Tong X. Effectiveness of traditional Chinese medicine Jinlida granules as an add-on therapy for type 2 diabetes: A system review and meta-analysis of randomized controlled trials. *J Diabetes*. (2019) 11:540–51. doi: 10.1111/1753-0407.12877

14. Zhang HY, Tian JX, Lian FM, Li M, Liu WK, Zhen Z, et al. Therapeutic mechanisms of traditional Chinese medicine to improve metabolic diseases via the gut microbiota. *BioMed Pharmacother*. (2021) 133:110857. doi: 10.1016/j.biopha.2020.110857

15. Tian J, Jin D, Bao Q, Ding Q, Zhang H, Gao Z, et al. Evidence and potential mechanisms of traditional Chinese medicine for the treatment of type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab*. (2019) 21:1801–16. doi: 10.1111/dom.13760

16. Safari M, Asadi A, Aryaeian N, Huseini HF, Shidfar F, Jazayeri S, et al. The effects of Melissa officinalis on depression and anxiety in type 2 diabetes patients with depression: a randomized double-blinded placebo-controlled clinical trial. *BMC Complement Med Ther*. (2023) 23:140. doi: 10.1186/s12906-023-03978-x

17. Li MZ, Gao TS, Shi YG, Li JJ, Ma R. Analysis of the evidence of newly diagnosed type 2 diabetes mellitus patients. *Liaoning J Traditional Chin Med*. (2012) 39:295–7. doi: 10.13192/j.ljtcm.2012.02.108.limzh.041

18. Li JJ, Gao TS, Ma R, Shi YG, Li MZ. Newly diagnosed type 2 diabetes trapped spleen pamp-heat and oxiadative stress. *J Liaoning Univ Traditional Chin Med*. (2010) 12:83–4. doi: 10.13194/j.jlunivtcm.2010.01.84.lijj.008

19. Shi J, Gao T. The Effect of Jianpi Lishi Tongluo Recipes to Inflammatory factors of the Overweight Patients with type 2 Diabetes. *Liaoning J Traditional Chin Med*. (2011) 38:2401–2. doi: 10.13192/j.ljtcm.2011.12.99.shij.036

20. Chen SY, Du RY. Effect of abdominal fat on insulin resistance and related metabolic indexes in obese patients with type 2 diabetes mellitus combined. *Chin J Public Health Eng*. (2019) 18:623–5. doi: 10.19937/j.issn.1671-4199.2019.04.055

21. Liu XW, Gao CH, Guan XF, Gao T. Pathogenesis and TCM therapeutic strategy of abnormal bone metabolism caused by diabetes mellitus. *J Liaoning Univ Traditional Chin Med*. (2020) 22:169–73. doi: 10.13194/j.issn.1673-842x.2020.05.041

22. Zang CX, Gao TS. Effect of keluoxin capsule on early hyperfiltration in diabetic kidney disease rats based on tubuloglomerular feedback mechanism. *Chin J Exp Traditional Med Formulae*. (2022) 28:102–11. doi: 10.13422/j.cnki.syfjx.20221241

23. Peng J, Yang YJ, Wang XH. Progress in exercise-induced improvements of leptin resistance in obese subjects and its mechanisms. *Prog Biochem Biophys*. (2021) 48:1023–30. doi: 10.16476/j.pibb.2020.0432

24. Zhu JZ, Zhao C, Sui YL, Liu YY, Qiao YB. Effects of leptin metabolism and inflammatory factors in diabetic rats. *Chin J Appl Physiol*. (2020) 36:197–201+227. doi: 10.12047/j.cjap.5960.2020.044

25. Lin QN, Guo NF, Shi Y, Yang YF. Study on mechanism of type 2 diabetes from spleen treatment based on intestinal flora. *J Liaoning Univ Traditional Chin Med*. (2023) 25:131–4. doi: 10.13194/j.issn.1673-842x.2023.06.027

26. Wang X, Pan Y, Wan H, Ba MY, Fu Y, Yan SX. Analysis of gut microbiomes and dietary patterns in patients with type a combination of 2 diabetes mellitus and obesity. *Chin J Dis Control Prev*. (2020) 24:761–6. doi: 10.16462/j.cnki.zhjbkz.2020.07.004

27. Han XY, Dou DQ, Yu JX, Yang YF, Shi Y. Effects of intestinal microbiota-bile acid pathway on type 2 diabetes mellitus. *Liaoning J Traditional Chin Med*. (2023) 50:216–220+229. doi: 10.13192/j.issn.1000-1719.2023.04.056

28. Li JX, Yang YF, Shi Y. Exploration of the correlation between the theory of earth stagnation and wood depression and insulin resistance in type 2 diabetes mellitus associated with the nuclear bile acid receptor FXR. *J Beijing Univ Traditional Chin Med*. (2022) 45:81–6. doi: 10.3969/j.issn.1006-2157.2022.01.012

29. Leng Y, Zhou X, Xie Z, Hu Z, Gao H, Liu X, et al. Efficacy and safety of Chinese herbal medicine on blood glucose fluctuations in patients with type 2 diabetes mellitus: A protocol of systematic review and meta-analysis. *Med (Baltimore)*. (2020) 99:e21904. doi: 10.1097/MD.0000000000021904

30. Zhou BCoorperative Meta-Analysis Group Of China Obesity Task Force. Predictive values of body mass index and waist circumference to risk factors of related diseases in Chinese adult population. *Chin J Epidemiol*. (2002) 23:5–10. doi: 10.3760/cma.j.issn.0254-6450.2002.01.103

31. Li H, Li YB. Interpretation of the international consensus on glucose targeted range time. *Chin J Diabetes Mellitus*. (2019) 11:825–7. doi: 10.3760/cma.j.issn.1674-5809.2019.12.012

32. Zhang LY. *Clinical Efficacy Observation of Clearing heat and Removing dampness in Treating type 2 Diabetes mellitus with Damp-heat Syndrome*. [master's thesis]. Beijing: Beijing University of Chinese Medicine (2016).

33. Pang GM, Kong LL, Pang KY, Li PH, Zhang F, Wang KF, et al. A retrospective cohort study on the clinical efficacy of real-world application of the He Zhong Reducing Turbidity and Regulating Glucose Drink in the treatment of obese type 2 diabetes mellitus with phlegm and turbidity in the middle blockage evidence. *Jiangxi Traditional Chin Med*. (2022) 53:30–3.

34. Pang GM, Cao QP, Li PH, Gao YG, Yao PY, Kong LL, et al. Clinical characterization of 546 cases of type 2 diabetes mellitus patients treated with pure traditional Chinese medicine "Disease-diagnosis-evidence-body-diagnosis diagnosis and treatment model"–a real-world retrospective study. *J Traditional Chin Med*. (2022) 63:1766–72. doi: 10.13288/j.11-2166/r.2022.18.012

35. Peng X, Chen S, Zhong L, Li Y, Wu C, Zhong L, et al. Cyclocarya paliurus leaves extracts alleviate metabolic phenotypes in Chinese T2DM patients by modulating gut microbiota and metabolites: a clinical randomized controlled trial. *Front Endocrinol (Lausanne)*. (2023) 14:1176256. doi: 10.3389/fendo.2023.1176256

36. Riedel S, Pheiffer C, Johnson R, Louw J, Muller CJF. Intestinal barrier function and immune homeostasis are missing links in obesity and type 2 diabetes development. *Front Endocrinol (Lausanne)*. (2022) 12:833544. doi: 10.3389/fendo.2021.833544

37. Pan J, Xu Y, Chen S, Tu Y, Mo Y, Gao F, et al. The effectiveness of traditional Chinese medicine jinlida granules on glycemic variability in newly diagnosed type 2 diabetes: A double-blinded, randomized trial. *J Diabetes Res*. (2021) 2021:6303063. doi: 10.1155/2021/6303063

38. Cheng Y, Lai YW, Gao TS. Meta-analysis on clinical efficacy of Chinese herbal medicine in tr eatment of type 2 diabetes mellitus with dampness heat and spleen deficiency. *Clin J Traditional Chin Med*. (2018) 30:264–9. doi: 10.16448/j.cjtcm.2018.0081

39. Liu ZZ, Weng HB, Zhang LJ, Pan LY, Sun W, Chen HX, et al. Bupleurum polysaccharides ameliorated renal injury in diabetic mice associated with suppression of HMGB1-TLR4 signaling. *Chin J Nat Med*. (2019) 17:641–9. doi: 10.1016/S1875-5364(19)30078-0

40. Sun CL, Geng CA, Huang XY, Ma YB, Zheng XH, Yang TH, et al. Bioassay-guided isolation of saikosaponins with agonistic activity on 5-hydroxytryptamine 2C receptor from Bupleurum chinense and their potential use for the treatment of obesity. *Chin J Nat Med*. (2017) 15:467–73. doi: 10.1016/S1875-5364(17)30070-5

41. Li YY, Lei GP, Dong S, Feng G. Research progress on modern pharmacological action of Radix bupleuri. *J Hainan Med Univ*. (2022) 28:1748–54. doi: 10.13210/j.cnki.jhmu.20210514.005

42. Dong HJ, Yao X, Mu Y, Ma SS, Geng YL, Liu F, et al. Investigation of the pharmacological activity and mechanism of Scutellaria baicalensis Georgi based on the network pharmacology method for explaining its traditional effect. *Shandong Sci*. (2019) 32:54–61. doi: 10.3976/j.issn.1002-4026.2019.05.006

43. Kim DS, Kim SH, Cha J. Antiobesity effects of the combined plant extracts varying the combination ratio of phyllostachys pubescens leaf extract and Scutellaria baicalensis root extract. *Evid Based Complement Alternat Med*. (2016) 2016:9735276. doi: 10.1155/2016/9735276

44. Da Silva Campelo M, Neto JFC, Lima ABN, das Chagas Neto FC, da Costa Gonzaga ML, de Aguiar Soares S, et al. Polysaccharides and extracts from Agaricus brasiliensis Murill-acomprehensive review. *Int J Biol Macromol*. (2021) 183:1697–714. doi: 10.1016/j.ijbiomac.2021.05.112

45. Yang YT, Wang R, Qian CC, Wu R, Ou JM. Progress in the study of chemical composition, pharmacological effects and prediction of quality markers of dark plum. *Chin Traditional Patent Med*. (2023) 45:1583–8.

46. Wang W, Liu R, Zhu Y, Wang L, Tang Y, Dou B, et al. YuNü-Jian attenuates diabetes-induced cardiomyopathy: integrating network pharmacology and experimental validation. *Front Endocrinol (Lausanne)*. (2023) 14:1195149. doi: 10.3389/fendo.2023.1195149

47. Huang YL, Xiang Q, Zou JJ, Wu Y, Yu R. Zuogui Jiangtang Shuxin formula Ameliorates diabetic cardiomyopathy mice via modulating gut-heart axis. *Front Endocrinol (Lausanne)*. (2023) 14:1106812. doi: 10.3389/fendo.2023.1106812

48. Maurya H, Mangal V, Gandhi S, Prabhu K, Ponnudurai K. Prophylactic antioxidant potential of gallic Acid in murine model of sepsis. *Int J Inflamm*. (2014) 2014:580320. doi: 10.1155/2014/580320

49. Cui WH, Wang YZ, Li ZZ. Studies on the chemical composition of dried ginger. *Chin Pharm J*. (2018) 53:1160–4. doi: 10.11669/cpj.2018.14.004

50. Zhou J, Yang WP, Li YL, Yang M, Lei ZX. Effects of Dried Ginger decoction on plasma angiotensin II, serum tumor necrosis factor alpha, malondialdehyde and nitric oxide in rats with Acute Myocardial Ischemia. *Lishizhen Med Materia Med Res*. (2014) 25:288–90. doi: 10.3969 /j.issn.1008-0805.2014.02.014

51. Long QJ, Xu XQ. Literature analysis on chemical composition, pharmacological actions and processing and curation of dried ginger. *Res Pract Chin Medicines*. (2015) 29:82–3. doi: 10.13728/j.1673-6427.2015.01.027

52. Xu Y, Su S, Wang T, Duan J, Wang Z. Progress in the study of chemical composition and pharmacological activity of cassia twig. *J Chin Medicinal Materials*. (2013) 36:674–8. doi: 10.13863/j.issn1001-4454.2013.04.031

53. Wu F, Jin PY, Liang WF. Mechanistic studies of cinnaldehydum in improving blood pressure and vascular function in hypertensive mice. *Chin J Evidence-Based Cardiovasc Med*. (2022) 14:994–996+1000. doi: 10.3969/j.issn.1674-4055.2022.08.24

54. Ghafouri A, Jafari Karegar S, Hajiluian G, Hosseini S, Shidfar S, Kamalinejad M, et al. The effects of aqueous and ethanolic extracts of Rheum ribes on insulin-resistance and apolipoproteins in patients with type 2 diabetes mellitus: a randomized controlled trial. *BMC Complement Med Ther*. (2023) 23:46. doi: 10.1186/s12906-023-03878-0

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EDITED BY
Jianzhong Xiao,
Tsinghua University, China

REVIEWED BY
Xianli Du,
Shandong Eye Institute, China
John Vincent Forrester,
University of Aberdeen, United Kingdom

*CORRESPONDENCE
Ming Li
lm@eye.ac.cn
Lele Cui
cll@eye.ac.cn
Fan Lu
lufan@eye.ac.cn

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Risk prediction of diabetic retinopathy based on visit-to-visit fasting blood glucose indices

Ying Ju[1], Zhengyang Guo[1], Jiaqi Ai[1], Kai Yang[1], Xiaoxuan Zhu[1], Keai Shi[1], Chunmei Li[1], Tianyun Yu[2], Yunfan Xiao[1], Binbin Su[1], Jinxia Yan[1], Ziyu Li[1], Wei Lian[1], Zhenqin Wang[1], Shasha Ding[1], Yudie Wang[1], Fan Lu[1*], Lele Cui[1*] and Ming Li[1*]

[1]National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, Wenzhou, China, [2]School of Optometry and Vision Science, University of New South Wales, Sydney, NSW, Australia

Objective: The long-term glucose monitoring is essential to the risk assessment of diabetic retinopathy (DR), the aim of this study was to investigate the predictive ability of visit-to-visit fasting blood glucose (FBG) indices on the risk of DR.

Methods: This was a community-based, cohort study conducted from 2013 to 2021. DR was diagnosed by digital fundus photography. The FPG indices included FBG, var. Associations of each FBG indices and DR were estimated using multinomial logistic regression models adjusting for confounders, and discrimination was determined by area under the curve (AUC). Predictive utility of different models was compared by changes in AUC, integrated discrimination improvement (IDI), and net reclassification index (NRI).

Results: This study analyzed 5054 participants, the mean age was 46.26 ± 11.44 years, and 2620 (51.84%) were women. After adjustment for confounders, the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for FBG, SD, CV, VIM, ARV, M-FBG, and cumulative FBG load were 1.62 (1.52—1.73), 2.74 (2.38—3.16), 1.78 (1.62—1.95), 1.11 (0.95—1.29), 1.72 (1.56—1.91), 2.15 (1.96—2.36), and 2.57 (2.31—2.85), respectively. The AUC of the model with separate cumulative FBG load and classical risk factors was 0.9135 (95%CI 0.8890—0.9380), and no substantive improvement in discrimination was achieved with the addition of other FBG indices once cumulative FBG load was in the model.

Conclusions: Cumulative FBG load is adequate for capturing the glucose-related DR risk, and the predictive utility of cumulative FBG load is not significantly improved by adding or replacing other FBG indices in the assessment of DR risk.

KEYWORDS

FBG index, risk prediction, diabetic retinopathy, cohort study, diabetic microvascular complication

1 Introduction

As the most common and specific microvascular complication of diabetes, diabetic retinopathy (DR) remains a leading cause of preventable vision impairment and blindness in working-age adults (1–4). The global diabetes prevalence in adults aged 20—79 years is expected to rise to 12.2% (783.2 million) by 2045, as estimated (5). Accordingly, the annual incidence of DR ranged from 2.2% to 12.7% and progression from 3.4% to 12.3%, respectively (6). Therefore, early identification of the onset of DR and further active and effective interventions to delay progression are essential to reduce DR-related risks.

Previous studies have established that long-term, sustained hyperglycemia is a key risk factor for DR (7). Furthermore, strong evidence suggests that intensive glucose control achieved through medication or therapy effectively prevents DR onset or delays its progression (8–10). Fasting blood glucose (FBG), a common metric for monitoring glycemic control, captures immediate blood glucose levels. Studies on the relationship between FBG levels and DR have primarily relied on single FBG data. Due to fluctuations, FBG monitoring at a single point may not capture long-term trends, reducing accuracy of DR risk assessment. Therefore, tracking FBG levels over time can provide a more reliable assessment of DR risk.

Recently, several visit-to-visit FBG indices, such as standard deviation (SD), coefficient of variation (CV), variation independent of the mean (VIM), average real variability (ARV), mean fasting blood glucose level (M-FBG), and cumulative FBG load, were calculated from multiple readings of FBG and documented to be associated with diabetic (macrovascular and microvascular) complications (11–15). However, most previous studies have focused on the relationship between FBG indices and cardiovascular complications (16, 17), diabetic nephropathy (18), and diabetes peripheral neuropathy (13, 14), and there are only few studies on DR (19, 20). Therefore, there is a need to explore whether these FBG indices can be used as predictors of DR risk and further identify the most informative predictors of these FBG indices in terms of DR risk.

Therefore, our study aimed to investigate the separate and joint predictive ability of different FBG indices for the risk of DR, thereby identifying DR and providing a robust basis for further glycemic control.

3 Methods

3.1 Study population

The data used in this study were obtained from the Jidong Eye Cohort Study (JECS). The JECS design was recorded as previously described. The participants were the general population consecutively recruited from the Jidong community (Tangshan City, northern China) from July 2013 to August 2014. From 2013 to 2021, the participants underwent five health screenings every one or two years. Routine screening included comprehensive laboratory tests (blood biochemistry and routine blood examinations) and a standardized questionnaire interview regarding demographic characteristics and medical history. Following routine screening, all participants underwent a comprehensive ophthalmological examination. Participants with less than three FBG tests, those lacking FBG tests from May 2019 to November 2021, and those with missing or unqualified fundus photography were excluded from the analysis (21, 22). This resulted in a final sample size of 5054 subjects for final analysis, as shown in online Supplementary Figure 1.

This study complied with the principles of the Declaration of Helsinki (revised in 2013). It was approved by the Ethics Committee of the Staff Hospital of Jidong Oil-field of Chinese National Petroleum (approval document 2018 YILUNZI 1) and the Ethics Committee of Wenzhou Medical University Affiliated Ophthalmology Hospital (2021-074-K-63-01). All subjects signed the informed consent.

3.2 Clinical and biological parameters

In this study, age, sex, educational level, income, smoking and drinking status, history of comorbidities, and current medication use were recorded using a standardized questionnaire. All participants underwent a comprehensive physical examination and laboratory tests. The education level was categorized into: “illiteracy or primary school or middle school” and “college graduate or above”. The average monthly income was categorized into “≤ ¥5,000” and “> ¥5,000”. In this study, hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, or self-reported hypertension history, or current use of antihypertensive medications. Dyslipidemia was defined by either low-density lipoprotein (LDL-C) ≥ 3.37 mmol/L, high density lipoprotein (HDL-C) < 1.04 mmol/L, total cholesterol (TC) ≥ 5.18 mmol/L, triglyceride (TG) ≥ 1.7 mmol/L, self-reported history of dyslipidemia, or current use of lipid-lowering medications.

3.3 FBG collection and calculation of longitudinal FBG indices

Fasting plasma glucose levels were measured in the early morning after at least 8 hours of food and water deprivation. Blood samples were collected from the antecubital vein (elbow vein). Following storage, the fasting plasma glucose levels were measured using an autoanalyzer employing the glucose oxidase method. The following four indices representing long-term glycemic variability were calculated: 1) SD: the standard deviation of FBG values; 2) CV: CV (%) = SD (mmol/L)/mean (mmol/L) ×100% 3) VIM: VIM= $100\times SD/mean^{\beta}$, β is the regression coefficient based on the ln of the SD over the ln of the mean; 4) ARV (23, 24). In our study, M-FBG was calculated as the average of the FBG values measured over time. Additionally, cumulative FBG load was determined by dividing the area under the curve (AUC) for FBG values ≥ 5.6 mmol/L divided by the AUC for all FBG values and then multiplied by 100 to achieve the percentage (25, 26).

3.4 Ophthalmic examination

All participants in our study underwent a complete ophthalmological examination between May 2019 and November 2021, including best-corrected visual acuity (BCVA) using a standard logarithmic visual acuity chart, the status of refraction using an auto refractometer (KR800; Topcon; Tokyo, Japan), axial length (AL) using a Lenstar 900 (Haag-Streit; Koeniz, Switzerland), and optical coherence tomography angiography (OCTA) images using a spectral-domain OCTA (RTVue XR Avanti with AngioVue; Optovue; Fremont, CA, United States). At least two independent ophthalmologists reviewed all the examination results. Digital fundus photography of each eye was performed by a trained ophthalmologist using a 45°non-mydriatic fundus camera (CR2AF; Canon; Tokyo, Japan). For image quality control, two trained ophthalmologists ensured that the images qualified for further analysis. Qualified fundus photographs were read by two experienced ophthalmologists double-blind, according to the International Clinical Diabetic Retinopathy (ICDR) Severity Scale (27). The diagnosis of DR was confirmed using digital fundus photography.

3.5 Statistical analysis

Continuous variables are expressed as mean (SD), as they were almost normally distributed, and categorical variables were expressed as numbers and percentages. Differences in baseline characteristics between the groups were compared using unpaired t-test or Wilcoxon rank sum test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Missing data were handled differently depending on the variable. For continuous variables like body mass index (BMI), we replaced missing values with the mean. For categorical variables like current smoking, current drinking, and hypertension, we used the median as the replacement value. The proportions of missing data for all covariates before imputation were less than 10%. Associations between different FBG indices were assessed using Spearman's correlations, both unadjusted and then sex and age were considered. Multinomial logistic regression models were used to estimate the relationship between each FBG index and DR. The DR models were adjusted for age, sex, educational level, income, current smoking, current drinking, hypertension, and dyslipidemia. The AUCs were used to assess the discrimination of different models with FBG indices. Changes in the AUC, integrated discrimination improvement (IDI) and net reclassification index (NRI) were calculated to compare the predictive ability of different models for the risk of DR. In addition, changes in Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were used to assess the improvement in goodness of model fit. We performed sensitivity analyses in subjects with more than three FBG tests and more than four FBG tests.

We expressed associations by βs and 95% confidence intervals (CIs) for all analyses. 2-tailed P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R 4.3.2(Packages included).

4 Results

4.1 Baseline characteristics

A total of 5054 participants with a mean age of 46.26 years (SD 11.44) were included in the final analysis, of whom 2620 (51.84%) were women. Table 1 shows the baseline characteristics of NO DR and DR groups. DR was observed in 158 (3.13%) participants. Participants in the DR group were more male, older and less educated, more likely to be current smokers and drinkers, had a higher prevalence of hypertension and hyperlipidemia, and had higher levels of BMI, FBG, SD, CV, ARV, M-FBG, and cumulative FBG load (Table 1).

Participants with higher FBG, SD, CV, ARV, M-FBG, and cumulative FBG load levels were more likely to be men, less educated, current smokers, current drinkers, and had a higher prevalence of hypertension and dyslipidemia (Supplementary Tables 1-7). The M-FBG and cumulative FBG load were highly correlated with FBG (r > 0.6) (Supplementary Table 8).

4.2 Multivariable association of different FBG indices with DR outcomes

Table 2 shows the relationships between different FBG indices and DR. The adjusted odds ratios (ORs) with 95%CIs for FBG, SD, per 1 SD increase in CV, per 1 SD increase in VIM, per 1 SD increase in ARV, M-FBG, and per 1 SD increase in cumulative FBG load were 1.62(1.52—1.73), 2.74(2.38—3.16), 1.78(1.62—1.95), 1.11 (0.95—1.29), 1.72(1.56—1.91), 2.15(1.96—2.36), and 2.57(2.31—2.85), respectively, after adjusting for age, sex, educational level, income, current smoking, current drinking, hypertension and dyslipidemia. Specifically, the SD and per 1 SD increase in the cumulative FBG load showed stronger links to DR.

4.3 Prediction of DR in addition to classical risk factors

Classical risk factors alone achieved reasonable discrimination for DR prediction (AUC 0.7703, 95%CI 0.7391—0.8015; Figure 1A). Adding any FBG index, except the VIM, further improved discrimination (Figure 1A). Among models with individual FBG index, discrimination and reclassification increased only when M-FBG or cumulative FBG load was added compared to the model with FBG (Tables 3; 4), and the model with separate cumulative FBG load achieved the highest discrimination (AUC 0.9135, 95%CI 0.8890-0.9380; Figure 1A, Table 3). When adding ARV or FBG and ARV to the model with separate cumulative FBG load, the discrimination improved modestly (changes in AUC +0.0013, 95%CI 0.0001—0.0025 and +0.0018, 95%CI 0.0004—0.0033; Figure 1B, Supplementary Table 12). However, adding ARV or FBG and ARV did not further improve the reclassification (Supplementary Table 13). There was no compelling evidence that adding other indices after adding the

TABLE 1 Participant characteristics at baseline.

Characteristics	Total (n=5054)	No DR (n=4896)	DR (n=158)	*P* value
Age, years	46.26(11.44)	46.00(11.38)	54.16(10.49)	<0.001
Female, n(%)	2620 (51.84)	2557 (52.23)	63 (39.87)	0.002
Educational level, n(%)				<0.001
Illiteracy/Primary School/Middle School	1472 (29.13)	1389 (28.37)	83 (52.53)	
College/University	3582 (70.87)	3507 (71.63)	75 (47.47)	
Income, n(%)				0.04
≤5000	4096 (81.04)	3958 (80.84)	138 (87.34)	
>5000	958 (18.96)	938 (19.16)	20 (12.66)	
Current smoking, n(%)	889 (17.59)	843 (17.22)	46 (29.11)	<0.001
Current drinking, n(%)	1096 (21.69)	1046 (21.36)	50 (31.65)	0.002
Hypertension, n(%)	1339 (26.49)	1249 (25.51)	90 (56.96)	<0.001
Dyslipidemia, n(%)	2923 (57.84)	2795 (57.09)	128 (81.01)	<0.001
BMI, kg/m^2	24.57(3.46)	24.52(3.46)	25.93(3.40)	<0.001
FBG, mmol/L	5.83(1.48)	5.72(1.20)	9.31(3.59)	<0.001
SD, mmol/L	0.63(0.59)	0.59(0.48)	1.87(1.57)	<0.001
CV, %	10.51(6.18)	10.21(5.59)	19.97(12.83)	<0.001
VIM, %	0.76(0.32)	0.76(0.31)	0.79(0.40)	0.18
ARV, %	13.36(7.71)	13.06(7.13)	22.71(15.48)	<0.001
M-FBG, mmol/L	5.66(1.09)	5.56(0.87)	8.50(2.57)	<0.001
cumulative FBG load, %	5.76(9.73)	4.95(8.10)	30.74(18.70)	<0.001

Data are presented as n (%) or means ± SD.
DR, diabetic retinopathy; BMI, body mass index; FBG, fasting blood glucose; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; ARV, average real variability; M-FBG, mean fasting blood glucose level.

TABLE 2 Associations of different FBG indices with DR in the logistic regression model.

	OR (95%CI)	Adjusted OR (95%CI)
FBG	1.73(1.63, 1.85)	1.62(1.52, 1.73)
SD	3.17(2.74, 3.66)	2.74(2.38, 3.16)
CV, per 1 SD Increase	1.93(1.75, 2.11)	1.78(1.62, 1.95)
VIM, per 1 SD Increase	1.11(0.95, 1.29)	1.11(0.95, 1.29)
ARV, per 1 SD Increase	1.84(1.66, 2.03)	1.72(1.56, 1.91)
M-FBG	2.35(2.15, 2.57)	2.15(1.96, 2.36)
cumulative FBG load, per 1 SD Increase	2.78(2.52, 3.07)	2.57(2.31, 2.85)

FBG, fasting blood glucose; DR, diabetic retinopathy; OR, odds ratio; CI, confidence interval; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; ARV, average real variability; M-FBG, mean fasting blood glucose level.
Adjusted for age, sex, educational level, income, current smoking, current drinking, hypertension, dyslipidemia, body mass index.

cumulative FBG load improved the goodness of model fit as measured by AIC and BIC (Supplementary Table 14).

Specifically, among all the models, the highest discrimination was observed when the FBG, ARV, and cumulative FBG load were added (AUC 0.9153, 95%CI 0.8914—0.9393]; Supplementary Table 9). Compared to the model with separate FBG, the discriminatory power and risk reclassification of model with FBG, ARV, and cumulative FBG load improved significantly (IDI 0.0630, 95%CI 0.0358—0.0901; NRI 0.1278, 95%CI 0.0434—0.2122; Supplementary Table 10). The goodness of model fit improved significantly as well (ΔAIC -99.6533; ΔBIC -86.5970; Supplementary Table 11). However, when compared to the model with separate cumulative FBG load, the discriminatory power and risk reclassification did not improve substantially (IDI 0.0027, 95% CI -0.0022—0.0076; NRI -0.0006, 95%CI -0.0399—0.0386; Supplementary Table 13), and the goodness of model fit showed the opposite trend (ΔAIC 1.9209; ΔBIC 14.9770; Supplementary Table 14).

4.4 Sensitivity analysis

Supplementary Tables 15, 16 show the discrimination of the different models among participants (n=3557 individuals) with

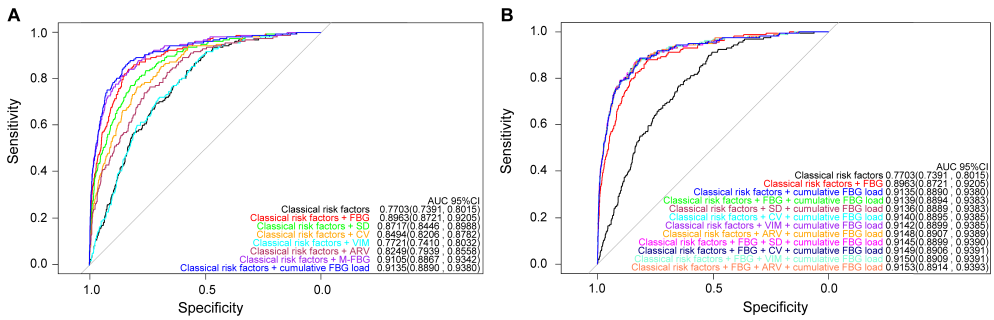

FIGURE 1
Prediction performance of the models. **(A)** Models with a separate FBG index. **(B)** Models with combined FBG indices.

more than three FBG tests and participants (n=1587 individuals) with more than four FBG tests. The AUCs with 95%CIs of the models with separate cumulative FBG load were 0.9209, 0.8937—0.9480 and 0.9317, 0.9004—0.9631. We observed similar discrimination in the three groups.

5 Discussion

In this study, we evaluated the predictive ability of various FBG indices for DR. This study showed that SD and per 1 SD increase in cumulative FBG load had stronger associations with the risk of DR

TABLE 3 Discrimination statistics for prediction of DR compared with the model with classical risk factors and FBG (n=5054).

Models	AUC (95%CI)	Changes in AUC(95%CI)	P value
Classical risk factors + FBG	0.8963(0.8721, 0.9205)	Reference	
Classical risk factors +SD	0.8717(0.8446, 0.8988)	-0.0246(-0.0403, -0.0089)	0.002
Classical risk factors +CV	0.8494(0.8206, 0.8782)	-0.0469(-0.0667, -0.0272)	<0.001
Classical risk factors +VIM	0.7721(0.7410, 0.8032)	-0.1242(-0.1504, -0.0980)	<0.001
Classical risk factors +ARV	0.8249(0.7939, 0.8558)	-0.0714(-0.0940, -0.0489)	<0.001
Classical risk factors +M-FBG	0.9105(0.8867, 0.9342)	0.0142(0.0043, 0.0240)	0.005
Classical risk factors +cumulative FBG load	0.9135(0.8890, 0.9380)	0.0172(0.0042, 0.0302)	0.009
Classical risk factors + FBG + SD	0.8993(0.8754, 0.9231)	0.0030(-0.0022, 0.0082)	0.26
Classical risk factors + FBG + CV	0.8958(0.8714, 0.9201)	-0.0005(-0.0012, 0.0002)	0.13
Classical risk factors + FBG + cumulative FBG load	0.9139(0.8894, 0.9383)	0.0176(0.0049, 0.0302)	0.007
Classical risk factors + SD + cumulative FBG load	0.9136(0.8889, 0.9383)	0.0173(0.0039, 0.0307)	0.01
Classical risk factors + CV + cumulative FBG load	0.9140(0.8895, 0.9385)	0.0177(0.0046, 0.0308)	0.008
Classical risk factors + ARV + cumulative FBG load	0.9148(0.8907, 0.9389)	0.0185(0.0056, 0.0315)	0.005
Classical risk factors + FBG + SD + cumulative FBG load	0.9145(0.8899, 0.9390)	0.0182(0.0052, 0.0311)	0.006
Classical risk factors + FBG + CV + cumulative FBG load	0.9149(0.8906, 0.9391)	0.0186(0.0059, 0.0312)	0.004
Classical risk factors + FBG + VIM + cumulative FBG load	0.9150(0.8909, 0.9391)	0.0187(0.0062, 0.0312)	0.003
Classical risk factors + FBG + ARV + cumulative FBG load	0.9153(0.8914, 0.9393)	0.0190(0.0065, 0.0316)	0.003

Classical risk factors: age, sex, BMI, educational level, income, current smoking, current drinking, hypertension, dyslipidemia.
DR, diabetic retinopathy; FBG, fasting blood glucose; AUC, area under the curve; CI, confidence interval; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; ARV, average real variability; M-FBG, mean fasting blood glucose level.

TABLE 4 Reclassification statistics for prediction of DR compared with the model with classical risk factors and FBG (n=5054).

Models	IDI (95% CI)	P value	NRI(Categorical) (95%CI)	P value
Classical risk factors + FBG	Reference		Reference	
Classical risk factors +SD	-0.0372(-0.0651, -0.0093)	0.009	-0.0751(-0.1465, -0.0037)	0.04
Classical risk factors +CV	-0.0861(-0.1173, -0.0549)	<0.001	-0.1615(-0.2292, -0.0938)	<0.001
Classical risk factors +VIM	-0.1618(-0.2016, -0.1221)	<0.001	-0.2442(-0.3120, -0.1763)	<0.001
Classical risk factors +ARV	-0.1030(-0.1413, -0.0647)	<0.001	-0.1788(-0.2530, -0.1047)	<0.001
Classical risk factors +M-FBG	0.0501(0.0215, 0.0787)	<0.001	0.1190(0.0418, 0.1963)	0.003
Classical risk factors +cumulative FBG load	0.0603(0.0312, 0.0894)	<0.001	0.1162(0.0295, 0.2028)	0.009
Classical risk factors + FBG + SD	-0.0003(-0.0053, 0.0048)	0.92	0.0000(-0.0248, 0.0248)	1.00
Classical risk factors + FBG + CV	0.0005(0.0000, 0.0010)	0.05	0.0000(0.0000, 0.0000)	1.00
Classical risk factors + FBG + cumulative FBG load	0.0614(0.0347, 0.0881)	<0.001	0.1288(0.0482, 0.2095)	0.002
Classical risk factors + SD + cumulative FBG load	0.0614(0.0299, 0.0928)	<0.001	0.1411(0.0502, 0.2320)	0.002
Classical risk factors + CV + cumulative FBG load	0.0623(0.0315, 0.0931)	<0.001	0.1407(0.0515, 0.2299)	0.002
Classical risk factors + ARV + cumulative FBG load	0.0618(0.0321, 0.0915)	<0.001	0.1280(0.0383, 0.2177)	0.005
Classical risk factors + FBG + SD + cumulative FBG load	0.0645(0.0368, 0.0922)	<0.001	0.1543(0.0674, 0.2413)	<0.001
Classical risk factors + FBG + CV + cumulative FBG load	0.0652(0.0376, 0.0928)	<0.001	0.1664(0.0800, 0.2527)	<0.001
Classical risk factors + FBG + VIM + cumulative FBG load	0.0643(0.0370, 0.0916)	<0.001	0.1415(0.0576, 0.2254)	<0.001
Classical risk factors + FBG + ARV + cumulative FBG load	0.0630(0.0358, 0.0901)	<0.001	0.1278(0.0434, 0.2122)	<0.001

Classical risk factors: age, sex, BMI, educational level, income, current smoking, current drinking, hypertension, dyslipidemia.
DR, diabetic retinopathy; FBG, fasting blood glucose; IDI, integrated discrimination improvement; CI, confidence interval; NRI, net reclassification improvement indexes; SD, standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; ARV, average real variability; M-FBG, mean fasting blood glucose level.

among these FBG indices. In addition, compared with other FBG indices, cumulative FBG load was a better predictor of DR. AUC analysis clearly showed that the model with separate cumulative FBG load was sufficiently qualified to capture the glucose-related DR risk. The predictive ability of model with separate cumulative FBG load were not improved by the replacement or addition with other FBG indices.

Compared with FBG, indices representing long-term glycemic control, such as M-FBG and cumulative FBG load, were more closely related to DR risk and simultaneously had better discrimination. Previous studies have shown that chronic, long-term glycemic exposure is a critical risk factor for diabetic complications (25). Unlike FBG, which offers a snapshot, long-term glucose control indices consider time, highlighting the impact of chronically high glucose levels on DR development. Moreover, maintaining stable glucose levels over time plays a key role in management of DR. Our study showed that compared with M-FBG, cumulative FBG load was more strongly associated with the risk of DR. Furthermore, cumulative FBG load was superior to the M-FBG in improving AUC, IDI, NRI, AIC, and BIC when added to a model with classical risk factors. Studies have shown that the M-FBG level is a good predictor of the development/progression of DR (19). Moreover, patients with a high average glucose level have an increased likelihood of adverse associations (18, 26). However, the M-FBG considers only the FBG level and time. When the average FBG level is below the threshold, it does not lead to DR (28, 29). Compared to the M-FBG, the cumulative FBG load considers the intensity, time, and emphasizes the proportion of the FBG load (17). Simultaneously, the cumulative FBG load introduced a blood glucose reference standard for prediabetes and emphasized the impact of FBG levels above the threshold on the retina (24). Our findings are consistent with those of a previous study which showed that a fasting blood glucose level of above 5.6 mmol/L was associated with a higher risk of cardiovascular disease and all-cause mortality (30). Several studies on cumulative FBG load support our findings. Previous studies have shown that a higher cumulative FBG load is associated with a higher risk of DM complications (17, 31). From the perspective of a clinical utility, cumulative FBG load is a better predictor of DR risk, as minor alterations in risk predictions can have substantial effects when applied to large populations.

While our study demonstrated little improvement in discrimination for other models compared to cumulative FBG load, a separate study in type 2 diabetics found that the coexistence of high glycemic variability and high glucose levels may exacerbate the independent risk of premature mortality (32). This inconsistency

with our results may be because glycemic variability mainly affects diabetic nephropathy (DN) rather than DR (33, 34). Although other FBG indices may have roles in some cases, our data suggests that a separate cumulative FBG load is adequate to predict the risk of DR. Therefore, as a simple measure of the level of FBG control at different time points, it can be considered for future risk prediction of DR.

Sensitivity analysis showed that the discrimination was similar among participants who had three or more FBG tests (n=5054 individuals), four or more FBG tests (n=3557 individuals), and five FBG tests (n=1587 individuals). The results showed that increasing the frequency of the FBG tests may not improve the prediction ability of these models. Therefore, from the perspective of the socioeconomic burden of the disease, appropriately reducing the frequency of FBG monitoring may not reduce the prediction efficiency.

This study is the first to use the cumulative FBG load to predict the risk of DR in a substantial community-based population. The strengths of this study include the use of detailed ophthalmic examinations, standardized questionnaires, biochemical analyses, and models that were fully adjusted for all common DR Risk factors. In addition, AUC was used to evaluate the model's prediction performance, which IDI, NRI, AIC, BIC further complemented to alleviate the possible limitations of a single model evaluation indicator.

However, our study has some limitations. The correlation of FBG indices with DR severity remains unclear as we did not stage DR according to severity. Besides, this study did not offer the baseline levels and the progress of DR, and we cannot draw a causal association between FBG indices and the occurrence and progression of DR. Further exploration of FBG indices on DR occurrence and progression prediction may be the purpose of future research. Additionally, the study participants were all from the Jidong community, and the applicability of our results to other ethnic populations requires further investigation. In the case of continuous variables, there may be potential differences when the mean is used in place of missing data. Finally, the analysis did not include potential confounders such as creatinine, AL, diopters, and residual confounding factors.

6 Conclusions

In conclusion, our study supports the idea that a separate cumulative FBG load is perfectly adequate for capturing the glucose-related DR risk, and the predictive utility of cumulative FBG load is not further substantively improved by the addition or replacement with other FBG indices in the assessment of DR risk. Our findings highlight the importance of achieving long-term normal FBG levels in glycemic management.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Staff Hospital of Jidong Oil-field of Chinese National Petroleum (approval document 2018 YILUNZI 1) and the Ethics Committee of Wenzhou Medical University Affiliated Ophthalmology Hospital (2021-074-K-63-01). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YJ: Data curation, Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. ZG: Data curation, Formal analysis, Writing – review & editing. JA: Data curation, Formal analysis, Writing – original draft. KY: Data curation, Formal analysis, Methodology, Writing – review & editing. XZ: Data curation, Formal analysis, Methodology, Writing – review & editing. KS: Methodology, Writing – review & editing. CL: Data curation, Formal analysis, Methodology, Writing – review & editing. TY: Conceptualization, Methodology, Writing – review & editing. YX: Methodology, Writing – review & editing. BS: Methodology, Writing – review & editing. JY: Methodology, Writing – review & editing. ZL: Data curation, Writing – review & editing. WL: Formal analysis, Methodology, Writing – review & editing. ZW: Formal analysis, Writing – review & editing. SD: Formal analysis, Methodology, Writing – review & editing. YW: Formal analysis, Writing – review & editing. FL: Funding acquisition, Resources, Visualization, Writing – review & editing. LC: Funding acquisition, Resources, Visualization, Writing – review & editing. ML: Conceptualization, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1420948/full#supplementary-material

References

1. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *N Engl J Med*. (2012) 366:1227–39. doi: 10.1056/NEJMra1005073

2. Steinmetz JD, Bourne RRA, Briant PS, Flaxman SR, Taylor HRB, Jonas JB, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Global Health*. (2021) 9:e144–60. doi: 10.1016/S2214-109X(20)30489-7

3. Papatheodorou K, Papanas N, Banach M, Papazoglou D, Edmonds M. Complications of diabetes 2016. *J Diabetes Res*. (2016) 2016:1–3. doi: 10.1155/2016/6989453

4. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. (2010) 376:124–36. doi: 10.1016/S0140-6736(09)62124-3

5. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

6. Sabanayagam C, Banu R, Chee ML, Lee R, Wang YX, Tan G, et al. Incidence and progression of diabetic retinopathy: a systematic review. *Lancet Diabetes Endocrinol*. (2019) 7:140–9. doi: 10.1016/S2213-8587(18)30128-1

7. Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJB, Klein CJ, et al. Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. *Diabetes Care*. (2006) 29:2282–8. doi: 10.2337/dc06-0525

8. Nathan DM, for the DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. *Diabetes Care*. (2014) 37:9–16. doi: 10.2337/dc13-2112

9. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. (2008) 358:2560–72. doi: 10.1056/NEJMoa0802987

10. Hirakawa Y, Arima H, Zoungas S, Ninomiya T, Cooper M, Hamet P, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care*. (2014) 37:2359–65. doi: 10.2337/dc14-0199

11. Tang X, Zhong J, Zhang H, Luo Y, Liu X, Peng L, et al. Visit-to-visit fasting plasma glucose variability is an important risk factor for long-term changes in left cardiac structure and function in patients with type 2 diabetes. *Cardiovasc Diabetol*. (2019) 18:50. doi: 10.1186/s12933-019-0854-9

12. Wang A, Liu X, Xu J, Han X, Su Z, Chen S, et al. Visit-to-visit variability of fasting plasma glucose and the risk of cardiovascular disease and all-cause mortality in the general population. *JAHA*. (2017) 6:e006757. doi: 10.1161/JAHA.117.006757

13. Pai Y-W, Lin C-H, Lee I-T, Chang M-H. Variability of fasting plasma glucose and the risk of painful diabetic peripheral neuropathy in patients with type 2 diabetes. *Diabetes Metab*. (2018) 44:129–34. doi: 10.1016/j.diabet.2018.01.015

14. Yang C-P, Li C-I, Liu C-S, Lin W-Y, Hwang K-L, Yang S-Y, et al. Variability of fasting plasma glucose increased risks of diabetic polyneuropathy in T2DM. *Neurology*. (2017) 88:944–51. doi: 10.1212/WNL.0000000000003682

15. Xu D, Fang H, Xu W, Yan Y, Liu Y, Yao B. Fasting plasma glucose variability and all-cause mortality among type 2 diabetes patients: a dynamic cohort study in Shanghai, China. *Sci Rep*. (2016) 6:39633. doi: 10.1038/srep39633

16. Bancks MP, Carson AP, Lewis CE, Gunderson EP, Reis JP, Schreiner PJ, et al. Fasting glucose variability in young adulthood and incident diabetes, cardiovascular disease and all-cause mortality. *Diabetologia*. (2019) 62:1366–74. doi: 10.1007/s00125-019-4901-6

17. Tian X, Chen S, Zhang Y, Zhang X, Xu Q, Xia X, et al. Association of cumulative blood glucose load with cardiovascular risk and all-cause mortality. *Diabetes Metab Syndrome: Clin Res Rev*. (2023) 17:102900. doi: 10.1016/j.dsx.2023.102900

18. Cardoso CRL, Leite NC, Moram CBM, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. (2018) 17:33. doi: 10.1186/s12933-018-0677-0

19. Zoppini G, Verlato G, Targher G, Casati S, Gusson E, Biasi V, et al. Is fasting glucose variability a risk factor for retinopathy in people with type 2 diabetes? *Nutr Metab Cardiovasc Dis*. (2003) 19:339–4. doi: 10.1016/j.numecd.2008.02.007

20. Gimeno-Orna JA, Castro-Alonso FJ, Boned-Juliani B, Lou-Arnal LM. Fasting plasma glucose variability as a risk factor of retinopathy in Type 2 diabetic patients. *J Diabetes its Complications*. (2003) 17:78–81. doi: 10.1016/S1056-8727(02)00197-6

21. Kim JA, Lee JS, Chung HS, Roh E, Lee Y-B, Hong S, et al. Impact of visit-to-visit fasting plasma glucose variability on the development of type 2 diabetes: A nationwide population-based cohort study. *Diabetes Care*. (2018) 41:2610–6. doi: 10.2337/dc18-0802

22. Wang Y. Visit-to-visit variability in fasting blood glucose predicts the new-onset heart failure: results from two large chinese cohorts. *Curr Probl Cardiol*. (2023) 48:1–26. doi: 10.1016/j.cpcardiol.2023.101842

23. Stewart AJ. Effects of β-blocker selectivity on blood pressure variability and stroke. *Neurology*. (2011). 77:731–7. doi: 10.1212/WNL.0b013e31822b007a

24. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: *standards of care in diabetes—2023*. *Diabetes Care*. (2023) 46:S19–40. doi: 10.2337/dc23-S002

25. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. (2001) 414:813–20. doi: 10.1038/414813a

26. Schreur V, Van Asten F, Ng H, Weeda J, Groenewoud JMM, Tack CJ, et al. Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. *Acta Ophthalmologica*. (2018) 96:459–64. doi: 10.1111/aos.13815

27. Wilkinson CP, Ferris FL, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. (2003) 110:1677–82. doi: 10.1016/S0161-6420(03)00475-5

28. Huru J, Leiviskä I, Saarela V, Liinamaa MJ. Prediabetes influences the structure of the macula: thinning of the macula in the Northern Finland Birth Cohort. *Br J Ophthalmol*. (2021) 105:1731–7. doi: 10.1136/bjophthalmol-2020-317414

29. Kirthi V, Zuckerman BP, Alam U, Bunce C, Hopkins D, Jackson TL. Associations between dysglycemia, retinal neurodegeneration, and microalbuminuria in prediabetes and type 2 diabetes. *Retina*. (2022) 42:442–9. doi: 10.1097/IAE.0000000000003337

30. Mongraw-Chaffin M, LaCroix AZ, Sears DD, Garcia L, Phillips LS, Salmoirago-Blotcher E, et al. A prospective study of low fasting glucose with cardiovascular disease events and all-cause mortality: The Women's Health Initiative. *Metabolism*. (2017) 70:116–24. doi: 10.1016/j.metabol.2017.02.010

31. Jin C, Li G, Rexrode KM, Gurol ME, Yuan X, Hui Y, et al. Prospective study of fasting blood glucose and intracerebral hemorrhagic risk. *Stroke*. (2018) 49:27–33. doi: 10.1161/STROKEAHA.117.019189

32. Liu Y, Xu H, Li J, Yang Y, Zhang J, Liu X, et al. Separate and combined effect of visit-to-visit glycaemic variability and mean fasting blood glucose level on all-cause mortality in patients with type 2 diabetes: A population-based cohort study. *Diabetes Obes Metab*. (2022) 24:2400–10. doi: 10.1111/dom.14826

33. Song K, Jeong J, Kim MK, Kwon H, Baek K, Ko S, et al. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. *J Diabetes Invest*. (2019) 10:745–52. doi: 10.1111/jdi.12953

34. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes. *Diabetes Care*. (2013) 36:2301–10. doi: 10.2337/dc12-2264

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EDITED BY
Jianzhong Xiao,
Tsinghua University, China

REVIEWED BY
Cosmin Mihai Vesa,
University of Oradea, Romania
Sueziani Binte Zainudin,
Sengkang General Hospital, Singapore

*CORRESPONDENCE
Fang Liu
f-liu@sjtu.edu.cn

†These authors have contributed equally to this work

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Flash glucose monitoring system help reduce the frequency of hypoglycemia and hypoglycemic fear behavior in type 1 diabetes patients

Lining Dong[1†], Junxian Li[1†], Yanyun Hu[1], Ruoting Chai[1], Ye Zhu[1], Liying Zhu[1], Nengguang Fan[1], Zhijian Zhang[1], Jiemin Pan[2], Jinhua Yan[3] and Fang Liu[1,2*]

[1]Department of Endocrinology and Metabolism, Shanghai General Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China, [2]Shanghai Key Laboratory of Diabetes, Department of Endocrinology & Metabolism, Shanghai Jiao-Tong University Affiliated Sixth People's Hospital, Shanghai Clinical Medical Center of Diabetes, Shanghai Key Clinical Center of Metabolic Diseases, Shanghai Institute for Diabetes, Shanghai, China, [3]Department of Endocrinology & Metabolism, The Third Affiliated Hospital of Sun Yat-Sen University, Guangdong, China

Objective: Hypoglycemia represents a serious acute complication in individuals with type 1 diabetes mellitus (T1DM). In order to more effectively identify and discriminate the occurrence of hypoglycemic events in patients with T1DM, this study aims to evaluate the impact of two distinct glucose monitoring systems—Flash Glucose Monitoring (FGM) and Continuous Glucose Monitoring (CGM)—on the management of blood glucose levels and the emotional responses associated with hypoglycemic episodes in individuals with T1DM.

Method: In this study, a total of 113 patients with type 1 diabetes mellitus were enrolled and allocated to two groups for the implementation of Glucose Monitoring Systems (GMS). The groups consisted of the FreeStyle Libre group (FGM, n=56) and the ipro2 group (CGM, n=57). Participants in both groups utilized GMS at least biannually and completed a set of three questionnaires: the Diabetes Monitoring and Treatment Satisfaction Questionnaire (DMTSQ), the Diabetes Specific Quality of Life (DQOL), and the Chinese Version of the Hypoglycemia Fear Survey II (CFHSII). Clinical data, CGM metrics, and questionnaire scores were collected at the initial visit and after a one-year follow-up period.

Results: The glucose coefficient of variation (GCV) and the standard deviation of blood glucose (SDBG) were independently associated with Time Below Range (TBR). Specifically, GCV could predict TBR ≥12%, with a cut-off point of 40.55. This yielded a specificity of 88.10% and a sensitivity of 68.18% in the overall patient population. For the FreeStyle Libre group and the iPro2 group, the cut-off points were 38.69 and 40.55, respectively, with specificities of 0.74 and 0.92, and sensitivities of 0.73 and 0.86, respectively. In the FreeStyle Libre group, where the frequency of use was greater than or equal to five times per year, the hypoglycemic episodes (time/month) and CHFSII-B scores were significantly reduced at follow-up compared to baseline (7.80 ± 10.25 vs 13.95 ± 14.87; 27.37 ± 11.05 vs 38.90 ± 21.61, respectively, all P <0.05).

Conclusion: The utilization of multiple Flash Glucose Monitoring (FGM) implementations proved to be valuable in discriminating the occurrence of hypoglycemia and mitigating the fear of hypoglycemic episodes in patients with type 1 diabetes. Within the parameters of Glucose Monitoring Systems (GMS), the glucose glycemic variability (GCV) was identified as a predictive factor for the risk of severe hypoglycemia (TBR > 12%). The optimal cut-off point for GCV was determined to be 40.55.

KEYWORDS

type 1 diabetes, hypoglycemia, flash glucose monitoring system, continuous glucose monitoring system, glucose coefficient of variation

1 Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder. According to the most recent nationwide population-based registry study, the estimated incidence of T1DM per 100,000 person-years across all age groups in China is 1.01 (1). Hypoglycemia represents an acute complication of T1DM, leading to both short-term and long-term physical adverse outcomes. The blood glucose management of patients with T1DM has an impact on the risk of complications (2). For example, poor glycemic control is associated with cardiac autoimmunity and may increase the risk of cardiovascular disease (CVD) (3) and fractures (4) in T1DM.Furthermore, it exerts a significant impact on psychosocial well-being, particularly by augmenting the fear of hypoglycemic episodes (5, 6). The adoption of higher hemoglobin A1c (HbA1c) targets is thought to diminish the risk of hypoglycemia (7). However, HbA1c reflects an average blood glucose level over the preceding 2-3 months and has a limited association with glycemic variability (8) and hypoglycemia (9). Conventional self-monitoring of blood glucose (SMBG) has been deemed inconvenient and insensitive for T1DM patients in the context of hypoglycemia prevention (10).

Continuous Glucose Monitoring (CGM) systems offer a convenient means of automatically recording interstitial fluid glucose concentrations at intervals of 5 to 15 minutes over several days. Previous evidence (11, 12) has demonstrated the benefits of CGM systems in glycemic control and the reduction of hypoglycemic episodes. Moreover, metrics of glycemic variability (GV) are emerging as valuable tools for the prediction of diabetic complications. For instance, Lu (13) reported that patients with more advanced diabetic retinopathy (DR) exhibited significantly reduced time spent within the glucose target range (TIR). Bragd et al (14) found that standard deviation of blood glucose (SDBG) not only showed significance in predicting the incidence of peripheral neuropathy, but also was a highly significant predictor of hypoglycemic unawareness in type 1 diabetes. In addition, Toschi et al (15) and Zhu et al (16)found that glucose coefficient of variation (GCV) from CGMs can identify individuals at higher risk for hypoglycemia compared with HbA1c in T1DM.

Time Below Range (TBR) represents the percentage of time per day that blood glucose levels are below 3.9 mmol/L, providing crucial insights into the duration of hypoglycemic episodes. Type 1 diabetes mellitus (T1DM) is characterized by significant glycemic fluctuations, making individuals with this condition more susceptible to hypoglycemia compared to those with type 2 diabetes. Flash Glucose Monitoring (FGM) systems, such as the FreeStyle Libre, are novel glucose monitoring technologies that provide continuous glucose data for up to 14 days per sensor wear, thereby enhancing the quality of life and satisfaction with diabetes monitoring and treatment among patients (17).

In light of these advancements, the present study aimed to investigate the association between TBR and glycemic variability (GV) in Chinese patients with T1DM by utilizing various Glucose Monitoring Systems (GMS). Additionally, the study sought to explore the impact of FGM on glycemic control and the fear of hypoglycemia after approximately one year of follow-up.

2 Methods

2.1 Study population

This study was conducted as a non-masked controlled trial, with participants, investigators, and study staff not being blinded to group allocation. A total of 120 patients with type 1 diabetes mellitus (T1DM) were recruited, and 113 of these were ultimately included in the study (Figure 1). The participants were recruited from the Departments of Endocrinology and Metabolism at Shanghai General Hospital, affiliated with Shanghai Jiao-Tong University School of Medicine; the Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital; and the Third Affiliated Hospital of Sun Yat-sen University. Recruitment and follow-up of patients occurred from March 2018 to May 2021.Inclusion criteria for participation were as follows: willingness to participate in the study; a confirmed diagnosis of T1DM with a history of insulin use for at least 3 months; an age of 6 years or older; the technical proficiency to utilize a glucose monitoring system; and agreement to perform self-monitoring of blood glucose

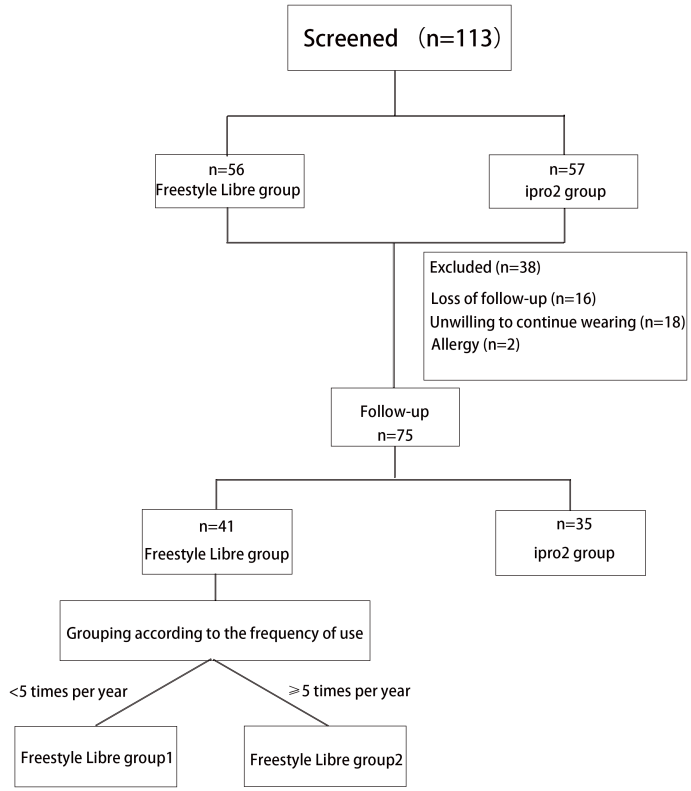

FIGURE 1
Flowchart of T1D patients recruitment and follow-up. A total of 113 patients with type 1 diabetes (T1D) were enrolled in this study following a screening process. Of these, 56 patients wore the FreeStyle Libre system, and 57 patients wore the iPro2 system. However, 38 patients were excluded from the study due to skin allergies (n=4), reluctance to continue wearing the device (n=18), and loss to follow-up (n=16). Consequently, 75 patients were followed up for approximately 1 year. Among these, 41 participants wore the FreeStyle Libre system, and 34 participants wore the iPro2 system. The FreeStyle Libre group was further divided into two subgroups based on wearing frequency: Group 1 (Worn less than five times per year) and Group 2 (Worn at least five times per year).

(SMBG) at least three times daily. Exclusion criteria included the following: a current diagnosis of hypoglycemia unawareness; a history of diabetic ketoacidosis or myocardial infarction within the preceding 6 months; known allergy to medical-grade adhesives; use of continuous glucose monitoring within the previous 4 months; pregnancy or intention to become pregnant; and receipt of oral steroid therapy.

The iPro2 group (n=57) utilized a retrospective Continuous Glucose Monitoring (CGM) system (Medtronic Inc., Northridge, CA) for a period of three consecutive days. The FreeStyle Libre group (n=56) employed the FreeStyle Libre system (Abbott Diabetes Care, Witney, UK) for a duration of fourteen consecutive days. Both groups were required to perform Glucose Monitoring Systems (GMS) assessments at least twice annually. Following a one-year follow-up period, a total of 74 patients completed the study.

The study protocol was ethically approved by the Institutional Review Board (IRB) of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, in compliance with the ethical principles outlined in the Declaration of Helsinki. Informed written consent was obtained from all participants prior to their inclusion in the study. This trial was registered with the Chinese Clinical Trial Registry (ClinicalTrials.gov) under the registration number ChiCTR1900025495, ensuring transparency and accountability in clinical research.

2.2 Clinical parameters collection

Prior to the commencement of Glucose Monitoring System (GMS) monitoring, comprehensive baseline data was collected from all subjects, encompassing demographic information such as age, sex, duration of diabetes, presence of diabetes-related complications, and details of insulin therapy. Additionally, anthropometric measurements were recorded, including height, weight, systolic and diastolic blood pressure. Body Mass Index (BMI) was calculated using the formula BMI = body weight (in kg)/height2 (in m2). A range of laboratory assessments was conducted, which included measurements of fasting plasma glucose, fasting C-peptide levels, HbA1c, a comprehensive lipid profile, and urine analysis.

2.3 CGMS parameters collection

Following the monitoring period, a suite of glycemic metrics was calculated, including Mean Blood Glucose (MBG), Time in Range (TIR), Time below Range (TBR), Time above Range (TAR), and measures of glycemic variability (GV). These metrics were calculated as follows:

- MBG: Defined as the average blood glucose level across all measured values.
- TIR: Represented the percentage of time during a 24-hour period that blood glucose levels remained within the target range of 3.9–10.0 mmol/L.
- TBR: Indicated the percentage of time during a 24-hour period that blood glucose levels were below 3.9 mmol/L.
- TAR: Measured the percentage of time during a 24-hour period that blood glucose levels exceeded 10.0 mmol/L.
- GV: This was quantified by metrics such as the standard deviation of blood glucose (SDBG), the glucose coefficient of variation (GCV), and the largest amplitude of glycemic excursion (LAGE). GCV was calculated by dividing SDBG by MBG. LAGE was defined as the difference between the maximum and minimum blood glucose levels observed during the monitoring period.

2.4 Questionnaire collection

Upon completion of the baseline and follow-up visits, during which the Glucose Monitoring System (GMS) was employed, patients were required to complete three questionnaires: the Diabetes Monitoring and Treatment Satisfaction Questionnaire (DMTSQ), the Diabetes Specific Quality of Life (DQOL), and the Chinese Version of the Hypoglycemia Fear Survey II (CHFSII). The CHFSII encompasses two subscales: the Behavior (CHFSII-B) and the Worry (CHFSII-W) subscales (18).

2.5 Statistical analysis

Data were presented as mean ± standard deviation (SD) for continuous variables and as percentages (%) for categorical variables. Comparisons between groups were conducted using the Chi-square test and the Mann-Whitney U test for categorical variables, and the Student's t test for continuous variables. The relationship between glycemic variability (GV) metrics and baseline characteristics was assessed using multiple stepwise linear regression analysis. The Receiver Operating Characteristic (ROC) curve was utilized to determine the cut-off value of the glucose coefficient of variation (GCV) for identifying the occurrence of abnormal Time Below Range (TBR) values (≥12%). Differences between baseline and follow-up data were evaluated using the Paired sample t test for continuous variables and the McNemar's test for categorical variables. All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 9.0. A two-sided P value < 0.05 was considered statistically significant.

3 Results

3.1 Participants characteristics

A total of 113 patients with type 1 diabetes mellitus (T1DM) were included in the study, with a gender distribution of 54 males and 59 females. The participants had a mean age of 35.7 ± 16.3 years and had been diagnosed with diabetes for a duration of 3.136 ± 3.032 years. The mean daily insulin dose was 31.59 ± 14.24 units, and the mean monthly frequency of hypoglycemic episodes was 7.531 ± 12.055. Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels were 8.52 ± 3.60 mmol/L and 7.58 ± 1.66%, respectively. Time in Range (TIR), Time above Range (TAR), Time below Range (TBR), Standard Deviation of Blood Glucose (SDBG), and Glucose Coefficient of Variation (GCV) were measured at 63.43 ± 22.50%, 29.86 ± 23.29%, 6.72 ± 9.79%, 2.95 ± 1.23, and 34.05 ± 11.14, respectively. Scores on the Chinese Version Hypoglycemia Fear Survey II (CHFSII) subscales Behavior (CHFSII-B) and Worry (CHFSII-W), as well as the Diabetes Specific Quality of Life (DQOL) and Diabetes Monitoring and Treatment Satisfaction Questionnaire (DMTSQ), were 25.94 ± 15.59, 14.20 ± 9.16, 99.39 ± 25.06, and 60.72 ± 18.40, respectively (Table 1).

The study involved 57 patients who were implanted with the iPro2 system (retrospective Continuous Glucose Monitoring, CGM) and 56 patients who were implanted with the FreeStyle Libre system (Flash Glucose Monitoring, FGM). Significant differences were observed in Time Below Range (TBR), Glucose Coefficient of Variation (GCV), and scores on the Chinese Version Hypoglycemia Fear Survey II Behavioral subscale (CHFSII-B) between the two groups. Specifically, the TBR, GCV, and CHFSII-B scores were found to be higher in the FGM group compared to the iPro2 group (Table 1).

3.2 The associated factors of TBR

In this study, Time Below Range (TBR) was found to be significantly correlated with Time Above Range (TAR), Mean Blood Glucose (MBG), Standard Deviation of Blood Glucose (SDBG), Glucose Coefficient of Variation (GCV), HbA1c, Fasting C-peptide levels, and scores on the Chinese Version Hypoglycemia Fear Survey II Behavioral subscale (CHFSII-B) in all patients with type 1 diabetes (Table 2). To further analyze the independent association factors of TBR, a multiple stepwise linear regression analysis was performed. The results indicated that GCV and SDBG were independent impact factors of TBR, after adjusting for other clinical confounding factors such as age, sex, body mass index (BMI), insulin dosage, duration of insulin use, fasting-C peptide levels, HbA1c, and other glycemic variability (GV) metrics (Table 3). Spearman correlation analysis revealed that GCV significantly correlated with TBR in both patient groups that wore the iPro2 and the FreeStyle Libre systems [correlation coefficients (r) = 0.693 and r = 0.463, respectively, all P < 0.001] (Figure 2).

3.3 The predictive value of GCV for TBR≥12%

According to the Chinese clinical guidelines for continuous glucose monitoring (19), Time Below Range (TBR) ≥12% was defined as the upper threshold of unacceptable hypoglycemia. Glucose Coefficient of Variation (GCV) and Standard Deviation of Blood Glucose (SDBG) were independently correlated with the

TABLE 1 Clinical characteristics and questionnaire scores of type 1 diabetes participants.

	All participants (*n* = 113)	Freestyle Libre group (n=56)	ipro2 group (n=57)	*p*
Male sex(%)	54,47.8%	25,44.6%	29,50.9%	0.509
Age (years)	35.7 ± 16.3	31.9 ± 17.4	39.4 ± 14.4	0.014
BMI (kg/m^2)	20.920 ± 2.984	20.322 ± 3.403	21.497 ± 2.406	0.037
SBP (mmHg)	113.443 ± 11.877	110.357 ± 10.949	116.474 ± 12.064	0.006
DBP (mmHg)	70.204 ± 9.163	68.161 ± 8.043	72.211 ± 9.805	0.018
FPG (mmol/l)	8.515 ± 3.604	7.986 ± 2.989	8.998 ± 4.051	0.144
PPG (mmol/l)	10.919 ± 4.915	9.839 ± 4.724	11.976 ± 4.920	0.040
Fasting C-peptide (ng/ml)	0.483 ± 0.591	0.503 ± 0.664	0.465 ± 0.520	0.744
TG (mmol/l)	0.788 ± 0.578	0.750 ± 0.319	0.822 ± 0.740	0.537
TC (mmol/l)	4.685 ± 0.833	4.624 ± 0.714	4.740 ± 0.932	0.491
HDL-C (mmol/l)	1.607 ± 0.443	1.593 ± 0.439	1.621 ± 0.450	0.750
LDL-C (mmol/l)	2.500 ± 0.684	2.389 ± 0.608	2.600 ± 0.738	0.125
Duration of diabetes (years)	3.136 ± 3.032	2.555 ± 2.052	3.707 ± 3.686	0.043
HbA1C (%)	7.581 ± 1.664	7.255 ± 1.433	7.907 ± 1.821	0.039
Hypoglycemia times (per month)	7.531±12.055	10.214 ± 15.279	4.895 ± 6.863	0.018
Insulin use dosage (units)	31.589 ± 14.244	29.535 ± 13.972	33.608 ± 14.342	0.129
Insulin use duration (years)	2.251 ± 2.609	1.953 ± 2.016	2.544 ± 3.073	0.230
TIR (3.9-10 mmol/L)	63.434 ± 22.501	63.714 ± 20.006	63.158 ± 24.887	0.896
TAR (>10 mmol/L)	29.858 ± 23.293	27.446 ± 22.096	32.228 ± 24.374	0.277
TBR (<3.9 mmol/L)	6.717 ± 9.787	8.839 ± 10.173	4.632 ± 8.900	0.022
MBG(mmol/L)	8.664 ± 2.357	8.320 ± 2.447	9.001 ± 2.237	0.125
SDBG(mmol/L)	2.949 ± 1.227	3.072 ± 1.358	2.843 ± 1.103	0.342
GCV(%)	34.054 ± 11.142	36.376 ± 9.165	32.059 ± 12.330	0.046
LAGE	10.435 ± 3.973	10.574 ± 3.826	10.292 ± 4.157	0.730
CHFSII-B score	25.941 ± 15.588	31.951 ± 19.034	20.341 ± 8.433	<0.001
CHFSII-W score	14.200 ± 9.157	15.439 ± 9.897	13.046 ± 8.358	0.231
DQOL score	99.386 ± 25.058	102.902 ± 23.422	95.952 ± 26.385	0.208
DMTSQ score	60.718 ± 18.402	60.135 ± 14.956	61.244 ± 21.213	0.792

CGM, Continuous glucose monitoring; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; TIR, Time in Range; TAR, Time above Range; TBR, Time below Range, MBG, Mean Blood Glucose; SDBG,standard deviation of blood glucose; GCV, glucose coefficient of variation; LAGE, largest amplitude of glycemic excursions; CHFSII-B/W,Chinese Version Hypoglycemia Fear Survey II- Behavior /Worry; DMTSQ, Diabetes Monitoring and Treatment Satisfaction Questionnaire; DQOL,Diabetes Specific Quality of Life.
a Data were expressed as mean ± standard deviation (SD) for continuous variables, and percentages (%) for categorical variables.

TBR level. Consequently, Receiver Operating Characteristic (ROC) curve analysis was employed to identify the cut-off value of GCV for predicting abnormal TBR (≥12%). In the overall cohort of type 1 diabetes mellitus (T1DM) subjects, the area under the curve (AUC) was 0.847 (95% Confidence Interval, 0.758-0.935; P=0.000), with a cut-off point of 40.55, yielding specificity of 88.10% and sensitivity of 68.18% (Figure 2A). In the FreeStyle Libre group, the AUC was 0.775 (95% CI, 0.638-0.912; P=0.002), with a cut-off point of 38.69, resulting in specificity of 73.53% and sensitivity of 73.33% (Figure 2B). In the iPro2 group, the AUC was 0.920 (95% CI, 0.793-1.000; P=0.000), with a cut-off point of 40.55, leading to specificity of 92.00% and sensitivity of 85.71% (Figure 3) (Table 4).

3.4 One year follow-up of T1DM who implemented with FGM

In this study, a one-year follow-up was conducted on 41 patients who used the FreeStyle Libre system. Clinical data, along with scores from the Chinese Version Hypoglycemia Fear Survey II

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(CFHSII), Diabetes Specific Quality of Life (DQOL), and Diabetes Monitoring and Treatment Satisfaction Questionnaire (DMTSQ), were reassessed. Based on the frequency of FreeStyle Libre use, patients were categorized into two groups: FreeStyle Libre Group 1, with low frequency use (<5 times per year, mean ± SD of 2.43 ± 0.51), and FreeStyle Libre Group 2, with high frequency use (≥5 times per year, mean ± SD of 22.10 ± 6.11).At baseline, there were no statistically significant differences between the two groups in terms of HbA1c, age, sex, Fasting Plasma Glucose (FPG), Body Mass Index (BMI), Lipid Profile, Insulin Daily Dose, Insulin Use Duration, and scores on the CFHSII-W subscale (all P values > 0.05). However, the frequency of hypoglycemic episodes (time/month) was significantly higher in FreeStyle Libre Group 2 compared to FreeStyle Libre Group 1 at baseline (5.38 ± 6.85 vs 13.95 ± 14.87, P < 0.05). Additionally, the CFHSII-B scores were significantly lower in FreeStyle Libre Group 2 compared to FreeStyle Libre Group 1 at baseline (25.78 ± 14.77 vs 38.90 ± 21.61, P < 0.05).A comparison of the clinical characteristics and questionnaire scores between FreeStyle Libre Group 1 and FreeStyle Libre Group 2 before and after follow-up revealed that the change in DQOL scores was significantly greater in FreeStyle Libre Group 2 compared to FreeStyle Libre Group 1 (11.79 ± 26.29 vs -9.41 ± 18.21, P < 0.05) (Table 5).

We compared the follow-up clinical characteristics and questionnaire scores with the baseline data for FreeStyle Libre Group 1 and FreeStyle Libre Group 2. In FreeStyle Libre Group 2, the frequency of hypoglycemic episodes (time/month) and scores on the Chinese Version Hypoglycemia Fear Survey II Behavioral subscale (CHFSII-B) were significantly lower at follow-up compared to baseline (13.95 ± 14.87 vs 7.80 ± 10.25; 38.90 ±

TABLE 2 Correlation analysis of variables with TBR in all T1DM.

Variables	*r*	*P*
TIR (3.9-10 mmol/L)	-0.124	0.191
TAR (>10 mmol/L)	-0.234	0.012
MBG(mmol/L)	-0.450	0.000
SDBG(mmol/L)	0.234	0.016
CV(%)	0.668	0.000
LAGE	0.098	0.342
HbA1c	-0.320	0.001
FPG	-0.142	0.140
PPG	-0.157	0.140
Fasting C-peptide	-0.255	0.007
Diabetic duration	0.033	0.731
age	-0.141	0.136
BMI	-0.078	0.415
Insulin daily dose	0.052	0.585
SBP	0.058	0.540
DBP	0.035	0.712
TC	-0.102	0.316
TG	-0.130	0.199
HDL	-0.058	0.565
LDL	-0.081	0.425
Sex	0.178	0.060
CHFSII-B	0.247	0.023
CHFSII-W	0.149	0.172
DQOL	0.052	0.643
DMTSQ	0.141	0.217

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; TIR, Time in Range; TAR, Time above Range ; TBR, Time below Range, MBG, Mean Blood Glucose; SDBG,standard deviation of blood glucose; CV,coefficient of variation; LAGE,largest amplitude of glycemic excursions; CHFSII-B/W,Chinese Version Hypoglycemia Fear Survey II- Behavior /Worry.;DMTSQ, Diabetes Monitoring and Treatment Satisfaction Questionnaire; DQOL, Diabetes Specific Quality of Life.

TABLE 3 Linear Regression Analysis of the GCV SDBG and TBR.

Model	Parameters	B(95%CI)	Standardized β	*P*
1	GCV	1.062	1.208	0.000
	SDBG	-6.103	-0.765	0.000
2	GCV	1.472	1.675	0.000
	SDBG	-10.923	-1.369	0.000
	MBG	1.714	0.421	0.015
3	GCV	1.479	1.626	0.000
	SDBG	-8.948	-1.095	0.000
	MBG	1.762	0.430	0.016
	LAGE	-0.718	-0.282	0.015
4	GCV	1.231	1.401	0.000
	SDBG	-9.914	-1.242	0.000
	TIR	-0.209	-0.490	0.000
5	GCV	1.260	1.433	0.000
	SDBG	-8.676	-1.087	0.000
	TAR	0.106	0.257	0.012

Model 1 was adjusted for age, sex, BMI, Insulin dosage, Insulin use duration, fasting C-peptide and HbA1c.
Model 2 includes all variables in Model 1 plus MBG.
Model 3 includes all variables in Model 1 plus LAGE and MBG.
Model 4 includes all variables in Model 1 plus TIR.
Model 5 includes all variables in Model 1 plus TAR.
BMI, body mass index;; HbA1c, glycosylated hemoglobin A1c; TIR, Time in Range; TAR, Time above Range ; TBR, Time below Range, MBG, Mean Blood Glucose; SDBG,standard deviation of blood glucose; CV,coefficient of variation.

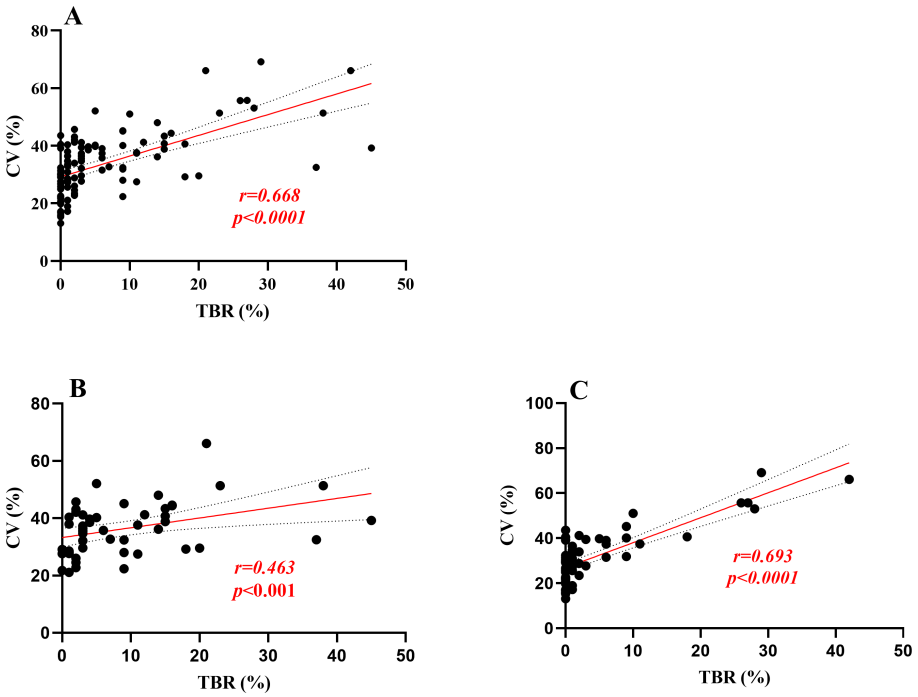

FIGURE 2
Linear regression analysis was performed for TBR and GCV. **(A)** means the correlation coefficient between TBR and GCV was 0.668 in all participants, p<0.0001;**(B, C)** means in Freestyle Libre group and Ipro2 group the correlation coefficient between TBR and GCV was 0.463,0.693, respectively, all P < 0.001].

21.61 vs 27.37 ± 11.05, respectively, all P<0.05). Additionally, the violin charts revealed that after follow-up, the distribution of hypoglycemic episodes (time/month) and CHFSII-B scores became more concentrated, with a narrower range between the maximum and minimum values (Figure 4).

In contrast, in FreeStyle Libre Group 1, there was no significant change in the frequency of hypoglycemic episodes (time/month) and CHFSII-B score. However, the Diabetes Specific Quality of Life (DQOL) score increased significantly (109.24 ± 19.87 vs 118.65 ± 23.20, P <0.05). Furthermore, the insulin daily dose increased significantly in both groups (P <0.05). Other variables, including triglycerides (TG) and fasting plasma glucose (FPG), did not show significant differences between the follow-up and baseline periods in either group (Table 6).

4 Discussion

In this study, we identified that Glucose Coefficient of Variation (GCV) and Standard Deviation of Blood Glucose (SDBG) serve as independent risk factors for Time Below Range (TBR) in the FreeStyle Libre (FGM) and Continuous Glucose Monitoring (CGM) parameters of patients with type 1 diabetes mellitus (T1DM). A high GCV is predictive of TBR ≥12%, with the most accurate prediction achieved at a GCV of 40.55%.

Patients with T1DM who were fitted with the iPro2 and FGM systems were followed up for one year. Our findings indicate that both FGM and iPro2 contribute to the timely detection of hypoglycemic episodes in T1DM patients. Although the Receiver Operating Characteristic (ROC) curve analysis demonstrated that iPro2 was more specific and sensitive than FGM in predicting TBR using GCV, the clinical parameters and questionnaire scores of patients using FGM before and after follow-up revealed that FGM use effectively reduced the monthly frequency of hypoglycemia and hypoglycemia-related fear behaviors. Furthermore, multiple FGM wearings exhibited a more pronounced effect on hypoglycemia monitoring.

Continuous Glucose Monitoring Systems (CGMS) have been extensively employed in clinical practice, with numerous studies conducted in patients with type 1 diabetes. These studies have provided valuable insights that have informed our research. For instance, Rama et al (9) identified the Glucose Coefficient of Variation (GCV) derived from CGMS (iPro2) and Self-Monitoring of Blood Glucose (SMBG) as the most effective discriminator of hypoglycemia (<3 mmol/L), with an Area Under the Curve (AUC) of 0.88. The optimal cut-off point was 44%, yielding a sensitivity of 81.3% and a specificity of 89%, thus offering the best discrimination of subjects with hypoglycemia among those with type 1 diabetes. Bragd et al (14) found that SDBG derived from SMBG was also a highly significant predictor of hypoglycemic unawareness (P = 0.001). Saisho (20) demonstrated that the SDBG derived from CGMS data was positively correlated with the duration of hypoglycemia (<3.9 mmol/L). Torimoto (21) indicated that the GCV derived from CGMS could serve as an indicator of hypoglycemia in type 2 diabetes, with an AUC of 0.756,

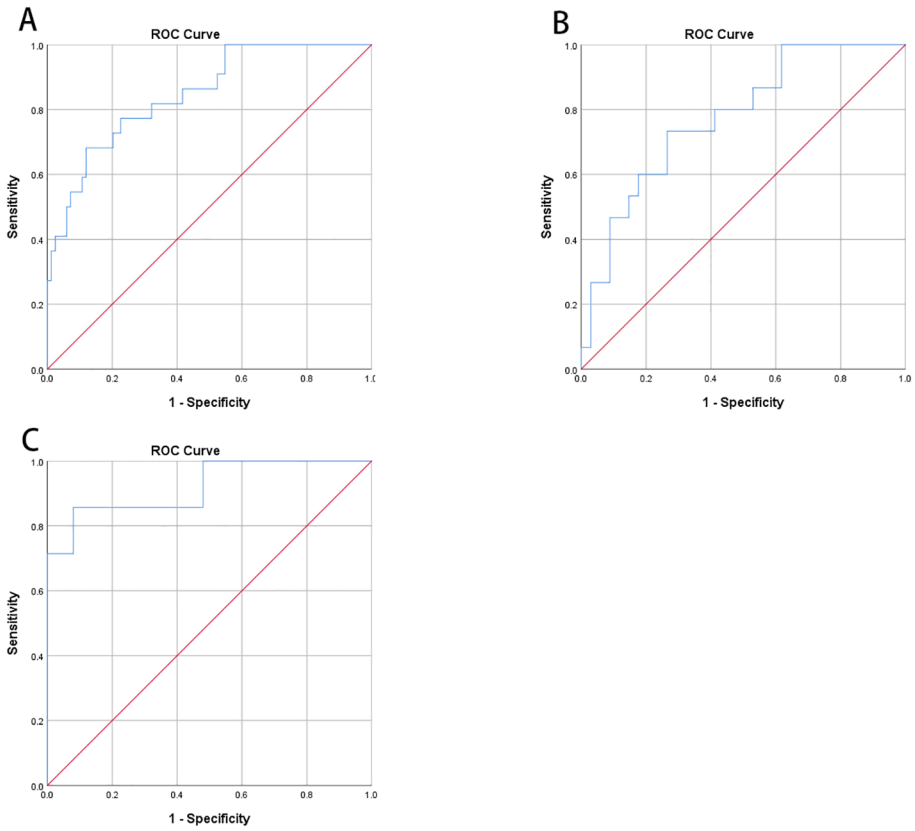

FIGURE 3
Receiver operating characteristic curve (ROC) analysis was used to know the cut-off point of GCV to predict abnormal TBR (≥12%). **(A)** In all T1DM subjects, area under the curve (AUC) of GCV was 0.847 (95%CI, 0.758-0.935; P<0.001) and the cut-off point was 40.55 with specificity 88.10% and sensitivity 68.18%, respectively. **(B)** In Freestyle Libre group, area under the curve (AUC) was 0.775 (95%CI, 0.638-0.912; P=0.002) and the cut-off point was 38.69 with specificity 73.53% and sensitivity 73.33%, respectively. **(C)** In Ipro2 group, AUC was 0.920 (95%CI, 0.793-1.000; P=0.000) the cut-off point was 40.55 with specificity 92.00% and sensitivity 85.71%, respectively (Table 4).

and the cut-off points for GCV in predicting hypoglycemia (<3.9 mmol/L) were 22%. Zhu et al (16) revealed that the GCV was strongly correlated with the percentage of time with glucose <70 mg/dL (<3.9 mmol/L) (r = 0.79; P < 0.0001) in youth with T1D.Toschi E et al (15) suggested that the GCV derived from CGMS could better identify individuals at higher risk for hypoglycemia compared to A1c alone.

Our research encompasses several unique and innovative aspects. Firstly, we compared the efficacy of two Glucose Monitoring Systems (GMS) in the recognition of hypoglycemia in patients with type 1 diabetes (T1D). The results revealed that both blood glucose monitoring systems were effective, with iPro2 demonstrating higher diagnostic sensitivity and specificity when TBR ≥ 12%. However, iPro2 is a retrospective blood glucose monitoring system, which can only reflect the blood glucose fluctuations over a span of 3 days and does not provide real-time guidance for the timely adjustment of hypoglycemic medications to reduce the duration of hypoglycemia. Secondly, our study evaluated the impact of FreeStyle Libre Monitoring (FGM) on quality of life and hypoglycemic fear behavior at baseline and follow-up. The findings indicated that the frequency of hypoglycemia was significantly reduced in the follow-up group, along with a significant decrease in the hypoglycemic fear behavior score. Rouhard et al. (22) conducted a retrospective study to assess the medium-term impact of FGM in T1DM and reported improvements in glycemic control, a slight reduction in daily insulin dose, an increase in diabetes satisfaction scores, and a decrease in hypoglycemic fear behavior scores. However, they did not observe a reduction in the frequency of hypoglycemia, particularly in well-controlled subjects. Thirdly, this study compared high-frequency FGM wear to low-frequency FGM for better glycemic control. Gomez-Peralta et al. (23) collected data on blood glucose variability, scanning frequency, and HbA1c in all Spanish individuals using Freestyle Libre to establish a Spain-specific relationship between testing frequency and glycemic parameters, and to demonstrate the associations of flash glucose monitoring with glycemic control under real-world settings. They found a positive correlation between high-frequency scanning and improved glycemic control. However, the large sample size may lead to an unfiltered sample, potentially resulting in biased outcomes. Urakami et al. (24) conducted a study on the effect of FGM on glycemic control in children and adolescents with T1D. They divided the subjects into high-frequency and low-frequency groups based on scanning frequency greater than 12 times/day, and found that scanning frequency was significantly positively correlated with TIR and negatively correlated with HbA1c. To date, more studies have focused on the influence of scanning frequency on glycemic control, while the

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TABLE 4 The characteristics of receiver operating characteristic curve.

ROC curve (Figure 2A)			CV(%)	ROC curve (Figure 2B)			CV(%)	ROC curve (Figure 2C)			CV(%)
Sensitivity	1 - Specificity	Youden's index	Cut-off point	Sensitivity	1 - Specificity	Youden's index	Cut-off point	Sensitivity	1 - Specificity	Youden's index	Cut-off point
0.682	0.155	0.527	40.16	0.733	0.353	0.380	37.48	0.857	0.140	0.717	39.60
0.682	0.143	0.539	40.30	0.733	0.324	0.410	37.81	0.857	0.120	0.737	39.94
0.682	0.131	0.551	40.44	0.733	0.294	0.439	38.26	0.857	0.100	0.757	40.29
0.636	0.119	0.517	40.68	0.667	0.265	0.402	39.03	0.714	0.080	0.634	40.94
0.636	0.119	0.517	40.68	0.667	0.265	0.402	39.03	0.714	0.080	0.634	40.94
0.591	0.119	0.472	40.95	0.600	0.265	0.335	39.46	0.714	0.060	0.654	42.40
0.591	0.107	0.484	41.20	0.600	0.235	0.365	39.95	0.714	0.040	0.675	44.40

a means the cut-off point of ROC curve. CV,coefficient of variation.

effect of wearing frequency on glycemic control remains underexplored. Our research contributes to this field by addressing this gap.

Our study also yielded some results that diverge from previous findings. For instance, Torimoto et al. (21) reported that Mean Blood Glucose (MBG) could predict hypoglycemia in type 2 diabetes mellitus (T2DM), with ROC curve analysis indicating that the optimal cut-off point for MBG in predicting hypoglycemia was 152 mg/dL (AUC = 0.826; 95% CI: 0.753–0.900). Contrary to this, in our study, MBG was not identified as an independent risk factor for Time Below Range (TBR), thus precluding its use for predicting abnormal TBR. We hypothesize that this discrepancy may be attributed to the more stable glycemic variability in T2DM compared to T1DM, making MBG a more suitable predictor of hypoglycemia in type 2 diabetes.

In our study, while HbA1c did not decrease following the use of FreeStyle (17) Libre Monitoring (FGM), the frequency of hypoglycemia was significantly reduced. This suggests that FGM may play a pivotal role in the management of hypoglycemia but that hyperglycemia management remains inadequate. Bolinder et al. found that FGM reduced the time adults with well-controlled T1DM spent in hypoglycemia (<3.9 mmol/L [70 mg/dL]) between baseline and 6 months. Laffel et al. (25) conducted a randomized clinical trial involving adolescents and young adults and reported a slight but statistically significant decrease in mean HbA1c from 8.9% at baseline to 8.5% at 26 weeks in the CGM group, whereas there was no change in HbA1c at baseline and 26 weeks in the BGM group. Karter et al. (26) included patients with both T1DM and T2DM in their retrospective study and found that the use of real-time CGM was associated with significantly lower HbA1c levels and lower rates of emergency department visits or hospitalizations for hypoglycemia compared to non-use.

The convenience of hospital-based intravenous blood glucose monitoring is limited, and self-monitoring of blood glucose (SMBG) is less convenient than Continuous Glucose Monitoring (CGM) due to its invasive nature. Despite the discrepancy between interstitial-fluid blood glucose monitoring and intravenous blood glucose monitoring, this difference does not significantly impact blood glucose management. Kumagai et al. (27) concluded that both the FreeStyle Libre Pro (FSL-Pro) and iPro2 systems are clinically acceptable, but glucose values tended to be lower when measured using the FSL-Pro compared to the iPro2.

This study exhibits several strengths. Firstly, within the context of Continuous Glucose Monitoring (CGM) data, we identified that the Glucose Coefficient of Variation (GCV) is independently associated with Time Below Range (TBR), with a cut-off point of 40.55 for abnormal TBR (≥12%). Secondly, we discovered a positive correlation between hypoglycemia-related worry and the frequency of hypoglycemic episodes, indicating that patients with greater concern about hypoglycemia are more inclined to wear a continuous glucose monitor frequently. Thirdly, the use of the Freestyle Libre Flash Glucose Monitoring (FGM) system at high frequency has been shown to decrease the incidence of hypoglycemia and alleviate hypoglycemia-related fear behaviors.

Certainly, the present study is not without limitations. Firstly, the study cohort comprises a relatively small sample size of follow-up patients with T1DM. Therefore, further research is warranted to

TABLE 5 Comparison between FGM groups before and after follow-up.

	FGM group 1 (n=21)	FGM group 2 (n=20)	*P*
Baseline			
Male sex(%)	8, 38.1%	8, 40%	*0.904*
Age	34.810 ± 15.964	25.050 ± 19.484	*0.087*
BMI	20.817 ± 3.625	18.836 ± 2.770	*0.057*
HbA1c	7.424 ± 1.557	6.858 ± 1.406	*0.237*
Fasting glucose (ng/mL)	8.414 ± 3.725	7.777 ± 2.520	*0.541*
Insulin daily dose	26.638 ± 13.661	31.703 ± 12.757	*0.228*
Insulin use duration	1.788 ± 1.654	1.370 ± 1.053	*0.339*
Hypoglycemic episodes (time /month)	5.381± 6.852	13.950 ± 14.873	*0.027*
CHFSII-B scores	25.778 ± 14.767	38.895 ± 21.610	*0.039*
CHFSII-W scores	14.500± 10.314	12.842 ± 7.719	*0.582*
DQOL scores	106.611 ± 22.264	105.053 ± 24.309	*0.840*
DMTSQ scores	58.938 ± 16.909	61.737 ± 12.701	*0.580*
TG	0.890 ± 0.399	0.658 ± 0.209	*0.049*
TC	4.564 ± 0.639	4.528 ± 0.688	*0.878*
HDL-c	1.507 ± 0.424	1.597 ± 0.454	*0.557*
LDL-c	2.338 ± 0.530	2.318 ± 0.625	*0.922*
Diabetic duration	2.510 ± 1.789	2.135 ± 1.621	*0.487*
Follow-up			
Implement times per year	2.430 ± 0.507	22.100 ± 6.112	0.000
ΔFPG(ng/mL)	0.284 ± 3.180	-1.263 ± 2.840	0.144
ΔTG	0.186 ± 0.512	-0.184 ± 1.022	0.202
ΔTC	-0.125 ± 0.810	-0.203 ± 0.883	0.803
ΔHDL-c	0.126 ± 0.675	0.000 ± 0.595	0.574
ΔLDL-c	-0.251 ± 0.706	-0.178 ± 0.641	0.768
ΔHbA1c(%)	-1.016 ± 2.006	-0.141± 0.743	0.090
Δ Insulin daily dose	-5.948 ± 11.671	-6.490 ± 8.374	0.867
Δ Hypoglycemic episodes (time /month)	-0.275 ± 10.081	6.150 ± 13.072	0.090
Δ CHFSII-B scores	3.353 ± 17.150	11.526 ±18.063	0.174
Δ CHFSII-W scores	-4.675 ± 10.994	0.895 ± 6.280	0.080
Δ DQOL scores	-9.412 ± 18.211	11.790 ± 26.292	0.009
Δ DMTSQ scores	2.200 ± 7.903	0.947 ± 12.117	0.732

BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; CHFSII-B/W, Chinese Version Hypoglycemia Fear Survey II- Behavior /Worry. DMTSQ, Diabetes Monitoring and Treatment Satisfaction Questionnaire; DQOL,Diabetes Specific Quality of Life. Δ means the difference between baseline and follow-up.

a. Data were expressed as mean ± standard deviation (SD) for continuous variables, and percentages (%) for categorical variables. ΔFPG = FPG baseline – FPG follow-up, and the others are the same way.

recruit a larger sample and extend the follow-up duration to validate the observed phenomena. Secondly, the absence of Continuous Glucose Monitoring (CGM) data from the follow-up visit precluded the analysis of changes in Time Below Range (TBR) and other glycemic variability (GV) metrics across the study groups. Thirdly, the one-year follow-up duration of this study limits its ability to assess the long-term impact of Flash Glucose Monitoring (FGM) on diabetes management.

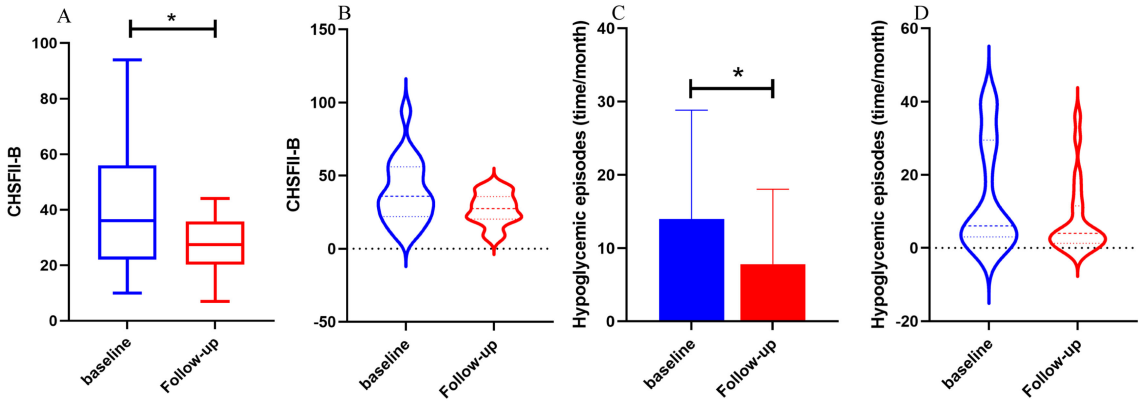

FIGURE 4
The comparison of hypoglycemic episodes, CFHSII-B between baseline and follow-up of Freestyle Libre group 2. FGM group 1 used Freestyle Libre at low frequency (<5 times per year) and FGM group 2 used Freestyle Libre at high frequency (≥ 5 times per year). In **(A, B)**, the CFHSII-B score of the follow-up group was significantly lower than baseline group, and the episodes of hypoglycemia in the follow-up group was significantly reduced compared with baseline in **(C, D)**, It can also be seen from the violin chart **(B, C)** that after follow-up, the distribution of hypoglycemia episodes (time/month) and CHFSII-B scores was more focused, and the gap between the maximum and minimum values was reduced.

5 Conclusions

In summary, the implementation of multiple Flash Glucose Monitoring (FGM) systems proved valuable in discriminating the occurrence of hypoglycemia and mitigating the fear-related behaviors in patients with type 1 diabetes. Among the Glucose Monitoring System (GMS) parameters, the Glucose Coefficient of Variation (GCV) emerged as a predictor of the risk of severe hypoglycemia (TBR > 12%), with an optimal cut-off point of 40.55. Consequently, for patients with T1DM whose blood glucose levels are prone to fluctuations, particularly adolescent patients, it is recommended to utilize real-time, non-invasive

TABLE 6 Intra-group comparison before and after follow-up.

FGM group 1 (n=21)				FGM group 2 (n=20)			
category	baseline	Follow-up	*P*	category	baseline	Follow-up	*P*
FPG(ng/mL)	8.576 ± 3.842	8.292 ± 3.208	0.717	FPG(ng/mL)	7.448 ± 2.306	8.711 ± 2.202	0.085
TG	0.855 ± 0.380	0.804 ± 0.404	0.586	TG	0.661 ± 0.204	0.912 ± 0.949	0.340
TC	4.561 ± 0.670	4.686 ± 0.774	0.574	TC	4.554 ± 0.662	4.758 ± 0.619	0.372
HDL-c	1.523 ± 0.403	1.579 ± 0.452	0.648	HDL-c	1.632 ± 0.470	1.718 ± 0.436	0.494
LDL-c	2.354 ± 0.565	2.604 ± 0.717	0.207	LDL-c	2.276 ± 0.627	2.453 ± 0.587	0.285
HbA1c(%)	7.500 ± 1.557	8.516 ± 2.162	0.041	HbA1c(%)	6.635 ± 0.841	6.777 ± 0.619	0.445
Insulin daily dose	26.570 ± 14.013	32.518 ± 18.640	0.034	Insulin daily dose	31.703 ± 12.757	38.193 ± 12.873	0.003
Hypoglycemic episodes (time /month)	5.250 ± 7.003	5.525 ± 8.081	0.904	Hypoglycemic episodes (time /month)	13.950 ± 14.873	7.800 ± 10.247	0.049
CHFSII-B scores	26.353 ± 15.012	23.000 ± 7.550	0.432	CHFSII-B scores	38.895 ± 21.610	27.368 ± 11.046	0.012
CHFSII-W scores	14.412 ± 10.625	19.059 ± 12.651	0.101	CHFSII-W scores	12.842 ± 7.719	11.947 ± 6.014	0.542
DQOL	109.235 ± 19.873	118.647 ± 23.200	0.049	DQOL	105.053 ± 24.309	93.263 ± 28.276	0.066
DMTSQ	55.333 ± 9.147	53.133 ± 9.403	0.299	DMTSQ	61.737 ± 12.701	60.263 ±12.041	0.615

BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, total triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; CHFSII-B/W, Chinese Version Hypoglycemia Fear Survey II- Behavior /Worry. DMTSQ, Diabetes Monitoring and Treatment Satisfaction Questionnaire; DQOL,Diabetes Specific Quality of Life.

FGM systems frequently to promptly identify the risk of severe or prolonged hypoglycemia. This approach can alleviate the psychological burden associated with hypoglycemia and enhance the quality of life within the T1DM population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

LD: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. JL: Writing – original draft, Methodology, Formal analysis, Data curation. YH: Writing – review & editing, Validation, Supervision, Formal analysis, Data curation. RC: Writing – review & editing, Data curation. YZ: Writing – review & editing, Data curation. LZ: Writing – review & editing, Supervision, Data curation. NF: Writing – review & editing, Visualization, Validation. ZZ: Writing – review & editing, Formal analysis. JP: Writing – review & editing, Data curation. JY: Writing – review & editing, Supervision, Data curation. FL: Writing – review & editing, Supervision, Methodology, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Weng J, Zhou Z, Guo L, Zhu D, Ji L, Luo X, et al. Incidence of type 1 diabetes in China, 2010-13: population based study. *BMJ (Clinical Res ed)*. (2018) 360:j5295. doi: 10.1136/bmj.j5295

2. Suh J, Choi Y, Oh JS, Song K, Choi HS, Kwon A, et al. Association between early glycemic management and diabetes complications in type 1 diabetes mellitus: A retrospective cohort study. *Prim Care Diabetes*. (2023) 17:60–7. doi: 10.1016/j.pcd.2022.12.006

3. Sousa GR, Pober D, Galderisi A, Lv H, Yu L, Pereira AC, et al. Glycemic control, cardiac autoimmunity, and long-term risk of cardiovascular disease in type 1 diabetes mellitus. *Circulation*. (2019) 139:730–43. doi: 10.1161/CIRCULATIONAHA.118.036068

4. Vavanikunnel J, Charlier S, Becker C, Schneider C, Jick SS, Meier CR, et al. Association between glycemic control and risk of fracture in diabetic patients: A nested case-control study. *J Clin Endocrinol Metab*. (2019) 104:1645–54. doi: 10.1210/jc.2018-01879

5. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab*. (2013) 98:1845–59. doi: 10.1210/jc.2012-4127

6. Driscoll KA, Raymond J, Naranjo D, Patton SR. Fear of hypoglycemia in children and adolescents and their parents with type 1 diabetes. *Curr Diabetes Rep*. (2016) 16:77. doi: 10.1007/s11892-016-0762-2

7. Karges B, Kapellen T, Wagner VM, Steigleder-Schweiger C, Karges W, Holl RW, et al. Glycated hemoglobin A1c as a risk factor for severe hypoglycemia in pediatric type 1 diabetes. *Pediatr Diabetes*. (2017) 18:51–8. doi: 10.1111/pedi.2017.18.issue-1

8. Derr R, Garrett E, Stacy GA, Saudek CD. Is HbA(1c) affected by glycemic instability? *Diabetes Care*. (2003) 26:2728–33. doi: 10.2337/diacare.26.10.2728

9. Rama Chandran S, Tay WL, Lye WK, Lim LL, Ratnasingam J, Tan ATB, et al. Beyond hbA1c: comparing glycemic variability and glycemic indices in predicting hypoglycemia in type 1 and type 2 diabetes. *Diabetes Technol Ther*. (2018) 20:353–62. doi: 10.1089/dia.2017.0388

10. Ajjan R, Slattery D, Wright E. Continuous glucose monitoring: A brief review for primary care practitioners. *Adv Ther*. (2019) 36:579–96. doi: 10.1007/s12325-019-0870-x

11. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet*. (2016) 388:2254–63. doi: 10.1016/S0140-6736(16)31535-5

12. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. Design and methods of a randomized trial of continuous glucose monitoring in persons with type 1 diabetes with impaired glycemic control treated with multiple daily insulin injections (GOLD study). *J Diabetes Sci Technol*. (2016) 10:754–61. doi: 10.1177/1932296816642578

13. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care*. (2018) 41:2370–6. doi: 10.2337/dc18-1131

14. Bragd J, Adamson U, Bäcklund LB, Lins PE, Moberg E, Oskarsson P. Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? *Diabetes Metab*. (2008) 34:612–6. doi: 10.1016/j.diabet.2008.04.005

15. Toschi E, Slyne C, Sifre K, O'Donnell R, Greenberg J, Atakov-Castillo A, et al. The relationship between CGM-derived metrics, A1C, and risk of hypoglycemia in older adults with type 1 diabetes. *Diabetes Care*. (2020) 43:2349–54. doi: 10.2337/dc20-0016

16. Zhu J, Volkening LK, Laffel LM. Distinct patterns of daily glucose variability by pubertal status in youth with type 1 diabetes. *Diabetes Care*. (2020) 43:22–8. doi: 10.2337/dc19-0083

17. Mitsuishi S, Nishimura R, Harashima SI, Kawamura T, Tsujino D, Koide K, et al. The effect of novel glucose monitoring system (Flash glucose monitoring) on mental well-being and treatment satisfaction in Japanese people with diabetes. *Adv Ther*. (2018) 35:72–80. doi: 10.1007/s12325-017-0649-x

18. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care*. (2011) 34:801–6. doi: 10.2337/dc10-1343

19. Bao Y, Chen L, Chen L, Dou J, Gao Z, Gao L, et al. Chinese clinical guidelines for continuous glucose monitoring (2018 edition). *Diabetes/Metabol Res Rev*. (2019) 35:e3152. doi: 10.1002/dmrr.v35.6

20. Saisho Y, Tanaka C, Tanaka K, Roberts R, Abe T, Tanaka M, et al. Relationships among different glycemic variability indices obtained by continuous glucose monitoring. *Primary Care Diabetes*. (2015) 9:290–6. doi: 10.1016/j.pcd.2014.10.001

21. Torimoto K, Okada Y, Hajime M, Tanaka K, Tanaka Y. Risk factors of hypoglycemia in patients with type 2 diabetes mellitus: A study based on continuous glucose monitoring. *Diabetes Technol Ther*. (2018) 20:603–12. doi: 10.1089/dia.2018.0017

22. Rouhard S, Buysschaert M, Alexopoulou O, Preumont V. Impact of flash glucose monitoring on glycaemic control and quality of life in patients with type 1 diabetes: A 18-month follow-up in real life. *Diabetes Metab Syndr*. (2020) 14:65–9. doi: 10.1016/j.dsx.2019.12.007

23. Gomez-Peralta F, Dunn T, Landuyt K, Xu Y, Merino-Torres JF. Flash glucose monitoring reduces glycemic variability and hypoglycemia: real-world data from Spain. *BMJ Open Diabetes Res Care*. (2020) 8:e001052. doi: 10.1136/bmjdrc-2019-001052

24. Urakami T, Yoshida K, Kuwabara R, Mine Y, Aoki M, Suzuki J, et al. Frequent scanning using flash glucose monitoring contributes to better glycemic control in children and adolescents with type 1 diabetes. *J Diabetes Investig*. (2022) 13:185–90. doi: 10.1111/jdi.13618

25. Laffel LM, Kanapka LG, Beck RW, Bergamo K, Clements MA, Criego A, et al. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: A randomized clinical trial. *JAMA*. (2020) 323:2388–96. doi: 10.1001/jama.2020.6940

26. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of real-time continuous glucose monitoring with glycemic control and acute metabolic events among patients with insulin-treated diabetes. *JAMA*. (2021) 325:2273–84. doi: 10.1001/jama.2021.6530

27. Kumagai R, Muramatsu A, Fujii M, Katakura Y, Ito K, Fujie K, et al. Comparison of glucose monitoring between Freestyle Libre Pro and iPro2 in patients with diabetes mellitus. *J Diabetes Investig*. (2019) 10:851–6. doi: 10.1111/jdi.12970

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EDITED BY
Åke Sjöholm,
Gävle Hospital, Sweden

REVIEWED BY
Hans-Michael Kaltenbach,
ETH Zürich, Switzerland
Daniela Lopes Gomes,
Federal University of Pará, Brazil

*CORRESPONDENCE
Ulrike Schierloh
schierloh.ulrike@me.com

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Fear of hypoglycemia and sleep in children with type 1 diabetes and their parents

Ulrike Schierloh[1]*, Gloria A. Aguayo[2], Muriel Fichelle[1], Cindy De Melo Dias[1], Anna Schritz[3], Michel Vaillant[3], Katharine Barnard-Kelly[4], Ohad Cohen[5], Inge Gies[6,7] and Carine de Beaufort[1]

[1]Department of Pediatric Diabetes and Endocrinology, Clinique Pédiatrique, Centre Hospitalier, Luxembourg, Luxembourg, [2]Deep Digital Phenotyping Research Unit, Department of Precision Health, Luxembourg Institute of Health, Strassen, Luxembourg, [3]Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen, Luxembourg, [4]Southern Health NHS Foundation Trust, Southampton, United Kingdom, [5]Institute of Endocrinology, Sheba Medical Center, Tel Hashomer, Israel, [6]Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Brussels, Brussels, Belgium, [7]Research Unit Research Group Growth and Development (GRON), Vrije Universiteit Brussel, Brussels, Belgium

Aims: To compare impact of pump treatment and continuous glucose monitoring (CGM) with predictive low glucose suspend (SmartGuard) or user initiated CGM (iscCGM) on sleep and hypoglycemia fear in children with type 1 Diabetes and parents.

Methods: Secondary analysis of data from 5 weeks pump treatment with iscCGM (A) or SmartGuard (B) open label, single center, randomized cross-over study was performed. At baseline and end of treatment arms, sleep and fear of hypoglycemia were evaluated using ActiGraph and questionnaires.

Results: 31 children (6-14 years, male: 50%) and 30 parents (28-55 years) participated. Total sleep minutes did not differ significantly for children (B vs. A: -9.27; 95% CI [-24.88; 6.34]; p 0.26) or parents (B vs. A: 5.49; 95% CI [-8.79; 19.77]; p 0.46). Neither daytime sleepiness nor hypoglycemia fear in children or parents differed significantly between the systems. Neither group met recommended sleep criteria.

Conclusion: Lack of sleep and fear of hypoglycemia remain a major burden for children with diabetes and their parents. Whilst no significant differences between the systems were found, future technology should consider psychosocial impacts of diabetes and related technologies on children and parents' lived experience to ensure parity of esteem between physical and mental health outcomes.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT03103867.

KEYWORDS

type 1 diabetes (T1D), children, parents, fear of hypoglycemia, sleep, sensor augmented pump, iscCGM

1 Introduction

The daily management of type 1 diabetes (T1D) is a 24/7 challenge for children and their caregivers and may have a major negative impact on their sleep and quality of life (1–3).

Fear of nocturnal hypoglycemia is common and a significant concern amongst parents of children with T1D (4–6), and is associated with enhanced attention to frequent checking of their children's glycemia or sensor values or to get up during the night (7, 8). Data show that fear of hypoglycemia can lead to chronic sleep disturbance for the parents as for their children with diabetes (9–11). This highly prevalent chronic sleep interruption can affect caregivers of children with T1D with negative effects on their daily functioning and well-being (12, 13).

New technologies have been introduced to facilitate and improve care with automated sensor-augmented pump (SAP) and predictive low glucose suspend and alerts (SmartGuard) or with user-initiated intermittently scanned continuous glucose monitoring (iscCGM, Freestyle libre).

SAP treatment leads to improved metabolic outcome (14). Alerts about hypo-and hyperglycemia are programmed in SAP in order to enable patients and their caregivers to react quickly to such information. The Minimed 640G pump with SmartGuard feature combines alerts with an automated insulin suspension to prevent hypoglycemia. The pump suspends insulin infusion when the sensor glucose (SG) is within 3.9 mmol/l (70 mg/dl) above the low limit and predicted to be 1.1 mmol/l (20 mg/dl) or lower above the low limit in 30 min. Glucose values and glucose trends are available on the pump screen (15).

A multicenter evaluation shows that SmartGuard technology significantly reduces the risk for hypoglycemia in pediatric diabetes patients without increasing HbA1c (16).

However, alerts may be perceived as intrusive and anxiety-inducing which can lead to diabetes distress and alert fatigue as well as nocturnal awakenings (8, 17).

Freestyle Libre 1 is a device measuring the interstitial glucose levels continuously. The results can be obtained when the patient/caregiver actively scans the sensor (iscCGM): no alerts are given for hypo-or hyperglycemic events, nor is information available when the sensor is not scanned. Data is lost when more than 8 hours elapse between scans. No communication exists between this glucose measurement and the insulin pump (15).

The evaluation of iscCGM being as safe as self-monitoring of blood glucose (SMBG) and having a better metabolic outcome than SMBG is demonstrated in children (18, 19).

The impact of these technologies on metabolic control has been studied before (20).

To our knowledge, no study has yet addressed the focus on comparing the impact of these two technologies on fear of hypoglycemia, quality and quantity of sleep in children and their caregivers. In this report we analyze these questions using questionnaires, sleep diaries and ActiGraph data in the QUEST trial (15).

2 Materials and methods

2.1 Ethics committee statement

This study was approved by the National Luxembourgish Ethics committee (CNER). Only pseudonymized data was used for the analysis.

2.2 Study design and randomization

The study had an open-label, single-center, randomized, two-period crossover design.

Each patient was randomly allocated; the sequence codes (A-B or B-A) were determined in advance (15).

2.3 Participants

Patients fulfilling the following inclusion criteria got included: age between 6 and 14 years, type 1 diabetes and on insulin pump treatment for at least 6 months and HbA1c ≤ 11% (≤ 96.72 mmol/mol) (30).

Exclusion criteria were physical or psychological disease likely to interfere with an appropriate conduct of the study and chronic sleep medication used by the patient or by the participant primary caregiver. Prior to enrollment, written informed consent was obtained from the parents and all children gave their informed assent (30).

2.4 Procedures

The participants were randomized either to treatment A, insulin pump Minimed 640G and independent iscCGM (Freestyle libre 1) or to treatment B, SAP with SmartGuard feature (Minimed 640G), each for 5 weeks. Following a 3 weeks washout period the participants crossed over to the other study arm for another 5 weeks.

No specific dietary advice was given.

The week before randomization as well as during the last 7 days of each treatment the participants and one of their caregivers (same reference person throughout the course of the study) wore a sleep device on the wrist (ActiGraph) and completed a sleep diary. Before the start and at the end of each treatment arm the subject and his caregiver were asked to fill in the questionnaires.

To evaluate the hypoglycemia fear, the Children's Hypoglycemia Survey (CHS) and Hypoglycemia Fear survey for parents were used. The Children's Hypoglycemia Survey (24 items) measures 3 areas of hypoglycemia fear: their general fear of hypoglycemia and its consequences, the children's fear of hypoglycemia in a specific situation, and the children's behavior to avoid hypoglycemia. The survey for parents is divided into 2

subscales-scores, one asking about parental worry about their child's hypoglycemia (15 items), and the other about behavior to prevent hypoglycemia for their child (11 items) (21–25).

Daytime sleepiness in the children and their caregiver were evaluated using the Epworth sleepiness scale, a self-administered questionnaire which provides a measurement of the subject's general level of daytime sleepiness (26). The Epworth Sleepiness Scale is defined based on questions about the chances to fall asleep in different situations. The score ranges from 0-24 with the following interpretation: score 0-5: lower normal daytime sleepiness/6-10: higher normal daytime sleepiness/11-12: mild excessive daytime sleepiness/13-15: moderate excessive daytime sleepiness/16-24: severe excessive daytime sleepiness (26).

The detailed conduct of the study was previously published (15).

The use of the two glucose measurement tools and the features of the Minimed 640G pump were explained during the dedicated training visit. All participants had access to a 24/7 diabetes hotline in case of technical or any other issues. Settings of the SmartGuard were standardized based on the current experience (20). The low limit was set at 3.4 mmol/l, with an insulin suspension at ≤7.3 mmol/l if the predicted value within 30 minutes was 4.5 mmol/l (15).

2.5 Methods

Randomization (ratio 1:1) was performed by a statistician with 4 blocks of 8 participants and equal treatment allocation based on prepared envelopes with the sequence code (A-B or B-A). In this randomized block design the sequence codes were randomly allocated to each block. This kind of design is used to minimize the effects of systematic error.

After consenting, the envelope was opened by the medical team to provide the participant with the allocated treatment sequence (15, 30).

Blinding was not possible for the participant nor the medical team.

A sample size of 36 patients with a minimum of 31 patients was calculated for a power of 80% (15).

To ensure data quality, double data entry was performed within Ennov Clinical software, and online logical controls were performed with correction of erroneous data values.

Hypoglycemia Index in children (subscales and Hypoglycemia Fear Survey in parent/caregiver (subscales for hypoglycemia worry and behavior) at baseline and at the end of each treatment arm were also analyzed by using a linear mixed model with the same independent parameters as described previously.

Total sleep (minutes) and total wake time (minutes) and number of awakenings during the last 7 days of each treatment arm were measured by ActiGraph, in children and in one of their caregivers. Sleep analysis was performed using ActiLife data analysis software. The detailed assessment of sleep patterns was previously published (15). The average sleep time per night for each visit was used as the outcome to compare the two different treatments. Additionally, the average number of awakenings and the average length of total wake time per night and visit was compared between the two devices. Where Actigraph measurement of sleep was divided into more than one sleep period (due to being awake and getting out of bed for more than 10 minutes), total sleep time (defined by ActiLife), time and number of awakenings (defined by ActiLife), number of get-ups (number of sleep periods - 1), and time of being out of bed (time from out of bed till sleep onset) was added up to have one measurement per night. Sleep time during the day (nap; went to bed between 12pm and 7pm) was excluded from the analysis. For number of awakenings and total wake time, the estimations of the ActiLife algorithm (Sadeh for children (10-25 years) and Cole-Kripke for adults) were used as outcomes (27, 28).

Time to bed, time out of bed and number of awakenings were also compared with the sleep diary and some parameters were adjusted according to the sleep diary if they seemed too unrealistic when calculated by ActiLife. We used the ActiLife settings for bedtime (5 consecutive asleep minutes) and wake time (first 10 consecutive minutes of awake time following a sleep period). The definition of sleep is based on the accelerometer data. If there is no movement for at least 5 minutes, the period is defined as sleep. Vacation time was not taken into account.

Characteristics of children and parents were presented using mean and standard deviations (SD) for continuous variables, median, 25% and 75% quartiles (Q1, Q3) for count variables and frequency and percentage for categorical variables. Characteristics for children are shown for the total study population and separated by treatment sequences. Z score BMI are calculated with the formula Z score = (X-m)/SD; X = BMI, m = mean, SD = standard deviation of BMI of the reference population (WHO growth reference (2006) data) with same sex and age (29).

Total sleep, quality of sleep (Epworth sleepiness scale and sleep diary) and number of awakenings were analyzed by using a linear mixed model and a naïve Fisher's Exact test with treatment given (A vs. B), treatment sequence (A-B vs. B-A) and period of treatment (week 5 vs. week 13) as fixed effects factors and patient as a random effect.

Least square means and their 95% confidence intervals (CI) from the linear mixed models were reported as adjusted mean average sleep time and adjusted average number of awakenings in children and parents.

All test were two-tailed and a p-value<0.05 was claimed statistically significant. RStudio 2021.09.2 was used for statistical analysis.

3 Results

32 children, 16 male (50%), between 6 -14 years with a mean HbA1c of 7.47%, (58.14 mmol/mol), SD 0.59, a mean diabetes duration of 5.91 years (SD 3.29), being on insulin pumps for 5.07 (SD 3.87) years, were included in this study. Metabolic outcome as primary endpoint was reported previously (30). One child dropped out of the study after the first visit at baseline, without wearing neither the ActiGraph nor filling out any of the questionnaires and sleep diaries. 31 children (16 males) completed the study.

30 caregivers (24 females, 28 – 55 years (mean 42.77 years, SD 5.96)) participated in the study.

One parent had two children included in the study, therefore only one questionnaire and sleep diary was filled out and one

Actigraph was worn by the parent. 28 parents and children answered all the questionnaires.

Table 1 (30) shows the demographic baseline values for study participants (31 children), Table 2 the data for the participating parents (30 caregivers).

3.1 Description of missing data

3.1.1 Children

For one child the glucose sensor values of the last visit are missing. For another child the questionnaire, sleep diary and ActiGraph data of the wash-out period are missing for visit 3. Two children did not return/fill out the questionnaire of visit 2. Two children did not completely fill out all questions at visit 3. The maximum percentage of missing data in the models was 6.5% for children (model including Epworth Sleepiness Scale).

3.1.2 Parents

The parent of the child whose data were missing for visit 3, had also no data for visit 3. One parent had missing data for the ActiGraph and the sleep diary for visit 2, 3 and 4. Two parents did not fill out/return the questionnaire at visit 2. One parent did not answer one question at visit 3. The maximum percentage of missing data in the models was 10% for parents (model including Epworth Sleepiness Scale).

3.2 Sleep data results

3.2.1 Total sleep time

Adjusted average sleep time for children in treatment A (pump and iscCGM) was 449.3 (95% CI [432.8; 465.7]) minutes per night (7.5 hours per night) and 440.0 (95% CI [423.6; 456.5]) minutes per night (7.3 hours per night) for treatment B (pump plus SmartGuard). No significant difference of total sleep time between devices was found (p-value 0.255).

For parents the adjusted average sleep time in treatment A was 413.8 (95% CI [395.4; 432.2]) minutes per night (6.9 hours) with a non-significant increase in sleep time of 5.5 minutes (95%CI [-8.8; 19.8]); p-value 0.46) for treatment B (419.3 (95% CI [400.9; 437.7])).

3.2.2 Number of awakenings

The adjusted average number of nocturnal awakenings in children in treatment A (pump and iscCGM) was 24.7 (95% CI [22.5; 26.9]) and 25.2 (95% CI [23.0; 27.3]) in treatment B (pump plus SmartGuard); no significant difference between the devices was found (p-value 0.64).

For parents the adjusted average number of nocturnal awakenings in treatment A was 16.3 (95% CI [14.5; 18.1]) compared to 16.1 (95% CI [14.3; 17.9]) in treatment B; no significant difference between the devices and number of awakenings was found (p-value 0.76).

TABLE 1 Descriptive baseline characteristics of the participating children (30).

	Mean (SD)/N (%)		
	Total (N = 31)	Sequence A-B (N = 14)	Sequence B-A (N = 17)
Age, years	10.5 (2.3)	11.2 (2.2)	10.7 (2.5)
Gender			
Female	15 (48%)	7 (50%)	8 (47%)
Male	16 (52%)	7 (50%)	9 (53%)
Ethnicity			
Caucasian	30 (97%)	13 (93%)	17 (100%)
African	1 (3%)	1 (7%)	0 (0%)
Height, cm	143.7 (14.6)	145.6 (15.2)	142.1 (14.4)
Weight, kg	42.8 (13.2)	44.1 (15.7)	41.8 (11.2)
BMI, kg/m^2	20.2 (3.1)	20.1 (3.9)	20.3 (2.5)
Z score BMI[a]	1.23 (0.6, 1.6)	1.2 (0.7, 1.5)	1.3 (0.6, 1.7)
HbA1c, %	7.5 (0.6)	7.6 (0.6)	7.3 (0.5)
HbA1c, mmol/mol	58.1 (6.5)	59.9 (6.9)	56.6 (5.9)
Diabetes duration, years[a]	5.6 (3.0, 8.2)	5.7 (3.7, 7.1)	5.6(2.9, 9.8)
Pump use, years[a]	4.0 (2.2, 8.3)	3.9 (2.4, 6.9)	4.5 (1.8, 9.1)

[a]Median (Q1, Q3).
Bold values indicate baseline characteristics.

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TABLE 2 Descriptive baseline characteristics of the participating parents.

	Mean (SD)/N (%)
N	30
Age, years	42.8 (6.0)
Gender	
Female	24 (80%)
Male	6 (20%)
Ethnicity	
Caucasian	29(97%)
African	1 (3%)
Height, cm	168.0 (9.7)
Weight, kg	77.4 (17.0)
BMI, kg/m^2	27.5 (6.2)

3.2.3 Number of nocturnal get-ups

The adjusted average number of nocturnal get-ups in children did not show a significant difference between the two devices: 0.35 (95% CI [0.23; 0.48]) in treatment A compared to 0.41 (95% CI [0.28; 0.54]) in treatment B; p-value: 0.25. The number of nocturnal get-ups in parents was 0.58 (95% CI [0.36; 0.80]) in device A compared to 0.64 (95% CI [0.43; 0.86]) in device B; no significant difference was found (p- value 0.35).

3.3 Questionnaire results

3.3.1 Hypoglycemia fear questionnaire

The score (Hypoglycemia Survey for children and for parent/caregiver with subscales for hypoglycemia worry and behavior) ranges from 0 = no fear to 104 high fear.

In the participating children, the adjusted mean for the hypoglycemia score was 55.1 (95% CI [51.7; 58.8]) for children in arm A. In treatment B, the score of hypoglycemia fear decreased by -0.8 (95% CI [-4.5; 2.9]), but no significant difference was observed between both devices (p-value = 0.67). In parents, the adjusted mean score was 40.67 (95% CI [33.1; 48.3]) in treatment A and decreased by -2.9 (95% CI [-7.0; 1.3]) points for device B. No significant difference for hypoglycemia fear was found between the devices (p= 0.18).

3.3.2 Epworth sleepiness scale

The participating children showed on average a less normal daytime sleepiness during baseline, device A, B and washout period (summary in Table 3) than their parents (Table 4). No significant difference of the Epworth's Sleepiness Scale and between device groups was found (p-value = 0.54). Also when only considering the 5-level interpretation scale of Epworth's Sleepiness Scale with a naive Fisher's Exact test, no significant differences was found between the devices (p = 0.90).

4 Discussion

In our real-life study neither children with type 1 diabetes nor their parents show a significant difference in either hypoglycemia

TABLE 3 Epworth's sleepiness scale interpretation by device (N (%)), children's answers.

	Baseline (N = 30)	Device A (N = 30)	wash-out (N = 29)	Device B (N = 28)
Lower normal daytime sleepiness	20 (67%)	17 (57%)	20 (69%)	17 (61%)
Higher normal daytime sleepiness	7 (23%)	7 (23%)	7 (24%)	7 (25%)
Mild excessive daytime sleepiness	1 (3%)	2 (7%)	0 (0%)	2 (7%)
Moderate excessive daytime sleepiness	2 (7%)	4 (13%)	1 (4%)	2 (7%)
Severe excessive daytime sleepiness	0 (0%)	0 (0%)	1 (4%)	0 (0%)

n, number of participants

TABLE 4 Epworth's sleepiness scale interpretation by device (N (%)), parent's answers.

	Baseline (N = 29)	Device A (N = 27)	wash-out (N = 29)	Device B (N = 27)
Lower normal daytime sleepiness	12 (41%)	10 (37%)	10 (35%)	12 (44%)
Higher normal daytime sleepiness	7 (24%)	9 (33%)	10 (35%)	9 (33%)
Mild excessive daytime sleepiness	4 (14%)	1 (4%)	4 (14%)	0 (0%)
Moderate excessive daytime sleepiness	2 (7%)	4 (15%)	1 (4%)	2 (7%)
Severe excessive daytime sleepiness	4 (14%)	3 (11%)	4 (14%)	4 (15%)

n, number of participants whose scores summed up to the respective sleepiness

fear, quality or quantity of sleep during the use of two different glucose monitoring systems with or without the alarm function and predictive low glucose suspend. The lack of change in hypoglycemia fear may explain why we do not observe a change in sleep quality and quantity. Whether this depends on the short duration of our intervention or on other factors that were no taken into account is uncertain. The time to get used to a new system and develop a confidence in its function may vary between individuals and for some the 5 weeks may have been insufficient (31).

In our study, the mean sleep data outcome of our participants (children or caregivers) was below the recommended sleep duration as published by the American Academy of Sleep medicine (AASM). According to the Consensus Statement of the AASM children (6 to 12 years of age) should sleep 9 to 12 hours per 24 hours and teenagers (13 to 18 years) 8 to 10 hours per 24 hours to promote optimal health (32). Sleep deprivation occurs. when an individual fails to get enough sleep. In healthy children, sleep deprivation is associated with worse cognitive functioning, school performance and more behavioral problems (33).

In our study, the children, slept on average between 1.2 and 1.5 hours less than the minimum recommended sleep, in both treatment arms.

Per night, they slept an average of 9 minutes longer in treatment A (pump and iscCGM) compared to treatment B, which was not significant.

For adults, the AASM and the Sleep Research Society recommend in their Consensus Statement at least 7 or more hours per night on a regular basis to promote optimal health (34). The parents in our study missed on average the minimum of recommended sleep slightly (6.89 hours in treatment A and 6.98 in treatment B). Unlike their children, the parents in our study slept an average of 5.5 minutes longer per night in treatment B (pump and SmartGuard).

According to the consensus statements, all participants in our study are considered to be sleep deprived (children more than their parents).

Caregivers of children with T1D are known to be frequently sleep deprived and to worry about their child's nighttime glucose (35). Sleep deprivation plays a role in different physiological processes influencing disease development (36). Treatment modalities, which can improve sleep quality and quantity, may have more impact on the general health and not only on diabetes outcome.

Sleep analysis and psycho-behavioral outcomes will have an added value in the evaluation of new technologies or new treatments and should be included as outcome parameter (37).

Future studies are needed to further explore the best use of new technologies and to offer a personalized medical approach.

5 Strength and limitations

The study is limited due to the constrained study duration and the number of participants. The study was powered for the primary outcome (percent of time spent in glucose target, TIT, (3.9 - 8 mmol/l) of treatment A and B during the final 7 days of the five-week device arm) (28).

The strength of the study derives from the fact that all data reflect the real world situation, as they were collected in free living at home. Another strength is the evaluation of sleep information with an objective method (Actigraphy) complemented with a sleep diary and not only based on self-reported data.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité National d'Ethique de Recherche Luxembourg. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

US: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft. GA: Conceptualization, Data curation, Methodology, Project administration, Software, Validation, Writing – review & editing. MF: Investigation, Resources, Writing – review & editing. CM: Investigation, Resources, Writing – review & editing. AS: Formal analysis, Software, Validation, Writing – review & editing. MV: Formal analysis, Methodology, Software, Validation, Writing – review & editing. KB-K: Methodology, Validation, Writing – review & editing. OC: Methodology, Validation, Writing – review & editing. IG: Supervision, Validation, Writing – review & editing. CB: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

Author OC was employed by the company Medtronic. Author CB got speakers honorarium and was part of the Medtronic Psychology e-learning Board.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Wood JR, Miller KM, Maahs DM, Beck RW, DiMeglio LA, Libman IM, et al. Most youth with type 1 diabetes in the T1 D Exchange Clinic Registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care*. (2013) 36:2035–7. doi: 10.2337/dc12-1959

2. Sinisterra M, Hamburger S, Tully C, Hamburger E, Jaser S, Streisand R. Young children with type 1 diabetes: sleep, health-related quality of life, and continuous glucose monitor use. *Diabetes Technol Ther*. (2020) 22:639–42. doi: 10.1089/dia.2019.0437

3. Whittemore R, Jaser S, Chao A, Jang M, Grey M. Psychological experience of parents of children with type 1 diabetes: a systematic mixed-studies review. *Diabetes Educ*. (2012) 38:562–79. doi: 10.1177/0145721712445216

4. Driscoll KA, Raymond J, Naranjo D, Patton SR. Fear of hypoglycemia in children and adolescents and their parents with type 1 diabetes. *Curr Diabetes Rep*. (2016) 16:77. doi: 10.1007/s11892-016-0762-2

5. Fernando A, Patel V. Fear of hypoglycaemia in pediatric diabetes: a literature review. *Br J Diabetes*. (2021) 21:36–42. doi: 10.15277/bjd.2021.286

6. Zhang L, Xu H, Liu L, Bi Y, Li X, Kan Y, et al. Related factors associated with fear of hypoglycemia in parents of children and adolescents with type 1 diabetes - A systematic review. *J Pediatr Nurs*. (2022) 66:125–35. doi: 10.1016/j.pedn.2022.05.022

7. Barnard K, Thomas S, Royle P, Noyes K, Waugh N. Fear of hypoglycaemia in parents of young children with type 1 diabetes: a systematic review. *BMC Pediatr*. (2010) 10:50. doi: 10.1186/1471-2431-10-50

8. Barnard KD, Oliver N, Adolfsson P, Aldred C, Kerr D. Is iatrogenic sleep disturbance worth the effort in Type 1 diabetes? *Diabetes Med*. (2015) 32:984–6. doi: 10.1111/dme.12699

9. Morrow T, Bhatia SH, Parmar AM, Baker L, Abadula F, Williamson D, et al. Sleep habits of early school-aged children with type 1 diabetes and their parents: family characteristics and diabetes management. *Behav Sleep Med*. (2022) 20(5):649–58. doi: 10.1080/15402002.2021.1977305

10. Barnard K, James J, Kerr D, Adolfsson P, Runion A, Sebedzija G. Impact of chronic sleep disturbance for people living with T1 diabetes. *J Diabetes Sci Technol*. (2016) 10:762–7. doi: 10.1177/1932296815619181

11. Jaser SS, Foster NC, Nelson BA, Kittelrud JM, DiMeglio LA, Quinn M, et al. T1D Exchange Clinic Network: Sleep in children with type 1 diabetes and their parents in the T1D Exchange. *Sleep Med*. (2017) 39:108–15. doi: 10.1016/j.sleep.2017.07.005

12. Lindström C, Aman J, Norberg AL. Parental burnout in relation to sociodemographic, psychosocial and personality factors as well as disease duration and glycaemic control in children with Type 1 diabetes mellitus. *Acta Paediatr*. (2011) 100:1011–7. doi: 10.1111/j.1651-2227.2011.02198.x

13. Carreon SA, Cao VT, Anderson BJ, Thompson DI, Marrero DG, Hilliard ME. [amp]]Igrave; don't sleep through the night`: Qualitative study of sleep in type 1 diabetes. *Diabetes Med*. (2022) 39:e14763. doi: 10.1111/dme.14763

14. Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, et al. SWITCH Study Group: The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia*. (2012) 55:3155–62. doi: 10.1007/s00125-012-2708-9

15. Schierloh U, Aguayo GA, Fichelle M, De Melo Dias C, Celebic A, Vaillant M, et al. Effect of predicted low suspend pump treatment on improving glycaemic control and quality of sleep in children with type 1 diabetes and their caregivers: the QUEST randomized cross-over study. *Trials*. (2018) 19:665. doi: 10.1186/s13063-018-3034-4

16. Biester T, Kordonouri O, Holder M, Remus K, Kieninger-Baum D, Wadien T, et al. Let the algorithm do the work": reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (Smart Guard) in pediatric type 1 diabetes patients. *Diabetes Technol Ther*. (2017) 19:173–82. doi: 10.1089/dia.2016.0349

17. Shivers JP, Mackowiak L, Anhalt H, Zisser H. Turn it off!": diabetes device alarm fatigue considerations for the present and the future. *J Diabetes Sci Tecnol*. (2013) 7:789–94. doi: 10.1177/193229681300700324

18. Edge J, Acerini C, Campbell F, Hamilton-Shield J, Moudiotis C, Rahman S, et al. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. *Arch Dis Child*. (2017) 102:543–9. doi: 10.1136/archdischild-2016-311530

19. Al Hayek AA, Robert AA, Al Dawish MA. Effectiveness of freestyle libre flash glucose monitoring system on diabetes distress among individuals with type 1 diabetes: A prospective study. *Diabetes Ther*. (2020) 11:927–37. doi: 10.1007/s13300-020-00793-2

20. Abraham MB, de Bock M, Paramalingam N, O'Grady MJ, Ly TT, George C, et al. Prevention of insulin-induced hypoglycemia in type 1 diabetes with predictive low glucose management system. *Diabetes Technol Ther*. (2016) 18:436–43. doi: 10.1089/dia.2015.0364

21. Clarke WL, Gonder-Frederick A, Snyder AL, Cox DJ. Maternal fear of hypoglycemia in their children with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab*. (1998) suppl 1:189–94. doi: 10.1515/jpem.1998.11.s1.189

22. Kamps JL, MC R, Varela RE. Development of a new fear of hypoglycemia scale: preliminary results. *J Pediatr Psychol*. (2005) 30:287–91. doi: 10.1093/jpepsy/jsi038

23. Gonder-Frederick L, Nyer M, Shepard JA, Vajda K, Clarke W. Assessing fear of hypoglycemia in children with Type 1 Diabetes and their parents. *Diabetes Manag (Lond)*. (2011) 1:627–39. doi: 10.2217/dmt.11.60

24. Haugstvedt A, Wentzel-Larsen T, Aarflot M, Rokne B, Graue M. Assessing fear of hypoglycemia in a population-based study among parents of children with type 1 diabetes - psychometric properties of the hypoglycemia fear survey - parent version. *BMC Endocr Disord*. (2015) 15:2. doi: 10.1186/1472-6823-15-2

25. Patton SR, Noser AE, Clements MA, Dolan LM, Powers SW. Reexamining the hypoglycemia fear survey for parents of young children in a sample of children using insulin pumps. *Diabetes Technol Ther*. (2017) 19:103–8. doi: 10.1089/dia.2016.0389

26. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*. (1991) 14:540–5. doi: 10.1093/sleep/14.6.540

27. Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep-wake identification: an empirical test of methodological issues. *Sleep*. (1994) 17:201–7. doi: 10.1093/sleep/17.3.201

28. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep*. (1992) 15:461–9. doi: 10.1093/sleep/15.5.461

29. World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. 1st ed. *Acta Paediatr Suppl*. (2006) 450:76–85.

30. Schierloh U, Aguayo GA, Schritz A, Fichelle M, De Melo Dias C, Vaillant MT, et al. Intermittent scanning glucose monitoring or predicted low suspend pump treatment: does it impact time in glucose target and treatment preference? The QUEST randomized crossover study. *Front Endocrinol (Lausanne)*. (2022) 13:870916. doi: 10.3389/fendo.2022.870916

31. Lally P, Van Jaarsveld CHM, Potts HWW, Wardle J. How are habits formed: Modelling habit formation in the real world. *Eur J Soc Psychol*. (2010) 40:998–1009. doi: 10.1002/ejsp.v40:6

32. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, et al. Recommended amount of sleep for pediatric populations: A consensus statement of the American academy of sleep medicine. *J Clin Sleep Med*. (2016) 12:785–6. doi: 10.5664/jcsm.5866

33. Astill RG, van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. *Psychol Bull*. (2012) 138:1109–38. doi: 10.1037/a0028204

34. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, et al. Recommended amount of sleep for a healthy adult: A joint consensus statement of the American academy of sleep medicine and sleep research society. *Sleep*. (2015) 38:843. doi: 10.5665/sleep.4716

35. Feeley CA, Clougherty M, Siminerio L, Charron-Prochownik D, Allende AL, Chasens ER. Sleep in caregivers of children with type 1 diabetes. *Diabetes Educ*. (2019) 45:80–6. doi: 10.1177/0145721718812484

36. Luyster FS, Strollo PJ, Zee PC, Walsh JK. Sleep: A health imperative. *Sleep*. (2012) 35:727–34. doi: 10.5665/sleep.1846

37. Bisio A, Brown SA, McFadden R, Pajewski M, Yu PL, DeBoer M, et al. Sleep and diabetes-specific psycho-behavioral outcomes of a new automated insulin delivery system in young children with type 1 diabetes and their parents. *Pediatr Diabetes*. (2021) 22(3):495–502. doi: 10.1111/pedi.13164

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EDITED BY
Lingling Xu,
Peking Union Medical College Hospital (CAMS), China

REVIEWED BY
Shenghui Ge,
Nanjing Medical University, China
Andrew Behnke,
Carilion Clinic, United States

*CORRESPONDENCE
Jianzhong Xiao
xjza01150@btch.edu.cn

†These authors have contributed equally to this work

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Accuracy of a novel calibratable real-time continuous glucose monitoring device based on FreeStyle libre in- and out-of-hospital

Zhenghao Wu[1,2†], Zhaoxiang Liu[1†], Wenhui Zhao[1], Shaocheng Wang[1], Liangbiao Gu[1] and Jianzhong Xiao[1*]

[1]Department of Endocrinology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, Beijing, China, [2]Department of Endocrinology, The Quzhou Affiliated Hospital of Wenzhou Medical University, Quzhou Peoples Hospital, Quzhou, Zhejiang, China

Objectives: Based on FreeStyle Libre, we designed QT AIR, an advanced real-time, calibrated Continuous Glucose Monitoring (CGM) device. This study aim to validate the consistency and clinical accuracy of the product by comparing the capillary blood glucose (CBG) with CGM data in both in-hospital and outpatient scenarios.

Methods: Results of CGM devices were compared with random capillary glucose values from users in both in-hospital and outpatient settings. The accuracy of CGMs was assessed through consistency analysis, Bland-Altman analysis, calculation of MARD and MAD, Consensus Error Grids, as well as analysis using the Continuous Glucose Deviation Interval and Variability Analysis (CG-DIVA).

Results: In outpatient setting, 1907 values from 138 users were analyzed. FreeStyle Libre data, QT AIR calibrated and uncalibrated data showed strong positive correlations with capillary blood glucose values. The MARD values for the FreeStyle Libre, uncalibrated QT AIR, and calibrated QT AIR groups were 18.33%, 20.63%, and 12.39%, respectively. Consensus Error Grid, reference values in Zone A: FreeStyle Libre: 69.75%, QT AIR uncalibrated: 67.80%, QT AIR calibrated: 87.62%. The Bland-Altman analysis results suggest that FreeStyle Libre exhibitsed a systematic underestimation of blood glucose levels, while QT AIR almost rectified the differences. In the in-Hospital setting, the MARD of QT AIR after calibration was reduced to 7.24%. The Consensus error grid analyses of the in-Hospital data revealed that 95% of the calibrated QT AIR values fell within Zone A, a significantly higher proportion than that of other two group. The CG-DIVA analysis of the calibrated QT AIR device showed a median bias of -0.49% and a between-sensor variability of 26.65%, both of which are significantly lower than the corresponding values observed for the FreeStyle Libre device.

Conclusions: We successfully transformed a retrospective CGM system into a real-time monitoring device. The monitoring accuracy of the device could be improved by calibration.

KEYWORDS

rtCGM, continuous glucose monitoring, accuracy, FreeStyle libre, calibrate

1 Introduction

Diabetes mellitus is a chronic metabolic disorder requiring long-term management (1). Currently, the population of diabetes is continuously increasing world-wide (2). The control of blood glucose (BG) has been shown to significantly reduce the complications of diabetes (3). Effective glycemic management relies upon close blood glucose monitoring. Continuous glucose monitoring (CGM) is an effective method that enables multi-day tracking of patients' blood glucose levels without frequent blood sampling (4). It helps in the detection of asymptomatic hypoglycemic (or hyperglycemic) events that might be ignored by a self-monitoring of peripheral blood glucose (SMBG) (5). Furthermore, it generates an ambulatory glucose profile for the patient. The time in range (TIR) of blood glucose, time above range (TAR), and time below range (TBR) provided by CGM has now become a recommended target for glycemic management according to multiple guidelines (6).

FreeStyle® Libre™ flash glucose monitoring (Abbott Diabetes Care, Alameda, CA) allows for convenient scanning to obtain instantaneous blood glucose readings and 14 days' glucose profiles (7). Additionally, it records the blood glucose fluctuations of the preceding 8 hours at 15-minute intervals. FreeStyle Libre holds a significant market share in developing countries, including Mainland China. However, as an intermittent-scanning CGM, it still presents certain limitations:1) FreeStyle Libre requires an intermittent scan for data at least every 8 hours and is a retrospective glucose monitor that cannot provide real-time monitoring (8, 9). 2) Its clinical accuracy might be marginally insufficient, with glucose levels tending to be lower compared to readings from traditional blood glucose testings (10, 11). We have developed the "QT AIR" based on FreeStyle Libre to solve the problems of consistency of glucose with SMBG, the inability to calibrate and the inability to synchronize data, which can synchronize, calibrate and monitor patients' blood glucose levels in real time. QT AIR is connected to FreeStyle Libre through a transfer hoop, capturing the electrical signal from FreeStyle Libre in real-time (Figure 1). Utilizing a proprietary intelligent algorithm, it promptly processes the data to generate glucose readings and subsequently transmits them to the cloud server. The QT APP available on both iOS and Android platforms, as well as the hospital's QT AIR management PDA, can be paired with fingertip glucose meters. This enables for the synchronization and recording of users' fingertip blood glucose measurements. Moreover, the fingertip glucose (FG) values are utilized to calibrate the monitoring readings of the QT AIR.

We aim to compare the consistency and clinical accuracy of clinical capillary blood glucose levels with the data obtained from Libre, QT AIR uncalibrated and QT AIR calibrated. This comparison will be conducted both in outpatient daily life settings and within the controlled environment of standard healthcare settings in hospitalized patients.

2 Methods

2.1 Patients

Adults with and without diabetes who wear QT AIR device and choose to consent to the use of the product to record blood glucose data were enrolled in this study.

The study encompasses two groups of participants:

a. Patients who wore QT AIR in outpatient settings (n = 138) from October 1, 2022, to March 31, 2023.

All device uers who electronically affirmed the QT APP End User License Agreement (EULA) were systematically enrolled in the randomized sampling framework.

b. Patients admitted to the Endocrinology Department at Beijing Tsinghua Chang Gung Hospital and wearing QT AIR (n = 38) from March, 2023, to March, 2024.

Eligible participants met the following criteria: (1) age ≥ 16 years with no gender restriction; (2) clinical indication for glycemic surveillance and willingness to maintain CGM device adherence for ≥7 consecutive days. Exclusion Criteria: (1) Required radiographic examinations (X-ray, MRI, or CT) or anticipated exposure to high-intensity radiation/electromagnetic fields during CGM application; (2) Presented with severe circulatory insufficiency; (3) Demonstrated documented hypersensitivity reactions to CGM sensor components; (4) Experienced acute metabolic complications including diabetic ketoacidosis (DKA); (5) Used pharmacotherapeutic agents with known interference potential on CGM or capillary blood glucose measurements.

2.2 Study design

Outpatient participants followed the instructions provided for wearing the Libre and the QT AIR. They downloaded the QT APP and activated and synchronized the devices through the app. Participants used their personal blood glucose meters, which were paired with the QT APP following authentication. This pairing process enables the automatic synchronization of self-measured fingertip blood glucose readings. Additionally, patients had the option to manually input their self-measured fingertip blood glucose values and corresponding test times into the QT APP. The reading in the stable blood glucose period (the glucose reading changes are lower than 0.05mmol/L·min) were utilized for calibrating the QT AIR data. During the wearing period, patients could have random fingertip blood glucose test. Before calibration, patients continued their daily routines and avoided strenuous exercise, eating, and injecting insulin for 3-4 hours, the blood glucose change rate should be less than 0.05 mmol/L·min. Concurrently, QT AIR uncalibrated data, QT AIR calibrated data, Libre readings, and fingertip blood glucose levels, were transmitted to and documented on a secure cloud-based server. In case of occurrences of hyperglycemia or hypoglycemia, the QT APP was able to alert the patients and provide feedback to healthcare providers, facilitating timely intervention to ensure comprehensive patient medical safety.

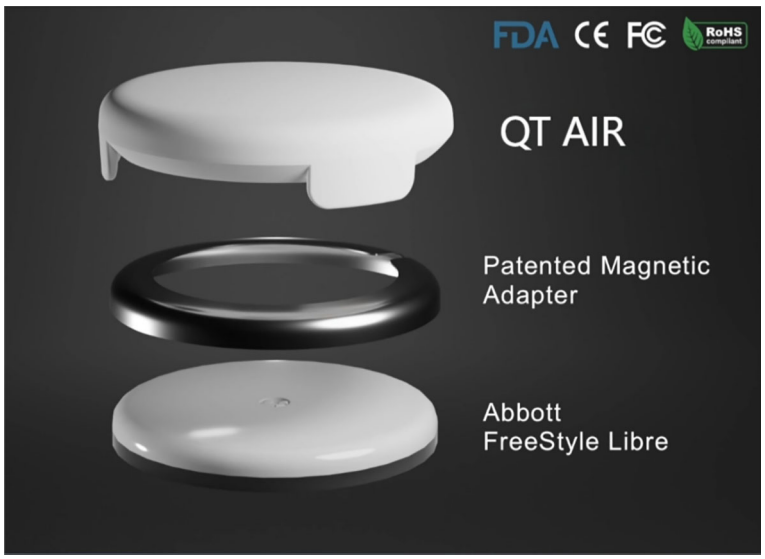

FIGURE 1
QT AIR 3D structure diagram.

In the hospital setting, with the assistance of professional staff, the Libre and QT AIR were worn on the outer side of the upper arm. After initiating the Libre, patient and device information was inputted into the hospital's internal glucose management platform. QT AIR device transmitted blood glucose readings to the hospital's server at one-minute intervals. During the monitoring process, nursing staff applied the standard blood glucose meter (Accu-Chek® Performa Connect) and utilized the same batch of blood glucose test strips for fingertip blood glucose measurements. All data will be systematically transmitted and recorded on the cloud server. If any hyperglycemic or hypoglycemic events occur, the hospital management platform will send immediate notifications to the doctor in charge. These notifications enable physicians to promptly intervene and make necessary adjustments to the treatment regimen.

Given that the FreeStyle Libre has a specified range of readings (2.2-27.8 mmol/L), data exceeding this range will be considered as output readings. The study will comprehensively compare the consistency and clinical accuracy of the data obtained from QT AIR uncalibrated, QT AIR calibrated, Libre readings, taking corresponding fingertip blood glucose values recorded at the matching time points as reference.

2.3 Statistical analysis

Statistical analysis was performed using GraphPad Prism 9.0.0 (GraphPad Software, San Diego, CA, USA). The data in accordance with normal distribution were expressed as mean ± standard deviation (). Since the glucose data violated the assumption of normality (assessed by Shapiro-Wilk/Kolmogorov-Smirnov test, $p<0.05$), Spearman's rank-order correlation was employed to evaluate the monotonic relationship between variables. Correlation analysis used Bland-Altman analysis (12); $p<0.05$ was considered as statistically significant. System error analysis used MAD (mean absolute difference) and MARD (mean absolute relative difference) (13); Clinical performance evaluation was conducted by analysis of the consensus error grid (14, 15); Plots and calculations were performed in "Python 3.11.1". Point accuracy is assessed using Continuous Glucose Deviation Interval and Variability Analysis (CG-DIVA) based on Food and Drug Administration requirements for integrated CGM systems (16) (Figure 2).

3 Results

3.1 The evaluation of the device's performance in outpatient settings

3.1.1 Correlation analysis

We have conducted an analysis of 1,907 paired data sets from 138 outpatient users, collected from the QT APP cloud server. The capillary glucose values of the users demonstrated significant and positive Spearman correlation with both Libre data and QT AIR data, before and after calibration ($p<0.0001$) (Shapiro-Wilk/Kolmogorov-Smirnov test, $p<0.001$). The correlation ranking of capillary blood glucose levels can be expressed as follows: QT AIR calibrated > Libre > QT AIR uncalibrated (Figure 3).

3.1.2 Difference analysis

The MARD for FreeStyle Libre was 18.33% ± 16.31%, while QT AIR uncalibrated has an MARD of 20.63% ± 15.92%. Remarkably, QT AIR calibrated exhibits a significantly superior performance

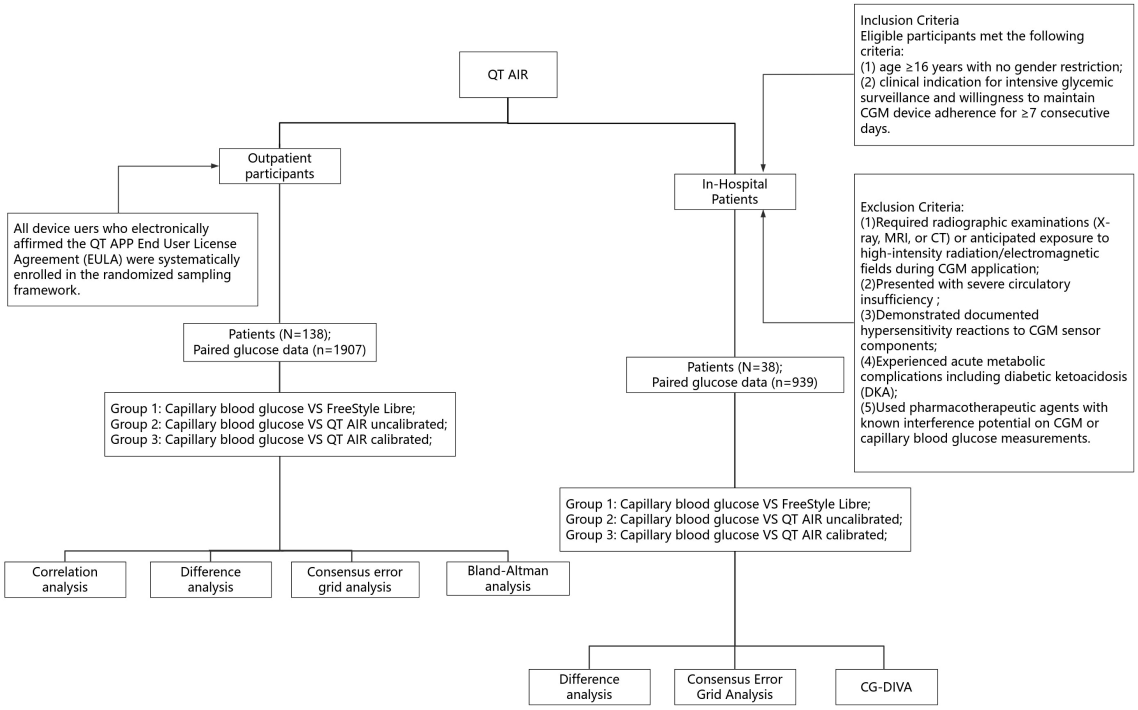

FIGURE 2
Flowchart of research procedures. CG-DIVA, Glucose Deviation Interval and Variability Analysis.

with an MARD of 12.39 ± 12.94%, outperforming the other two groups (overall $p < 0.0001$).

Further analysis involved stratifying the data based on capillary glucose values.The MAD was used for error comparison in the hypoglycemic group (BG ≤ 3.9 mmol/L,136 samples). The MARD was calculated for the hyperglycemic group (BG > 10.0 mmol/L, 170 samples) and optimal glycemic groups (4.0-10.0 mmol/L, 1601 samples). The results showed that the MAD of QT AIR calibrated data closely approximated that of Libre and significantly outperformed the uncalibrated data in the hypoglycemic group. In the non-hypoglycemic range (BG > 3.9 mmol/L), the MARD values of QT AIR calibrated were significantly better than both the Libre and the uncalibrated group, with Libre slightly surpassing the uncalibrated group (Table 1).

3.1.3 Consensus error grid analysis

Consensus error grid analysis, an improved version of Clarke error grid analysis, addresses partition incoherence and other limitations to enhance accuracy assessment. The study's results revealed that the proportions of values falling within regions A and B for FreeStyle Libre, QT AIR calibrated, and QT AIR uncalibrated were all over 99%. However, when focusing on the specific Zone A, the ratio of QT AIR calibrated (87.62%) was significantly superior to that of Libre (69.74%) and QT AIR uncalibrated (67.80%). Remarkably, none of the three exhibited samples in regions D and E, indicating their good performance in avoiding clinically dangerous errors (Figure 4, Table 2).

3.1.4 Bland-Altman analysis

The Bland-Altman plot was generated with the mean value of capillary glucose and CGM data as the x-axis and the difference between capillary blood glucose and CGM (BG - CGM) as the y-axis. As shown in Figure 5, the mean difference in FreeStyle Libre was 0.8834 mmol/L, signifying an overall underestimation of FreeStyle Libre compared to capillary glucose data. The mean difference and standard deviation of QT AIR calibrated were significantly lower than those of Libre and QT AIR uncalibrated (Table 3).

3.2 The evaluation of the device's performance in hospital settings

3.2.1 In-hospital patients characteristics

The clinical characteristics of 38 randomly selected inpatients are as follows: among them, 27 were male and 11 were female, with a mean age of (53.32 ± 17.93) years (range: 18 to 84 years). Among the patients, there were 17 cases of type 1 diabetes, 16 cases of type 2 diabetes, 2 case of reactive hypoglycemia, and 3 cases of latent autoimmune diabetes in adults (LADA). Among these patients, 28 were undergoing insulin therapy, with an average daily insulin dosage of 26.72 ± 22.22 IU. The patients had an average body mass index (BMI) of (24.05 ± 4.62) kg/m^2 and an average diabetes duration of approximately 11 years (ranging from 1 week to 35 years). The mean value of glycated hemoglobin (HbA1c) was 9.12 ± 2.77% (Table 4).

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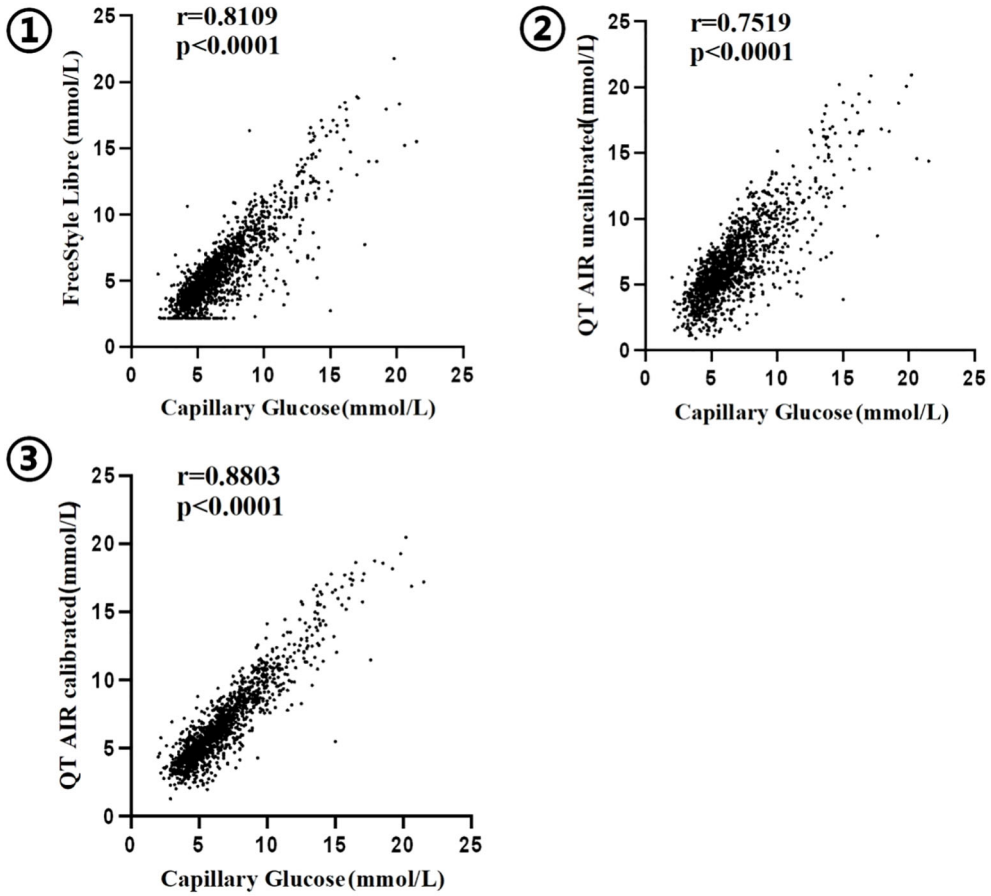

FIGURE 3
Correlation between capillary blood glucose and CGM ① FreeStyle Libre; ② QT AIR uncalibrated; ③ QT AIR calibrated;.

3.2.2 Analysis of blood glucose measurement difference among in-hospital patients

A total of 939 capillary blood glucose data points from in-hospital patients were collected for analysis. The MARD for FreeStyle Libre was calculated as 13.72% ± 14.57%, the uncalibrated QT AIR exhibited a MARD of 13.00% ± 12.44%, and the calibrated QT AIR yielded a significantly improved MARD of 7.27% ± 7.45%. The statistical analysis showed a significant difference among these MARD values ($p<0.0001$).

3.2.3 Consensus error grid analysis of blood glucose among in-hospital patients

As illustrated in Figure 6, Table 5, the consensus error grid analysis for in-hospital patients revealed that approximately 99% of

TABLE 1 Comparison of MAD and MARD Values Among FreeStyle Libre, Uncalibrated QT AIR, and Calibrated QT AIR in different capillary glucose ranges among Out-of-Hospital Patients.

Capillary glucose range	Sample (n)	FreeStyle Libre	QT AIR uncalibrated	QT AIR calibrated	P value*	P value#
≤3.9mmol/L MAD(mmol/L)	136	0.774 ± 0.6322	0.9204 ± 0.6841	0.7432 ± 0.7311	0.0093	0.7069
4.0-10.0mmol/L MARD(%)	1601	17.97 ± 15.84	20.25 ± 15.08	11.67 ± 10.99	<0.0001	<0.0001
>10.0mmol/L MARD(%)	170	18.13 ± 15.85	18.51 ± 15.17	10.51 ± 9.2	0.6128	<0.0001
>3.9mmol/L MARD(%)	1771	17.98 ± 15.83	20.08 ± 15.1	11.56 ± 10.84	0.0009	<0.0001
Overall MARD(%)	1907	18.33 ± 16.31	20.63 ± 15.92	12.39 ± 12.94	<0.0001	<0.0001

MAD, mean absolute difference. MARD, mean absolute relative difference. *comparison between QT AIR uncalibrated and FreeStyle Libre; #comparison between QT AIR calibrated and FreeStyle Libre.

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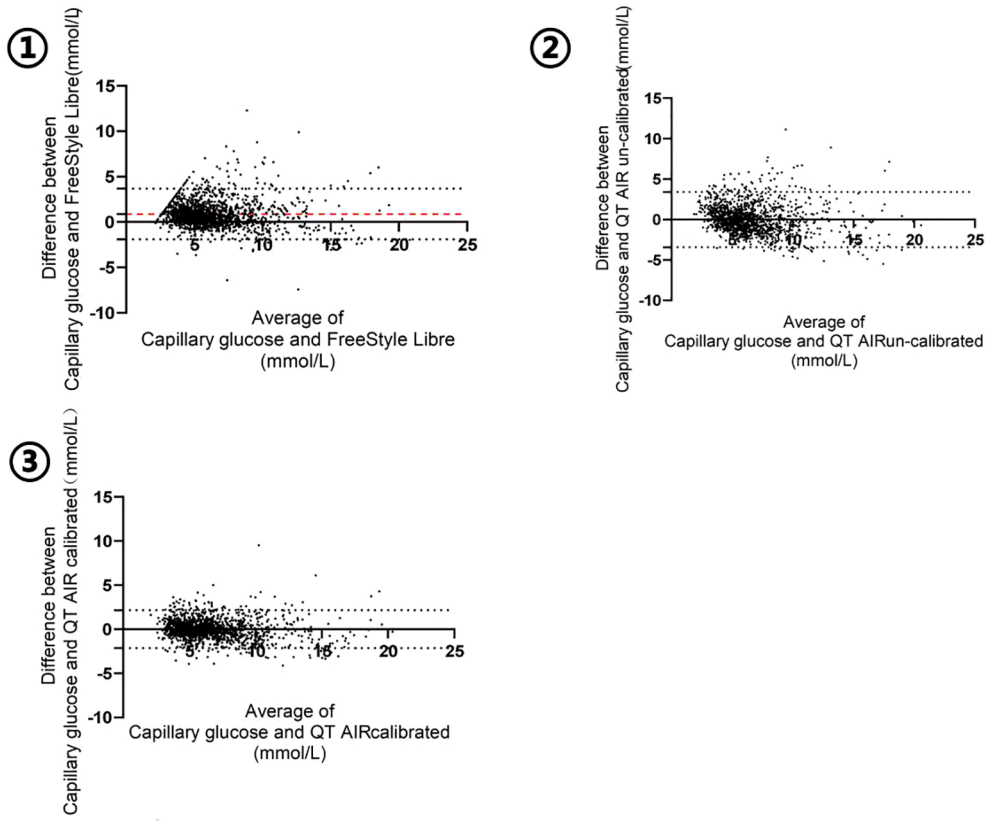

FIGURE 4
Consensus error grid of Out-of-Hospital Patients. ①comparison between FreeStyle Libre and capillary glucose; ②comparison between QT AIR uncalibrated and capillary glucose; ③comparison between QT AIR calibrated and capillary glucose.

the data points from Libre, uncalibrated QT AIR, and calibrated QT AIR fell within the A+B zones. Similar to the outpatient results, the calibrated QT AIR exhibited a substantial improvement with 94.89% of its data points falling within the A zone, surpassing the 78.70% of Libre and the 79.45% of uncalibrated QT AIR.

3.2.4 Point accuracy

The CG-DIVA results are shown in the Figure 7. Figures 7A–C, show the overall distribution of CGM reading biases across different glucose ranges. Overall median biases were -9.40%, -9.36%, and -0.49% for Libre, QT AIR uncalibrated, and calibrated, respectively. Figures 7D–F shows the variability of different representative sensors across various glucose levels, with an overall between sensor variability range of 60.17%, 62.40%, and 26.65% for Libre, QT AIR uncalibrated, and calibrated, respectively.

4 Discussion

The CGM detects blood glucose through a series of interstitial fluid glucose measurement. It is very helpful for diabetic patients to optimize their treatment regimens (17). CGM systems are

TABLE 2 Consensus error grid of out-of-hospital patients.

	FreeStyle Libre		QT AIR uncalibrated		QT AIR calibrated	
	Sample (n)	Percentage (%)	Sample (n)	Percentage (%)	Sample (n)	Percentage (%)
A	1330	69.75	1293	67.80	1671	87.62
B	559	29.31	596	31.26	224	11.75
C	18	0.94	18	0.94	12	0.63
D	0	0.00	0	0.00	0	0.00
E	0	0.00	0	0.00	0	0.00
A+B	1889	99.06	1889	99.06	1895	99.37

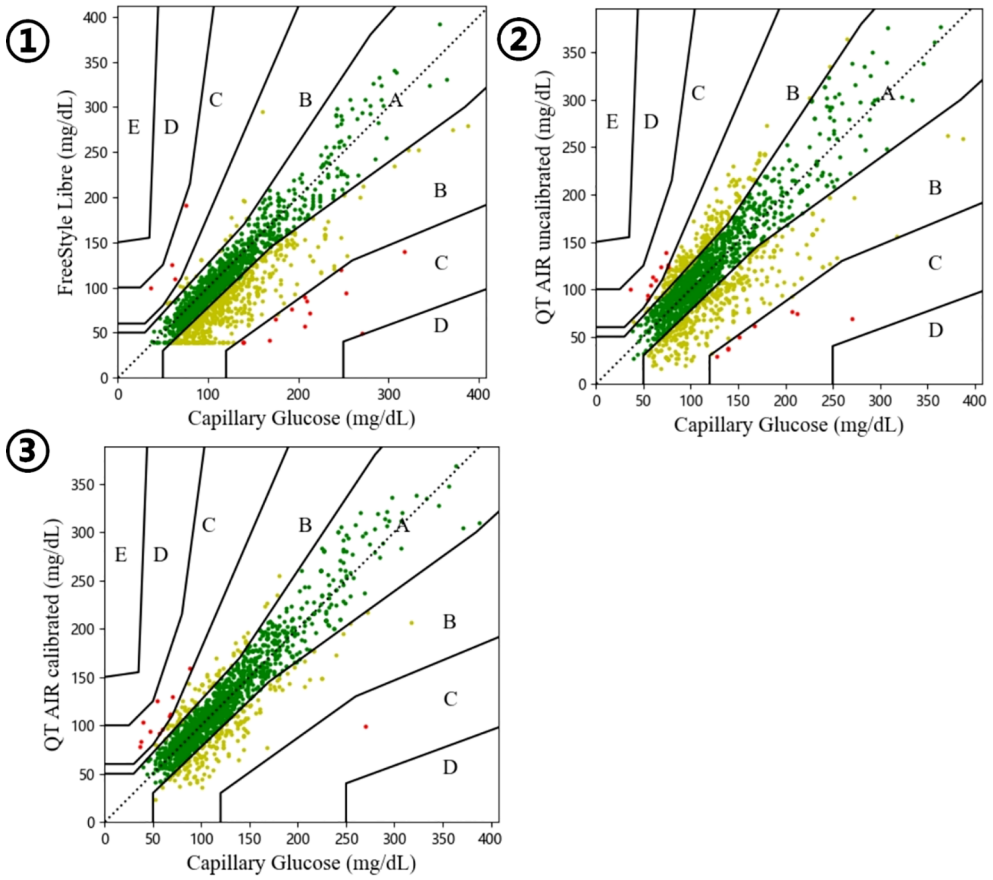

FIGURE 5
Bland-Altman analysis of FreeStyle Libre, QT AIR calibrated and uncalibrated among Out-of-Hospital Patients.

categorized into retrospective and real-time dynamic glucose monitoring systems. Real-time CGM devices provide a real-time glucose reading and glucose change trend. It not only facilitates convenient glucose information retrieval but also enables the anticipation of hyperglycemic or hypoglycemic events. As a result, users are empowered to promptly adjust their glycemic management strategies, thereby increase their TIR and improving overall glycemic control (18). However, FreeStyle Libre, a widely used intermittently scanned CGMs in China and other developing countries, operates as a retrospective system. Based on this technical foundation, our research team developed QT AIR to address these limitations. QT AIR upgraded Libre to a calibratable real-time continuous blood glucose monitoring device.

TABLE 3 Bland-Altman analysis of FreeStyle Libre, QT AIR calibrated and uncalibrated among Out-of-Hospital Patients.

	FreeStyle Libre	QT AIR uncalibrated	QT AIR calibrated
Bias (mmol/L)	0.8834	-0.01517	0.006137
SD of bias	1.423	1.741	1.094
95%CI (mmol/L)	(-1.906,3.673)	(-3.427,3.397)	(-2.137,2.150)

TABLE 4 Characteristics of study subjects.

Variable	Subjects (N=38)
Gender	
Male, N (%)	27 (71.05)
Female, N (%)	11 (28.95)
Diagnosis	
Type 1, N (%)	17 (44.74)
Type 2, N (%)	16 (42.11)
Reactive hypoglycemia, N (%)	2 (5.26)
LADA, N (%)	3 (7.89)
Therapy	
Insulin therapy, N (%)	28 (73.68)
Oral hypoglycemic agents or non-pharmacologically intervened, N (%)	10 (26.32)
Age, mean ± SD, years	53.32 ± 17.93
BMI, mean ± SD, kg/m2	24.05 ± 4.62
HbA1c, %	9.12 ± 2.77

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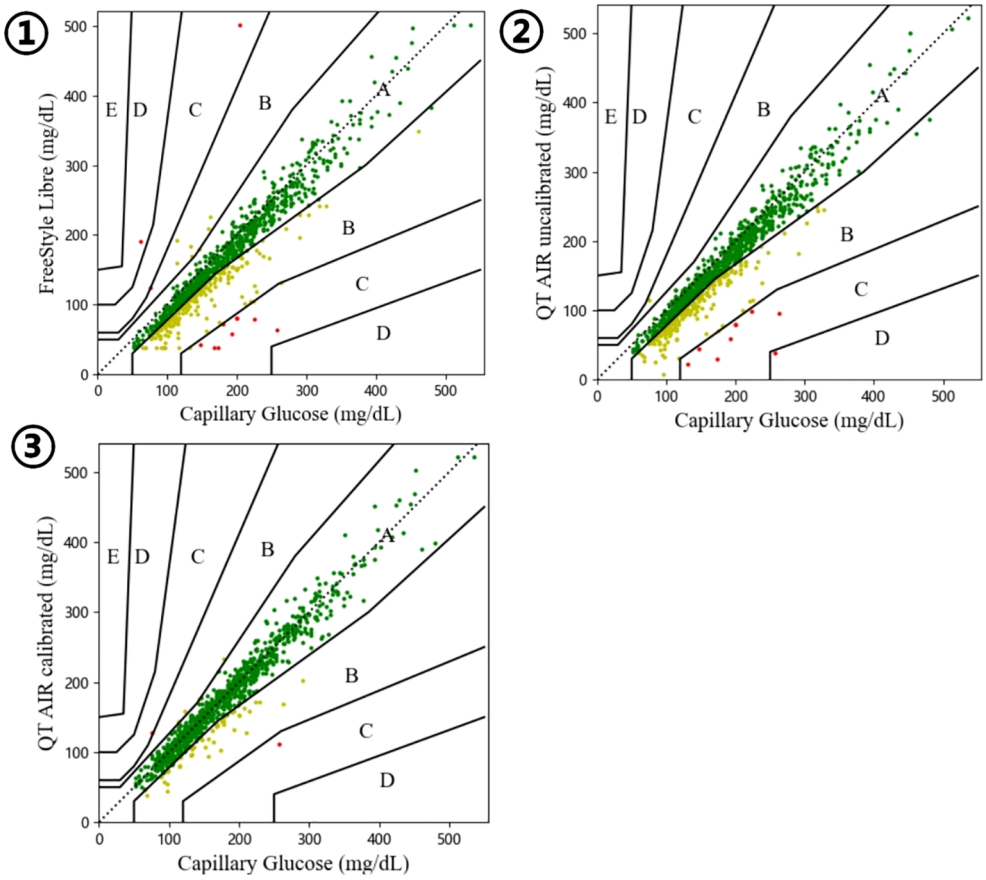

FIGURE 6
Consensus error grid among In-Hospital Patients. ①comparison between FreeStyle Libre and capillary glucose; ②comparison between QT AIR uncalibrated and capillary glucose; ③comparison between QT AIR calibrated and capillary glucose.

Capillary blood glucose, obtained from fingertip capillaries, remains an irreplaceable clinical prominence as the most commonly employed glycemic reference metric in both patients' daily lives and clinical blood glucose management practices (19). Considering its reliablility and convienence, we utilize CBG as the benchmark for comparing the values obtained from CGM systems.

The evaluation of the accuracy of CGM systems encompasses two aspects: numerical accuracy and clinical accuracy assessment. In terms of numerical accuracy, the consistency analysis results reveal significant correlations among all three groups of outpatient users—Libre, calibrated QT AIR, and uncalibrated QT AIR. Among these, calibrated QT AIR exhibits the highest degree of correlation. The Bland-Altman analysis serves as a quantitative and directional means of assessing the consistency between two different measurement methods. In the comparison between FreeStyle Libre readings and capillary blood glucose values, it is evident that the Libre generally underestimates the blood glucose. This observation aligns with conclusions drawn from other relevant

TABLE 5 Consensus error grid among In-hospital patients.

Zone	FreeStyle Libre		QT AIR uncalibrated		QT AIR calibrated	
	Sample (n)	Percentage (%)	Sample (n)	Percentage (%)	Sample (n)	Percentage (%)
A	739	78.70	746	79.45	891	94.89
B	188	20.02	184	19.59	46	4.90
C	11	1.17	8	0.85	2	0.21
D	1	0.11	1	0.11	0	0.00
E	0	0.00	0	0.00	0	0.00
A+B	927	98.72	930	99.04	937	99.79

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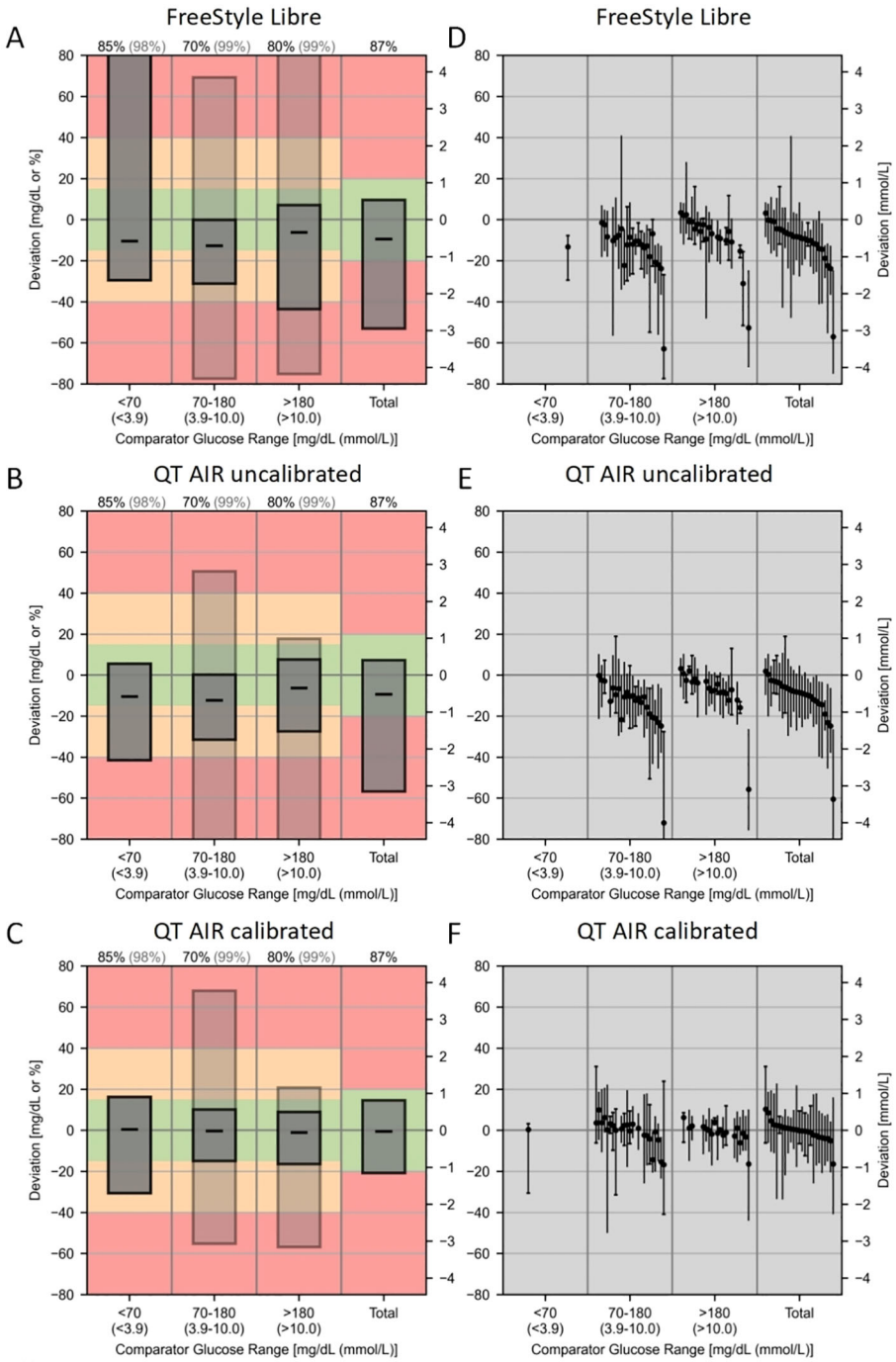

FIGURE 7
Continuous Glucose Deviation Interval and Variability Analysis (CG-DIVA) of FreeStyle Libre, QT AIR uncalibrated, and calibrated. **(A–C)**: Provides an absolute bias comparison for glucose levels <70 mg/dL and a relative bias comparison for all other glucose levels, referencing the right axis scale. Consistency rates (AR) are used to evaluate the other glucose ranges, referencing the left axis scale.The bias intervals are shown as light/dark gray boxes, indicating the expected range of biases. The median bias is represented by a black dashed line. The coverage of the bias intervals, i.e., the percentage of biases falling within the intervals, is set according to the requirements defined by the U.S. Food and Drug Administration (FDA) and is printed at the top of the figure.The dark gray box represents standard I, and the light gray box represents standard II, corresponding to the percentage colors of the bias ranges at the top.The colored background indicates the degree of bias and is based on the limits of standards I and II. The green range represents standard I, the yellow range, which includes the green, represents standard II, and the red indicates exceeding the standard requirements. **(D–F)**: Each sensor is described by the range of bias within the median and the 90% range, and sensors are ranked by median bias within the overall glucose range, with black solid dots representing the median positions.

studies (10, 11). Comparatively, the differences between QT AIR monitoring values and capillary blood glucose values are less pronounced, with the average difference narrowing further after calibration. MARD is the measure of choice for evaluating the accuracy of CGM systems. Calibrated QT AIR exhibits a significant reduction in MARD values when compared to both Libre and uncalibrated QT AIR. In the outpatient setting, among the FreeStyle Libre, uncalibrated QT AIR and calibrated QT AIR, Consensus error grid analyses demonstrated data distribution exceeding 97% in zones A+B. Furthermore, after the calibration of QT AIR, the data within zone A rising from less than 70% to over 80%, resulting in a noteworthy enhancement in clinical accuracy within the context of daily outpatient scenarios. Building upon the factory calibration of FreeStyle Libre, QT AIR introduces capillary blood calibration to further refine data accuracy, thereby facilitating superior monitoring outcomes for users.

In the context of outpatient CGM device utilization, inaccuracies in measurement data may stem from various factors, including improper self-application of the sensor, intricate physical activities leading to suboptimal sensor adherence, and other related issues. Moreover, the accuracy of capillary blood glucose values, utilized as a calibration reference, could be influenced by variances in the patient's self-sampling techniques, inconsistent skin disinfection procedures, and variations in the quality of testing instruments (20, 21). Therefore, our data collection was conducted among inpatients as well, with the assistance of specialized nursing staff, to ensure proper device placement, conduct regular checks of device functionality, and implement standardized procedures for capillary blood sampling. These measures were undertaken to mitigate potential data inaccuracies arising from procedural variations. In the hospital setting, the MARD of FreeStyle Libre was 13.72%, which closely approximates the official claim of 11.4%. However, after rigorous capillary blood calibration, the MARD of QT AIR decreased significantly to 7.27%, surpassing FreeStyle Libre with factory calibration. Additionally, this MARD value was lower than the reported 9.2% for subsequent iterations of FreeStyle Libre (22, 23). Previous studies have demonstrated that the MARD values of Dexcom G7 were 8.2% or 9.1%, compared with 9.4% for Guardian™ Sensor 3 (24, 25). After calibration, QT AIR exhibited comparable performance to these market-leading glucose monitoring systems. In terms of clinical accuracy, similar to the results of outpatients, the Consensus error grid analysis revealed that the predominant data points for all three groups fell within zones A and B. However, after calibration, QT AIR improved the proportion of data points in zone A from approximately 80% to 94.89%. This outcome underscores the remarkable clinical accuracy of QT AIR, underscoring its potential to deliver monitoring outcomes akin to capillary blood glucose levels when subjected to meticulous adherence to wearing protocols and rigorous data calibration procedures. CG-DIVA results show that after algorithm optimization and calibration, the QT AIR significantly improved the point accuracy of Libre and reduced the variability between devices and within devices. Furthermore, the calibrated QT AIR's point accuracy has approached the benchmark required for an Integrated-CGM system.

Our study has certain limitations. In the outpatient study, there is a potential occurrence of inadequate sensor adherence. However, we addressed this concern by implementing data collection within a separated population, well monitored inpatients, and got a consistent result. The sample size in the hospital data collection was limited. We did not incorporate a gold standard reference such as venous blood for comparison.

5 Conclusion

In summary, we have successfully upgraded the intermittently scannedCGM device to a real-time CGM device and introduced capillary blood calibration to enhance accuracy. From the results, QT AIR demonstrated statistically significant enhancements in both data accuracy and clinical accuracy after calibration, surpassing the performance of FreeStyle Libre and achieving parity with leading CGM devices.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Tsinghua Changgung Hospital (Beijing, China; Approval No. 23571-6-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZW: Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. ZL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. WZ: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. SW: Conceptualization, Methodology, Project administration, Validation, Writing – review & editing. LG: Data curation, Investigation, Methodology, Validation, Writing – review & editing. JX: Data curation, Formal analysis, Investigation, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1466358/full#supplementary-material

References

1. Standards of medical care in diabetes-2022 abridged for primary care providers. *Clin Diabetes*. (2022) 40:10–38. doi: 10.2337/cd22-as01

2. Lovic D, Piperidou A, Zografou I, Grassos H, Pittaras A, Manolis A. The growing epidemic of diabetes mellitus. *Curr Vasc Pharmacol*. (2020) 18:104–9. doi: 10.2174/1570161117666190405165911

3. The Prevention of Diabetes Mellitus. *JAMA*. (2021) 325(2):190. doi: 10.1001/jama.2020.17738

4. Galindo RJ, Aleppo G. Continuous glucose monitoring: the achievement of 100 years of innovation in diabetes technology. *Diabetes Res Clin Pract*. (2020) 170:108502. doi: 10.1016/j.diabres.2020.108502

5. Bolli GB. Hypoglycaemia unawareness. *Diabetes Metab*. (1997) 23 Suppl 3:29–35. doi: 10.5114/pedm.2018.80994

6. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19-0028

7. Blum A. Freestyle libre glucose monitoring system. *Clin Diabetes*. (2018) 36:203–4. doi: 10.2337/cd17-0130

8. Freckmann G, Pleus S, Grady M, Setford S, Levy B. Measures of accuracy for continuous glucose monitoring and blood glucose monitoring devices. *J Diabetes Sci Technol*. (2019) 13:575–83. doi: 10.1177/1932296818812062

9. Edelman SV, Argento NB, Pettus J, Hirsch IB. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. *Diabetes Care*. (2018) 41:2265–74. doi: 10.2337/dc18-1150

10. Zhang Y, Liu X, Zhang J, Fu J, Li S, Chen S, et al. Evaluation for the feasibility and accuracy of freestyle libre flash glucose monitoring system used by covid-19 patients in intensive care unit. *J Diabetes*. (2021) 13:603–5. doi: 10.1111/1753-0407.13181

11. Aberer F, Hajnsek M, Rumpler M, Zenz S, Baumann PM, Elsayed H, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. *Diabetes Obes Metab*. (2017) 19:1051–5. doi: 10.1111/dom.12907

12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. (1986) 1:307–10. doi: 10.1016/S0140-6736(86)90837-8

13. Reiterer F, Polterauer P, Schoemaker M, Schmelzeisen-Redecker G, Freckmann G, Heinemann L, et al. Significance and reliability of mard for the accuracy of cgm systems. *J Diabetes Sci Technol*. (2017) 11:59–67. doi: 10.1177/1932296816662047

14. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care*. (1987) 10:622–8. doi: 10.2337/diacare.10.5.622

15. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. *Diabetes Care*. (2000) 23:1143–8. doi: 10.2337/diacare.23.8.1143

16. Eichenlaub M, Stephan P, Waldenmaier D, Pleus S, Rothenbühler M, Haug C, et al. Continuous glucose deviation interval and variability analysis (Cg-diva): A novel approach for the statistical accuracy assessment of continuous glucose monitoring systems. *J Diabetes Sci Technol*. (2024) 18(4)::857–65. doi: 10.1177/19322968221134639

17. Rodbard D. Continuous glucose monitoring: A review of recent studies demonstrating improved glycemic outcomes. *Diabetes Technol Ther*. (2017) 19:S25–s37. doi: 10.1089/dia.2017.0035

18. Préau Y, Galie S, Schaepelynck P, Armand M, Raccah D. Benefits of a switch from intermittently scanned continuous glucose monitoring (Iscgm) to real-time (Rt) cgm in diabetes type 1 suboptimal controlled patients in real-life: A one-year prospective study (§). *Sensors (Basel)*. (2021) 21:6131. doi: 10.3390/s21186131

19. Heinemann L, Freckmann G, Koschinsky T. Considerations for an institution for evaluation of diabetes technology devices to improve their quality in the European Union. *J Diabetes Sci Technol*. (2013) 7:542–7. doi: 10.1177/193229681300700230

20. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol*. (2009) 3:903–13. doi: 10.1177/193229680900300438

21. Freckmann G, Jendrike N, Baumstark A, Pleus S, Liebing C, Haug C. User performance evaluation of four blood glucose monitoring systems applying ISO 15197:2013 accuracy criteria and calculation of insulin dosing errors. *Diabetes Ther*. (2018) 9:683–97. doi: 10.1007/s13300-018-0392-6

22. Alva S, Bailey T, Brazg R, Budiman ES, Castorino K, Christiansen MP, et al. Accuracy of a 14-day factory-calibrated continuous glucose monitoring system with advanced algorithm in pediatric and adult population with diabetes. *J Diabetes Sci Technol*. (2022) 16:70–7. doi: 10.1177/1932296820958754

23. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technol Ther*. (2015) 17:787–94. doi: 10.1089/dia.2014.0378

24. Garg SK, Kipnes M, Castorino K, Bailey TS, Akturk HK, Welsh JB, et al. Accuracy and safety of dexcom G7 continuous glucose monitoring in adults with diabetes. *Diabetes Technol Ther*. (2022) 24:373–80. doi: 10.1089/dia.2022.0011

25. Christiansen MP, Garg SK, Brazg R, Bode BW, Bailey TS, Slover RH, et al. Accuracy of a fourth-generation subcutaneous continuous glucose sensor. *Diabetes Technol Ther*. (2017) 19:446–56. doi: 10.1089/dia.2017.0087

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EDITED BY
Åke Sjöholm,
Gävle Hospital, Sweden

REVIEWED BY
Cosmin Mihai Vesa,
University of Oradea, Romania
Alberto Casertano,
University of Naples Federico II, Italy
Sethu Reddy,
Central Michigan University, United States

*CORRESPONDENCE
Hafiz Rashid Hussain
rashid.hussain@uos.edu.pk
Abdul Malik
amoinuddin@ksu.edu.sa

†PRESENT ADDRESS
Nabeel Ahmed,
School of Pharmacy, Kunming Medical University, Kunming, Yunnan, China

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Fear of hypoglycemia: a key predictor of sleep quality among the diabetic population

Hafiz Rashid Hussain[1*], Nabeel Ahmed[1†], Muhammad Waseem Akram[2], Faisal Gulzar[3], Jawad Akbar Khan[4], Muhammad Asad[5], Sana Tahseen[1], Tanveer Ahmed[6], Abdul Malik[7*], Suhail Akhtar[8], Ayesha Shahid[1], Mah Noor[1], Maryam Pervaiz[1] and Muneeb Ur Rahman[1]

[1]College of Pharmacy, University of Sargodha, Sargodha, Pakistan, [2]School of Economics, University of Wollongong, Wollongong, NSW, Australia, [3]Rai Foundation Pharmacy College, Sargodha, Pakistan, [4]Riphah Institute of Pharmaceutical Sciences, Riphah International University, Lahore, Pakistan, [5]Cadson College of Pharmacy, Kharian, Pakistan, [6]Ahmad Polyclinic and Diabetic Center, Sargodha, Pakistan, [7]Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia, [8]Department of Biochemistry, A.T. Still University of Health Sciences, Kirksville, MO, United States

Introduction: Every one in seven people with Type-I or Type-II diabetes suffers from fear of hypoglycemia (FOH). Its impact on quality of life, glycemic control, and health outcomes is well studied. However, its relationship with sleep quality remains underexplored, particularly in developing societies. We hypothesize that FOH is a key predictor of sleep quality in Type-I and Type-II patients with diabetes and, therefore, needs detailed investigation.

Methods: A multicentric study was conducted across five cities and six centers of Punjab. Data from 310 diabetes patients were analyzed using the Hypoglycemia Fear Survey-II (HFS-II) Scale and the Pittsburgh Sleep Quality Index (PSQI). Statistical analyses explored subgroup variations, correlations, regression models, and receiver operator curve (ROC) estimation.

Results: The study reports 57.70% of patients with poor sleep among whom 47% had elevated FOH. Sleep quality, age, gender, diabetes duration, and insulin route significantly correlated with FOH ($p < 0.05$), while glycemic control and insulin use did not. Binary logistics regression showed that for every one-unit increase in FOH, the odds of experiencing poor sleep increased by approximately 3.7% ($p < 0.001$; OR 1.037). Five out of seven sleep components (sleep quality, efficiency, disturbance, medication use, and daytime dysfunction) were significantly related to FOH. We hypothesize that FOH might specifically influence the quality rather than the initiation or termination of the sleep cycle. ROC analysis revealed that HFS-II may be better at diagnosing poor sleep in patients than by chance ($p < 0.001$) with an AUC of 0.691.

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Conclusion: FOH is a key predictor of sleep quality among patients with diabetes. Healthcare providers should prioritize patient education targeting common FOH concerns and assess patients with disturbed sleep for elevated FOH levels, as it may contribute to sleep disturbances.

KEYWORDS

fear of hypoglycemia, quality of sleep, diabetes mellitus, HFS-II scale, PSQI

1 Introduction

Diabetes is characterized as an increased blood glucose level that is caused by either a defect in insulin action, insulin secretion, or both, causing various metabolic disorders (1, 2). It is one of the most prevalent diseases across the world with an increasing incidence in Pakistan. The most recent data provided by the International Diabetes Foundation (IDF) has shown a 30.8% prevalence of diabetes in the Pakistani adult population, where every 1 in 4 persons is affected by diabetes (3).

Patients with diabetes are required to maintain a balance between their medication and food intake. This balance is essential to avoid poor glycemic control on one side and hypoglycemia on the other side. Hypoglycemia, although acute, yet is one of the most serious acute adverse outcomes of anti-diabetic treatments (4). It can be manifested as either autonomic symptoms (trembling, palpitations, sweating, tingling) or neuroglycopenic symptoms (difficulty concentrating, confusion, drowsiness, vision changes, difficulty speaking) (5). Generally, the symptoms can be alleviated by the administration of fast-acting carbohydrates and do not require any assistance (level 1 and level 2 hypoglycemia), however, if left unrecognized or unaddressed it may lead to a severe form of hypoglycemia (level 3, requiring aid) resulting in loss of consciousness, seizure, coma, or even death (6). These potentially fatal consequences create a psychological state of mind in diabetes patients known as the fear of hypoglycemia (FOH).

FOH is defined as "the degree of fear associated with episodes of hypoglycemia and their negative consequences" (7). It is one of the most common psychological manifestations associated with hypoglycemia (8–10).

The state of hypoglycemic fear induces behavioral changes in patients with diabetes to prevent the occurrence of hypoglycemic episodes and thus the consequences. These include having additional meals (11), snacking at night (12), stress-induced eating, decreased physical activity (13), maintaining higher blood glucose levels (14, 15), and mismanagement of insulin doses (11, 16–18). These behaviors can potentially lead to impaired glycemic control (10), reduced quality of life (19, 20), suboptimal diabetes management (21, 22), and development of microvascular complications (7, 22).

Along with these physical behaviors, FOH is also manifested psychologically. Evidence shows that FOH is related to anxiety and depression in patients with diabetes (23). These psychological states are closely linked with sleep quality (24, 25). Similarly, research shows that the improvement in blood glucose monitoring technologies has significantly reduced FOH and improved quality of life, including sleep quality, in these patients (26, 27). Therefore, FOH is a potential factor that may affect the quality of sleep in patients with diabetes.

Only a few studies are available worldwide that have assessed this correlation in patients with diabetes (15, 28), but the data on the Pakistani population is scarce. It has also been reported that there is a high prevalence of sleep disturbances among the diabetes population in Pakistan. The results were confirmed in a recent (and by far the first) study by Farooque et al. where 57% of the patients were found to be poor sleepers (Global PSQI Score > 5) in a sample of 329 patients (29). However, the reasons remain unexplored as in the aforementioned study (29), there was no association found between poor sleep and glycemic control which necessitates further research in this area. In light of this, the present study aims to determine if FOH is a key predictor of sleep quality, describe the relationship between FOH and sleep components, and describe factors associated with FOH for targeted interventions.

2 Methodology

2.1 Study setting and design

This study employed a multicenter cross-sectional research design spanning six months (April 2023 to September 2023). Data was collected from multiple healthcare settings of the Punjab province of Pakistan viz. Ahmad Diabetes and Foot Center, Sargodha; District Headquarter Hospital (DHQ), Sargodha; Non-Communicable Disease Clinic (NCD), DHQ Hospital Jhelum; DHQ Hospital Hafizabad; Tehsil Headquarter Hospital, Lalamusa; and Fatima Memorial Hospital, Sambrial.

2.2 Ethics approval

Ethical approval was obtained on April 19, 2023, from the Ethical Review Committee at the University of Sargodha (Reference Number SU/ORIC/799).

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2.3 Study tools

The study employed two pre-validated questionnaires, viz. the Hypoglycemia Fear Survey (HFS-II) (30) and the Pittsburgh Sleep Quality Index (PSQI) (31). The HFS-II consists of 33 items divided among two sub-scales i.e., the behavior scale (HSF-B, 15 items) and the worry scale (HFS-W, 18 items). It is used to measure different aspects of fear related to hypoglycemia. Each item on the scale carries five Likert points from 0-4 marked as 'Never', 'Rarely', 'Sometimes', 'Often,' and 'Almost always', respectively. Patients were classified into "elevated fear" or "non-elevated fear" groups based on the elevated item (EI) endorsement criterion (32). The criterion describes patients as having elevated fear if they score '≥3' for more than one item on HFS-W.

The PSQI, with its 19 items, is a widely used tool to assess the sleep quality of patients over the past month based on self-reporting (31). Initial scoring of the scale generates seven components i.e., subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, medication use, and daytime dysfunction. Each component is scored from 0-3 (0 being the best and 3 being the worst score), and when all seven are cumulated, a global score is generated from '0-21'. The patients were categorized into "good sleep health (PSQI ≤ 5)" or "poor sleep health (PSQI > 5)" groups based on the global score (31). Prior permissions were obtained from the relevant bodies/persons to use these questionnaires in this study.

2.4 Study participants

A total of 310 participants were enrolled from different centers, as mentioned above. Inclusion criteria comprised patients with Type-I or Type-II diabetes, diabetes duration of ≥ 1 year, good cognitive skills, and willingness to participate. Exclusion criteria included pregnancy-related diabetes, mental illness history, and other conditions hindering communication.

Patients were approached during healthcare visits, and provided with study details, and those agreeing to participate gave written informed consent. Selected patients were then interviewed thoroughly for the baseline demographics, HFS-II, and PSQI questionnaires and responses were marked accordingly.

2.5 Statistical analysis

The statistics were applied using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Data analysis involved descriptive statistics for means, frequencies, and percentages. The non-normal distribution of dependent variables (HFS-II Total Score and PSQI Global Score) led to the use of non-parametric tests like Kruskal-Wallis and Mann-Whitney tests for significance testing regarding age, gender, education, diabetes duration, and insulin use.

Spearman's correlation was used to analyze the relationship between fear of hypoglycemia (HFS-II) and sleep quality (PSQI). A binary logistic regression was subsequently performed, treating PSQI as a dichotomous variable for further exploration, with fear of hypoglycemia and insulin use as predictor variables. Finally, ROC curve analysis was conducted to evaluate the diagnostic ability of HFS-II (FOH) in measuring poor sleep quality. The output data on the assumption analysis of regression, normality testing, and ROC curve analysis can be found in the Supplementary File.

3 Results

3.1 Population characteristics

Table 1 summarizes the population's characteristics. The largest age group was 41-60 years (30.9%), with 65.5% female and 34.5%

TABLE 1 Sample characteristics of study participants.

Variable	Values	Frequency (%)
Age (Years)	≤ 40	70 (22.6%)
	41-60	190 (61.3%)
	> 60	50 (16.1%)
Gender	Male	107 (34.5%)
	Female	203 (65.5%)
Education	Primary (5 years)	75 (24.2%)
	Middle (8 years)	72 (23.2%)
	Matric (10 years)	88 (28.4%)
	Inter (12 years)	38 (12.3)
	Graduate (14/16 years)	37 (11.9%)
Duration of Diabetes (Years)	< 5	124 (40.0%)
	5 - 10	93 (30.0%)
	> 10	93 (30.0%)
BSF (mg/dL)	Mean	181.91 (SD = 70.364)
BSR (mg/dL)	Mean	268.20 (SD = 92.178)
Glycemic Control	Poor Glycemic Control (FPG > 130 mg/dL)	181 (58.4%)
	Good Glycemic Control (FPG 80 - 130 mg/dL)	60 (19.4%)
	Data Unavailable	69 (22.3%)
Patients on Insulin		155 (50.0%)
Patients on Insulin Secretagogues		53 (17.1%)
Patients on Insulin and Insulin Secretagogue		15 (4.8%)
Method of Insulin Administration	Syringe	127 (41.0%)
	Penfil	45 (14.5%)
	Pump	1 (0.3%)

BSF, Blood Sugar Fasting; BSR, Blood Sugar Random; FPG, Fasting plasma glucose.

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male participants. Most had 10 years of education (28.4%), while 11.9% were graduates. Around 40.0% were diagnosed with diabetes in the last 5 years, and 30.0% had diabetes for over 10 years. Mean fasting blood sugar (BSF) was 181.91 mg/dL (SD 70.36), and random blood sugar (BSR) was 268.20 mg/dL (SD 92.17). Notably, 58.4% had poor glycemic control (BSF > 130 mg/dL). Type-I diabetes patients constituted 50% of the sample, primarily using syringes for insulin (41.0%). Additionally, 17.1% used insulin secretagogues and 4.8% used both insulin and insulin secretagogues.

3.2 HFS-II scores

The mean HFS-II total score was 25.18 (SD 23.24) on a scale of 0 – 132. Mean scores on HFS-B and HFS-W scales were 15.40 (SD 13.64) and 9.77 (SD 12.48) respectively. The most rated items on HFS-B and HFS-W have been listed in Table 2. Using the EI criterion (32), we identified 120 patients (38.7%) having an elevated FOH as they scored '≥ 3' for more than one item on HFS-W.

3.3 FOH in different population groups

The scores of HFS-II, HFS-B, and HFS-W have been presented in Table 3. Participant's gender, diabetes duration, and method of insulin administration were significantly related to the FOH scores. The mean HFS-II score was significantly higher in the female gender (M = 27.40 (SD 22.42)) than in males (M = 20.95 (SD 24.28)). Nearly 75% of the females had an elevated fear of hypoglycemia. The most feared items among females related to hypoglycemia were 'made sure there were other people around,' 'stayed at home more than I liked,' and 'made sure I had someone with me when I went out.' Male participants differed only in item ('ate large snacks').

Duration of diabetes appears to have a positive correlation with the FOH as the mean HFS-II scores are highest in patients with a duration of > 10 years. Though the overall difference in the groups is marginally significant (p = 0.047), the pairwise comparison highlights a more substantial difference of means between the groups '< 5 years' and '> 10 years' (p = 0.016).

Finally, the way the patients administer insulin seems to have a significant impact on their FOH. The fear is more prevalent among patients using traditional methods such as insulin syringes (M = 29.40; SD 25.04) than those using modern technologies such as penfills (M = 16.17; SD 18.60). No solid inference can be derived from the scores of patients on insulin pumps due to their small proportion.

Glycemic control (good or bad), insulin *vs* non-insulin users, and the educational status of the participants did not appear to influence the FOH levels significantly. However, the fear was higher in patients with good glycemic control (M = 30.63 (SD 28.53)), use of insulin (M = 26.22 (SD 24.59)), and lower educational level (M = 26.25 (SD 23.16)).

TABLE 2 Most rated items on HFS-II Scale by the study participants.

Scale	Items	Mean (SD)
HFS-B	Stayed at home more than I liked (HFS-B9)	1.55 (1.63)
	Made sure there were other people around me (HFS-B11)	1.50 (1.54)
	Made sure I had someone with me when I went out (HFS-B5)	1.38 (1.50)
	Limited my out-of-town travel (HFS-B6)	1.38 (1.50)
HFS-W	Difficulty thinking clearly (HFS-W12)	1.18 (1.57)
	Feeling lightheaded or dizzy (HFS-W13)	0.83 (1.21)
	No one to help during hypoglycemia (HFS-W8)	0.77 (1.23)
	Becoming upset and difficult (HFS-W18)	0.77 (1.29)

SD, standard deviation; HFS-B, behavior subscale of hypoglycemia fear survey; HFS-W, worry subscale of hypoglycemia fear survey; BG, blood glucose.

3.4 Sleep quality in different population groups

The mean PSQI score was 7.11 (SD 4.31) where 57.7% (179) of the participants were poor sleepers (PSQI > 5) and 42.3% (131) had better sleep (PSQI ≤ 5). Age, gender, diabetes duration, use of oral hypoglycemic agents, glycemic control, and insulin regimen were not related to sleep quality significantly ($p > 0.05$). The use of insulin only, however, had a significant impact on the quality of sleep (p = 0.047). The proportion of poor sleep health was higher in all patients with diabetes without regard to their therapeutic regimens i.e., insulin, insulin secretagogues, or both medications. However, sleep health was relatively more compromised in patients using insulins in combination with insulin secretagogues (73.3% poor sleep health). Among other groups, sleep health was more compromised in patients aged between 21-30 years (78.6%), females (59.6%), diabetes duration > 10 years (62.4%), penfil users (57.8%), and those having a good glycemic control (65.0%) (Table 3). Interestingly, the FOH also seems to be higher within the same population groups particularly '21-30 years old', 'females', 'diabetes duration >10 years', and 'good glycemic control' (Table 3), setting up a base for a more in-depth relation between these two variables explained as follows.

3.5 Comparison of FOH and sleep quality

The sleep outcomes were measured as Global PSQI Score (sleep health) and seven sleep components (Table 4). A Spearman's correlation between FOH and sleep health showed a highly significant positive monotonic relation between the two variables ($p < 0.001$, $r_s = 0.397$, n = 310). The relationship with behavior and

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TABLE 3 Fear of hypoglycemia and sleep quality in different population groups.

		The outcome of the HFS-II Total Score			*p*-value*	PSQI Outcomes		*p*-value**
		Mean Total HFS-II	Mean HFS-B	Mean HFS-W		Good Sleep Health	Poor Sleep Health	
Age (years)	≤ 40	26.31 (SD 24.99)	15.58 (SD ± 13.48)	10.73 (SD 13.71)	0.488	29 (41.4%)	41 (58.6%)	0.711
	41-60	24.03 (SD 22.33)	14.58 (SD 13.19)	9.44 (SD 11.94)		80 (42.6%)	110 (57.9%)	
	> 60	27.98 (SD 24.28)	18.30 (SD 15.36)	9.68 (SD 12.89)		22 (44%)	28 (56%)	
Gender	Male	20.95 (SD 24.28)	12.69 (SD 14.04)	8.26 (SD 12.44)	**0.002**	49 (45.8%)	58 (54.2%)	0.074
	Female	27.40 (SD 22.42)	16.84 (SD 13.23)	10.56 (SD 12.45)		82 (40.4%)	121 **(59.6%)**	
Educational Status	Primary	24.62 (SD 24.21	14.33 (SD 14.38)	10.29 (SD 12.81)	0.881	41 (54.7%)	34 (45.3%)	0.054
	Middle	25.69 (SD 26.28)	15.56 (SD 15.07)	10.12 (SD 14.14)		28 (38.9%)	44 (61.1%)	
	Matric	26.25 (SD 23.16)	17.00 (SD 13.55)	9.25 (SD 11.94)		28 (68.2%)	60 (68.2%)	
	Inter	24.76 (SD 19.98)	14.31 (SD 10.59)	10.44 (SD 12.47)		15 (39.5%)	23 (60.5%)	
	Graduate	23.18 (SD 18.83)	14.62 (SD 12.43)	8.56 (SD 9.82)		19 (51.4%)	18 (48.6%)	
Duration of Diabetes (years)	< 5	21.51 (SD 21.43)	13.23 (SD 12.26)	8.28 (SD 11.71)	**0.047**	54 (43.5%)	70 (56.5%)	0.951
	5-10	27.03 (SD 25.31)	16.06 (SD 13.98)	10.96 (SD 14.09)		42 (45.2%)	51 (54.8%)	
	> 10	28.21 (SD 23.01)	17.65 (SD 14.71)	10.55 (SD 11.66)		35 (37.6%)	58 **(62.4%)**	
Method of Insulin Use	Syringe	29.40 (SD 25.04)	17.70 (SD 14.68)	11.69 (SD 13.22)	< **0.001**	57 (44.9%)	70 (55.1%)	0.673
	Penfil	16.17 (SD 18.60)	11.75 (SD 13.13)	4.42 (SD 8.06)		19 (42.2%)	26 **(57.8%)**	
	Pump	37.00	37.00	0.00		1 (100%)	0	
Glycemic Control	Poor	22.40 (SD 19.38)	14.34 (SD 12.52)	8.06 (SD 10.27)	0.088	83 (45.9%)	98 (54.1%)	0.137
	Good	30.63 (SD 28.53)	19.01 (SD 15.27)	11.61 (SD 15.46)		21 (35.0%)	39 **(65.0%)**	
Patients Taking Insulin Only		26.22 (SD 24.59)	16.77 (SD 14.72)	9.45 (SD 12.52)	0.535	72 (46.5%)	83 **(53.5%)**	**0.047**
Patients Taking Insulin Secretagogues Only		21.28 (SD 21.69)	12.52 (SD 12.47)	8.75 (SD 11.61)	0.204	25 (47.2%)	28 (52.8%)	0.959
Patients Taking Both Medications		24.46 (SD 20.67)	12.06 (SD 12.80)	12.40 (SD 12.72)	0.752	4 (26.7%)	11 **(73.3%)**	0.237

HFS-II, hypoglycemia fear survey-II; HFS-B, Hypoglycemia fear survey-behavior scale; HFS-W, Hypoglycemia fear survey-worry Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; FPG, Fasting plasma glucose.

*Significance was measured between the said variable (age, gender, etc.) and total HFS-II score.

**Significance was measured between the said variable (age, gender, etc.) and the PSQI global score.

Bold values indicate statistical significance, measured as $p < 0.05$ that we have already mentioned within methodology & results.

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TABLE 4 Relationship between FOH and sleep.

Parameter	Responses	Mean FOH Score	Non-Elevated FOH	Elevated FOH	Significance with FOH*
PSQI Global	Good Sleep Health (PSQI ≤ 5)	16.41 (SD 17.07)	95 (72.5%)	36 (27.5%)	**< 0.001**
	Poor Sleep Health (PSQI > 5)	31.59 (SD 25.04)	95 (53.1%)	84 (46.9%)	
Subjective Sleep Quality	Very Good	21.14 (SD 19.68)	73 (67.0%)	36 (33.0%)	**0.007**
	Fairly Good	22.85 (SD 22.35)	63 (63.6%)	36 (36.4%)	
	Fairly Bad	32.96 (SD 27.18)	27 (51.9%)	25 (48.1%)	
	Very Bad	30.48 (SD 25.39)	27 (54.0%)	23 (46.0%)	
Latency	0	23.03 (SD 22.69)	69 (63.9%)	39 (36.1%)	0.145
	1-2	23.85 (SD 23.20)	50 (64.1%)	28 (35.9%)	
	3-4	25.04 (SD 21.24)	42 (60.0%)	28 (40.0%)	
	5-6	31.55 (SD 26.23)	29 (53.7%)	25 (46.3%)	
Duration	> 7 hours	25.07 (SD 23.76)	87 (62.1%)	53 (37.9%)	0.626
	6-7 hours	24.35 (SD 23.32)	44 (56.4%)	34 (43.6%)	
	5-6 hours	23.80 (SD 23.22)	27 (67.5%)	13 (32.5%)	
	< 5 hours	27.75 (SD 22.18)	32 (61.5%)	20 (38.5%)	
Efficiency	> 85%	23.03 (SD 23.50)	133 (65.2%)	71 (34.8%)	**0.017**
	75-84%	26.29 (SD 22.50)	17 (63.0%)	10 (37.0%)	
	65-74%	19.57 (SD 20.67)	6 (85.7%)	1 (14.3%)	
	< 65%	31.38 (SD 22.24)	34 (47.2%)	38 (52.8%)	
Disturbance	0	7.07 (SD 7.64)	13 (100%)	0 (0%)	**< 0.001**
	1 - 9	16.95 (SD 18.66)	110 (73.8%)	39 (26.2%)	
	10 - 18	31.97 (SD 22.57)	60 (49.6%)	61 (50.4%)	
	19 - 27	48.85 (SD 26.68)	7 (25.9%)	20 (74.1%)	
Medication	Not during the past month	20.96 (SD 19.99)	149 (65.1%)	80 (34.9%)	**< 0.001**
	Less than once a week	23.88 (SD 18.55)	23 (65.7%)	12 (34.3%)	
	Once or twice a week	46.76 (SD 27.15)	12 (46.2%)	14 (53.8%)	
	Three or more times a week	47.70 (SD 31.85)	6 (30.0%)	14 (70.0%)	
Day Time Dysfunction	0	15.95 (SD 17.53)	96 (74.4%)	33 (25.6%)	**< 0.001**
	1 - 2	23.05 (SD 20.13)	53 (61.6%)	33 (38.4%)	
	3 - 4	38.14 (SD 22.96)	33 (47.1%)	37 (52.9%)	
	5 - 6	43.80 (SD 32.25)	8 (32.0%)	17 (68.0%)	

*The significance was measured between the categorical sleep components and HFS-II total scores.
Bold values indicate statistical significance, measured as p < 0.05 that we have already mentioned within methodology & results.

worry dimensions of HFS-II scale was equally significant ($p < 0.001$, $r_s = 0.379$; $p < 0.001$, $r_s = 0.304$ respectively). Notably, the correlation was positive, meaning the PSQI score increases with the increments in HFS-II scores. Moreover, the mean HFS-II scores were higher among patients with poor sleep health compared to those with good sleep health (Table 4). In addition, among the 179 patients with poor sleep health, 46.9% had an elevated FOH according to the EI criterion.

Going ahead, we attempted to understand the relationship between FOH and the sleep components to highlight grey areas in overall sleep health. The relationship of five out of seven components was significant *($p < 0.05$)*. These were subjective sleep quality, sleep efficiency, sleep disturbance, sleep medications, and daytime dysfunction. Sleep latency and duration showed an insignificant relationship with FOH. With few exceptions, the mean FOH scores as well as the proportion of elevated fear tend to rise

with the worsening outcome of each sleep component. For example, a 'fairly bad' subjective sleep quality in patients is associated with 48.1% elevated FOH compared to 36.4% for 'fairly good' sleep quality. A similar trend is followed in other components except for the sleep duration where a relatively large deviation can be seen.

3.6 Relationship between FOH and sleep quality

To further understand the nature of the relationship between FOH and sleep quality, logistic regression analysis was performed between the two variables (Table 5). The global PSQI score (continuous scale, 0-21) was converted into a binary variable 'sleep health' with two outputs, good sleep health (PSQI ≤ 5) and poor sleep health (PSQI > 5), to perform a binary logistic regression. The 'HFS-II score' (continuous variable) was added as the independent variable with 'insulin use (dichotomous)' as a covariate since it was found to be significantly related to sleep quality (Table 3). The model demonstrated an overall satisfactory fit, as evidenced by the -2 Log Likelihood value of 382.370 and the Cox & Snell R Square (12.1%) and Nagelkerke R Square (16.2%). For the predictor variable "Fear of hypoglycemia," the coefficient (B) was 0.036, and the Wald chi-square test yielded a statistically significant result (χ^2 (1) = 29.387, $p < 0.001$). The odds ratio (Exp (B)) was 1.037, suggesting that for every one-unit increase in fear of hypoglycemia, the odds of experiencing poor sleep increased by approximately 3.7%. As for "Insulin use," the coefficient (B) was -0.440, and the Wald chi-square test produced a p-value of 0.073, indicating marginal significance. The odds ratio (Exp(B)) for insulin use was 0.644, suggesting that individuals using insulin had approximately 60% lower odds of experiencing poor sleep compared to those not using insulin.

3.7 Diagnostic ability of FOH to predict poor sleep quality – receiver operating characteristic (ROC) curve analysis

ROC curve analysis is a graphical representation used to evaluate the diagnostic ability of a binary classifier system. In the present case, the ROC curve analysis was conducted to evaluate the diagnostic accuracy of three scales—HFS-B (Behavior score), HFS-W (Worry score), and HFS-T (Total HFS score)—in identifying poor sleep quality (Table 6, Figure 1). The dataset comprised 179 cases with severe sleep difficulty and 131 cases without. The Area Under the Curve (AUC) values were 0.691 for the Total HFS Score, 0.681 for the HFS-B Scores, and 0.647 for the HFS-W Scores, with all p-values being < 0.001. This indicates that all three scales are significantly better than chance at distinguishing between individuals with and without severe sleep difficulty. Following this, we analyzed sensitivity and 1 – specificity values of the three scales at a cutoff value of 3.5. The total HFS-II score showed the highest sensitivity, followed by HFS-B and HFS-W. However, as a trade-off between sensitivity and specificity, HFS-B appears to be more optimal with a specificity of 83.8% and a false-positive rate of 61.1%.

4 Discussion

This is the first study examining the FOH among patients with diabetes and its influence on the quality of sleep in Pakistan. While the clinical practice is intensely oriented to reducing glycemic levels, the resultant hypoglycemic events and associated psychological implications are often ignored. FOH is one of the most common psychological manifestations of hypoglycemia. It is known to impact behavioral and worry patterns in individuals with diabetes. However, its impact on psychological states, such as sleep, is still in its infancy. Few studies that examined this particular relationship were related to Type-I patients (28) or adolescents (33).

In our study, with the inclusion of both Type-I and Type-II diabetics and no age restriction, the mean HFS-II score is 25.18 (SD 23.24) which is relatively lower compared to similar studies measuring FOH (10, 30, 34, 35). However, like our study, some other studies have also reported lower mean values for HFS scores (36). The EI criterion classified 120 individuals (38.7%) as having an elevated FOH which is relatively higher than other studies by Hajos et al. (32) (26%) and Majanovic et al. (37) (11.1%). The mean differences as well as fear characteristics could be attributed to the population differences in these studies.

In our study, FOH was higher in younger age (<10 – 30 years) as supported by other studies (35, 38, 39). Also, higher FOH was seen in patients above 60 years which is also evident from the literature (10, 11). We have also noted that the most vulnerable age groups with respect to FOH are those below 40 years and above 50 years. However, we agree with the interpretation of

TABLE 5 Logistic regression predicting sleep health from FOH and insulin use.

Predictor	*B*	Wald χ^2	*p*	Odds Ratio	95% CI for EXP(B)	
					Lower	Upper
Total HFS Score	0.036	29.387	< 0.001	1.037	1.023	1.050
Patients Taking Insulin Only	-0.440	3.212	0.073	0.644	0.398	1.042
Constant	-0.293	1.845	0.174	0.746		

TABLE 6 Diagnostic performance of Total HFS, HFS-B, and HFS-W scores for identifying poor sleep quality using ROC.

Test Result Variable	AUC	Std. Error	p-value	95% CI (Lower)	95% CI (Upper)	Cutoff	Sensitivity	1 - Specificity
Total HFS Score	0.691	0.030	0.000	0.632	0.749	3.5000	0.888	0.779
HFS-B Scores	0.681	0.031	0.000	0.621	0.741	3.5000	0.838	0.611
HFS-W Scores	0.647	0.031	0.000	0.587	0.708	3.5000	0.654	0.466

Martyn-Nemet et al. (40) that there is no consistent pattern of FOH with regard to age and that the relationship with age is complex. For gender comparisons, FOH was higher in females which are in uniform agreement with the previous literature (38, 41, 42).

Education seems to have a positive impact on the FOH. The fear is higher among participants with lower educational levels and vice versa. This appears to be a negative correlation as reported by Gonder-Fredrick et al. (30), however, we could not perform a direct correlation statistic due to the categorical nature of our variable. The relationship, nonetheless, remains insignificant and consistent with other studies (41).

Duration of diabetes was significantly associated with FOH in our study. The scores of HFS-II increased with the increase in the duration of diabetes. The findings are consistent with previous studies by Hongmei et al. (43) and Erol and Enc (41) where a positive correlation existed between the course of disease (diabetes) and FOH. Opposite findings also surfaced in some populations where there was no correlation between duration of diabetes and FOH or the FOH decreased with an increase in the duration of diabetes (30, 44).

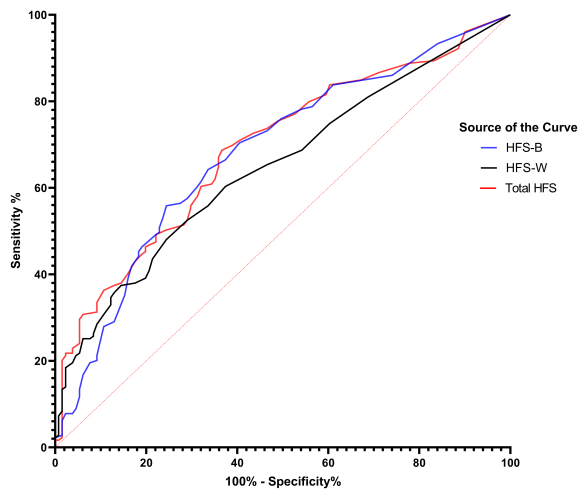

FIGURE 1
ROC Curves of fear of hypoglycemia scores predicting sleep quality in patients with diabetes. This figure shows ROC curves for components of the Fear of Hypoglycemia Survey (HFS) in predicting sleep quality among patients with diabetes. The blue curve (HFS-B) represents the behavioral component, the black curve (HFS-W) represents the worry component, and the red curve (Total HFS) represents the combined score. The diagonal red dashed line indicates no discrimination (AUC = 0.5). Higher AUC values denote better predictive accuracy.

The impact of glycemic control on FOH is debated. Some studies suggest improved glycemic control is associated with increased FOH (35, 40, 45), while others show higher FOH in patients with poor control (36). In our study, glycemic control showed a marginally insignificant relationship with FOH. However, patients with good control (FPG 80-130 mg/dL) were more likely to have FOH than those with poorer control (FPG > 130 mg/dL). Tight control lowers glucose levels intensively, raising hypoglycemia risk and concerns. Regular glucose monitoring and insulin dose management are key, especially in T2DM.

The FOH did not differ significantly among insulin users and those on oral anti-diabetic agents. However, the proportion of FOH was greater among insulin users compared to other groups. Studies have found a similar pattern of FOH among Type-I and Type-II diabetes patients, that is, individuals with T1DM have more FOH than individuals with T2DM, but the difference is not statistically significant (35, 36, 41).

As for the technology used for insulin administration, our data suggested that FOH was more prevalent in those administering insulin via syringes than those using pen fills. This means that technology infuses confidence and security among patients and is a reliable tool for reducing FOH. These results are consistent with a previous study showing that FOH was higher in patients using multiple-dose injection treatment compared to those receiving insulin via pump (38). However, in our study patients on insulin pumps showed a higher proportion of FOH but given the small number of users, the results cannot be generalized.

The relationship between FOH and sleep appears to be fairly significant. The univariate analysis as well as the multivariate logistic regression found the relationship significant. Moreover, five out of seven PSQI sleep components showed a statistically significant link with FOH. Sleep latency and sleep duration were not significantly linked with FOH. This generates the hypothesis that the FOH may not affect the initiation or termination of the sleep cycle rather it is more specifically linked with the quality of sleep. This could be disturbed sleep ($p < 0.001$), less efficient sleep ($p = 0.017$), medication-dependent sleep ($p < 0.001$), or sleep leading to daytime dysfunction ($p < 0.001$). These findings represent a novel contribution to the existing literature, signaling a need for further exploration and in-depth investigation into the specific mechanisms through which FOH manifests its impact on the qualitative aspects of sleep.

The ROC curve estimation also provided some novel insights into utilization of HFS-II scores in determining the quality of sleep. The results revealed that the HFS scores were better at predicting sleep quality than by chance. However, we couldn't determine a

specific cut-off score for a reliable diagnosis as the false positive rates were high. For the sake of comparison, a cut-off value of 3.5 was selected, which was closest to the maximum possible score on one item. This approach showed that the HFS-B scale was better at predicting poor sleep quality than the other forms of the scale in terms of sensitivity and specificity. This could be because of the underlying condition that the means of the HFS-B scores were higher in our study participants (15.40 (SD 13.64)) compared to the HFS-W scores (9.77 (SD 12.48)) indicating that fear derived from behavioral aspects may be more limiting towards sleep quality. However, the findings need clinical support to reflect more authenticity.

The identification of these nuanced relationships provides a foundation for targeted interventions aimed at improving sleep quality in individuals grappling with the psychological challenges associated with FOH. As the field advances, this newfound understanding paves the way for tailored strategies that encompass both glycemic control and psychological well-being in the holistic care of patients with diabetes. Further research endeavors should delve into the intricate dynamics of FOH and its implications on sleep, contributing to the evolving landscape of diabetes management and patient-centric care.

The strength of this study is that, for the first time, it provides comprehensive data on FOH in the diabetes population of Pakistan. While most of the studies utilize only the worry scale of HFS-II, we used the complete 33-item HFS-II scale in our sample population. Another strength of the study is that patients with both T1DM and T2DM were included in this study, unlike previous studies where the choice was selective. Finally, the study outlines an in-depth association between FOH and sleep quality and evaluates the diagnostic ability of FOH in terms of sleep quality. Moreover, it proposes a new hypothesis that the FOH may influence not the initiation and termination of the sleep cycle but its quality in an individual.

5 Conclusion

In conclusion, this study sheds light on the underexplored issue of FOH in the Pakistani population with diabetes, revealing its significant impact on both psychological well-being and sleep quality. The findings underscore the prevalence of FOH, with particular vulnerability among younger and older age groups, females, syringe users, and those with longer diabetes durations. Notably, FOH is closely linked with poor sleep quality, emphasizing the need for holistic diabetes management that addresses both glycemic control and psychological aspects. Healthcare practitioners should prioritize patient education and counseling, targeting the most common FOH concerns identified in this study. Furthermore, patients with disturbed sleep should be assessed for an elevated level of FOH as it could be a contributing factor to poor sleep quality. Future research should develop validated methods to better understand the intricate relationship between FOH and sleep disturbances.

6 Limitations

The cross-sectional design, missing confounding variables (e.g., history of hypoglycemic episodes, comorbidities e.g., obesity), and a higher proportion of female participants are some of the limitations of this study. Moreover, the data on glycemic control was generated from a single value of either BSR or BSF, which may not reflect the chronic condition of glycemic control. HbA1c could have been a better measure; however, we could not find enough data for this. Additionally, the PSQI tool assesses sleep quality over a relatively short period (past month) and may not capture long-term sleep patterns accurately. Furthermore, using HFS-II scores alone to classify patients into “elevated fear” or “non-elevated fear” groups may oversimplify FOH, which varies in intensity and impact among individuals. Similarly, future studies are also recommended to explore the relationship between fear of hypoglycemia and sleep quality in patients on non-hypoglycemic therapies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Institutional Review Board (IRB), University of Sargodha. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HH: Conceptualization, Methodology, Resources, Supervision, Validation, Writing – review & editing, Writing – original draft. NA: Formal analysis, Investigation, Writing – original draft. MWA: Formal analysis, Software, Validation, Writing – review & editing, Writing – original draft. FG: Resources, Supervision, Writing – review & editing, Writing – original draft. JK: Writing – original draft, Formal analysis, Writing – review & editing. MA: Resources, Visualization, Writing – review & editing, Writing – original draft. ST: Resources, Visualization, Writing – original draft. TA: Project administration, Supervision, Writing – review & editing, Writing – original draft. AM: Resources, Supervision, Validation, Writing – review & editing, Writing – original draft. SA: Resources, Supervision, Validation, Writing – review & editing, Writing – original draft. AS: Formal analysis, Validation, Writing – original draft. MN: Data curation, Writing – original draft. MP: Data curation, Writing – original draft. MU: Data curation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1456641/full#supplementary-material

References

1. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. (2009) 32:S62–7. doi: 10.2337/DC09-S062

2. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. (2014) 37:S81–90. doi: 10.2337/dc14-S081

3. International Diabetes Federation. Pakistan - International diabetes federation (2021). Available online at: https://idf.org/our-network/regions-and-members/middle-east-and-north-africa/members/Pakistan/ (Accessed August 21, 2023).

4. Almomani HY, Pascual CR, Grassby P, Ahmadi K. Effectiveness of the SUGAR intervention on hypoglycaemia in elderly patients with type 2 diabetes: A pragmatic randomised controlled trial. *Res Soc Adm Pharm*. (2023) 19:322–31. doi: 10.1016/j.sapharm.2022.09.017

5. Clayton D, Woo V, Yale JF. Hypoglycemia. *Can J Diabetes*. (2013) 37:S69–71. doi: 10.1016/j.jcjd.2013.01.022

6. Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. *Diabetes Care*. (2023) 46:S19–40. doi: 10.2337/DC23-S002

7. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*. (2007) 68:10–5. doi: 10.1016/j.pec.2007.05.003

8. Anarte MT, Carreira M, MaChado A, Domínguez M, Tapia MJ, Valdés S, et al. Identification of risk factors for suffering fear of hypoglycemia in type 1 diabetes mellitus patients. *Scand J Psychol*. (2014) 55:554–7. doi: 10.1111/sjop.12158

9. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. *Diabetes Med*. (2013) 30:1126–31. doi: 10.1111/dme.12247

10. Wang Y, Zeng Z, Ding J, Yuan R, Wang R, Zhang Y, et al. Fear of hypoglycaemia among patients with type 2 diabetes mellitus: a cross-sectional study. *Sci Rep*. (2021) 11:7971. doi: 10.1038/S41598-021-86954-0

11. Böhme P, Bertin E, Cosson E, Chevalier N. Fear of hypoglycaemia in patients with type 1 diabetes: Do patients and diabetologists feel the same way? *Diabetes Metab*. (2013) 39:63–70. doi: 10.1016/j.diabet.2012.10.006

12. Desjardins K, Brazeau AS, Strychar I, Rabasa-Lhoret R. Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes? *Diabetes Obes Metab*. (2014) 16:577–87. doi: 10.1111/dom.12232

13. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. (2008) 31:2108–9. doi: 10.2337/dc08-0720

14. Martyn-Nemeth P, Quinn L, Penckofer S, Park C, Hofer V, Burke L. Fear of hypoglycemia: Influence on glycemic variability and self-management behavior in young adults with type 1 diabetes. *J Diabetes Complications*. (2017) 31:735–41. doi: 10.1016/j.jdiacomp.2016.12.015

15. Martyn-Nemeth P, Phillips SA, Mihailescu D, Farabi SS, Park C, Lipton R, et al. Poor sleep quality is associated with nocturnal glycemic variability and fear of hypoglycemia in adults with type 1 diabetes. *J Adv Nurs*. (2018) 74:2373. doi: 10.1111/JAN.13765

16. Di Battista AM, Hart TA, Greco L, Gloizer J. Type 1 diabetes among adolescents: reduced diabetes self-care caused by social fear and fear of hypoglycemia. *Diabetes Educ*. (2009) 35:465–75. doi: 10.1177/0145721709333492

17. Fidler C, Elmelund Christensen T, Gillard S, Nordisk NA, Samantha Gillard D. Hypoglycemia: An overview of fear of hypoglycemia, quality-of-life, and impact on costs. *J Med Econ*. (2011) 14:646–55. doi: 10.3111/13696998.2011.610852

18. Martyn-Nemeth P, Quinn L, Hacker E, Park H, Kujath AS. Diabetes distress may adversely affect the eating styles of women with type 1 diabetes. *Acta Diabetol*. (2014) 51:683–6. doi: 10.1007/s00592-014-0575-1

19. Davis RE, Morrissey M, Peters JR, Wittrup-Jensen K, Kennedy-Martin T, Currie CJ. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin*. (2005) 21:1477–83. doi: 10.1185/030079905X61929

20. Rossi MC, Nicolucci A, Ozzello A, Gentile S, Aglialoro A, Chiambretti A, et al. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. *Nutr Metab Cardiovasc Dis*. (2019) 29:736–43. doi: 10.1016/J.NUMECD.2019.04.009

21. Gonder-Frederick LA, Vajda KA, Schmidt KM, Cox DJ, Devries JH, Erol O, et al. Examining the behaviour subscale of the hypoglycemia fear survey: An international study. *Diabetes Med*. (2013) 30:603–9. doi: 10.1111/dme.12129

22. Krawczyk J, Duda-Sobczak A, Zozulińska-Ziółkiewicz D. Fear of hypoglycaemia — from normality to pathology. Diagnostic criteria and therapeutic directions. *Clin Diabetol*. (2020) 9:487–92. doi: 10.5603/DK.2020.0046

23. Polonsky WH, Davis CL, Jacobson AM, Anderson BJ. Correlates of hypoglycemic fear in type I and type II diabetes mellitus. *Heal Psychol*. (1992) 11:199–202. doi: 10.1037//0278-6133.11.3.199

24. Shan W, Peng X, Tan W, Zhou Z, Xie H, Wang S. Prevalence of insomnia and associations with depression, anxiety among adults in guangdong, China: A large-scale cross-sectional study. *Sleep Med*. (2024) 115:39–47. doi: 10.1016/j.sleep.2024.01.023

25. Lee S-A, Im K, Seo JY, Jung M. Association between sleep apnea severity and symptoms of depression and anxiety among individuals with obstructive sleep apnea. *Sleep Med*. (2023) 101:11–8. doi: 10.1016/j.sleep.2022.09.023

26. Cobry EC, Bisio A, Paul Wadwa R, Breton MD. Improvements in parental leep, fear of hypoglycemia, and diabetes distress with use of an advanced hybrid closed-loop system. *Diabetes Care*. (2022) 45:1292–5. doi: 10.2337/dc21-1778

27. Speight J, Choudhary P, Wilmot EG, Hendrieckx C, Forde H, Cheung WY, et al. Impact of glycaemic technologies on quality of life and related outcomes in adults with type 1 diabetes: A narrative review. *Diabetes Med*. (2023) 40:e14944. doi: 10.1111/dme.14944

28. Suteau V, Saulnier PJ, Wargny M, Gonder-Frederick L, Gand E, Chaillous L, et al. Association between sleep disturbances, fear of hypoglycemia and psychological well-being in adults with type 1 diabetes mellitus, data from cross-sectional VARDIA study. *Diabetes Res Clin Pract*. (2020) 160:107988. doi: 10.1016/J.DIABRES.2019.107988

29. Farooque R, Herekar F, Iftikhar S, Patel MJ. The frequency of poor sleep quality in patients with diabetes mellitus and its association with glycemic control. *Cureus*. (2020) 12:e11608. doi: 10.7759/cureus.11608

30. Gonder-Frederick LA, Schmidt KM, Vajda KA, Greear ML, Singh H, Shepard JA, et al. Psychometric properties of the hypoglycemia fear survey-II for adults with type 1 diabetes. *Diabetes Care*. (2011) 34:801–6. doi: 10.2337/DC10-1343

31. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

32. Hajós TRS, Polonsky WH, Pouwer F, Gonder-Frederick L, Snoek FJ. Toward defining a cutoff score for elevated fear of hypoglycemia on the hypoglycemia fear survey worry subscale in patients with type 2 diabetes. *Diabetes Care*. (2014) 37:102–8. doi: 10.2337/DC13-0971

33. Hitt TA, Hershey JA, Olivos-Stewart D, Forth E, Stuart F, Garren P, et al. The impact of fear of hypoglycaemia on sleep in adolescents with type 1 diabetes. *Diabetes Med*. (2023) 40:e15066. doi: 10.1111/dme.15066

34. Glocker V, Bachmann S, Hess M, Szinnai G, Burckhardt MA. Fear of hypoglycemia and quality of life in young people with type 1 diabetes and their parents in the era of sensor glucose monitoring. *Front Endocrinol (Lausanne)*. (2022) 13:958671/BIBTEX. doi: 10.3389/FENDO.2022.958671/BIBTEX

35. Hapunda G, Abubakar A, Pouwer F, van de Vijver F. Correlates of fear of hypoglycemia among patients with type 1 and 2 diabetes mellitus in outpatient hospitals in Zambia. *Int J Diabetes Dev Ctries*. (2020) 40:619–26. doi: 10.1007/S13410-020-00835-2

36. Lam AYR, Xin X, Tan WB, Gardner DSL, Goh SY. Psychometric validation of the hypoglycemia fear survey-II (HFS-II) in Singapore. *BMJ Open Diabetes Res Care*. (2017) 5:e000329. doi: 10.1136/bmjdrc-2016-000329

37. Al AA, Asirvatham H, Robert A, Braham Besher RB, Issa A, Al Sabaan FS. Predictive risk factors for fear of hypoglycemia and anxiety-related emotional disorders among adolescents with type 1 diabetes. *Med Princ Pract*. (2015) 24:222–30. doi: 10.1159/000375306

38. Majanovic SK, Janez A, Lefterov I, Tasic S, Cikac T. The real-life effectiveness and care patterns of diabetes management study for Balkan Region (Slovenia, Croatia, Serbia, Bulgaria): a multicenter, observational, cross-sectional study. *Diabetes Ther*. (2017) 8:929–40. doi: 10.1007/s13300-017-0288-x

39. Graue M, Iversen MM, Wentzel-Larsen T, Rokne B, Haugstvedt A. Assessing fear of hypoglycemia among adults with type 1 diabetes–psychometric properties of the Norwegian version of the Hypoglycemia Fear Survey II. *Nor Epidemiol*. (2013) 23:75–81. doi: 10.5324/nje.v23i1.1605

40. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. *J Diabetes Complications*. (2016) 30:167–77. doi: 10.1016/j.jdiacomp.2015.09.003

41. Erol O, Enc N. Hypoglycemia fear and self-efficacy of Turkish patients receiving insulin therapy. *Asian Nurs Res (Korean Soc Nurs Sci)*. (2011) 5:222–8. doi: 10.1016/J.ANR.2011.12.001

42. Gjerløw E, Bjørgaas MR, Nielsen EW, Olsen SE, Åsvold BO. Fear of hypoglycemia in women and men with type 1 diabetes. *Nurs Res*. (2014) 63:143–9. doi: 10.1097/NNR.0000000000000020

43. Hongmei X, Chun M, Di B. Assessing fear of hypoglycemia and related factors in patients with type 2 diabetes mellitus. *Chin J Diabetes Mellit*. (2018) 10:735–9.

44. Beléndez M, Hernández-Mijares A. Beliefs about insulin as a predictor of fear of hypoglycaemia. *Chronic Illn*. (2009) 5:250–6. doi: 10.1177/1742395309346464

45. Bloomgarden ZT, Einhorn D. Hypoglycemia in type 2 diabetes: Current controversies and changing practices. *Front Endocrinol (Lausanne)*. (2012) 3:66. doi: 10.3389/fendo.2012.00066

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EDITED BY
Åke Sjöholm,
Gävle Hospital, Sweden

REVIEWED BY
Tarik A. A. A. Elhadd,
Hamad Medical Corporation, Qatar
Rayaz A. Malik,
Weill Cornell Medicine, Qatar

*CORRESPONDENCE
Abdullah M. Alguwaihes
aalguwaihes@ksu.edu.sa

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Altered Ramadan fasting glycemic profiles of adults with type 1 diabetes reveal strong evidence of underestimated insulin adjustments: a 3-year observational study in Arab settings

Abdullah M. Alguwaihes[1,2]*, Ebtihal Y. Alyusuf[3], Areej Alrajeh[4], Metib Alotaibi[5] and Mohammed E. Al-Sofiani[1,6]

[1]Division of Endocrinology, Department of Internal Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [2]Dallah Hospital, Diabetes Center, Riyadh, Saudi Arabia, [3]Division of Endocrinology, Department of Internal Medicine, Salmaniya Medical Complex, Manama, Bahrain, [4]Department of Internal Medicine, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia, [5]University Diabetes Center, King Saud University Medical City, Riyadh, Saudi Arabia, [6]Division of Endocrinology, Diabetes & Metabolism, The Johns Hopkins University, Baltimore, MD, United States

Background: Adults with type 1 diabetes (T1D) who fast during Ramadan remain a severely understudied population in terms of changes in glycemic control, making evidence-based recommendations for insulin adjustments difficult in this age-group. To fill this gap, we aimed to prospectively observe the changes in glycemic control of young adults with T1D who fast during Ramadan.

Methods: In this 3-year prospective study, we enrolled participants with T1D with flash glucose monitoring (FGM) data during the Ramadan periods of 2020-2022. CGM data for 4 weeks before, during, and after Ramadan were collected and analyzed. A sub-cohort of age-matched non-DM participants (N=49) who fasted during the Ramadan of 2022 were included for comparison.

Results: A total of 76 participants were enrolled, of whom only 39 (19 males and 20 females, mean age 28.1 ± 8.4 years) completed the three-year follow-up. The mean duration of diabetes among these participants was 11.5 ± 8.9 years. Ten (26%) patients were on insulin pump, and 22 (56%) patients received Ramadan-focused education at baseline. Pooled glycemic trends during Ramadan showed two main abnormal glucose spikes: after Iftar (between 16:00-18:00 and 18:00-20:00), with a difference of 15.5mg/dL, and after Suhoor (between 0:00-2:00h to 4:00-6:00), with a difference of 18.8mg/dL. These abnormal glycemic indices persisted a month after Ramadan. In parallel, these glucose spikes were also observed in non-DM participants, but remained within normal limits.

Conclusions: Ramadan fasting among adults with T1D in SA is associated with deterioration in glycemic control, with the highest glucose spikes observed after Iftar and Suhoor. These hyperglycemic episodes were most prominent during

Ramadan and persisted for at least a month after. The present real-time evidence warrants the need to review insulin adjustments in this understudied group, focusing on high risk patients with T1D, including those with history of overindulgent behavior during Ramadan.

KEYWORDS

Ramadan, intermittent fasting, type 1 diabetes, Saudi Arabia, flash glucose monitoring, continuous glucose monitoring

1 Introduction

Ramadan is a holy Islamic month during which Muslims observe fasting from dusk until dawn and abstain from food or drink (1). Suhoor, the pre-dawn meal, is the meal consumed before fasting begins, while Iftar is the meal that marks the moment to break the fast at sunset. While intermittent fasting has been shown to offer several benefits (2, 3), it differs from Ramadan fasting in terms of flexibility of fasting days, the latter being stricter as it has to be implemented for a month. Ramadan in Saudi Arabia (SA) is associated with extravagant changes in lifestyle and eating habits; people tend to consume larger portions, including higher consumption of traditional sweets and sweetened beverages which are culturally driven (4–6). Furthermore, sleeping patterns are reversed during Ramadan in SA, resulting in lower physical activity and higher levels of evening cortisol, leading to a paradoxical increase in insulin resistance (7, 8).

For patients with type 1 diabetes (T1D) who choose to fast during Ramadan, as they need to re-adjust insulin doses and timing to minimize the risk of abnormal glycemic changes (9). Moreover, because of the long duration of absolute fasting particularly during summer, additional risks should be considered in patients with T1D, including dehydration, hypoglycemia, and possibly an increased risk of diabetic ketoacidosis (10–12). Despite medical and religious exemptions, a considerable number of T1D patients insist on fasting (1, 13). An epidemiological study across several Muslim countries estimated that 42.8% of Muslims with T1D fast for ≥ 15 days and this was highest in SA at 71.6% (12). A recent survey that included T1D patients and conducted during the coronavirus pandemic found that 71.1% of respondents intended to fast (14). However, only 26.8% managed to fast for the full month, while 45% fasted for more than 21 days. Additionally, 60.7% of participants reported hypoglycemia episodes (14). Several guidelines recommended against fasting during Ramadan for high-risk T1D patients due to lack of available evidence (9, 10, 15). Nevertheless, some studies have shown that it can be safely accomplished in selected patients (16, 17).

Novel technologies seem to provide promising benefits for T1D patients fasting during Ramadan (9, 15). Real-time continuous glucose monitoring (RT-CGM) and flash glucose monitoring systems (FGM) provide comprehensive evaluation of glucose measurements and variability, enabling patients and healthcare professionals to make better-informed decisions (18–23). Additionally, insulin pumps may help individuals with T1D maintain better clinical outcomes (13, 24). Despite the high prevalence of fasting during Ramadan among patients with T1D, there remains a significant gap in the understanding of the impact of this type of fasting on glycemic control, notably among adults with T1D. To fill this gap, we examined the changes in glycemic control among adult patients with T1D who attempted to fast before, during, and after Ramadan and how these changes may have differed from the glycemic changes in non-T1D individuals.

2 Methods

2.1 Study design and participants

This is a real-world observational study that initially included 79 outpatients with T1D who had FGM data during 4 weeks pre-Ramadan, 4 weeks during Ramadan, and 4 weeks post-Ramadan during 2020, 2021 and 2022, at the diabetes clinics of King Saud University Medical City (KSUMC), Riyadh, Saudi Arabia. The inclusion criteria for the study were patients with T1D, aged ≥15 years, who intended to fast during one or more of the Ramadan periods of the three years of the study, and had available FGM data. We excluded patients with T2D, patients with T1D who didn't attempt fasting during Ramadan or with no FGM data during Ramadan in any of the study periods. Moreover, 49 healthy individuals without diabetes were included in Ramadan 2022. The participants without diabetes were recruited from hospital staff and patients' companions who consented to wear the sensor for Two weeks during Ramadan 2022 and share their data for the study. Demographic and clinical data such as age, gender, medications, comorbidities, duration of diabetes, HbA1c, and the status of receiving focused-Ramadan education were extracted from the electronic medical records for all participants with T1D. The total fasting hours per day during Ramadan can vary within a year and from year to year. However, the fasting hours during the three study years were around 14.5 hours per day starting at around 04:00 h and ending at around 18:30 h. By the end of the study, 39 participants (19 males and 20 females) remained and were included for analysis

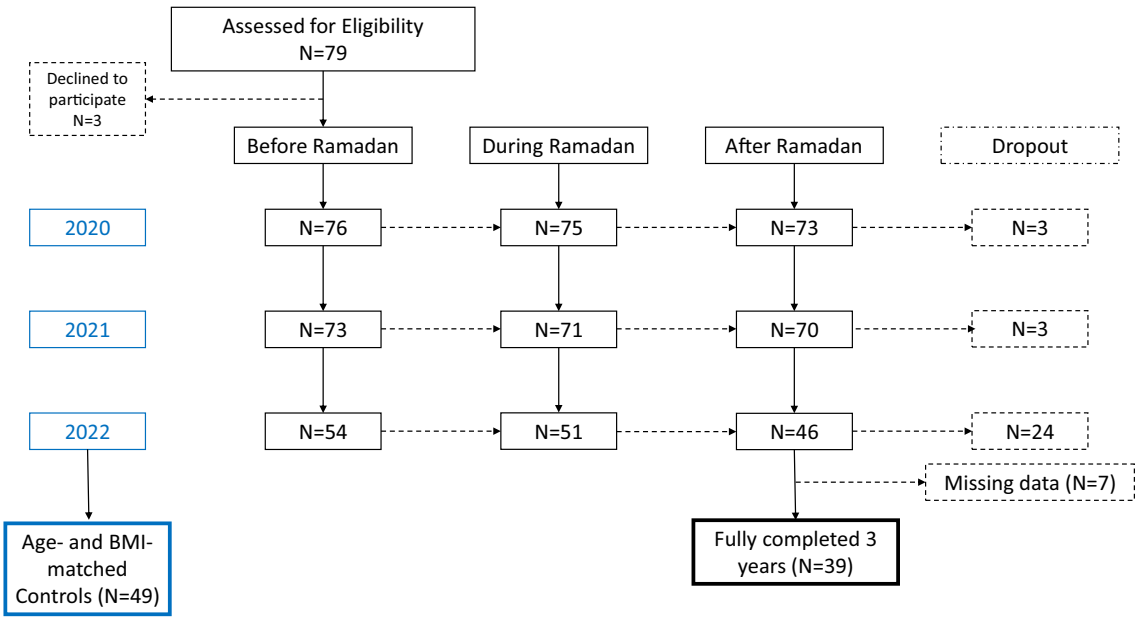

FIGURE 1
Flowchart of participants.

(see Figure 1). It is worthy to note that the sudden drop of participants in the last year (2022) was primarily due to the limited availability of sensors, and not necessarily due to dropouts. The study was approved by the institutional review board College of Medicine, King Saud University Riyadh, Saudi Arabia (Ref 21/0439/IRB).

2.2 Glycemic measures using flash glucose monitoring

All participants used the first generation Freestyle Libre 14-day System (Abbott Diabetes Care, Alameda, CA) which is a factory-calibrated flash glucose monitoring sensor with a mean absolute relative difference of 11.4% (25). In this study, we utilized CGM glycemic metrics with their widely accepted definitions including average sensor glucose, glucose management indicator (GMI), time in range (TIR) (i.e. glucose: 70–180 mg/dl), time above range level 1 (TAR-1) (i.e. glucose: 181–250 mg/dl), TAR level 2 (TAR-2) (i.e. glucose: >250 mg/dL), time below range level 1 (TBR-1) (i.e. glucose: 54–70 mg/dl), TBR level 2 (TBR-2) (i.e. glucose: <54 mg/dl), glycemic variability, as measured by the coefficient of variation (CV), sensor active time, and the number of daily scans, which were obtained from the Freestyle LibreView platform (26).

2.3 Assessment of glycemic outcomes

The following CGM metrics were evaluated in all the study participants at 4 weeks pre-, 4 weeks during, and 4 weeks post-Ramadan: Average sensor glucose, GMI, TIR, TAR-1, TAR-2, TBR-1, TBR-2, sensor active time, and the number of daily scans. Average sensor glucose throughout the day during each of the study periods, pre-, during, and post-Ramadan, were analyzed by looking at the patterns and trends of sensor average glucose changes during the day hours and postprandial hours. For controls (individuals without diabetes), similar CGM metrics were only reported during the month of Ramadan. For this group, sensor average glucose throughout the day during Ramadan of 2022 was analyzed by looking at the patterns and trends of sensor average glucose changes during the day hours and postprandial hours. Moreover, laboratory HbA1c within the normal range were required from this group at enrollment.

2.4 Statistical analysis

Analyses were conducted using SPSS software version 28.0 Descriptive statistics, such as mean ± SD for continuous variables and frequencies and percentages for categorical variables, were reported. Repeated measures analysis of variance (ANOVA) was used to compare differences over time. The estimated marginal means and estimated differences from the model were reported as the estimated mean with a 95% confidence interval (CI). All reported p-values are two-tailed, and $p<0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

The study included a total of 39 T1D participants out of 79 who started in 2020, with 20 (51%) of them being female. The mean age

of the participants was 28.1 ± 8.4 years, and the mean duration of diabetes was 11.5 ± 8.9 years. Additionally, 10 (26%) participants were on insulin pump, and 22 (56%) had medical record documentation that they received Ramadan-focused education since 2020. Complete CGM data for all three years of the study was available for all participants. Table 1 presents the baseline characteristics and number of participants with T1D. Moreover, the study included 49 age-and BMI-matched participants (34 females or 69%). The participants had a mean age of 27.4 ± 8.0 years. The mean BMI was 24.0 ± 4.5 kg/m^2, and the mean HbA1c was 5.2 ± 0.3%.

3.2 Glycemic indices overtime in people with T1D

A comparison of glycemic metrics across the three years of the study period is shown in Table 2. Insulin doses received before and during Ramadan were highest in 2022 as compared to previous years (p-values 0.02 and 0.01, respectively). There were no significant differences observed over time in terms of Aspart use, daily and suggested insulin doses before and during Ramadan, ICR as well as pre- and post-BMI over time. In terms of glycemic indices, mean HbA1c was worst before Ramadan of 2020 (8.7 ± 1.9) for all participants, which was significantly higher than successive years (p=0.02). On the other hand, mean glucose variability was highest in 2022 as compared to previous years (p=0.01). The rest of the glycemic indices were comparable over time (Table 2).

Figure 2 shows the mean glycemic pattern of T1D participants before, during and after Ramadan for each year while Figure 3 shows the pooled data for 3 successive Ramadan. In both figures, 2 abnormal glucose spikes have been consistently observed overtime and in pooled analysis, all of which occurred during the period of Ramadan. In the pooled data (Figure 3) before Ramadan, the two-hour time bucket with the lowest average glucose level was observed at 10:00-12:00 h (159.2 ± 26.2), whereas the highest average glucose level was observed at 22:00-24:00 h [176.1 ± 27.4] (not mentioned in table). During Ramadan, the lowest average glucose level was observed at 14:00-16:00 h (157.8 mg/dL ± 25.8). The highest average glucose levels were observed after Iftar at 20:00-22:00 h (185.5 ± 27.6), and after Suhoor at 4:00-6:00 h (191.1 ± 27.1). Glycemic trends during Ramadan showed that the highest glucose spike occurred after Iftar, between 16:00-18:00 h and 18:00-20:00 h, with a difference value of 15.5 mg/dL and after Suhoor (between 0:00-2:00h to 4:00-6:00), with a difference of 18.8mg/dL (not shown tables). Glycemic values before, during and after Ramadan for each successive year are presented in Supplementary Table S1.

With respect to other CGM indices, no significant differences were seen in TAR1, TAR2, TIR, TBR1 and TBR2 before, during and after Ramadan of the years 2020 and 2021. In 2022 however, TAR1 and TAR2 were observed to be significantly higher during Ramadan than before and after (p-values 0.008 and 0.007, respectively). In parallel, TIR and TBR1 were also significantly lower during the Ramadan as compared to before and after (p-values 0.001 and <0.001, respectively), with TBR2 during Ramadan also being significantly lower only during before Ramadan of 2022 (p=0.02) (Supplementary Table S2). Pooled time indices showed no significant differences. Time in ranges over time were presented as Figure 3.

TABLE 1 Characteristics of participants.

Parameter	T1D	Controls
N (M/F)	39	49
Male/Female	19/20	15/34
Age (years)	28.1 ± 8.4	27.4 ± 8.0
Type 1 Diabetes duration (years)	11.5 ± 8.9	–
Body mass index (kg/m^2)	25.3 ± 4.4	24.0 ± 4.5
HbA1c (%)	8.7 ± 1.9	5.2 ± 0.3
Insulin Delivery Modality		
Pump	10 (26)	–
Multiple Daily Injections	29 (74)	–

Data presented as frequencies (%) and mean ± standard deviation.

3.3 Impact of Ramadan fasting on glycemic indices in individuals without diabetes during Ramadan

Figure 4 shows the glycemic indices of control participants during the Ramadan of 2022. The lowest average glucose level was observed at 16:00-18:00 h (85.8 ± 7.8). The highest average glucose level after Iftar was observed at 18:00-20:00 h (103.6 ± 10.7), and the glucose change between the lowest and highest average glucose was 17.8 mg/dL (16.1 to 19.5) (Supplementary Table S1).

4 Discussion

In this real-world study, findings revealed a tendency for patients and/or their physicians to adopt an overprotective behavior to avoid hypoglycemia during Ramadan leading to an increase in time spent above the recommended glycemic range and a decrease in time spent within and below the target range. The pattern of glucose fluctuation (timing of the lowest and highest average glucose level) seen on FGM confirms the significant changes in lifestyle taking place during Ramadan in Saudi Arabia. The pattern of glucose levels during Ramadan, as observed in the present study, is consistent with previous studies (27–29). The average glucose levels slightly rise two hours before the Iftar meal, which could be attributed to the waning effect of the basal insulin dose and/or the increase in stress hormones due to prolonged fasting. Following the Iftar meal, there was a sharp increase in average glucose levels with a pronounced excursion that lasted for four hours, followed by a moderate decrease. The same pattern was observed after the Suhoor meal, with an increase in average glucose levels to the same extent and duration as the Iftar meal. During

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TABLE 2 Changes in glycemic indices overtime.

	2020	2021	2022	P-value
N	39			
Received Ramadan Education	22 (56)	26 (67)	16 (41)	
Insulin dose before Ramadan	26.4 ± 12.4	25.1 ± 9.3	28.4 ± 10.3	0.02
Suggested Insulin dose in Ramadan	23.1 ± 12.3	23.0 ± 9.3	25.8 ± 8.7	0.01
Aspart dose before Ramadan	27.4 ± 10.0	30.4 ± 9.4	35.6 ± 17.0	0.16
Suggested Aspart dose in Ramadan	19.6 ± 6.5	19.4 ± 7.6	29.6 ± 9.1	0.16
Daily total insulin dose before Ramadan	55.3 ± 19.1	58.5 ± 17.0	70.7 ± 23.9	0.32
Suggested total insulin dose for Ramadan	41.6 ± 14.2	43.4 ± 17.7	62.4 ± 16.5	0.38
Pre-BMI (kg/m^2)	25.3 ± 4.4	25.6 ± 4.3	26.6 ± 4.8	0.09
Post-BMI (kg/m^2)	25.2 ± 4.5	25.5 ± 4.3	27.9 ± 4.6	0.33
HbA1c Before Ramadan	8.7 ± 1.9	7.8 ± 1.0	7.5 ± 0.9	0.02
Active Time Sensor	82.0 ± 21.0	81.9 ± 22.9	88.6 ± 12.1	0.08
Glucose (mg/dl)	167.2 ± 39.9	165.9 ± 30.8	166.9 ± 30.6	0.94
GMI	7.2 ± 0.8	7.2 ± 0.7	7.3 ± 0.7	0.89
GMI mmol	55.7 ± 8.9	55.7 ± 7.3	56.3 ± 7.9	0.92
Glucose Variability	37.9 ± 7.6	36.7 ± 6.5	39.2 ± 6.2	0.01
Daily Scans	10.7 ± 6.8	10.2 ± 7.3	10.8 ± 8.7	0.84

Data presented as mean ± standard deviation; p-value significant at <0.05.

fasting, glucose levels gradually declined, reaching their lowest average at 14:00-16:00 h. This pattern was significantly different from that observed outside of Ramadan in several ways. First, the post-meal amplitude of glucose excursion during Ramadan was much higher. Second, there were higher fluctuations during Ramadan, and the difference between the lowest and highest average glucose was significantly greater. Third, contrary to the general assumption that TBR would be higher during Ramadan due to prolonged fasting (18), TBR was lower in this study in only the last year of the 3-year observation (2022). Consequently, GMI and

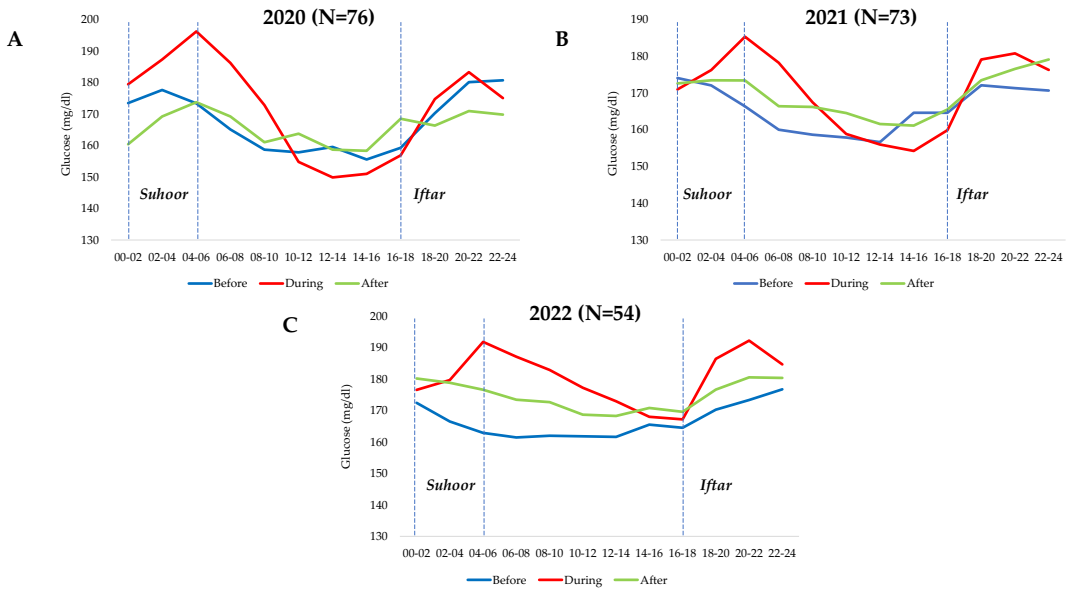

FIGURE 2
Average 24-hour glycemic pattern of T1D participants before, during and after Ramadan (2020-2022). **(A)** 2020. **(B)** 2021. **(C)** 2022.

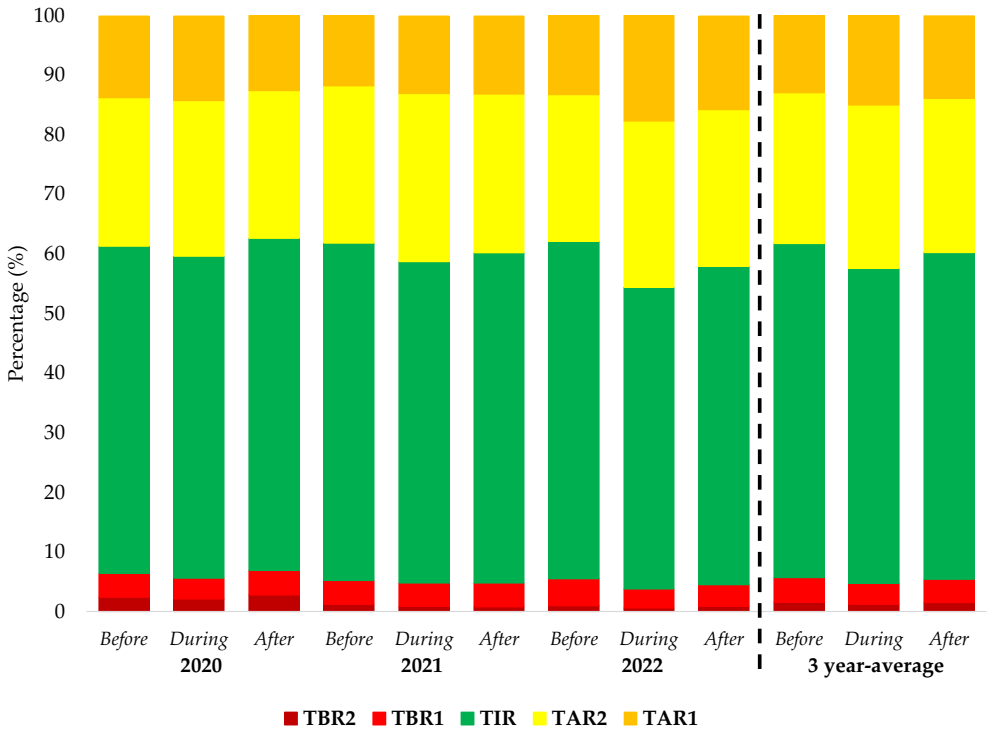

FIGURE 3
Time in ranges before, during and after Ramadan of the years 2020, 2021 and 2022.

TAR were all significantly higher during Ramadan than before and after of the same year.

The FGM data during Ramadan in healthy participants without T1D showed a similar pattern of glucose changes, albeit within normal, suggesting that the changes we are observing in patients with T1D is not only due to miscalculated/mismatched insulin requirement but also to the largely underestimated effect of cultural habits and diet taking place during Ramadan. As expected, not only the amplitude of postprandial hyperglycemia is greater in T1D patients, but also the duration of hyperglycemia which subjects patients with T1D to complications. The postprandial glucose excursion during Ramadan in healthy participants is similar to that reported in a previous study without Ramadan fasting (30). In patients with T1D, not only insulin management is important but also the effect of cultural diet on their glucose should be taken in consideration.

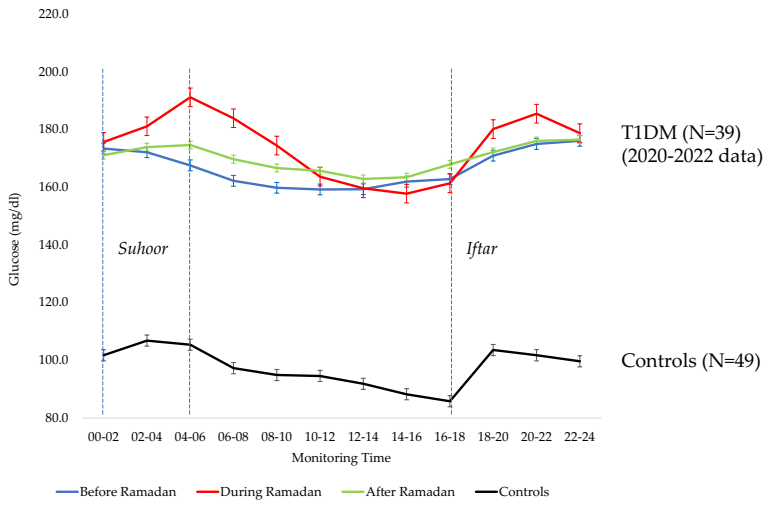

FIGURE 4
Pooled glycemic metrics of T1D participants before, during and after Ramadan versus Controls.

In the present study, the glucose trends during Ramadan exhibit the lowest average glucose levels between 14:00 to 16:00 h, which may be the time associated with a higher risk of hypoglycemia. Therefore, patients should be educated to frequently check their glucose levels during this time period, avoid strenuous physical activity, and respond immediately to any symptoms of hypoglycemia (27). It is highly important to bear in mind that patients living with T1D are prone to hypoglycemia unawareness. Previous research has found that patients with T1D spent an average of 1.39 hours per fasting day in hypoglycemia, with 8% of cases documented as severe yet asymptomatic (18).

The DAR-MENA T1D showed similar rates of confirmed and symptomatic hypoglycemia during Ramadan compared to before Ramadan (4). Other studies reported no increase in the time spent in hypoglycemia during Ramadan, but found no significant differences in terms of average glucose, GMI, or TAR (31–36). The present study found similar observations in the first 2 years of the study, with the final year showing significant differences in all time range indices. It is worthy to note that compared to years 2020 and 2021, most pandemic restrictions were lifted in Saudi Arabia from March 2022, a month before Ramadan, with all restrictions removed in June 2022. This complete removal of preventive measures that led to heightened social mobility, full opening of the fast food and dining industry, as well as outdoor recreational activities may have partially, but not fully explain, the differences observed in that year.

The present study results showed better glycemic control when compared to a previous study of glycemia during Ramadan in patients with T1D, which reported a TIR of 42%, TAR of 48%, and TBR of 10%. The study reached the same conclusion that there is a higher rate of hyperglycemia than hypoglycemia related to Ramadan fasting (27).

The unique addition of the current study is providing insight to what happens after Ramada. Although the values of the glycemic metrics improved during the month after Ramadan, they did not return to pre-Ramadan levels completely. Hence, fasting during Ramadan was associated with at least two months of disturbance in glycemic control, which highlights the need to reshape the conventional perception of Ramadan fasting as a risk factor for only hypoglycemia. More efforts and attention should made for the period after Ramadan not to prolong the duration spent in hyperglycemia.

The present study has some limitations. First, because this was a real-world study, we could not control or adjust dietary intake diversity among participants, which may have influenced our results. Second, we did not collect data on the timing and reasons for fast-breaking or hypoglycemic events, as well as insulin types used and day-to-day dose adjustments made. Finally, not all patients had complete data for the entire three-year period, but we reported estimated means and confidence intervals to illustrate the effect size of changes.

Despite these limitations, our study provides valuable insights into glucose profiles before, during, and after Ramadan fasting in adult patients with T1D using FGM. One of the strengths of this study is that it focused solely on patients with type 1 diabetes, young adults in particular, filling the needed data for an understudied population in T1D. Additionally, this study included patients' data for three years, providing a more robust dataset.

The results of the current study have important clinical implications for patients with T1D and medical professionals alike since robust data for adults with T1D are scarce. Diabetes education and management strategies should be individualized and include diet and cultural habits for Ramadan, insulin dosing and timing tailored for Ramadan to help T1D patients safely fast, and counseling on after-Ramadan management.

5 Conclusions

This real-world observational study provided a unique and comprehensive look at the glycemic changes among young adults with T1D who attempted to fast before, during, and after Ramadan in SA, and revealed how Ramadan fasting can be associated with deterioration in glycemic control that starts during Ramadan and extends for at least one month afterwards. Attention should be directed to hyperglycemia during Ramadan and the month after Ramadan as well. A particular attention should be made to the underestimation of insulin requirements for Iftar and Suhoor meals and this may vary based on risk profile and history of overindulgent behavior during Ramadan.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by institutional review board, College of Medicine, King Saud University Riyadh, Saudi Arabia (Ref 21/0439/IRB). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AMA: Conceptualization, Data curation, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EA: Data curation, Investigation, Resources, Writing – review & editing. AA: Data curation, Writing – review & editing. MA: Resources, Writing – review & editing. MA-S: Methodology, Resources, Visualization, Writing – review & editing.

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Conflict of interest

AMA has served on an advisory panel for Medtronic, Novonordisk, Eli Lilly, Vital Air, and Sanofi and has received honoraria for speaking from AstraZeneca, Eli Lilly, Medtronic, Novo Nordisk, and Sanof. AMA has received research support from AstraZeneca and Novo Nordisk and provided medical consultations to Eli Lilly. MA has served on an advisory panel for Eli Lilly, and Algorithm and has received honoraria for speaking from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, and Sanofi. MA has received research support from Novo Nordisk. MA-S: has served on an advisory panel for Medtronic, Insulet, Abbott, VitalAire, Sanofi and has received honoraria for speaking from Abbott, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, VitalAire; and provided medical consultations to Eli Lilly.

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Supplementary material

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References

1. Ahmed SH, Chowdhury TA, Hussain S, Syed A, Karamat A, Helmy A, et al. Ramadan and diabetes: A narrative review and practice update. *Diabetes Ther*. (2020) 11:2477–520. doi: 10.1007/s13300-020-00886-y

2. Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. *Am J Clin Nutr*. (2015) 102:464–70. doi: 10.3945/ajcn.115.109553

3. Santos HO, Macedo RCO. Impact of intermittent fasting on the lipid profile: Assessment associated with diet and weight loss. *Clin Nutr ESPEN*. (2018) 24:14–21. doi: 10.1016/j.clnesp.2018.01.002

4. Al Awadi FF, Echtay A, Al Arouj M, Sabir Ali S, Shehadeh N, Al Shaikh A, et al. Patterns of diabetes care among people with type 1 diabetes during ramadan: an international prospective study (DAR-MENA T1DM). *Adv Ther*. (2020) 37:1550–63. doi: 10.1007/s12325-020-01267-4

5. Eltoum N, Washi S, Al Twaim A. Dietary habits and nutrients intake of diabetic adolescents during Ramadan fasting. *Int J Food Nutr Public Health*. (2014) 7:25–40. doi: 10.47556/J.IJFNPH.7.1.2014.3

6. Alamoudi R, Alsubaiee M, Alqarni A, Aljaser S, Saleh Y, Salam A, et al. Attitudes and habits of patients with type 1 diabetes during fasting Ramadan. *J Clin Transl Endocrinol*. (2018) 14:1–4. doi: 10.1016/j.jcte.2018.09.001

7. Bahijri S, Borai A, Ajabnoor G, Abdul Khaliq A, AlQassas I, Al-Shehri D, et al. Relative metabolic stability, but disrupted circadian cortisol secretion during the fasting month of Ramadan. *PloS One*. (2013) 8:e60917. doi: 10.1371/journal.pone.0060917

8. Ajabnoor GM, Bahijri S, Borai A, Abdulkhaliq AA, Al-Aama JY, Chrousos GP. Health impact of fasting in Saudi Arabia during Ramadan: association with disturbed circadian rhythm and metabolic and sleeping patterns. *PloS One*. (2014) 9:e96500. doi: 10.1371/journal.pone.0096500

9. Deeb A, Elbarbary N, Smart CE, Beshyah SA, Habeb A, Kalra S, et al. ISPAD Clinical Practice Consensus Guidelines: Fasting during Ramadan by young people with diabetes. *Pediatr Diabetes*. (2020) 21:5–17. doi: 10.1111/pedi.12920

10. Hassanein M, Afandi B, Yakoob Ahmedani M, Mohammad Alamoudi R, Alawadi F, Bajaj HS, et al. Diabetes and ramadan: practical guidelines 2021. *Diabetes Res Clin Pract*. (2022) 185:109185. doi: 10.1016/j.diabres.2021.109185

11. Alshahrani M, Alraddadi A. Incidence of diabetic ketoacidosis during Ramadan compared with non-fasting months in King Saud Medical City, Riyadh, Saudi Arabia. *J Family Med Prim Care*. (2022) 11:3905. doi: 10.4103/jfmpc.jfmpc_2004_21

12. Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care*. (2004) 27:2306–11. doi: 10.2337/diacare.27.10.2306

13. Loh HH, Lim LL, Loh HS, Yee A. Safety of Ramadan fasting in young patients with type 1 diabetes: A systematic review and meta-analysis. *J Diabetes Investig*. (2019) 10:1490–501. doi: 10.1111/jdi.13054

14. Hassanein M, Alamoudi RM, Kallash MA, Aljohani NJ, Alfadhlu EM, Tony LE, et al. Ramadan fasting in people with type 1 diabetes during COVID-19 pandemic: The DaR Global survey. *Diabetes Res Clin Pract*. (2021) 172:108626. doi: 10.1016/j.diabres.2020.108626

15. Ibrahim M, Davies MJ, Ahmad E, Annabi FA, Eckel RH, Ba-Essa EM, et al. Recommendations for management of diabetes during Ramadan: update 2020, applying the principles of the ADA/EASD consensus. *BMJ Open Diabetes Res Care*. (2020) 8. doi: 10.1136/bmjdrc-2020-001248

16. Muammar T, Fojas EGF, Helal R, Lessan N. Ramadan fasting among older children and adolescents with type 1 diabetes mellitus: A real-world study from the UAE. *Front Nutr*. (2022) 9:786678. doi: 10.3389/fnut.2022.786678

17. Al-Khawari M, Al-Ruwayeh A, Al-Doub K, Allgrove J. Adolescents on basal-bolus insulin can fast during Ramadan. *Pediatr Diabetes*. (2010) 11:96–100. doi: 10.1111/j.1399-5448.2009.00544.x

18. Afandi B, Kaplan W, Majd L, Roubi S. Rate, Timing, and Severity of hypoglycemia in adolescents with Type 1 diabetes during ramadan fasting: A study with freestyle libre flash glucose monitoring system. *Ibnosina J Med Biomed Sci*. (2018) 10:9–11. doi: 10.4103/ijmbs.ijmbs_73_17

19. Alguwaihes AM, Alotaibi N, Alotaibi M, Masry N, Safarini S. The use of miniMed780G system is associated with stable glycemic control in people with type 1 diabetes before, during, and after ramadan: an observational study. *J Diabetes Res*. (2025) 2025:4144787. doi: 10.1155/jdr/4144787.19

20. Tootee A, Larijani B. Ramadan fasting and diabetes, latest evidence and technological advancements: 2021 update. *J Diabetes Metab Disord*. (2021) 20:1003–9. doi: 10.1007/s40200-021-00804-4

21. Al-Ozairi E, El Samad A, Al Kandari J, Aldibbiat AM. Intermittent fasting could be safely achieved in people with type 1 diabetes undergoing structured education and advanced glucose monitoring. *Front Endocrinol (Lausanne)*. (2019) 10:849. doi: 10.3389/fendo.2019.00849

22. Hassanein M, Abdelgadir E, Bashier A, Rashid F, Saeed MA, Khalifa A. The role of optimum diabetes care in form of Ramadan focused diabetes education, flash glucose monitoring system and pre-Ramadan dose adjustments in the safety of Ramadan fasting in high risk patients with diabetes. *Diabetes Res Clin Pract*. (2019) 150:288–95. doi: 10.1016/j.diabres.2018.12.013

23. Al-Agha AE, Kafi SE, Zain Aldeen AM, Khadwardi RH. Flash glucose monitoring system may benefit children and adolescents with type 1 diabetes during fasting at Ramadan. *Saudi Med J*. (2017) 38:366–71. doi: 10.15537/smj.2017.4.18750

24. Alamoudi R, Alsubaiee M, Alqarni A, Saleh Y, Aljaser S, Salam A, et al. Comparison of insulin pump therapy and multiple daily injections insulin regimen

in patients with type 1 diabetes during ramadan fasting. *Diabetes Technol Ther*. (2017) 19:349–54. doi: 10.1089/dia.2016.0418

25. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technol Ther*. (2015) 17:787–94. doi: 10.1089/dia.2014.0378

26. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. (2019) 42:1593–603. doi: 10.2337/dci19-0028

27. Alfadhli EM. Higher rate of hyperglycemia than hypoglycemia during Ramadan fasting in patients with uncontrolled type 1 diabetes: Insight from continuous glucose monitoring system. *Saudi Pharm J*. (2018) 26:965–9. doi: 10.1016/j.jsps.2018.05.006

28. Teoh ST, Hussain S, Hong JYH. Glycaemic changes among children and adolescents with type 1 diabetes mellitus before and during ramadan fasting using continuous glucose monitoring. *J ASEAN Fed Endocr Soc*. (2022) 37:49–59. doi: 10.15605/jafes.037.02.08

29. Lessan N, Hannoun Z, Hasan H, Barakat MT. Glucose excursions and glycaemic control during Ramadan fasting in diabetic patients: Insights from continuous glucose monitoring (CGM). *Diabetes Metab*. (2015) 41:28–36. doi: 10.1016/j.diabet.2014.11.004

30. González-Rodríguez M, Pazos-Couselo M, García-López JM, Rodríguez-Segade S, Rodríguez-García J, Túñez-Bastida C, et al. Postprandial glycemic response in a non-diabetic adult population: the effect of nutrients is different between men and women. *Nutr Metab (Lond)*. (2019) 16:46. doi: 10.1186/s12986-019-0368-1

31. Kaplan W, Afandi B, Al Hassani N, Hadi S, Zoubeidi T. Comparison of continuous glucose monitoring in adolescents with type 1 diabetes: Ramadan versus non-Ramadan. *Diabetes Res Clin Pract*. (2017) 134:178–82. doi: 10.1016/j.diabres.2017.10.010

32. Al Hayek AA, Robert AA, Al Dawish MA. Evaluating the impact of Ramadan fasting on ambulatory glucose profile among patients with type 1 diabetes using Flash Glucose Monitoring System: A comparative study. *Diabetes Metab Syndr*. (2022) 16:102472. doi: 10.1016/j.dsx.2022.102472

33. Alawadi F, Alsaeed M, Bachet F, Bashier A, Abdulla K, Abuelkheir S. Impact of provision of optimum diabetes care on the safety of fasting in Ramadan in adult and adolescent patients with type 1 diabetes mellitus. *Diabetes Res Clin Pract*. (2020) 169:108466. doi: 10.1016/j.diabres.2020.108466

34. Yan J, Zhou Y, Zheng X, Zheng M, Lu J, Luo S. Effects of intermittently scanned continuous glucose monitoring in adult type 1 diabetes patients with suboptimal glycaemic control: A multi-centre randomized controlled trial. *Diabetes Metab Res Rev*. (2023) 39:e3614. doi: 10.1002/dmrr.3614

35. Marcovecchio ML. Complications of acute and chronic hyperglycemia. *US Endocrinol*. (2017) 13:17. doi: 10.17925/USE.2017.13.01.17

36. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. *Am J Med Sci*. (2016) 351:201–11. doi: 10.1016/j.amjms.2015.11.011

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EDITED BY
Ma Jianhua,
Nanjing Medical University, China

REVIEWED BY
Bianca Leca,
University Hospitals Coventry and Warwickshire NHS Trust, United Kingdom
Paul Nsiah,
University of Cape Coast, Ghana

*CORRESPONDENCE
Dan Liu
liudandan303114@163.com
Na Li
Lina721124@163.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work

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To assess the impact of individualized strategy and continuous glucose monitoring on glycemic control and mental health in pregnant women with diabetes

Mengxue Liu[1†], Tong Chen[1†], Shuai Wang[2], Na Li[1*‡] and Dan Liu[1*‡]

[1]Department of Endocrinology and Metabolism, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China, [2]Department of Health Services and Management, Dalian Neusoft University of Information, Dalian, Liaoning, China

Objective: To assess the impact of individualized strategy and continuous glucose monitoring (CGM) on glycemic control and mental health(anxiety, depression, pregnancy-related anxiety and diabetes specific quality of life during pregnancy) in patients with diabetes in pregnancy (DIP).

Methods: In this study, 80 pregnant women diagnosed with type 2 diabetes mellitus (T2DM) complicated with pregnancy or gestational diabetes mellitus (GDM) were enrolled. Participants were randomly assigned to either CGM group or self-monitoring of blood glucose (SMBG) group. Blood glucose was regularly monitored for 14 days to guide and adjust hypoglycemic treatment (lifestyle or hypoglycemic agents) of the patients in time. Baseline characteristics were collected after enrollment. Self-rating anxiety scale (SAS), self-rating depression scale (SDS), pregnancy-related anxiety questionnaire (PAQ), diabetes specific quality of life scale (DSQL) were used to evaluate the anxiety, depression, pregnancy-related anxiety and quality of life. Glycemic parameters and scale scores were collected before and after individualized strategy.

Results: FBG and 2hPBG significantly decreased post-intervention in both groups (P<0.001). In the CGM group, the scores of SAS (39.59 ± 7.10 vs 37.15 ± 6.28), PAQ (24.15 ± 6.45 vs 22.59 ± 5.65) and DSQL (47.44 ± 9.01 vs 43.20 ± 9.00) after individualized strategy were significantly lower than those before individualized strategy ($P<0.05$). The SAS scale scores and PAQ scale scores were positively correlated with blood glucose levels ($P<0.05$).

Conclusion: The individualized strategy encompasses an insulin titration protocol guided by CGM, coupled with structured lifestyle modifications that address dietary patterns, physical activity and more, combined with short-term glucose monitoring can exert a positive effect on glycemic improvement in the

short term and meet the requirements of glycemic control in pregnancy, which has important clinical significance. The combined use of individualized strategy and CGM improves glycemic control and may have protective effects on psychological well-being.

Clinical Trial Registration: https://www.chictr.org.cn, identifier ChiCTR2200060719.

KEYWORDS

diabetes in pregnancy, gestational diabetes mellitus, continuous glucose monitoring, anxiety, depression, quality of life

1 Introduction

Diabetes in pregnancy (DIP) is a condition characterized by abnormal glucose metabolism during pregnancy, which includes both pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM). PGDM denotes that a pregnant woman was diagnosed with diabetes mellitus (DM) prior to pregnancy. GDM is defined as the first occurrence or detection of impaired glucose tolerance during pregnancy. The prevalence of DIP in the U.S. ranges from 6.0% to 9.0%, with GDM constituting 90.0% of cases (1). According to the diagnostic criteria of the International Diabetes and pregnancy Research Group (IADPSG), a study in China in 2013 showed that the incidence of GDM was 17.5% (2). Hyperglycemia in pregnancy can lead to a variety of adverse pregnancy outcomes, such as macrosomia, shoulder dystocia, stillbirth, neonatal respiratory distress syndrome, neonatal hypoglycemia, etc. (1, 3), and is associated with an increased risk of maternal and fetal long-term complications such as type 2 diabetes mellitus (T2DM) (4, 5).

Pregnant women are more likely to be affected psychologically due to changes in physical and social psychological state, with anxiety and depression being more common (6). The global prevalence of prenatal anxiety and depression varied from 6.0% to 57.0% and 8.5% to 44.4%, respectively (7–9). On the other hand, anxiety and depression can cause hypothalamus-pituitary-adrenal dysfunction and then cause abnormal glucose tolerance or insulin resistance (IR) through sympathetic nerve activation (10, 11). GDM is more prone to anxiety and depression (12, 13). Hyperglycemia during pregnancy contributes to anxiety and depression through multiple mechanisms, including lack of awareness of the disease, worry about the health problems of future generations, stress response and so on. Anxiety can affect the mother's emotional balance and fetal development, and it can also lead to low birth weight, premature birth and other adverse pregnancy outcomes (14–16). Therefore, it is crucial to pay attention to the psychological status of patients with DIP. It is worth mentioning that PGDM and GDM are significantly different in terms of clinical manifestations, treatment measures and clinical prognosis. In addition, the characteristics of glucose metabolism are different at different gestational ages, so it is necessary to analyze the difference of mental health status between them.

Blood glucose monitoring plays an indispensable role in the blood glucose strategy of patients with DM. The most widely used blood glucose monitoring method in a clinic is self-monitoring of blood glucose (SMBG), based on capillary glucose testing. Whereas SMBG can only reflect the instantaneous capillary blood glucose level at that time but cannot recall the overall trend and fluctuation of blood glucose, and some patients cannot stand the pain of fingertip blood glucose monitoring and the economic burden related to blood glucose monitoring. Continuous glucose monitoring (CGM) is a new blood glucose monitoring method that has been used in clinics in recent years, which reflects the whole-day blood glucose level and blood glucose fluctuation by measuring the blood glucose concentration in tissue fluid. The daily glucose trend chart, glucose fluctuation trend and other related data can be obtained to encourage both doctors and patients to evaluate the blood glucose more thoroughly and assist in adjusting of the hypoglycemic treatment to achieve the targets of blood glucose control. CGM and SMBG were used in this study to better understand the blood glucose level of patients with DIP, provide reference for individualized strategy and evaluate the efficacy, anxiety, depression and quality of life of individualized strategy combined with blood glucose monitoring.

2 Materials and methods

2.1 Participants and study design

This study enrolled 80 pregnant women who met the diagnosis of DIP (including PGDM and GDM) in the outpatient clinic of the First Affiliated Hospital of Dalian Medical University from June 2022 to July 2022 (Figure 1). This study was approved by the ethics committee of the First Affiliated Hospital of Dalian Medical University. The inclusion criteria included: 1) 18–45 years old; 2) singleton pregnancy; 3) no previous history of mental illness; 4) voluntary use of CGM or SMBG, who have good understanding and

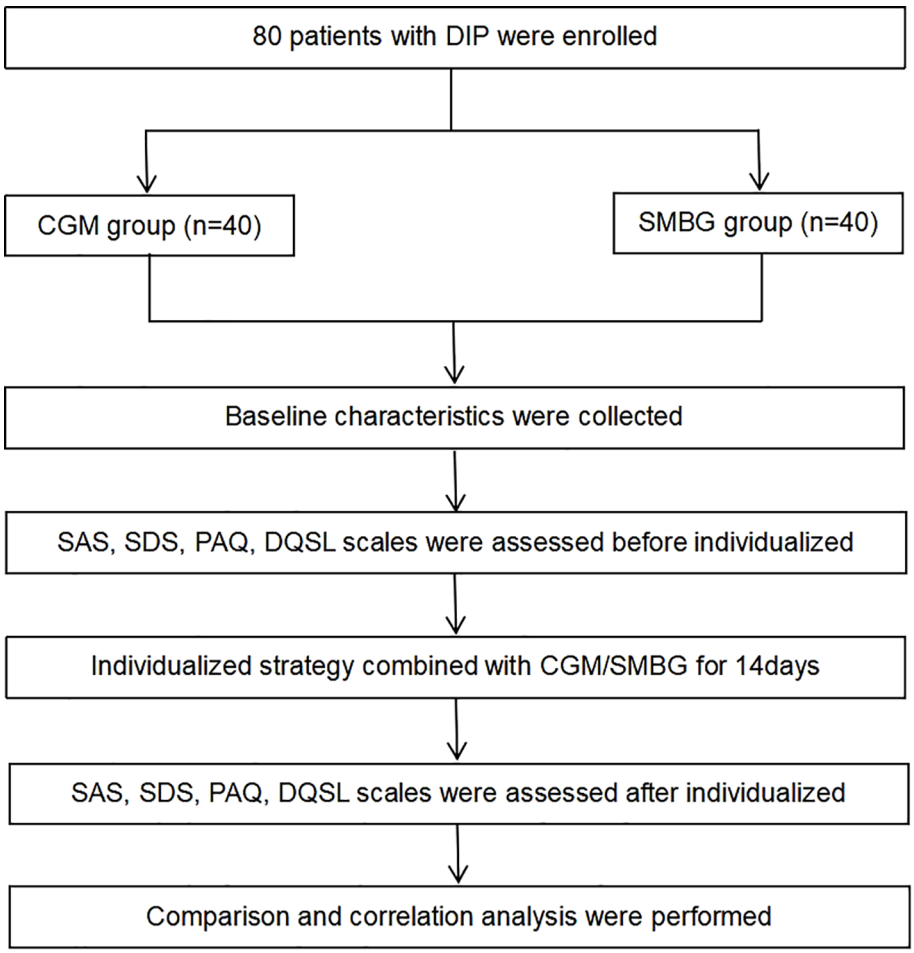

FIGURE 1
Flowchart of material and methods.

communication skills. The exclusion criteria included: 1) anxiety or depression diagnosed before pregnancy; 2) recently experienced severe stress events, complicated with infection, heart failure, kidney insufficiency, or other serious complications; 3) poor compliance. The participants were randomly divided into the CGM group and the SMBG group. The pregnant women in the CGM group used FreeStyle Libre (Abbott Diabetes Care Ltd) to dynamically monitor their blood glucose for 14 consecutive days. By using the scanner, patients can obtain an immediate glucose value, nearly 8 hours of glucose data and a glucose change trend, and the system can automatically save an average of blood glucose every 15 minutes, recording a total of 96 blood glucose values per day, and finally obtaining a 14-day glucose trend chart. The pregnant women in the SMBG group, on the other hand, utilized a home blood glucose meter to track changes in peripheral blood glucose, and recorded fasting and 2-hour postprandial blood glucose for 14 days.

Fasting blood glucose (FBG) and 2 hours postprandial blood glucose (2hPBG) were recorded using CGM or SMBG. To minimize bias, all participants received standardized instructions from the same endocrinologist. Patients sent recorded blood glucose and daily exercise and diet information to the endocrinologist every 1 to 3 days through the WeChat app (application) during the study period. The endocrinologist then gives patients timely lifestyle advice, including diet, exercise instructions and insulin dose adjustments, based on blood glucose control targets during pregnancy. According to American Diabetes Association, blood glucose targets during pregnancy: FPG or pre-prandial blood glucose ≤ 5.3mmol/L, 1h post-prandial ≤ 7.8mmol/L, 2h post-prandial ≤ 6.7mmol/L.

2.2 Hypoglycemic treatment guidance

The dietary principle is the principle of low-glycemic load. Maintain weight gain within a reasonable range through a low-glycemic load diet to avoid hypoglycemia, hyperglycemia and diabetic ketosis. Individual nutrient intake includes: 1) protein: ensure adequate intake of high-quality protein, such as eggs, skim milk, fish and shrimp, beef, mutton, pork, tofu, skinless poultry, etc., which are conducive to the growth and development of the fetus. 2) fat: a high-fat diet is challenging to digest and increases the burden of insulin; limit the intake of high-fat and high-cholesterol foods. 3) carbohydrates: regular and quantitative, preferably buckwheat, oats, whole wheat, brown rice and other hypoglycemic effects; eat less stuffing, noodles, porridge, etc.; avoid desserts, sweets, drinks and

excessive intake of fruits rich in monosaccharides. 4) inorganic salts and vitamins: vegetables, nuts, fruits and lean meat are recommended as sources of vitamins, calcium, magnesium and trace elements.

Reasonable diet combined with personalized exercise can effectively reduce blood glucose. Before instructing pregnant women to exercise, first exclude patients with contraindications for exercise during pregnancy, such as heart disease, threatened premature delivery, low progesterone, threatened abortion, fetal intrauterine growth restriction, placental abnormalities, cervical dysfunction, etc. The recommended way of exercise is aerobic exercise such as walking, exercise time in half an hour to one hour after meal, the duration of activity is about 20–30 minutes, to avoid hypoglycemia caused by excessive activity.

After lifestyle interventions, patients with DIP who still failed to achieve blood glucose control targets were treated with insulin based on lifestyle modification. The first choice for basic insulin is hypodermic injection of insulin detemir before bedtime. Insulin glargine or intermediate-acting insulin (Novolin N) should be used instead in the event of an allergic reaction. In addition, the preferred pre-prandial short-acting insulin is insulin aspart subcutaneously injected 5 minutes before meals, and insulin lispro should be used if allergic. During pregnancy, the insulin dose was modified based on blood glucose control targets.

2.3 Baseline characteristics

Baseline characteristics of DIP patients were collected, including age, gestational age, prepregnancy body mass index (BMI), pregnancy type (primipara or multipara), history of abortion, family history of diabetes, glycosylated hemoglobin (HbA1c), hypoglycemic regimen.

TABLE 1 Comparison of baseline characteristics between the CGM group and the SMBG group.

Parameters	CGM group (n=40)	SMBG group (n=40)	*P* value
Age (years)	33.38 ± 3.89	32.43 ± 4.36	0.307
Gestation age (weeks)	22.25 ± 8.47	20.95 ± 8.31	0.490
Prepregnancy BMI (kg/m^2)	27.12 ± 4.51	27.32 ± 5.13	0.854
Type [n (%)]			0.648
PGDM	17 (42.50%)	15 (34.50%)	
GDM	23 (57.50%)	25 (62.50%)	
Pregnancy type [n (%)]			0.152
Primipara	24 (60.0%)	30 (75.0%)	
Multipara	16 (40.0%)	10 (25.0%)	
History of abortion [n (%)]	20 (50.0%)	18 (45.0%)	0.654
Family history of diabetes [n (%)]	25 (62.5%)	26 (65.0%)	0.816
FBG (mmol/L)	6.81 ± 2.38	6.74 ± 1.49	0.867
2hPBG (mmol/L)	9.89 ± 3.11	8.86 ± 2.76	0.121
HbA1c (%)	6.55 ± 1.80	6.27 ± 1.26	0.431
Hypoglycemic treatment			0.491
Insulin	26 (65.0%)	23 (57.5%)	
Lifestyle	14 (35.0%)	17 (42.5%)	

Data are presented as mean ± SD or number (%).
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; BMI, body mass index; PGDM, pregestational diabetes mellitus; GDM, gestational diabetes mellitus; FBG, fasting blood glucose; 2hPBG, 2 hours postprandial blood glucose; HbA1c, glycosylated hemoglobin.

2.4 Assessment of glycemic control

FBG and 2hPBG were collected from patients with DIP before and after individualized strategy. CGM-measurements and glycemic variability parameters included time in range (TIR), time above range (TAR), time below range (TBR), average glucose (AG), estimated HbA1c, standard deviation of blood glucose (SDBG), mean amplitude of glucose excursions (MAGE) and coefficient of variation (CV) were also collected.

2.5 Assessment of anxiety, depression and quality of life

Anxiety, depression, pregnancy-related anxiety and diabetes specific quality of life scales were assessed in patients before and after individualized strategy respectively. In this study, patients' anxiety, depression and quality of life were evaluated by applying self-rating anxiety scale (SAS) (17), self-rating depression scale (SDS) (18), pregnancy-related anxiety questionnaire (PAQ) (19), diabetes specific quality of life scale (DSQL) (20). These scales have been transformed into Chinese versions and are widely used in China with good reliability and validity (21–23). There are 20 items in SAS and SDS, respectively. SAS standard points ≥ 50 were anxiety and SDS standard points ≥ 53 were depression, according to Chinese norms. The PAQ scale, compiled by Chinese scholars, has a total of 13 items, including three aspects of pregnant women worried about fetal health, delivery process and self-care. The total score ≥ 24 was pregnancy-related anxiety, with a higher total score indicating a higher level of pregnancy-related anxiety. The DSQL scale evaluated the quality of life of patients with DIP from physical, psychological, social relations and treatment dimensions, a total of 27 items, with a lower total score indicating a higher level of quality of life.

2.6 Statistical analysis

Statistical analysis was performed using Statistical Package of Social Sciences (SPSS) 26. Data normality was evaluated before using parametric tests. Data with normal distribution were

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TABLE 2 Comparison of baseline characteristics between PGDM and GDM patients.

Parameters	PGDM (n=32)	GDM (n=48)	*P* value
Age (years)	32.28 ± 3.95	33.31 ± 4.24	0.227
Gestation age (weeks)	18.50 ± 7.73	23.67 ± 8.20*	0.006
Prepregnancy BMI (kg/m^2)	28.11 ± 4.55	26.62 ± 4.92	0.175
Pregnancy type [n (%)]			0.436
Primipara	20 (62.50%)	34 (70.83%)	
Multipara	12 (37.50%)	14 (29.17%)	
History of abortion [n (%)]	16 (50%)	22 (45.83%)	0.715
Family history of diabetes [n (%)]	27 (84.375%)	24 (50%)*	0.002
FBG (mmol/L)	7.92 ± 2.31	6.01 ± 1.23*	<0.001
2hPBG (mmol/L)	10.82 ± 3.35	8.42 ± 2.26*	<0.001
HbA1c (%)	7.40 ± 1.89	5.75 ± 0.76*	<0.001
Hypoglycemic treatment			<0.001
Insulin	31 (96.875%)	18 (37.5%)	
Lifestyle	1 (3.125%)	30 (62.5%)	

Data are presented as mean ± SD or number (%).
PGDM, pregestational diabetes mellitus; GDM, gestational diabetes mellitus; BMI, body mass index; FBG, fasting blood glucose; 2hPBG, 2 hours postprandial blood glucose; HbA1c, glycosylated hemoglobin. *P value<0.05 was considered significant.

expressed by mean ± standard deviation ($\bar{x}$± s), and data with non-normal distribution were expressed by medians, and count data were expressed by [n (%)]. T-test was used for continuous variables to compare the difference between the two groups, chi-square test and Fisher's exact test were used for categorical variables to compare the difference between the two groups. Within-group differences were compared with paired t-test. Pearson correlation analysis was used to analyze the correlation between scale score and other data. All the tests were performed by two-sided test, with a P value<0.05 as the statistical difference evaluation standard.

3 Results

A total of 80 eligible women completed study, including 40 women in the CGM group and 40 women in the SMBG group. Among the 80 participants, 32 had PGDM (all with T2DM), while 48 had GDM.

3.1 Baseline characteristics

3.1.1 Comparison of baseline characteristics between the CGM group and the SMBG group

The mean age of DIP patients was 32.90 ± 4.13 years old, and there were 27 (33.75%) patients ≥ 35 years old. The mean pre-pregnancy BMI of the patients was 27.22 ± 4.80kg/m^2, and there were 49 patients (61.3%) with pre-pregnancy BMI>25kg/m^2. There were 51 patients (63.8%) with a family history of diabetes. There were no statistically significant differences between the CGM group and the SMBG group in age, gestational age, pre-pregnancy BMI, type of DIP, pregnancy type, proportion of abortion history, proportion of family history of diabetes, FBG, 2hPBG, hypoglycemic treatment and HbA1c (P>0.05) (Table 1). There was no difference in baseline between the two groups, indicating comparability of data between the two groups.

3.1.2 Comparison of baseline characteristics between PGDM patients and GDM patients

There were 32 patients (40.0%) with PGDM and 48 patients (60.0%) with GDM. There were no significant differences in age, pre-pregnancy BMI, pregnancy type and proportion of abortion history between PGDM patients and GDM patients (P>0.05). The gestational age of PGDM patients was smaller than that of GDM patients, while the proportion of family history of diabetes, FBG, 2hPBG, HbA1c and the proportion of insulin used were significantly higher than those of GDM patients, with statistical significance (P<0.05) (Table 2). This indicated that PGDM presents more significant blood glucose fluctuations and more severe hyperglycemia compared to GDM.

3.2 Glycemic parameters

3.2.1 Comparison of glycemic parameters before and after individualized strategy

FBG and 2hPBG of the two groups after individualized strategy by different blood glucose monitoring methods (CGM or SMBG) were significantly lower than those before individualized strategy (P<0.001) (Table 3), indicating that individualized strategy exerted a positive effect on glycemic improvement in the short term.

3.2.2 Glycemic variability parameters

Compared with GDM patients, glycemic variability parameters calculated by CGM included TAR, AG, estimated HbA1c, SDBG and MAGE of PGDM patients were significantly higher and TBR

TABLE 3 Comparison of FBG and 2hPBG before and after individualized strategy.

Blood Glucose	CGM group (n=40)			SMBG group (n=40)		
	before	after	*P* value	before	after	*P* value
FBG (mmol/L)	6.81 ± 2.38	5.39 ± 0.63*	<0.001	6.74 ± 1.49	5.71 ± 1.04*	<0.001
2hPBG (mmol/L)	9.89 ± 3.11	6.87 ± 0.96*	<0.001	8.86 ± 2.76	6.95 ± 1.23*	<0.001

Data are presented as mean ± SD.
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; FBG, fasting blood glucose; 2hPBG, 2 hours postprandial blood glucose; *P value<0.05 was considered significant.

TABLE 4 Comparison of glycemic variability parameters between PGDM patients and GDM patients in the CGM group.

Glycemic variability parameters	PGDM (n=17)	GDM (n=23)	*P* value
TIR (%)	87.00 (69.00, 92.00)	89.00 (71.00, 93.00)	0.741
TAR (%)	7.00 (4.00, 29.00)	1.00 (0, 9.00)*	0.013
TBR (%)	1.00 (0, 4.00)	9.00 (3.00, 27.00)*	0.006
AG (mmol/L)	6.71 ± 1.43	5.37 ± 0.76*	0.001
estimated HbA1c (%)	5.85 ± 0.92	5.01 ± 0.49*	0.002
SDBG (mmol/L)	1.61 ± 0.20	1.21 ± 0.29*	0.003
MAGE (mmol/L)	3.02 ± 0.15	2.44 ± 0.67*	0.003
CV (%)	24.90 ± 3.43	22.78 ± 3.14	0.158

Data are presented as mean ± SD, mean (interquartile range).
PGDM, pregestational diabetes mellitus; GDM, gestational diabetes mellitus; TIR, time in range; TAR, time above range; TBR, time below range; AG, average glucose; HbA1c, glycosylated hemoglobin; SDBG, standard deviation of blood glucose; MAGE, mean amplitude of glucose excursions; CV, coefficient of variation. *P value<0.05 was considered significant.

was significantly lower (P<0.05); there were no significant difference in TIR and CV between PGDM and GDM (P>0.05) (Table 4). PGDM exhibited higher blood glucose than GDM, with significant blood glucose fluctuation and more severe hyperglycemia.

3.3 The score of SAS, SDS, PAQ and DSQL scales

Among patients with DIP, 7.5% had anxiety, 17.5% had depression, 5.0% had anxiety and depression, and 45.0% had pregnancy-related anxiety.

3.3.1 Comparison of scale scores between the CGM group and the SMBG group before and after individualized strategy

Before and after individualized strategy, there were no significant differences in SAS, SDS, PAQ and DSQL scores between the CGM group and the SMBG group (P>0.05) (Table 5).

In the CGM group, the scores of SAS, PAQ and DSQL after individualized strategy were significantly lower than those before individualized strategy (P<0.05) (Figure 2); the SDS score were lower than that before individualized strategy, but the difference was not statistically significant (P>0.05) (Table 6). In the SMBG group, the scores of PAQ after individualized strategy were significantly lower than that before individualized strategy (P<0.05); the scores of SAS, SDS and DSQL scales after individualized strategy had no statistical difference compared with those before individualized strategy (P>0.05) (Table 6), indicating that CGM is superior to SMBG in improving anxiety and quality of life.

3.3.2 Comparison of scale scores between PGDM patients and GDM patients before and after individualized strategy

In the CGM or SMBG group, there were no statistical differences in SAS, SDS, PAQ and DSQL scale scores between PGDM patients and GDM patients in before and after individualized strategy (P>0.05) (Table 7).

In the CGM group, the scores of SAS, SDS, PAQ and DSQL in PGDM patients after individualized strategy were not significantly different from those before individualized strategy, while the scores of SAS and DSQL in GDM patients were significantly lower than those before individualized strategy (P<0.05) (Figure 3); the scores of SDS and PAQ were lower than those before individualized strategy, but there was no significant difference (P>0.05) (Table 8).

In the SMBG group, the scores of PAQ in patients with PGDM were significantly lower than those before individualized strategy (P<0.05), while the scores of SAS, SDS, PAQ and DSQL in GDM patients after individualized strategy were not significantly different from those before individualized strategy (P>0.05) (Table 8). In

TABLE 5 Comparison of inter-group scale scores between the CGM group and the SMBG group before and after individualized strategy.

Scale	Before			After		
	CGM group (n=40)	SMBG group (n=40)	*P* value	CGM group (n=40)	SMBG group (n=40)	*P* value
SAS	39.75 ± 7.11	39.28 ± 8.54	0.788	37.35 ± 6.22	39.03 ± 7.90	0.296
SDS	43.45 ± 11.21	44.55 ± 8.92	0.629	42.20 ± 9.82	45.20 ± 8.66	0.151
PAQ	24.28 ± 6.48	24.18 ± 5.75	0.942	22.73 ± 5.65	22.30 ± 5.74	0.739
DSQL	47.73 ± 8.93	45.45 ± 7.57	0.223	43.40 ± 9.02	44.83 ± 9.43	0.492

Data are presented as mean ± SD.
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; SAS, self-rating anxiety scale; SDS, self-rating depression scale; PAQ, pregnancy-related anxiety questionnaire; DSQL, diabetes specific quality of life scale..

addition, the degree of blood glucose elevation and fluctuation in patients with GDM is less than that in PGDM.

3.3.3 Correlation analysis between SAS, SDS, PAQ, DSQL scale scores and other parameters before individualized strategy

The score of SAS scale was positively correlated with HbA1c, FBG in patients with DIP, and the score of PAQ scale was positively correlated with FBG, indicating that patients with higher blood glucose level tend to have higher anxiety scores. The scores of SDS and DSQL were not significantly correlated with gestational age, age, HbA1c, FBG, 2hPBG and prepregnancy BMI (Table 9).

4 Discussion

Due to physiological factors such as hormone fluctuations, as well as increased sensitivity to family, social and other factors, pregnant women are prone to adverse emotions such as anxiety and depression. In this study, the probabilities of anxiety, depression, anxiety and depression in DIP patients were 7.5%, 17.5% and 5.0%, respectively, which was similar to the probabilities of anxiety, depression, anxiety and depression in early pregnancy found by Tang et al. (7.7%, 10.5%, 4.8%) (24). But Other studies have shown that about 12.0% of pregnant women experience depression and up to 22.0% experience anxiety in late pregnancy (25, 26). Studies reported that the prevalence of maternal depression and anxiety was as high as 27.0% and 24.0%, respectively (27, 28). We emphasize the importance of routine psychological assessment and intervention in the management of DIP.

In addition, Compared with normal GDM pregnant women, GDM pregnant women with anxiety and depression are more prone to adverse outcomes in terms of blood glucose, delivery mode and maternal and infant outcomes during pregnancy (13). A study showed a significant increase in anxiety and depression symptoms among pregnant women during the COVID-19 pandemic, which could have long-term effects on their offspring (59). According to statistics, the probability of depression in patients with DM was 3 times higher than that in healthy people, and the incidence of depression in patients with T1DM was as high as 12.0% (29). Patients with T2DM had a high incidence of anxiety and depression, and patients with adverse emotions had poor compliance, which was detrimental to disease management (60).

Studies have shown that anxiety and depression may be risk factors for GDM (30, 31), but there is no unified conclusion on the correlation between anxiety, depression and GDM at present. Anxiety and depression can lead to hormone imbalance in the body, which seriously affects pregnancy outcomes and blood glucose control of GDM. In addition to physiological factors, psychological factors such as anxiety and depression are also important causes of GDM (32, 33). Anxiety and depression can lead to chronic hypothalamic-pituitary-adrenal (HPA) axis hyperfunction, resulting in increased cortisol release and IR (34), increasing the risk of GDM in pregnant women. At the same time, GDM increases the susceptibility of pregnant women to anxiety and depression, and the likelihood of prenatal or postpartum depression is 2–4 times higher than that without GDM (35–38), which may be related to their awareness of poor blood glucose control and pregnancy complications and adverse pregnancy outcomes (39, 40). However, some studies suggest that anxiety and depression do not increase the probability of GDM in pregnant women (41–44), nor does GDM increase the risk of prenatal or postpartum depression (45, 46).

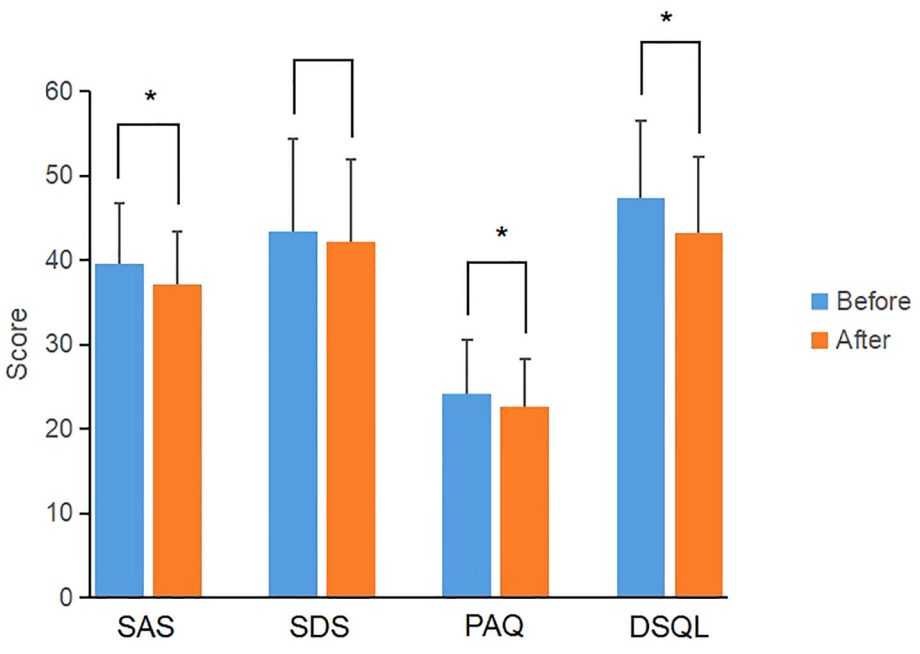

FIGURE 2
Comparison of scale scores of the CGM group before and after individualized strategy. *P value<0.05 was considered significant.

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TABLE 6 Comparison of within-group scale scores between the CGM group and the SMBG group before and after individualized strategy.

Scale	CGM group (n=40)			SMBG group (n=40)		
	Before	After	*P* value	Before	After	*P* value
SAS	39.75 ± 7.11	37.35 ± 6.22*	0.003	39.28 ± 8.54	39.03 ± 7.90	0.802
SDS	43.45 ± 11.21	42.20 ± 9.82	0.157	44.55 ± 8.92	45.20 ± 8.66	0.558
PAQ	24.28 ± 6.48	22.73 ± 5.65*	0.020	24.18 ± 5.75	22.30 ± 5.74*	0.022
DSQL	47.73 ± 8.93	43.40 ± 9.02*	<0.001	45.45 ± 7.57	44.83 ± 9.43	0.575

Data are presented as mean ± SD.
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; SAS, self-rating anxiety scale; SDS, self-rating depression scale; PAQ, pregnancy-related anxiety questionnaire; DSQL, diabetes specific quality of life scale. *P value<0.05 was considered significant.

With the implementation of the three-child policy, it is urgent to pay attention to the psychological status of pregnancy and avoid adverse pregnancy outcomes under the guidance of demand. In addition, pregnancy-related anxiety refers to a kind of anxiety and painful emotional experience caused by pregnancy to pregnant women (47). Feng et al. found that pregnancy-related anxiety accounted for 59.1% of GDM patients (48). In this study, the incidence of pregnancy-related anxiety in patients with DIP was 45%, which was higher than that of 31% of normal pregnant women at mid-pregnancy and 29% at late-pregnancy (49).

One study identified three sources of anxiety and depression in patients with GDM: the diagnosis of GDM and perceptions of high-risk pregnancies; glycemic control during dietary intervention; the fear of maternal and infant complications. The study identified the fear of pregnancy complications as the most significant source of stress for GDM. In addition, pregnant women who received insulin treatment were more stressed than those who received dietary intervention only (45). This is consistent with the recent study of Lee et al. (50), which exacerbates patients' concerns about treatment because of the relationship between insulin and hypoglycemia events. Horsch et al. believed that anxiety was related to FBG (3), which was consistent with the findings of this study that anxiety was positively correlated with HbA1c, FBG, and pregnancy-related anxiety was positively correlated with FBG and 2hPBG. Through the analysis of the three aspects of worrying about fetal health, delivery process and self-care contained in the PAQ scale, it was found that the pregnancy-related anxiety of DIP patients mainly originated from worrying about the physical health of the fetus.

Clinical application of CGM can reduce the risk of hypoglycemia and hyperglycemia as well as blood glucose variability and improve the quality of life of patients (51). CGM contributed to a significant improvement in diabetes specific quality of life in T1DM adults (52). However, one study suggested that the use of well-standardized, structured SMBG could reduce depressive symptoms in a large number of moderately depressed or distressed T2DM patients with poor glycemic control (53). There is no study to observe the effects of individualized strategy through CGM on anxiety, depression and quality of life in DIP patients. This study found that scores on the SAS and PAQ scales were positively correlated with blood glucose parameters, suggesting that effective glycemic control may play a crucial role in mitigating psychological distress in DIP patients. Additionally, this study verified that an individualized strategy combined with CGM can improve anxiety, pregnancy-related anxiety, and diabetes-specific quality of life. The reasons considered are mainly that CGM is easy to monitor blood glucose in patients, which can quickly and painlessly obtain blood glucose value, predict the trend of glucose change, timely detect occult blood glucose abnormalities (hyperglycemia or

TABLE 7 Comparison of inter-group scale scores between PGDM patients and GDM patients before and after individualized strategy.

Scale	CGM group (n=40)						SMBG group (n=40)					
	Before			After			Before			After		
	PGDM (n=17)	GDM (n=23)	*P* value	PGDM (n=17)	GDM (n=23)	*P* value	PGDM (n=15)	GDM (n=25)	*P* value	PGDM (n=15)	GDM (n=25)	*P* value
SAS	39.82 ± 7.11	39.70 ± 7.26	0.956	38.12 ± 6.85	36.78 ± 5.82	0.510	41.87 ± 8.04	37.72 ± 8.61	0.139	40.27 ± 7.05	38.28 ± 8.42	0.449
SDS	43.53 ± 12.48	43.39 ± 10.46	0.970	43.88 ± 11.16	40.96 ± 8.76	0.359	45.87 ± 9.52	43.76 ± 8.64	0.477	44.00 ± 8.86	45.92 ± 8.64	0.504
PAQ	24.41 ± 7.05	24.17 ± 6.18	0.910	22.82 ± 5.50	22.65 ± 5.87	0.926	24.73 ± 6.45	23.84 ± 5.40	0.640	21.73 ± 5.80	22.64 ± 5.80	0.635
DSQL	47.35 ± 8.98	48.00 ± 9.09	0.824	44.29 ± 11.41	42.74 ± 6.96	0.596	47.33 ± 7.04	44.32 ± 7.79	0.228	46.47 ± 10.47	43.84 ± 8.82	0.401

Data are presented as mean ± SD.
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; PGDM, pregestational diabetes mellitus; GDM, gestational diabetes mellitus; SAS, self-rating anxiety scale; SDS, self-rating depression scale; PAQ, pregnancy-related anxiety questionnaire; DSQL, diabetes specific quality of life scale.

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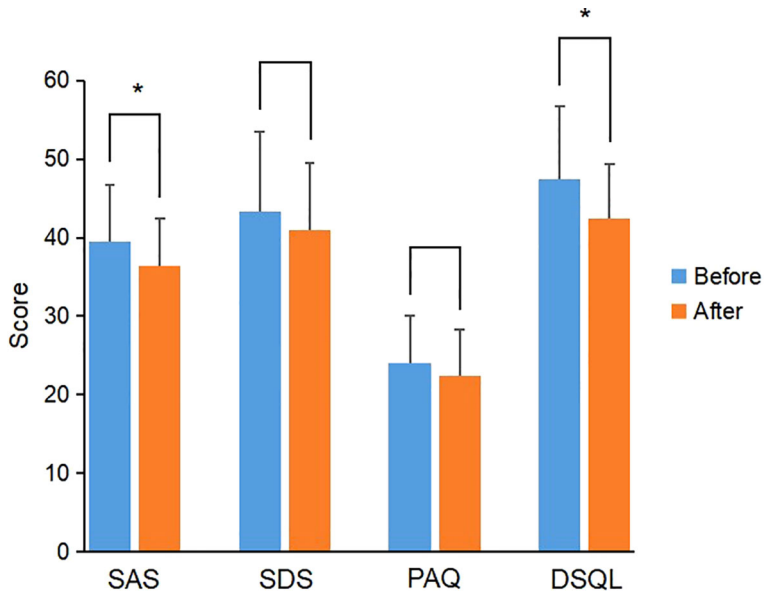

FIGURE 3
Comparison of scale scores of GDM patients before and after individualized strategy in the CGM group. *P value<0.05 was considered significant..

hypoglycemia), adjust lifestyle and hypoglycemic treatment and optimize treatment effects. Therefore, CGM shows advantages over traditional SMBG in improving anxiety and quality of life. However, no significant improvement in depression was found for the following reasons: the results of this study did not find any correlation between SDS scale scores and blood glucose parameters; there were many factors considering the causes of depression in DIP; the duration of monitoring blood glucose by CGM was short (14 days), and the effect of improving patients' depression was limited in a short time. In addition, we also found that individualized strategy with CGM played a more significant role in improving anxiety and quality of life in patients with GDM compared with patients with PGDM, probably because most patients with PGDM had taken lifestyle intervention combined with oral drugs or insulin before pregnancy and had a certain degree of understanding of the disease. In addition, the degree of blood glucose elevation and blood glucose fluctuation in GDM patients was less than that in PGDM, so that the results may be better after individualized strategy. Hence, they had a higher acceptance of the disease than patients with GDM and could accept hypoglycemic treatment psychologically, which can improve the anxiety and quality of life of patients to some extent. However, we did not find any improvement in pregnancy-related anxiety in GDM patients in the CGM group, and we hypothesized that this improvement might be supported by larger sample size. Besides, we also indicated improvement in pregnancy-related anxiety in PGDM patients in the SMBG group, as PAQ scores correlated with glycemic parameters. In summary, blood glucose levels are related

TABLE 8 Comparison of within-group scale scores between PGDM patients and GDM patients before and after individualized strategy.

Scale	CGM group (n=40)						SMBG group (n=40)					
	PGDM (n=17)			GDM (n=23)			PGDM (n=15)			GDM (n=25)		
	Before	After	*P*	Before	After	*P*	Before	After	*P*	Before	After	*P*
SAS	39.82 ± 7.11	38.12 ± 6.85	0.176	39.70 ± 7.26	36.78 ± 5.82*	0.008	41.87 ± 8.04	40.27 ± 7.05	0.251	37.72 ± 8.61	38.28 ± 8.42	0.685
SDS	43.53 ± 12.48	43.88 ± 11.16	0.747	43.39 ± 10.46	40.96 ± 8.76	0.063	45.87 ± 9.52	44.00 ± 8.86	0.243	43.76 ± 8.64	45.92 ± 8.64	0.147
PAQ	24.41 ± 7.05	22.82 ± 5.50	0.158	24.17 ± 6.18	22.65 ± 5.87	0.069	24.73 ± 6.45	21.73 ± 5.80*	0.028	23.84 ± 5.40	22.64 ± 5.80	0.251
DSQL	47.35 ± 8.98	44.29 ± 11.41	0.144	48.00 ± 9.09	42.74 ± 6.96*	<0.001	47.33 ± 7.04	46.47 ± 10.47	0.715	44.32 ± 7.79	43.84 ± 8.82	0.674

Data are presented as mean ± SD.
CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; PGDM, pregestational diabetes mellitus; GDM, gestational diabetes mellitus; SAS, self-rating anxiety scale; SDS, self-rating depression scale; PAQ, pregnancy-related anxiety questionnaire; DSQL, diabetes specific quality of life scale. * *P* value<0.05 was considered significant.

TABLE 9 Correlation analysis between scale scores and other parameters.

Parameters	SAS		SDS		PAQ		DSQL	
	r	*P* value	r	*P* value	r	*P* value	r	*P* value
Gestation age	-0.212	0.059	0.006	0.961	-0.173	0.125	-0.106	0.350
Age	0.057	0.614	0.048	0.674	-0.083	0.464	-0.010	0.932
HbA1c	0.239	0.033	0.093	0.413	0.187	0.097	0.178	0.115
FBG	0.246	0.028	0.151	0.182	0.231	0.039	0.172	0.127
2hPBG	0.146	0.197	0.074	0.512	0.203	0.070	0.180	0.110
Prepregnancy BMI	-0.082	0.468	0.035	0.757	0.094	0.406	-0.020	0.861

SAS, self-rating anxiety scale; SDS, self-rating depression scale; PAQ, pregnancy-related anxiety questionnaire; DSQL, diabetes specific quality of life scale. HbA1c, glycosylated hemoglobin; FBG, fasting blood glucose; 2hPBG, 2 hours postprandial blood glucose; BMI, body mass index. *P* value<0.05 was considered significant.

to the mental health of pregnant women, and good control of blood glucose can improve mental status.

The potential mechanisms underlying the effect of CGM on mental health could be expanded through hypothetical pathways. The proposed dual-pathway model integrates "physiological feedback", "psychosocial mediators" and bidirectional feedback loops. 1) Physiological Feedback a. Glycemic Stability and Stress Response: The hypothalamic-pituitary-adrenal axis is thought to play a vital role in glucose homeostasis and diabetes. Stress reduces glucose and total cholesterol (TC) levels in female rats under the same behavioral tests (54). While human studies exhibit lower TIR with higher serum cortisol (P< 0.001) in T2DM patients (55). b. Neurotransmitter Modulation: CGM-driven hypoglycemia prevention preserves tryptophan availability for serotonin synthesis. Compared with the TIR-H (TIR > 70%) group, the TIR-L (TIR< 50%) group exhibits lower serum levels of 5-hydroxy-L-tryptophan and more (56). c. Psychosocial Mediators: CGM can enhance precise monitoring of diabetes symptoms associated with dysglycemia, diabetes-related complications, and mental conditions within the realm of precision medicine (57). 2) Pychosocial Mediators a. Self-Efficacy and Cognitive Liberation: CGM empowers patients to predict glycemic trends, reducing "decision fatigue" from frequent self-monitoring and enhancing confidence in "daily activities". b. Anxiety Mitigation: Animals that have previously experienced recurrent hypoglycemia exhibit an increase in norepinephrine levels in the amygdala during hypoglycemia, accompanied by increased anxiety (58). 3) Bidirectional Feedback Loops: Emerging models suggest a virtuous cycle, CGM-enhanced glycemic control → improved mood → better adherence → sustained glycemic benefits (Figure 4).

The innovation of this study is that it is the first to explore the positive significance of individualized strategy combined with CGM on anxiety and diabetes specific quality of life in patients with DIP. The limitations of this study include: 1) This trial was a single-center study; 2) The sample size of this study was small, and the analysis of risk factors for anxiety and depression is limited; 3) The duration of the study was only 14 days to meet the clinical requirements of smoothly lowering blood glucose in the short term, and the improvement of blood glucose and partial psychological status was observed. However, if the individualized strategy combined with CGM was longer, its effect on the improvement of psychological status and quality of life might be more obvious, and its clinical significance on the physical and mental regulation of patients would be more significant.

Although this study has confirmed the short-term psychological benefits of CGM, several unresolved issues persist. Future research should focus on the following areas.

1) Extend the follow-up period to assess the persistence of psychological benefits. Future research should include long-term longitudinal studies (such as/e.g. 1–3 years postpartum) to determine whether the psychological protective effects of CGM are enduring and to explore whether they reduce the risk of postpartum depression; 2) Explore the Impact of CGM on Different Subgroups of DIG. It may impose a different psychological burden compared to GDM and PGDM (such as/e.g, T1DM or T2DM). Future studies should stratify the analysis of the differential impact of CGM on these subgroups and assess whether

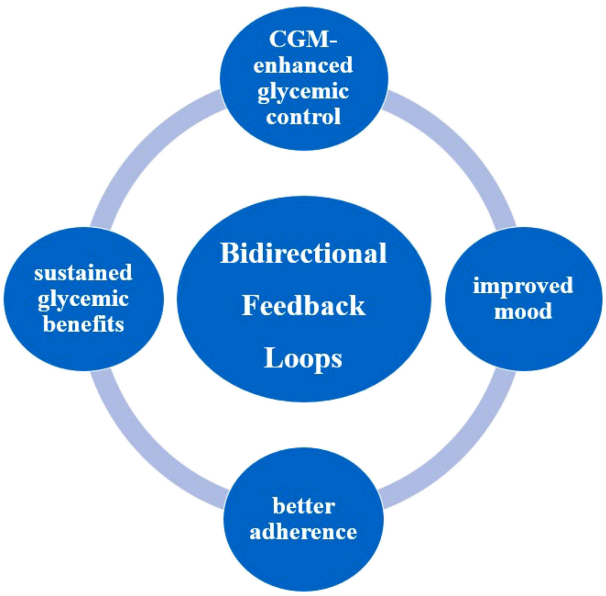

FIGURE 4
Bidirectional feedback loops.

psychological support strategy need to be tailored accordingly; 3) Combine digital psychological intervention and optimize the clinical utility of CGM. Real-time data can be integrated with mobile health technology, such as developing an AI-based emotional warning system that provides immediate psychological counseling when abnormal blood glucose fluctuations are detected, or recommends relaxation training, thus forming a "blood glucose-psychological" dual management model; 4) Focus on the clinical significance of CGM beyond blood glucose control. Currently, the assessment of CGM primarily concentrates on metabolic indicators, including HbA1c, TIR, etc. Moving forward, a broader range of psychosocial indicators should be incorporated to comprehensively evaluate the clinical value of CGM.

In conclusion, the combination of individualized strategy and regular blood glucose monitoring (CGM or SMBG) enables DIP patients to achieve better blood glucose control in the short term and avoid the effects of hyperglycemia on the fetus and pregnant woman. As for the management of gestational diabetes, it is crucial to pay attention to the patient's mental health along with the patient's blood glucose level. CGM appears to be an effective tool for glycemic control and may contribute to improved mental health in DIP patients. A multidisciplinary approach, integrating endocrinology, obstetrics, and mental health support, is essential for optimizing DIP management. We call on researchers, clinicians, and policymakers to jointly advance the following actions. Incorporate mental health indicators into the clinical assessment system of CGM; Conduct multicenter, long-term follow-up studies to clarify the impact of CGM on postpartum mental states; Develop intelligent management tools that integrate CGM with psychological support to optimize the overall care model for DIP.

5 Conclusion

The individualized strategy combined with short-term glucose monitoring can positively impact glycemic improvement in the short term and meet the requirements of glycemic control in pregnancy, which has important clinical significance. The combined use of individualized strategy and CGM improves glycemic control and may have protective effects on psychological well-being.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was given by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University with the following reference number: PJ-KS-KY-2022-113(X). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ML: Investigation, Methodology, Writing – review & editing. TC: Investigation, Methodology, Writing – original draft. SW: Supervision, Writing – review & editing. DL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NL: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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References

1. Practice bulletin no. 180: gestational diabetes mellitus. *Obstet Gynecol.* (2017) 130: e17–37. doi: 10.1097/AOG.0000000000002159

2. Zhu WW, Yang HX, Wei YM, Yan J, Wang ZL, Li XL, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. *Diabetes Care.* (2013) 36:586–90. doi: 10.2337/dc12-1157

3. Rosenstein MG, Cheng YW, Snowden JM, Nicholson JM, Doss AE, Caughey AB. The risk of stillbirth and infant death stratified by gestational age in women with gestational diabetes. *Am J Obstet Gynecol.* (2012) 206:309 e1–7. doi: 10.1016/j.ajog.2012.01.014

4. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes.* (2000) 49:2208–11. doi: 10.2337/diabetes.49.12.2208

5. England LJ, Dietz PM, Njoroge T, Callaghan WM, Bruce C, Buus RM, et al. Preventing type 2 diabetes: public health implications for women with a history of gestational diabetes mellitus. *Am J Obstet Gynecol.* (2009) 200:365 e1–8. doi: 10.1016/j.ajog.2008.06.031

6. Consonni EB, Calderon IM, Consonni M, De Conti MH, Prevedel TTs, Rudge MV. A multidisciplinary program of preparation for childbirth and motherhood: maternal anxiety and perinatal outcomes. *Reprod Health.* (2010) 29:728. doi: 10.1186/1742-4755-7-28

7. Biaggi A, Conroy S, Pawlby S, Pariante CM. Identifying the women at risk of antenatal anxiety and depression: A systematic review. *J Affect Disord.* (2016) 191:62–77. doi: 10.1016/j.jad.2015.11.014

8. Coll CVN, da Silveira MF, Bassani DG, Netsi E, Wehrmeister FC, Barros FC, et al. Antenatal depressive symptoms among pregnant women: Evidence from a Southern Brazilian population-based cohort study. *J Affect Disord.* (2017) 209:140–6. doi: 10.1016/j.jad.2016.11.031

9. Ghaffar R, Iqbal Q, Khalid A, Saleem F, Hassali MA, Baloch NS, et al. Frequency and predictors of anxiety and depression among pregnant women attending tertiary healthcare institutes of Quetta City, Pakistan. *BMC Womens Health.* (2017) 17:51. doi: 10.1186/s12905-017-0411-1

10. Ravid E, Salzer L, Arnon L, Eisner M, Wiznitzer A, Weller A, et al. Is there an association between maternal anxiety propensity and pregnancy outcomes? *BMC Pregnancy Childbirth.* (2018) 18:287. doi: 10.1186/s12884-018-1925-8

11. Berge LI, Riise T. Comorbidity between type 2 diabetes and depression in the adult population: directions of the association and its possible pathophysiological mechanisms. *Int J Endocrinol.* (2015) 2015:164760. doi: 10.1155/2015/164760

12. Varner M. Improving the effectiveness of lifestyle interventions for gestational diabetes mellitus prevention (what would Janus do)? *BJOG.* (2019) 126:321. doi: 10.1111/1471-0528.15489

13. OuYang H, Chen B, Abdulrahman AM, Li L, Wu N. Associations between gestational diabetes and anxiety or depression: A systematic review. *J Diabetes Res.* (2021) 2021:9959779. doi: 10.1155/2021/9959779

14. Berle JØ, Mykletun A, Daltveit AK, Rasmussen S, Holsten F, Dahl AA. Neonatal outcomes in offspring of women with anxiety and depression during pregnancy. A linkage study from The Nord-Trondelag Health Study (HUNT) and Medical Birth Registry of Norway. *Arch Womens Ment Health.* (2005) 8:181–9. doi: 10.1007/s00737-005-0090-z

15. Graignic-Philippe R, Dayan J, Chokron S, Jacquet AY, Tordjman S. Effects of prenatal stress on fetal and child development: a critical literature review. *Neurosci Biobehav Rev.* (2014) 43:137–62. doi: 10.1016/j.neubiorev.2014.03.022

16. Hanley GE, Oberlander TF. Neurodevelopmental outcomes following prenatal exposure to serotonin reuptake inhibitor antidepressants: a "social teratogen" or moderator of developmental risk? *Birth Defects Res A Clin Mol Teratol.* (2012) 94:651–9. doi: 10.1002/bdra.23032

17. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics.* (1971) 12:371–9. doi: 10.1016/S0033-3182(71)71479-0

18. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry.* (1965) 12:63–70. doi: 10.1001/archpsyc.1965.01720310065008

19. Zhu J, Li Y, Wang R, Zhang J, Liu C, Li H, et al. The mediating role of family functions between pregnancy-related anxiety and sleep quality: A cross-sectional study. *Nat Sci Sleep.* (2024) 16:279–89. doi: 10.2147/NSS.S443612

20. Yu Y, Feng L, Shao Y, Tu P, Wu HP, Ding X, et al. Quality of life and emotional change for middle-aged and elderly patients with diabetic retinopathy. *Int J Ophthalmol.* (2013) 6:71–4. doi: 10.3980/j.issn.2222-3959.2013.01.15

21. Zhang P, Lou P, Chang G, Chen P, Zhang L, Li T, et al. Combined effects of sleep quality and depression on quality of life in patients with type 2 diabetes. *BMC Fam Pract.* (2016) 17:40. doi: 10.1186/s12875-016-0435-x

22. Tao M, Gao J. Reliability and validity of revised self rating Anxiety Scale. *Chin J Nerv Ment Dis.* (1994) 20(5):3. doi: CNKI:SUN:ZSJJ.0.1994-05-022

23. Lee HC, Chiu HF, Wing YK, Leung CM, Kwong PK, Chung DW. The Zung Self-rating Depression Scale: screening for depression among the Hong Kong Chinese elderly. *J Geriatr Psychiatry Neurol.* (1994) 7:216–20. doi: 10.1177/089198879400700404

24. Tang Y, Lan X, Zhang Y, Zhou F, Cai C, Zhang J, et al. Anxiety and depression on gestational diabetes mellitus in early pregnancy. *Wei Sheng Yan Jiu.* (2020) 49:179–84. doi: 10.19813/j.cnki.weishengyanjiu.2020.02.002

25. Palladino CL, Singh V, Campbell J, Flynn H, Gold KJ. Homicide and suicide during the perinatal period: findings from the National Violent Death Reporting System. *Obstet Gynecol.* (2011) 118:1056–63. doi: 10.1097/AOG.0b013e31823294da

26. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord.* (2017) 219:86–92. doi: 10.1016/j.jad.2017.05.003

27. Ecklund-Flores L, Myers MM, Monk C, Perez A, Odendaal HJ, Fifer WP. Maternal depression during pregnancy is associated with increased birth weight in term infants. *Dev Psychobiol.* (2017) 59:314–23. doi: 10.1002/dev.21496

28. Alqahtani AH, Al Khedair K, Al-Jeheiman R, Al-Turki HA, Al Qahtani NH. Anxiety and depression during pregnancy in women attending clinics in a University Hospital in Eastern province of Saudi Arabia: prevalence and associated factors. *Int J Womens Health.* (2018) 10:101–8. doi: 10.2147/IJWH.S153273

29. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord.* (2012) 142 Suppl:S8–21. doi: 10.1016/S0165-0327(12)70004-6

30. Byrn M, Penckofer S. The relationship between gestational diabetes and antenatal depression. *J Obstet Gynecol Neonatal Nurs.* (2015) 44:246–55. doi: 10.1111/1552-6909.12554

31. Horsch A, Kang JS, Vial Y, Ehlert U, Borghini A, Marques-Vidal P, et al. Stress exposure and psychological stress responses are related to glucose concentrations during pregnancy. *Br J Health Psychol.* (2016) 21:712–29. doi: 10.1111/bjhp.12197

32. Bowers K, Laughon SK, Kim S, Mumford SL, Brite J, Kiely MZ, et al. The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort in the United States. *Paediatr Perinat Epidemiol.* (2013) 27:323–8. doi: 10.1111/ppe.12057

33. Gilbert L, Gross J, Lanzi S, Quansah DY, Puder J, Horsch A. How diet, physical activity and psychosocial well-being interact in women with gestational diabetes mellitus: an integrative review. *BMC Pregnancy Childbirth.* (2019) 19:60. doi: 10.1186/s12884-019-2185-y

34. Robinson DJ, Coons M, Haensel H, Vallis M, Yale JF. Diabetes and mental health. *Can J Diabetes.* (2018) 42 Suppl:1S130–S141. doi: 10.1016/j.jcjd.2017.10.031

35. Hjelm K, Berntorp K, Frid A, Åberg A, Apelqvist J. Beliefs about health and illness in women managed for gestational diabetes in two organisations. *Midwifery.* (2008) 24:168–82. doi: 10.1016/j.midw.2006.12.008

36. Hirst JE, Tran TS, Do MA, Rowena F, Morris JM, Jeffery HE. Women with gestational diabetes in Vietnam: a qualitative study to determine attitudes and health behaviours. *BMC Pregnancy Childbirth.* (2012) 12:81. doi: 10.1186/1471-2393-12-81

37. Hinkle SN, Buck Louis GM, Rawal S, Zhu Y, Albert PS, Zhang C. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. *Diabetologia.* (2016) 59:2594–602. doi: 10.1007/s00125-016-4086-1

38. Azami M, Badfar G, Soleymani A, Rahmati S. The association between gestational diabetes and postpartum depression: A systematic review and meta-analysis. *Diabetes Res Clin Pract.* (2019) 149:147–55. doi: 10.1016/j.diabres.2019.01.034

39. Kim C, Brawarsky P, Jackson RA, Fuentes-Afflick E, Haas JS. Changes in health status experienced by women with gestational diabetes and pregnancy-induced hypertensive disorders. *J Womens Health (Larchmt).* (2005) 14:729–36. doi: 10.1089/jwh.2005.14.729

40. Dalfra MG, Nicolucci A, Bisson T, Bonsembiante B, Lapolla A. Quality of life in pregnancy and post-partum: a study in diabetic patients. *Qual Life Res.* (2012) 21:291–8. doi: 10.1007/s11136-011-9940-5

41. Martini J, Knappe S, Beesdo-Baum K, Lieb R, Wittchen HU. Anxiety disorders before birth and self-perceived distress during pregnancy: associations with maternal depression and obstetric, neonatal and early childhood outcomes. *Early Hum Dev.* (2010) 86:305–10. doi: 10.1016/j.earlhumdev.2010.04.004

42. Bayrampour H, Salmon C, Vinturache A, Tough S. Effect of depressive and anxiety symptoms during pregnancy on risk of obstetric interventions. *J Obstet Gynaecol Res.* (2015) 41:1040–8. doi: 10.1111/jog.12683

43. Ghimire U, Papabathini SS, Kawuki J, Obore N, Musa TH. Depression during pregnancy and the risk of low birth weight, preterm birth and intrauterine growth restriction-an updated meta-analysis. *Early Hum Dev.* (2021) 152:105243. doi: 10.1016/j.earlhumdev.2020.105243

44. Dayan J, Creveuil C, Marks MN, Conroy S, Herlicoviez M, Dreyfus M, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. *Psychosom Med.* (2006) 68:938–46. doi: 10.1097/01.psy.0000244025.20549.bd

45. Arafa A, Dong JY. Depression and risk of gestational diabetes: A meta-analysis of cohort studies. *Diabetes Res Clin Pract.* (2019) 156:107826. doi: 10.1016/j.diabres.2019.107826

46. Hui AL, Sevenhuysen G, Harvey D, Salamon E. Stress and anxiety in women with gestational diabetes during dietary management. *Diabetes Educ.* (2014) 40:668–77. doi: 10.1177/0145721714535991

47. Blackmore ER, Gustafsson H, Gilchrist M, Wyman C, G O'Connor T. Pregnancy-related anxiety: Evidence of distinct clinical significance from a prospective longitudinal study. *J Affect Disord*. (2016) 197:251–8. doi: 10.1016/j.jad.2016.03.008

48. Fu F, Yan P, You S, Mao X, Qiao T, Fu L, et al. The pregnancy-related anxiety characteristics in women with gestational diabetes mellitus: why should we care? *BMC Pregnancy Childbirth*. (2021) 21:424. doi: 10.1186/s12884-021-03887-2

49. Zhou C, Weng J, Tan F, Wu S, Ma J, Zhang B, et al. Pregnancy-related anxiety among Chinese pregnant women in mid-late pregnancy under the two-child policy and its significant correlates. *J Affect Disord*. (2020) 276:272–8. doi: 10.1016/j.jad.2020.07.099

50. Lee KW, Ching SM, Hoo FK, Ramachandran V, Chong SC, Tusimin M, et al. Prevalence and factors associated with depressive, anxiety and stress symptoms among women with gestational diabetes mellitus in tertiary care centres in Malaysia: a cross-sectional study. *BMC Pregnancy Childbirth*. (2019) 19:367. doi: 10.1186/s12884-019-2519-9

51. Rodbard D. Continuous glucose monitoring: A review of recent studies demonstrating improved glycemic outcomes. *Diabetes Technol Ther*. (2017) 19:S25–37. doi: 10.1089/dia.2017.0035

52. Polonsky WH, Hessler D, Ruedy KJ, Beck RW. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. *Diabetes Care*. (2017) 40:736–41. doi: 10.2337/dc17-0133

53. Fisher L, Polonsky W, Parkin CG, Jelsovsky Z, Amstutz L, Wagner RS. The impact of blood glucose monitoring on depression and distress in insulin-naive patients with type 2 diabetes. *Curr Med Res Opin*. (2011) 27 Suppl:339–46. doi: 10.1185/03007995.2011.619176

54. da Silva CC, Lazzaretti C, Fontanive T, Dartora DR, Bauereis B, Gamaro GD. Estrogen-dependent effects on behavior, lipid-profile, and glycemic index of ovariectomized rats subjected to chronic restraint stress. *Behav Processes*. (2014) 103:327–33. doi: 10.1016/j.beproc.2014.01.022

55. Liang Y, Liang J, Jiang W, Wang W, Yang X, Liu Y, et al. Stronger association between morning serum cortisol level and diurnal time in range in type 2 diabetes? *Diabetol Metab Syndr*. (2024) 16:290. doi: 10.1186/s13098-024-01515-5

56. Ma L, Liu J, Deng M, Zhou L, Zhang Q, Xiao X. Metabolomics analysis of serum and urine in type 1 diabetes patients with different time in range derived from continuous glucose monitoring. *Diabetol Metab Syndr*. (2024) 16:21. doi: 10.1186/s13098-024-01257-4

57. Hermanns N, Ehrmann D, Kulzer B, Klinker L, Haak T, Schmitt A. Somatic and mental symptoms associated with dysglycaemia, diabetes-related complications and mental conditions in people with diabetes: Assessments in daily life using continuous glucose monitoring and ecological momentary assessment. *Diabetes Obes Metab*. (2025) 27:61–70. doi: 10.1111/dom.15983

58. McNay E. Recurrent hypoglycemia increases anxiety and amygdala norepinephrine release during subsequent hypoglycemia. *Front Endocrinol (Lausanne)*. (2015) 6:175. doi: 10.3389/fendo.2015.00175

59. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G. Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic. *J Affect Disord*. (2020) 277:5–13. doi: 10.1016/j.jad.2020.07.126

60. Dong D, Lou P, Wang J, Zhang P, Sun J, Chang G, et al. Interaction of sleep quality and anxiety on quality of life in individuals with type 2 diabetes mellitus. *Health Qual Life Outcomes*. (2020) 18:150. doi: 10.1186/s12955-020-01406-z

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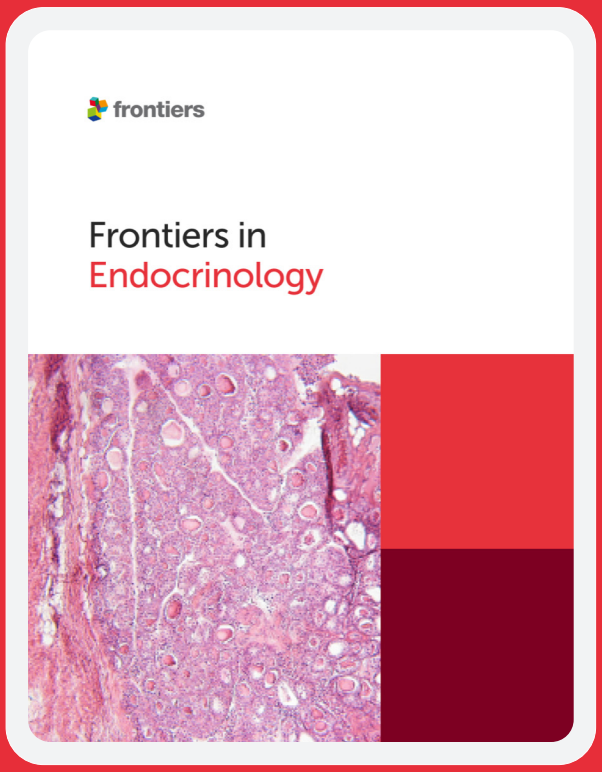

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