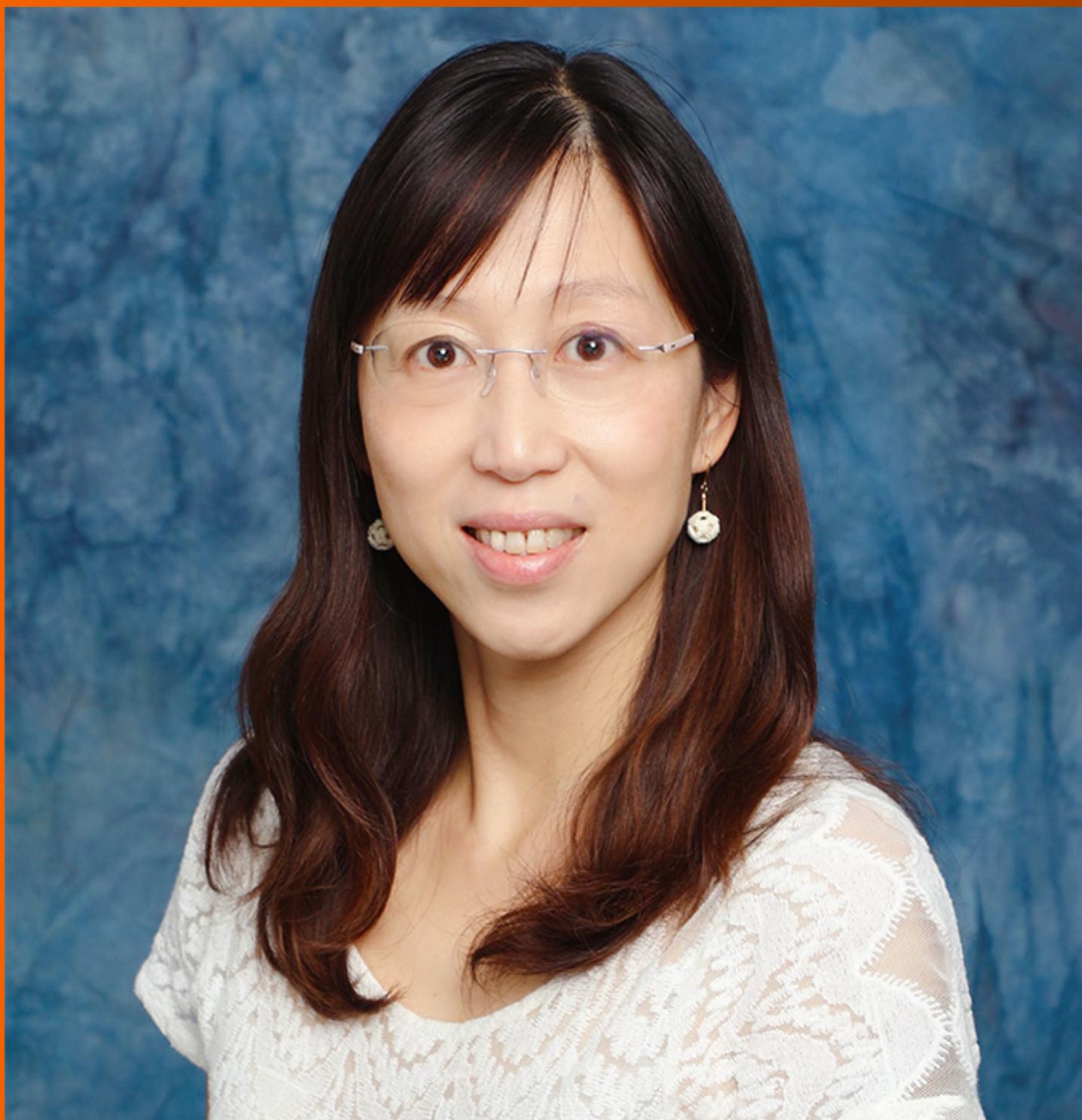


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ABOUT COVER

Editorial board member of *World Journal of Diabetes*, Dr. Luo-Hua Jiang is a biostatistician with a unique combination of expertise in biostatistics, epidemiology, and diabetes research. She obtained her MD degree from Peking University (China) and PhD in Biostatistics from the University of California Los Angeles (United States). She has led a series of investigations examining the relationship of diabetes with mental health and conducted multilevel analysis of the translational effects of lifestyle intervention to prevent diabetes among American Indians and Alaska Natives (AIs/ANs). She has also been funded by the National Institute of Diabetes and Digestive and Kidney Diseases to assess the comparative effectiveness of a diabetes case management intervention in AI/AN communities. She has authored and co-authored more than 80 publications. (L-Editor: Filipodia)

AIMS AND SCOPE

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, etc..

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJD* as 3.247; IF without journal self cites: 3.222; Ranking: 70 among 143 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yu-Jie Ma; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

December 15, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Exenatide once weekly combined with metformin reduced glycemic variability in type 2 diabetes by using flash glucose monitoring system

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Author contributions: Liu YF and Zhang Y designed the study and revised the manuscript; Li Y and Han MM drafted the initial manuscript; Li Y, Han MM, and He Q analyzed and interpreted the data; Liu ZA, Liang D, Hou JT, Li Y, Han MM, and He Q conducted the study and collected the data. All authors read and approved the final manuscript for publication.

Supported by National Natural Science Foundation of China, No. 81770776 and No. 81973378; Cultivate Scientific Research Excellence Programs of Higher Education Institutions in Shanxi, No. 2019KJ022; and Special Project for Transformation and Guidance of Scientific and Technological Achievements in Shanxi Province, No. 201804D131044.

Institutional review board statement: The study was reviewed and approved by the

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Abstract

BACKGROUND

Multiple studies demonstrate that fluctuating blood glucose level produces greater damage compared with sustained hyperglycemia. Flash glucose monitoring system is an effective method in documenting blood glucose variability, contributing to better glucose management and reduced hypoglycemic event occurrence.

AIM

To investigate the improvement in glycemic variability (GV), blood glucose level, and metabolic indexes of patients with type 2 diabetes mellitus after combined treatment of exenatide once weekly (EXQW) and metformin.

METHODS

Twenty-five patients with type 2 diabetes mellitus suffering from poor blood glucose control under metformin treatment were recruited. The recruited patients were prescribed with oral metformin only (maintaining a dosage of metformin at ≥ 1500 mg/day) for 2 wk (screening period), and then given EXQW (2 mg, subcutaneous injection) for 12 wk (experimental period). The flash glucose monitoring system was used to document blood glucose values during the screening period and the last 2 wk of the experimental period.

Ethics Committee of the First Hospital of Shanxi Medical University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Endocrinology and metabolism

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 27, 2020

Peer-review started: June 27, 2020

First decision: September 18, 2020

Revised: October 9, 2020

Accepted: October 26, 2020

RESULTS

Four patients were excluded for various reasons, yielding a total of 21 patients, including 17 males and 4 females, with an average age of 48.8 years, who completed this study. The estimated glycated hemoglobin, mean blood glucose, fasting and postprandial blood glucose levels, and percentage of blood glucose above 7.8 mmol/L decreased compared to those at baseline ($P = 0.003$, 0.003 , 0.008 , 0.010 , 0.014 , 0.017 , and 0.005 , respectively), while the percentage of blood glucose between 3.9 and 7.8 mmol/L significantly increased ($P = 0.005$). Parameters of GV including standard deviation of blood glucose, mean amplitude of glycemic excursions, mean of daily difference, area under the curve difference between percentiles 25 and 75, and area under the curve difference between percentiles 10 and 90 were significantly lower compared to that of baseline ($P = 0.017$, 0.006 , 0.000 , 0.024 , 0.036 , respectively). The durations of blood glucose below 3.9 mmol/L during the day and nocturnal periods significantly increased after treatment ($P = 0.041$ and 0.028 , respectively), but there was no significant increase in severe hypoglycemia (< 3.0 mmol/L) compared with that at baseline ($P = 0.207$). In addition, some metabolic indicators improved after EXQW treatment.

CONCLUSION

EXQW combined with metformin can effectively improve blood glucose levels, reduce GV, and improve metabolic indicators. However, there is still a risk of nocturnal hypoglycemia, and careful attention should be paid to patients with EXQW treatment.

Key Words: Flash glucose monitoring; Glycemic variability; Type 2 diabetes mellitus; Exenatide once weekly

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Core Tip: In this study, flash glucose monitoring system was used not only to observe the hypoglycemic effect of and the improvement of glycemic variability by exenatide once weekly in combination with metformin, but also to accurately assess the specific time period for the improvement of blood glucose and the time when the occurrence of hypoglycemia was concentrated. The results indicated that the combination of these drugs significantly improved fasting blood glucose, but the risk of increasing hypoglycemia, especially at night, should be cautioned.

Citation: Li Y, Han MM, He Q, Liu ZA, Liang D, Hou JT, Zhang Y, Liu YF. Exenatide once weekly combined with metformin reduced glycemic variability in type 2 diabetes by using flash glucose monitoring system. *World J Diabetes* 2020; 11(12): 654-665

URL: <https://www.wjgnet.com/1948-9358/full/v11/i12/654.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v11.i12.654>

INTRODUCTION

Achieving and maintaining blood glucose levels within normal range is an integral part of diabetes mellitus (DM) management, in which blood glucose monitoring plays an indispensable role. Glycated hemoglobin (HbA1c) is a long-term blood glucose indicator, providing useful information about the most recent 2-3 mo blood glucose levels. However, patients with similar or identical HbA1c results may have different glucose variability (GV) profiles. GV condition in patients with DM has gained wide attention in recent years, because it is a more reliable indicator for a wide range of acute or chronic diabetes-related complications^[1,2]. Current studies have demonstrated that compared to persistent hyperglycemia, fluctuating hyperglycemia can cause greater damage to the blood vessels and endothelial tissue.

Flash glucose monitoring system (FGMS) can be used to continuously measure interstitial fluid blood glucose level over a period of 10 to 14 d. Compared to the

Article in press: October 26, 2020**Published online:** December 15, 2020**P-Reviewer:** Athyros VG, Koch T, Nakajima K**S-Editor:** Zhang H**L-Editor:** Wang TQ**P-Editor:** Ma YJ

continuous glucose monitoring system, the FGMS is factory calibrated without the alert function for the risk of hyperglycemia and hypoglycemia^[3], and available data revealed that the FGMS is an effective method in documenting blood glucose variability, contributing to better glucose management and reduced hypoglycemic event occurrence^[4,5].

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been demonstrated to significantly improve blood glucose level, blood lipid profile, and weight in patients with DM, which are a class of safe and effective hypoglycemic medications due to their glucose-dependent hypoglycemic property without increasing the risk of hypoglycemia. In addition, the safety of GLP-1RAs in the cardiovascular system has been verified, specifically, the LEADER study^[6] has shown that liraglutide, as a kind of GLP-1RA, has a significant protective effect on the cardiovascular system. Exenatide once-weekly (EXQW), a long-acting GLP-1RA, can significantly improve metabolic disorders *in vivo*. Considering the reduced frequency of injections and discomfort experience, EXQW has become an effective and convenient therapy that can improve patients' quality of life and compliance^[7]. Therefore, we hypothesized that the combination of EXQW and metformin can bring significant clinical benefits for DM management.

As the aims of this study, the clinical and therapeutic effects of combined EXQW and metformin treatment in type 2 DM (T2DM) patients were evaluated by using dynamic glucose monitoring and metabolic indicators. Based on the FGMS data, we analyzed and compared the GV-related indices, and hypoglycemic incidence between baseline and end points.

MATERIALS AND METHODS

This is a pre-post study involving the same group of patients, conducted at the First Hospital of Shanxi Medical University from June 2018 to March 2019. This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University (2018K007). All patients were informed of the objective of the study and signed a written informed consent form.

Study population

Twenty-five patients with T2DM, whose blood glucose was poorly controlled by metformin monotherapy, were recruited. These patients were selected according to the following criteria: (1) Patients were diagnosed with T2DM for 2 to 10 years, based on the DM diagnosis standards published by the World Health Organization in 1999, and their ages ranged from 18 to 70 years old; (2) Measured HbA1C $\geq 7.0\%$ but $< 11.0\%$; (3) Patients receiving monotherapy of metformin for at least 3 mo (daily metformin dosage ≥ 1500 mg) with unsatisfactory blood glucose control; and (4) Patients with an estimated glomerular filtration rate > 60 mL/min/1.73 m².

The exclusion criteria were as follows: (1) Patients with contraindications according to the instructions on EXQW, or who had a history of allergy to any other excipients; (2) Patients received insulin therapy for more than 7 d consecutively within 1 year before the screening (excluding those taking insulin therapy for acute diseases or operations); (3) Patients with a history of acute or chronic pancreatitis; (4) Patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2; (5) Patients suffering from serious gastrointestinal diseases; and (6) Patients who could not cooperate with the researcher because of poor compliance or mental disorders, unwilling to communicate, or having difficulty in expressing thoughts.

Study interventions

This study comprised of two periods, namely, a 2-wk screening period and a 12-wk experiment period. During the screening period, the recruited patients' profiles comprising height, weight, waist circumference, and other basic information were compiled. Thereafter, all patients were provided with the standard diabetes health education and relevant training on the FGMS. It is recommended that all subjects have meals at 8:00, 13:00, and 18:00 each day. According to the Dietary Guidelines for Type 2 Diabetes in China and Guidelines for the Prevention and Control of Type 2 Diabetes in China, the patients were instructed to eat 50%-65% carbohydrate, 20%-30% fat, and 15%-20% protein every day, and they were given 150 min of moderate-intensity aerobic exercise every week.

During the 2-wk screening period, the patients were prescribed with oral metformin

only (maintaining a dosage of metformin at ≥ 1500 mg/day). At the end of the screening period, EXQW was prescribed at 2 mg *via* subcutaneous injection, administered at a fixed time every week. The combined drug therapy continued for 12 wk.

FGMS was used in the screening period and the last 2 wk of the experimental period. The sensor of an FGMS device was placed under the skin of patient's upper arm with the help of professional medical staff. The patients were asked to avoid strenuous exercise and long hours of bathing or swimming to prevent the sensor from detaching. Additionally, the patients were required to obtain complete blood glucose data at least once every 8 h using the separate touchscreen reader device.

Endpoints

The primary endpoint of this study was to evaluate the change of GV after 12-wk treatment relative to the baseline by using an FGMS, and the secondary end points were blood glucose control and the occurrence of hypoglycemia. In addition, changes in some biochemical indicators were also observed. Pancreatic islet function and insulin resistance (IR) were assessed using homeostasis model assessment (HOMA)^[8]: $\text{HOAM-}\beta = 20 \times \text{FINS} / (\text{FBG} - 3.5)$, and $\text{HOMA-IR} = \text{FBG} \times \text{FINS} / 22.5$.

Flash glucose monitoring system data

The FGMS records blood glucose values every 15 min, and the information has to be scanned at least once every 8 h for data compilation. Therefore, 96 continuous blood glucose level values could be obtained for every 24 h. After wearing the FGMS for 10 to 14 d, the patients' baseline blood glucose data and automatically-generated ambulatory glucose profile (AGP) were captured by the commercial software in the FGMS device. Should there be missing values in the baseline blood glucose data, they will be replaced by the average blood glucose value nearing the missing value.

Based on the FGMS data, we calculated some parameters of GV, including mean amplitude of glycemic excursion (MAGE), mean of daily difference (MODD), coefficient of variation (CV), standard deviation of blood glucose (SDBG), large amplitude of glycemic excursion, area under the curve (AUC) difference between percentiles 25 and 75 (area of IQR), and AUC difference between percentiles 10 and 90 (area of IDR). The automatically generated AGPs were used as parameters for blood glucose control, including estimated HbA1c, mean blood glucose (MBG), time in range (TIR) (3.9-7.8 mmol/L), time out of range (TOR), percentage of time below 3.9 mmol/L, percentage of time between 3.9-7.8 mmol/L, and percentage of time above 7.8 mmol/L. At the same time, fasting (6:00-8:00) and postprandial (8:00-10:00, 13:00-15:00, and 18:00-20:00) blood glucose levels were extracted for specific analysis. The means of blood glucose in each time period were plotted into a line graph and the AUCs were calculated accordingly. In addition, two different hypoglycemic cutoffs, less than 3.9 mmol/L and 3.0 mmol/L, were used during the day (6:00-24:00) and nocturnal periods (0:00-6:00). The parameters of GV and blood glucose levels were obtained using SigmaPlot 12.5 version for Windows and SPSS version 23.0 software, except that some of them were provided by AGP.

Statistical analysis

SPSS version 23.0 software was used for statistical analyses. Data are reported as the mean \pm SD for normally distributed continuous variables and median (inter-quartile range) for the non-normally distributed continuous variables. Paired-sample *t*-tests or Wilcoxon signed rank test were performed to compare the data between start and the end of this intervention study. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the patients

Twenty-five subjects were recruited for this study, of whom two failed to complete the study and two failed to obtain FGMS data. Finally, a total of 21 subjects were involved in this study, including 17 males and 4 females. The mean age of participants was 48.8 ± 8.4 years (range, 33-66 years). The mean duration of diabetes was 5.3 ± 2.1 years (range, 2-10 years). All patients wore the FGMS devices for a total of 284 d for the baseline period and 309 d after 12-wk treatment. Baseline characteristics of the participants are shown in Table 1.

Table 1 Baseline characteristics of patients (mean \pm SD)

Variable	Total (21)
Age (yr)	48.8 \pm 8.4
Duration of diabetes (yr)	5.3 \pm 2.1
Gender (female/male)	4/17
BMI (kg/m ²)	26.7 \pm 1.6
Smoking (%)	71.4
Hypertension (%)	66.7
Macrovascular complications (%)	19.0
Microvascular complications (%)	38.1

BMI: Body mass index.

Effectiveness of exenatide once weekly in glycemic control

Overall, after 12 wk of combined drug therapy, blood glucose levels improved significantly compared with baseline values, as shown in [Table 2](#). The estimated HbA1c, MBG, and TOR decreased after treatment ($P = 0.003$, 0.003 , and 0.005 , respectively), while TIR increased ($P = 0.005$).

Percentage of time in different target ranges

As shown in [Figure 1](#), the percentage of time below 3.9 mmol/L and percentage of time above 7.8 mmol/L significantly decreased ($P = 0.035$ and 0.005 , respectively), while percentage of time between 3.9-7.8 mmol/L significantly increased ($P = 0.005$) after 12 wk of combination therapy compared with that at baseline.

Glycemic variability alterations

After intervention treatment, GV improved significantly compared to baseline value. Parameters representing within-day GV (SDBG and MAGE) and day-to-day GV (MODD) decreased significantly ($P = 0.017$, 0.006 , and 0.000 , respectively). Further extraction and analysis of GV parameters for daytime and night showed that the values of MAGE and MODD were reduced during the daytime as well as at night ($P = 0.010$, 0.020 , 0.001 , and 0.007 , respectively). Moreover, AUC difference between percentiles 25 and 75 (area of IQR) and AUC difference between percentiles 10 and 90 (area of IDR) narrowed ($P = 0.024$ and 0.036 , respectively). However, there was no significant difference in CV or large amplitude of glycemic excursion. Detailed information is shown in [Table 3](#).

Area under the curve of fasting and postprandial blood glucose

The results are shown in [Figure 2](#). Fasting and postprandial glucose levels significantly decreased after treatment compared with those at baseline ($P = 0.008$, 0.010 , 0.014 , and 0.017 , respectively).

Duration of hypoglycemia

As shown in [Table 4](#), when the interstitial fluid blood glucose less than 3.9 mmol/L was considered as hypoglycemia, the durations of hypoglycemia during the whole day and the nocturnal period (0:00-6:00) increased significantly compared with those at baseline ($P = 0.041$ and 0.028 , respectively), while the duration of hypoglycemia during the daytime (6:00-24:00) showed no significant difference ($P = 0.157$). For the hypoglycemic cutoff point of 3.0 mmol/L, the durations of hypoglycemia did not increase throughout the day, during the daytime (6:00-24:00), or during the nocturnal period (0:00-6:00).

Comparison of metabolic indicators

After 12-wk combined therapy, mean weight of patients decreased from 78.1 ± 8.3 to 77.3 ± 8.5 kg ($P = 0.008$), and mean waist circumference decreased from 100.8 ± 9.2 to 99.5 ± 8.5 cm ($P = 0.021$). Besides, the significantly decreased HOMA-IR and significant increased HOMA- β than those at baseline indicated an improvement in insulin resistance and pancreatic islets function. Results are shown in [Table 5](#).

Table 2 Blood glucose level and time in range at baseline and 12 wk [mean \pm SD or median (interquartile range)]

Variable	Baseline	12 wk	P value
eHbA1c (%)	8.4 \pm 1.4	7.0 \pm 1.3	0.003
MBG (mmol/L)	10.8 \pm 2.3	8.6 \pm 2.0	0.003
TIR (h)	6.1 \pm 5.9	11.5 \pm 5.8	0.005
TOR (h)	17.9 \pm 5.9	12.5 \pm 5.8	0.005

eHbA1c: Estimated glycated hemoglobin; MBG: Mean blood glucose; TIR: Time in range; TOR: Time out of range.

Table 3 Parameters of glycemic variability at baseline and 12 wk [mean \pm SD or median (interquartile range)]

Variable		Baseline	12 wk	P value
SDBG (mmol/L)		2.8 \pm 0.8	2.3 \pm 0.6	0.017
CV (%)		26.3 \pm 5.4	26.3 \pm 3.5	0.997
MAGE (mmol/L)	Overall	5.7 \pm 1.3	4.5 \pm 1.1	0.006
	During day	5.8 \pm 1.2	4.6 \pm 1.3	0.010
	At night	4.7 \pm 1.8	3.6 \pm 1.2	0.020
MODD (mmol/L)	Overall	2.8 \pm 1.2	1.6 \pm 0.4	0.000
	During day	2.9 \pm 1.1	1.8 \pm 0.5	0.001
	At night	1.8 (1.1-3.9)	1.0 (0.6-1.5)	0.007
LAGE (mmol/L)	Overall	15.2 \pm 2.6	13.5 \pm 3.2	0.092
	During day	14.8 \pm 2.8	13.1 \pm 3.3	0.127
	At night	9.7 \pm 3.6	8.5 \pm 2.4	0.258
AUC of IQR		5017.5 \pm 1932.8	3877.1 \pm 1001.1	0.024
AUC of IDR		9713.2 \pm 2782.2	8015.9 \pm 2208.2	0.036

AUC of IDR: Area under the curve between percentiles 10 and 90; AUC of IQR: Area under the curve between percentiles 25 and 75; CV: Coefficient of variation; LAGE: Large amplitude of glycemic excursion; MAGE: Mean amplitude of glycemic excursion; MODD: Mean of daily difference; SDBG: Standard deviation of blood glucose.

Table 4 Duration of hypoglycemia at baseline and after treatment [median (interquartile range)]

Variable	Before trial	After trial	P value
Hypoglycemia cutoff: 3.9 mmol/L			
Throughout the day (min)	0 (0-2.3)	1.1 (0-22.0)	0.041
During day (min)	0 (0-1.3)	0 (0-3.0)	0.157
At night (min)	0 (0-0)	1.1 (0-10.0)	0.028
Hypoglycemia cutoff: 3.0 mmol/L			
Throughout the day (min)	0 (0,0)	0 (0, 0)	0.207
During day (min)	0 (0,0)	0 (0, 0)	0.197
At night (min)	0 (0-0)	0 (0, 0)	0.465

DISCUSSION

This study explored the effects of EXQW combined with metformin treatment on GV, blood glucose levels, hypoglycemia, and some metabolic indicators in patients with T2DM. A recent study has revealed that exenatide twice daily and metformin could jointly improve GV profile^[9]. The present study extended this prior research by

Table 5 Comparison of metabolic indicators before and after treatment (mean ± SD)			
Variable	Baseline	12 wk	P value
Weight (kg)	78.1 ± 8.3	77.3 ± 8.5	0.008
Waist circumference (cm)	100.8 ± 9.2	99.5 ± 8.5	0.021
HOMA-IR	4.8 ± 2.2	4.0 ± 1.9	0.033
HOMA-β	41.2 ± 24.1	64.4 ± 51.6	0.046

HOMA-IR: Homeostasis model assessment insulin resistance; HOMA-β: Homeostasis model assessment beta cell.

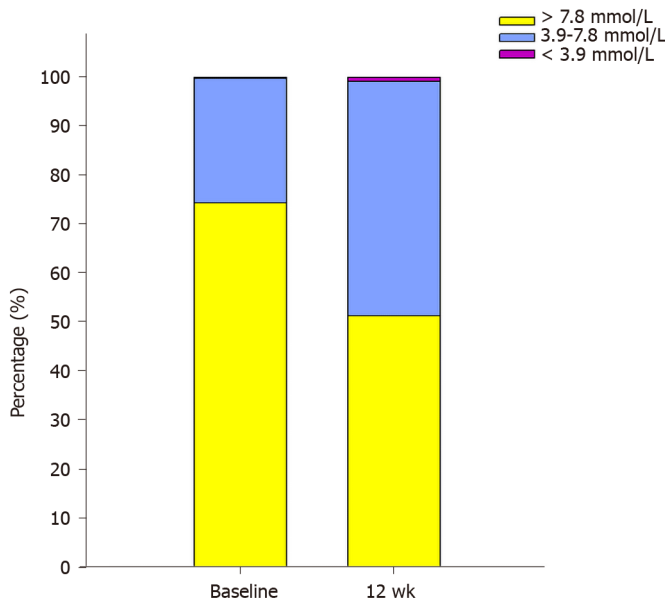


Figure 1 PT1, PT2, and PT3 at baseline and 12 wk. PT1: Percentage of time below 3.9 mmol/L; PT2: Percentage of time between 3.9-7.8 mmol/L; PT3: Percentage of time above 7.8 mmol/L. *P* = 0.035, 0.005, and 0.005, respectively, after 12-wk treatment vs baseline.

demonstrating that the combination of EXQW and metformin could significantly improve GV and blood glucose control. Additionally, the therapeutic effects on weight loss, waist circumference reduction, and improvement of islet function were also evident.

In this research, an FGMS was used to acquire continuous blood glucose levels in 10 to 14 d to assess GV, blood glucose control, and duration of hypoglycemia in T2DM patients with combined EXQW and metformin treatment. This new-type glucose monitoring system consists of a subcutaneous sensor and an independent reader. It is easy to wear and is almost pain free. Besides, its invisibility and portability have provided much convenience for patients who have trouble in monitoring blood glucose levels consistently. A prospective study applied FGMS in adults with T2DM and suggested that FGMS usage could improve blood glucose control, reduce the incidence of hypoglycemia, and improve patients' quality of life^[10]. Besides, FGMS has high user satisfaction and is a convenient option for patients requiring intensive glucose monitoring.

EXQW is a long-acting GLP-1RA, which is usually injected subcutaneously at 2 mg per week. A prospective study observed the therapeutic effect of EXQW combined with a standard dosage of metformin, suggesting that this treatment can effectively decrease HbA1c and fasting blood glucose levels, and improve carotid intima-media thickness^[11].

According to this study, after 12-wk EXQW and metformin combination treatment, estimated HbA1c, MBG, and TOR significantly decreased, while TIR significantly increased, indicating that the overall blood glucose control was better compared to that at baseline. TIR is an important index for the effectiveness in blood glucose control. When TIR is lowered, it suggests the existence of hypoglycemia or hyperglycemia. The relationship between TIR and macro- and micro-vascular

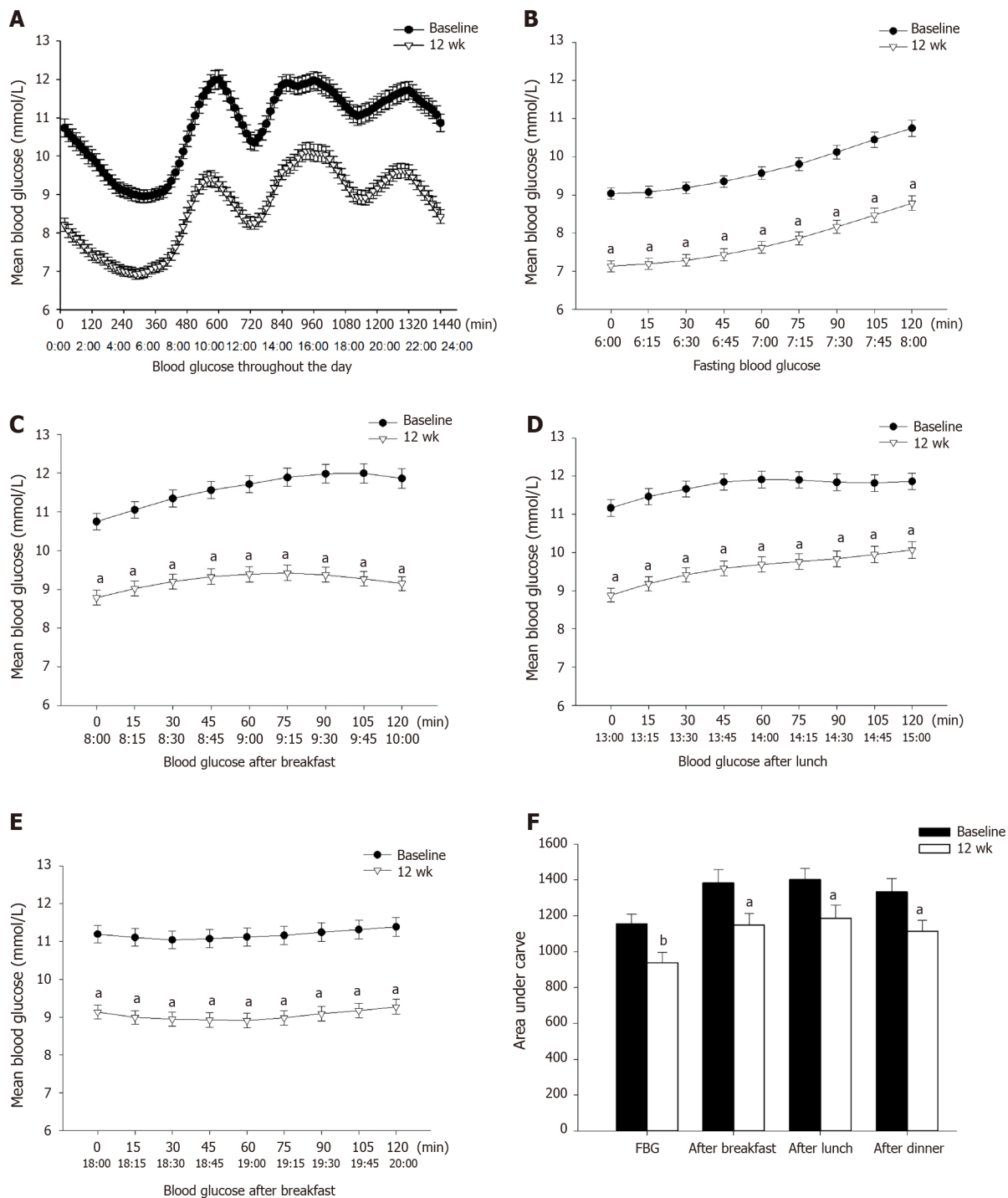


Figure 2 Comparison of mean blood glucose and the area under curves of fasting and postprandial blood glucose at baseline and after treatment. A: Mean blood glucose from 0:00 to 24:00; B: Mean blood glucose from 6:00 to 8:00; C: Mean blood glucose from 8:00 to 10:00; D: Mean blood glucose from 13:00 to 15:00; E: Mean blood glucose from 18:00 to 20:00; F: Area under the curves of each time period. The data are denoted as mean \pm SD. ^a $P < 0.05$, ^b $P < 0.01$, after 12-wk treatment vs baseline.

complications has been confirmed by previous researchers^[12,13]; hence, the reduction of TIR helps to delay the progression of diabetes.

In recent years, evidence-based medicine has achieved significant progress; there are new findings suggesting that unstable GV is more dangerous than the mere hyperglycemia^[14,15]. GV is considered unstable when the blood glucose levels fluctuate between peaks and troughs, increasing the risks of inflammation, oxidative stress, and damage to the endothelial cells^[16]. Therefore, GV is closely related to multiple complications in diabetes and is also a risk factor independent of blood glucose level. Our study revealed that the combination treatment of EXQW and metformin for 12 wk could improve the general GV (MBG and CV), within-day GV (SDBG and MAGE),

and day-to-day GV (MODD). Besides, the AUC difference between percentiles 25 and 75 (area of IQR) and AUC difference between percentiles 10 and 90 (area of IDR) narrowed. By comparing the changes in MAGE and MODD at daytime and at night to those at baseline, we found that these indicators improved significantly. A randomized placebo-controlled research using continuous glucose monitoring system to assess GV found that EXQW could not only improve blood glucose level but also reduce GV^[17], which is consistent with the results of this study.

Researchers have demonstrated that GV is a powerful independent predicting factor for patients with T2DM and acute coronary syndrome^[18]. Another study has also found that long-term follow-up of GV is probably a more reliable index compared to HbA1c in assessing the future risk of macro- and micro-vascular complications in patients with T2DM^[19]. Owing to the relatively short period of this study, follow-up on the occurrence of relevant complications could not be carried out. However, it can be inferred that EXQW in combination with metformin slows down the progression of diabetes-related complications by improving GV.

We specifically analyzed the blood glucose levels and AUCs at four different time periods. It revealed that EXQW can significantly reduce fasting blood glucose and achieve satisfactory blood glucose after breakfast, lunch, and dinner. Therefore, as a long-acting GLP-1RA, EXQW has a significant effect on the control of fasting blood glucose and exerts a certain effect on the control of postprandial blood glucose.

In this research, we calculated the durations of hypoglycemia below 3.9 mmol/L and 3.0 mmol/L, respectively. Results show that EXQW combined with metformin increased the durations of hypoglycemia (< 3.9 mmol/L) throughout the day and during the night (0:00-6:00), without any obvious increase of hypoglycemia during daytime (6:00-24:00). Further analysis of the duration of blood glucose below 3.0 mmol/L showed that severe hypoglycemia did not increase for the day, at daytime or night. Hypoglycemia causes anxiety and fear in patients, and severe hypoglycemia tends to occur at night. However, nocturnal hypoglycemia is usually asymptomatic and difficult to monitor, which often results in patients not getting timely and appropriate severe hypoglycemia management. GLP-1RA promotes insulin secretion in a glucose-dependent manner and inhibits glucagon secretion, contributing to a low risk of hypoglycemia. However, we should still be vigilant against the occurrence of nocturnal hypoglycemia, though the risk of hypoglycemia due to GLP-1RA is relatively low.

In addition to lowering blood glucose, we also found that HOMA-IR decreased after treatment, while HOMA- β increased. This indicates that EXQW could not only lower blood glucose, but also contribute to the repair of damaged pancreatic islet function and reduce the resistance of peripheral tissues to insulin, which is consistent with the findings of Bunck *et al*^[20].

In this study, changes in the body weight and waist circumference of patients were recorded. After 12 wk of treatment, both body weight and waist circumference were reduced compared to those at baseline, which is consistent with previous findings on using EXQW to improve body weight and waist circumference^[12,21,22]. We are informed that EXQW reduces body weight and waist circumference mainly through inhibition of the appetite, extended digestion in the stomach, and reduction in calorie intake.

Nevertheless, this study has several limitations, one of which is the lack of a control group. Moreover, it was a single-center study involving a small number of patients and a short observation period that limited the evaluation of certain essential treatment indicators. Meanwhile, the poor compliance of some patients or force majeure resulted in some missing data on blood glucose levels. To overcome these study limitations, a multi-center study could be carried out, with higher number of subjects, extended period of observation, and enhanced education to improve patient compliance.

CONCLUSION

In summary, EXQW in combination with metformin could effectively improve blood glucose levels and reduce GV. It has a remarkable effect on the control of fasting blood glucose and also exerts certain effect on the blood glucose levels after three meals in a day. While GV is more stable throughout the day, we also found that the GV parameters of day and night times were reduced. Although the risk of severe hypoglycemia in EXQW is relatively low, there is still a risk of nocturnal hypoglycemia, which requires careful attention. In addition, EXQW has a variety of effects other than lowering blood glucose, such as alleviating insulin resistance,

improving islet function, and reducing body weight and waist circumference. Therefore, it has a good clinical application prospect for the treatment of patients with T2DM.

ARTICLE HIGHLIGHTS

Research background

Multiple studies demonstrate that fluctuating blood glucose level produces greater damage compared with sustained hyperglycemia. Flash glucose monitoring system (FGMS) is an effective method in documenting blood glucose variability, contributing to better glucose management and reduced hypoglycemic event occurrence.

Research motivation

A dynamic blood glucose monitoring system was used to observe the blood glucose characteristics of type 2 diabetes patients during the use of exenatide once weekly (EXQW) combined with metformin.

Research objectives

As the aims of this study, the clinical and therapeutic effects of combined EXQW and metformin treatment in type 2 diabetes patients were evaluated by using FGMS and metabolic indicators. Based on the FGMS data, we analyzed and compared the glycemic variability-related indices, and hypoglycemic incidence between baseline and end points.

Research methods

This study is a pre-post study involving the same group of patients. Patients wore FGMS twice during the screening period (oral metformin monotherapy) and the experimental period (EXQW combined with metformin), respectively, and the changes of blood glucose characteristics and related metabolic indexes at baseline and endpoint were observed.

Research results

After 12 wk of combined treatment, hyperglycemia was controlled, especially fasting blood glucose, and postprandial blood glucose levels were also reduced. The percentage of time in range (3.9-7.8 mmol/L) increased and the percentage of time out of range decreased. The fluctuation of blood glucose was more stable than baseline, and there were statistically significant differences in standard deviation of blood glucose, mean amplitude of glycemic excursion, mean of daily difference, area under the curve of IQR, and area under the curve of IDR. After treatment of EXQW combined with metformin, the duration of hypoglycemia (< 3.9 mmol/L) increased, mainly at night, but the duration of severe hypoglycemia (< 3.0 mmol/L) did not increase. In addition, metabolic indexes such as body weight and waist circumference were improved.

Research conclusions

The combination of EXQW and metformin can effectively control hyperglycemia, reduce glycemic variability, and improve metabolic indexes. By analyzing FGMS data during different time periods, EXQW was found to significantly improve fasting and postprandial glucose without increasing the incidence of severe hypoglycemia (< 3.0 mmol/L) events, but still with an increased risk of nocturnal hypoglycemia.

Research perspectives

This study has its limitations, and we expect that a multi-center, large-sample study should be carried out.

ACKNOWLEDGEMENTS

We are grateful to all the study subjects for their participation.

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