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ORIGINAL RESEARCH

To Assess Liraglutide's Therapeutic Effect in Patients with Type 2 Diabetes Mellitus Using Flash Glucose Monitoring System

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Purpose: Liraglutide, a type of glucagon-like peptide-1 receptor agonist, has significant anti-hyperglycaemic activity without increasing the incidence of hypoglycaemia. In addition, it can improve β-cell function and insulin resistance. The flash glucose monitoring system (FGMS) is a novel method to document consecutive and detailed interstitial glucose levels, further reflecting blood glucose levels. This study aimed to investigate the therapeutic effect of liraglutide on blood glucose management (glucose variability, hyperglycaemia, and the incidence of hypoglycaemia), β-cell function, and insulin resistance in patients with diabetes.

Patients and Methods: Thirty-three patients with type 2 diabetes mellitus were recruited in this study. On the basis of metformin monotherapy, these patients received liraglutide add-on treatment for 3 months. The FGMS was used to document glucose levels before and after add-on treatment. Parameters of glucose variability, blood glucose levels at specific time periods, and the incidence of hypoglycaemia were assessed according to FGMS data and compared before and after liraglutide add-on treatment. Further, β-cell function and insulin resistance were assessed and compared before and after liraglutide add-on treatment.

Results: According to FGMS monitoring data, liraglutide add-on treatment significantly improved general, within-day, and day-to-day glucose variability and the glucose-target-rate. Further, the specifically analysed blood glucose levels at different time periods showed that blood glucose levels significantly decreased at nocturnal, fasting, and postprandial periods after add-on treatment. The incidence of hypoglycaemia was comparable during the whole day, daytime, and night-time according to the prespecified cutoffs (3.9 mmol/L and 3.0 mmol/L) before and after add-on treatment. Analysis of other assessed parameters revealed significant differences in glycosylated hemoglobin A1c and fasting blood glucose levels as well as parameters of β-cell function and insulin resistance before and after add-on treatment.

Conclusion: In type 2 diabetes mellitus, liraglutide treatment can effectively decrease glucose variability and ameliorate hyperglycaemia without increasing the incidence of hypoglycaemia. In addition, liraglutide can significantly improve the β-cell function and insulin resistance.

Keywords: glucagon-like peptide-1 receptor agonist, glucose variability, glucose target rate, time in range, β-cell function, insulin resistance

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Introduction

Owing to its increasing prevalence and incidence, diabetes mellitus has always been a focal point of the general interest and a facing challenge worldwide. Due to its progressive nature, an optimum management should be individualised and modified

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along the course, in a complementary manner of maximum glycaemic effect and minimum adverse episodes. The commonly used antidiabetic agents such as insulin secretagogues or insulin are efficacious, but they confer a major risk of severe hypoglycaemia events. Liraglutide,[1] a newly developed human glucagon-like peptide-1 (GLP-1) receptor agonist, contributed to hyperglycaemia amelioration in a strictly glucose-dependent manner without increasing the incidence of hypoglycaemia. A seminal review on a series of Phase III trials has provided strong evidence regarding the therapeutic effect of liraglutide as monotherapy or in combination with other oral antidiabetic drugs on blood glucose levels, β-cell function, incidence of hypoglycaemia, and weight loss.[2] Since then, a series of notable studies have provided data supporting its superiority in these aspects.[3–5]

The flash glucose monitoring system (FGMS) is a new sensor-based scanning glucose monitoring system that indirectly reflects the blood glucose levels by detecting interstitial fluid glucose concentrations. It is convenient, visual, and easy to operate compared to the traditional self-monitoring blood glucose or continuous glucose monitoring system.[6,7] Emerging data have confirmed the accuracy and safety of FGMS as well as its high patient acceptability and satisfaction.[8–10] In this study, the FGMS was used for continuous glucose monitoring and providing blood glucose values throughout the day, allowing blood glucose control assessed from dynamic glucose monitoring perspective, and offering reliable and new insights into the therapeutic effect of liraglutide.

In this study, the FGMS was used to monitor the blood glucose alterations, including glucose variability (GV), blood glucose levels of specific periods, and the incidence of hypoglycaemic, in patients with type 2 diabetes mellitus (T2DM) before and after liraglutide add-on treatment, initiated due to poor glycemic control for >2 months on metformin monotherapy (1.5 g per day). Furthermore, β-cell function and insulin resistance (IR) were also assessed in these patients. In this study, we have provided real-world evidence and guidance for the clinical application of liraglutide in patients with T2DM.

Patients and Methods

The study was conducted at the First Hospital of Shanxi Medical University from August 2018 to April 2021. The study protocol was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the First Hospital of Shanxi Medical University (2018K008), and patients provided informed consent.

Subjects

Patients with T2DM (diagnosed according to the 1999 World Health Organization's Diabetes Diagnostic Criteria), who volunteered to receive liraglutide treatment for better blood glucose management, were enrolled in this study. The inclusion criteria were as follows: diabetes duration of 2–10 years; metformin (≥1.5 g per day) monotherapy with poor glycaemic control; age between 18 and 70 years; baseline glycosylated hemoglobin A1c (HbA1c) level between 7% and 10%; and body mass index >24 kg/m^2. Patients with diabetic nephropathy stage ≥IV, those with severe liver and renal insufficiency, those with thyroid diseases or a family history of medullary thyroid carcinoma, and those with a history of pancreatitis and pancreatic tumours were excluded.

Methods

All the recruited patients received diabetes health education and wore the FGMS to monitor glucose levels for 2 weeks. After FGMS monitoring, these patients were treated with liraglutide for 3 months, during which the current hypoglycaemic regimen was continued (metformin: 1.5 g per day), and other GLP-1 receptor agonists and dipeptidyl peptidase-IV inhibitors could not be used. The recommended starting liraglutide dose was 0.6 mg daily, which was adjusted every week in the first month until a final dose of 1.8 mg per day. All patients were treated with liraglutide 1.8 mg per day for the next 2 months. After the 3-month add-on treatment, the FGMS was used for 2 weeks to monitor blood glucose levels in these patients. Due to the inaccuracy of FGMS monitoring data at the first day of installation or other unexpected events, it was difficult to achieve a complete 2-week monitoring data. In total, 349-day and 364-day monitoring data were collected before and after add-on treatment, respectively. During the study period, all patients were requested to comply with a diabetic diet and exercise regimen. The meal was offered at 7:00, 12:00, and 18:00 during the day, consisting of 50% of carbohydrates, 35% of fats, and 15% of protein, with a caloric intake ratio of 2:4:4. A 30-minute exercise regimen (eg, walk, jogging, or biking) was recommended after a meal three to five times a week.

In addition, the levels of the following indices were tested before and after liraglutide add-on treatment:

HbA1c, fasting blood glucose (FBG, mmol/L), and fasting insulin (FINS, μIU/mL). The IR and β-cell function were assessed using homeostasis model assessment (HOMA)-IR, quantitative insulin sensitivity check index (QUICKI), fasting glucose-to-insulin ratio (G/I), and HOMA-β.

Statistical Processing

SPSS 19.0 and Sigmaplot 12.5 software were used for statistical analysis and graph construction. $P < 0.05$ was considered statistically significant. All values are expressed as mean±standard error of mean unless otherwise stated. Some data are expressed as median (first quartile, third quartile) due to the wide distribution.

The FGMS data were used to calculate the following parameters: 24-hour mean of blood glucose (24hMBG) and coefficient variable (CV) representing general GV; standard deviation of blood glucose (SDBG), mean amplitude of glycaemic excursions (MAGE) and large amplitude of glycaemic excursions (LAGE) indicating within-day GV; mean of daily differences (MODD), area of interquartile range (IQR), and area of interdecile range (IDR) showing day-to-day GV; and percentile time (PT, PT1: blood glucose level <3.9 mmol/L; PT2: 3.9–10 mmol/L; and PT3: >10 mmol/L), time in range (TIR), and time out of range (TOR) representing the glucose-target-rate. These parameters were compared before and after add-on treatment using a *t*-test (for normally distributed data) or the Mann–Whitney test (for skewed data). The normal range of the blood glucose levels was set as 3.9–10.0 mmol/L.

The blood glucose levels were specifically analysed at five periods before and after add-on treatment, including nocturnal period (0:00–6:00), fasting period (6:00–7:00), and postprandial periods (7:00–9:00, 12:00–14:00, and 18:00–20:00). The mean blood glucose level at each time point in each patient were drawn as multiple-line and scatter diagram and the area under the curve (AUC) of each analysed period was calculated. A *t*-test or the Mann–Whitney test was used to compare the AUC in each time period before and after add-on treatment.

The incidence of hypoglycaemia was evaluated during three time periods, including the whole day (0:00–24:00), daytime (6:00–24:00), and night-time (0:00–6:00). A blood glucose <3.9 mmol/L or 3.0 mmol/L were used as the cut–off. A *t*-test or the Mann–Whitney test was used to compare the incidence of hypoglycaemia during the time periods before and after add-on treatment.

The parameters of IR and β-cell function were calculated using the following formulas: HOMA-IR = (FBG×FINS)/22.5; QUICKI = 1/[(logFINS)+(logFBG)]; G/I = FBG/FINS; and HOMA-β = (20×FINS)/(FBG–3.5). These indices, HbA1c, FBG, and FINS were compared before and after add-on treatment using a *t*-test or the Mann–Whitney test.

Results

General Characteristics of the Recruited Patients

The clinical characteristics of the patients are showed in Table 1. A total of 33 patients (18 males and 15 females) aged (50.061±0.774) years with a duration of diabetes mellitus of 6.455±0.329 years were enrolled.

Glucose Variability

The parameters representing general GV showed that 24hMBG was significantly decreased after add-on treatment compared to that before ($P < 0.001$), while CV was comparable before and after add-on treatment (Figure 1). Parameters of within-day GV indicated significantly lower SDBG and LAGE after add-on treatment than that before ($P < 0.001$, and $P = 0.002$, respectively); however, no significant difference was found in MAGE before and after treatment (Figure 2). Regarding day-to-day GV, significant differences were identified in MODD ($P = 0.002$), and areas of IQR ($P < 0.001$) and IDR ($P = 0.001$) before and after add-on treatment (Figure 2). Indices representing the glucose-target-rate revealed significantly decreased PT3 and TOR and significantly increased PT2 and TIR after add-on treatment compared to that before. However, PT1 was not significantly different before and after add-on treatment, implying that liraglutide treatment satisfied the antidiabetic effect without increasing the incidence of hypoglycaemia (Figure 1).

Blood Glucose Levels at Different Time Periods

According to Figure 3A, there was a great tendency of reduced general blood glucose level after add-on treatment compared to that before. Further comparison of the blood glucose levels at specific periods before and after add-on treatment showed significantly decreased blood glucose levels during nocturnal, fasting, and postprandial periods (Figure 3).

Table 1 General Characteristics of the Recruited Subjects

Parameters	Values
Gender (male:female)	18:15
Age (years)	50.061±0.774
Duration of diabetes (years)	6.455±0.329
Body mass index (kg/m^2)	27.509±0.759
Metformin dose (g/day)	1.5

Note: Part of the data were denoted as mean±standard error of mean.

Hypoglycaemia Incidence

There was no marked difference revealed in the incidence of hypoglycaemia episodes during the whole day, daytime, and night-time according to the prespecified cutoffs (3.9 mmol/L and 3.0 mmol/L) before and after add-on treatment (Table 2).

Metabolic Indicators

The results of the metabolic indicators are showed in Table 3. There was no significant difference in body mass index before and after treatment. A significant difference was identified in the parameters of HbA1c, and FBG before and after add-on treatment ($P < 0.001$, and $P = 0.003$, respectively). The parameters of IR revealed that significantly decreased HOMA-IR ($P = 0.003$) and G/I ($P = 0.012$), and increased QUICKI ($P = 0.024$) after add-on treatment compared to that before. Comparison of HOMA-β before and after add-on treatment indicated a significant difference ($P < 0.001$). No significance was found in FINS levels before and after treatment. Taken together, these results demonstrated significantly improved general blood glucose levels, IR, and β-cell function.

Discussion

Diabetes mellitus is a complex entity, characterized by IR and progressive β-cell deterioration, manifested as hyperglycaemia state, usually accompanied with a constellation of complications. There is overwhelming evidence for the involvement of IR and hyperglycaemia in the pathogenesis

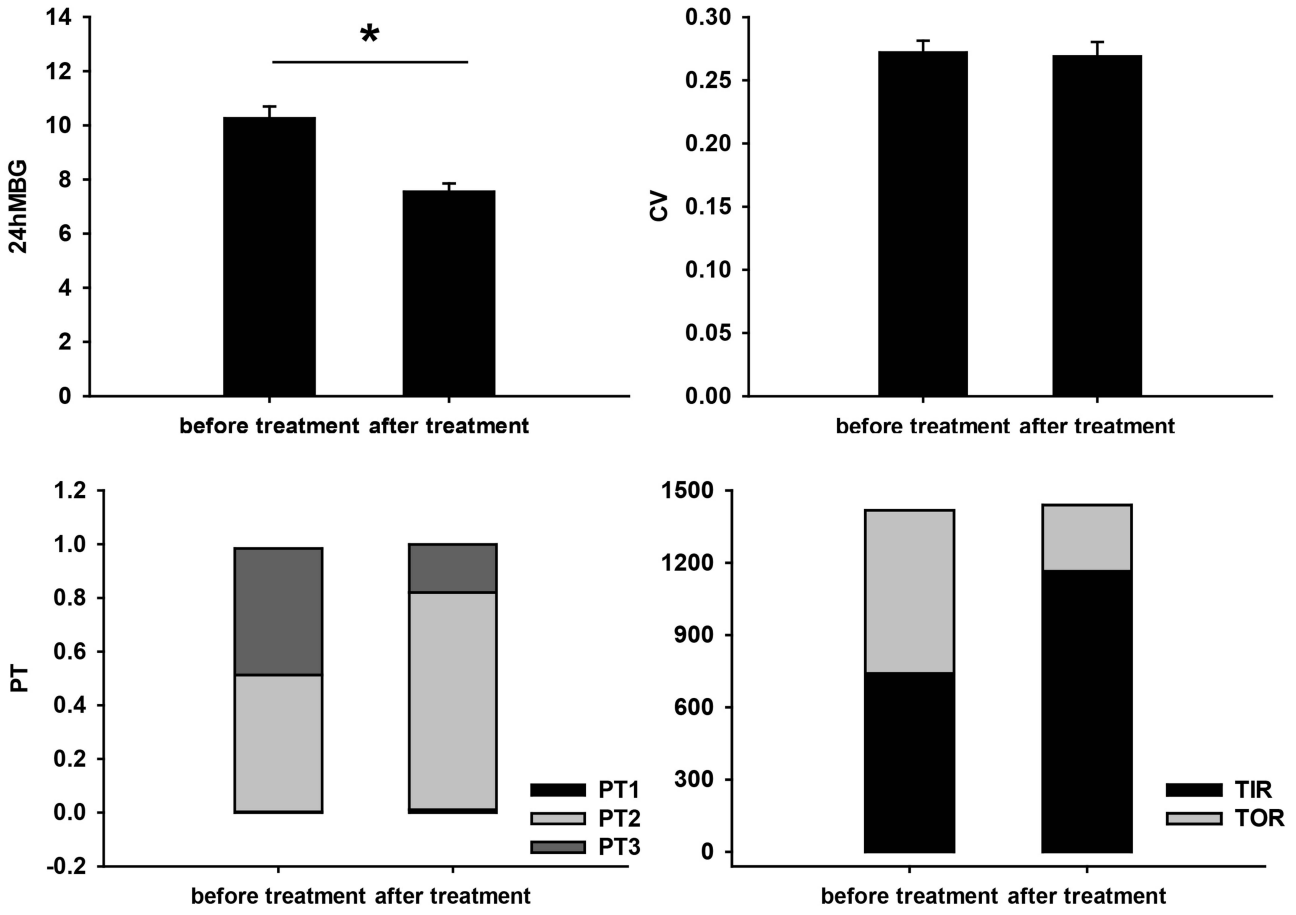

Figure 1 Comparison of general GV and the glucose-target-rate before and after liraglutide add-on treatment. The values are presented as mean±SEM. *Represents significant difference (P<0.05).

Abbreviations: GV, glucose variability; SEM, standard error of mean.

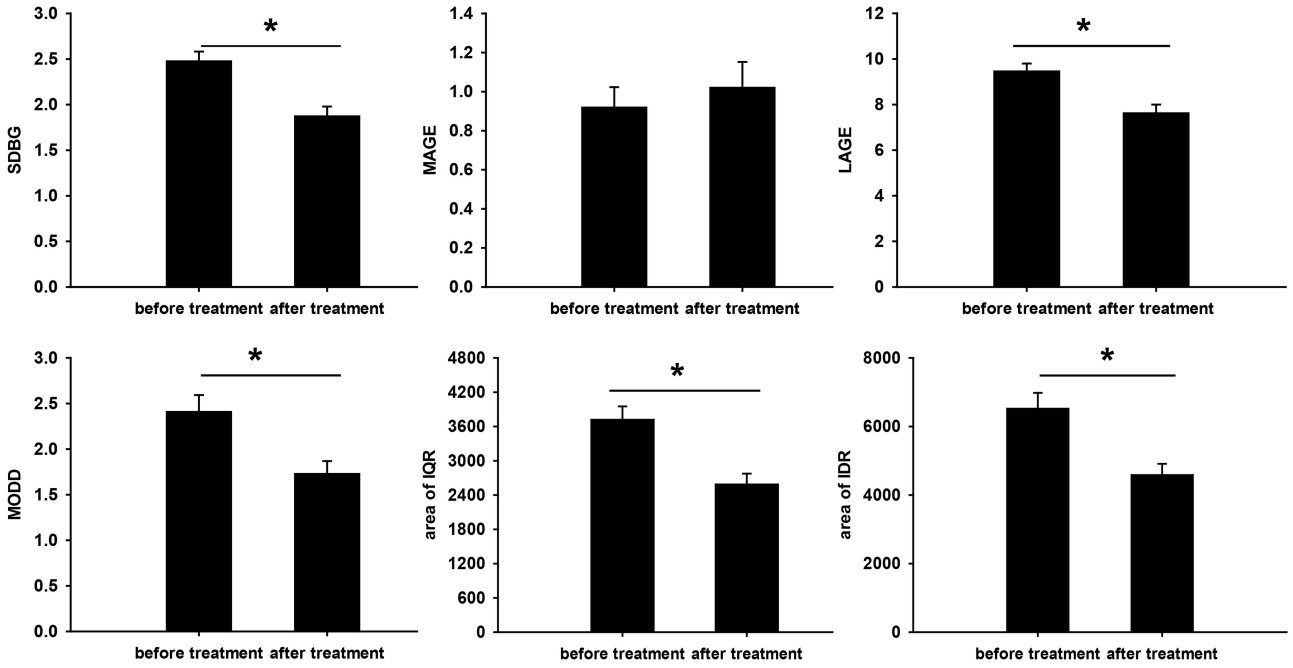

Figure 2 Comparison of within-day and day-to-day GV before and after liraglutide add-on treatment. The values are presented as mean±SEM. *Represents significant difference (P<0.05).
Abbreviations: GV, glucose variability; SEM, standard error of mean.

of vascular endothelial injury, inflammation reaction, and oxidative stress, and ensuing micro- and macro-angiopathy in patients with diabetes.[11] Another perspective that should be underlined was the valued role of GV in this setting, which is an emerging field that is attracting the interests of many researchers.[12,13] Reducing GV, namely the amplitude, frequency, and duration of the upward and downward glucose fluctuations, is a key component of the glucose–lowering therapy. Over the past few years, a considerable body of evidence from studies has indicated improved prognosis of diabetes-related complications when to intervene in GV and maintain a stable glycaemic state.[14] In addition, some proof has suggested the major and indispensable role of hypoglycaemia in the progression of diabetes and its complications.[15] Therefore, in patients with diabetes, simply controlling of blood glucose within the normal range may have a preventive effect on disease progression, but it is clinically crucial to pay attention to other contributors, in particular GV and occurrence of hypoglycemia.

Liraglutide, a novel GLP-1 receptor agonist, has fuelled considerable interests worldwide due to its safe and effective hypoglycaemic effect, and various clinical benefits. Large amounts of researches have provided ground for its therapeutic effects.[2–5] Recently, the dual GLP-1/glucagon receptor agonists, SAR425899, sparked much interest in the scientific community. Comparison investigation studies were performed between liraglutide and SAR425899, showing comparable blood glucose improvement and higher enhancement of β-cell function with SAR425899 in patients with obesity and T2DM.[16] In addition, clinical studies comparing liraglutide with other GLP-1 receptor agonists have reported inconsistent results.[5,17,18] Therefore, this study explored the liraglutide's therapeutic effect from a continuous glucose monitoring perspective, promising to offer real-world credence for its widespread application.

Analysis of GV parameters revealed that liraglutide add-on therapy decreased the general, within-day, and day-to-day GV, and improved the glucose target rate. Our findings are consistent with those of previous researches and further expanded and added credence to previous findings in this area. In the past few years, ever-growing researches demonstrated the decreased GV with liraglutide treatment, focusing on the indices of MAGE, LAGE, MODD, and SD.[14] This study provided novel evidence on general, within-day, and day-to-day GV, and the glucose-target-rate as a proper reference for clinical practice.

To date, the majority of evidence collected suggests the involvement of fluctuating blood glucose levels in the pathogenesis of diabetic complications, via increased production of reactive oxygen species and

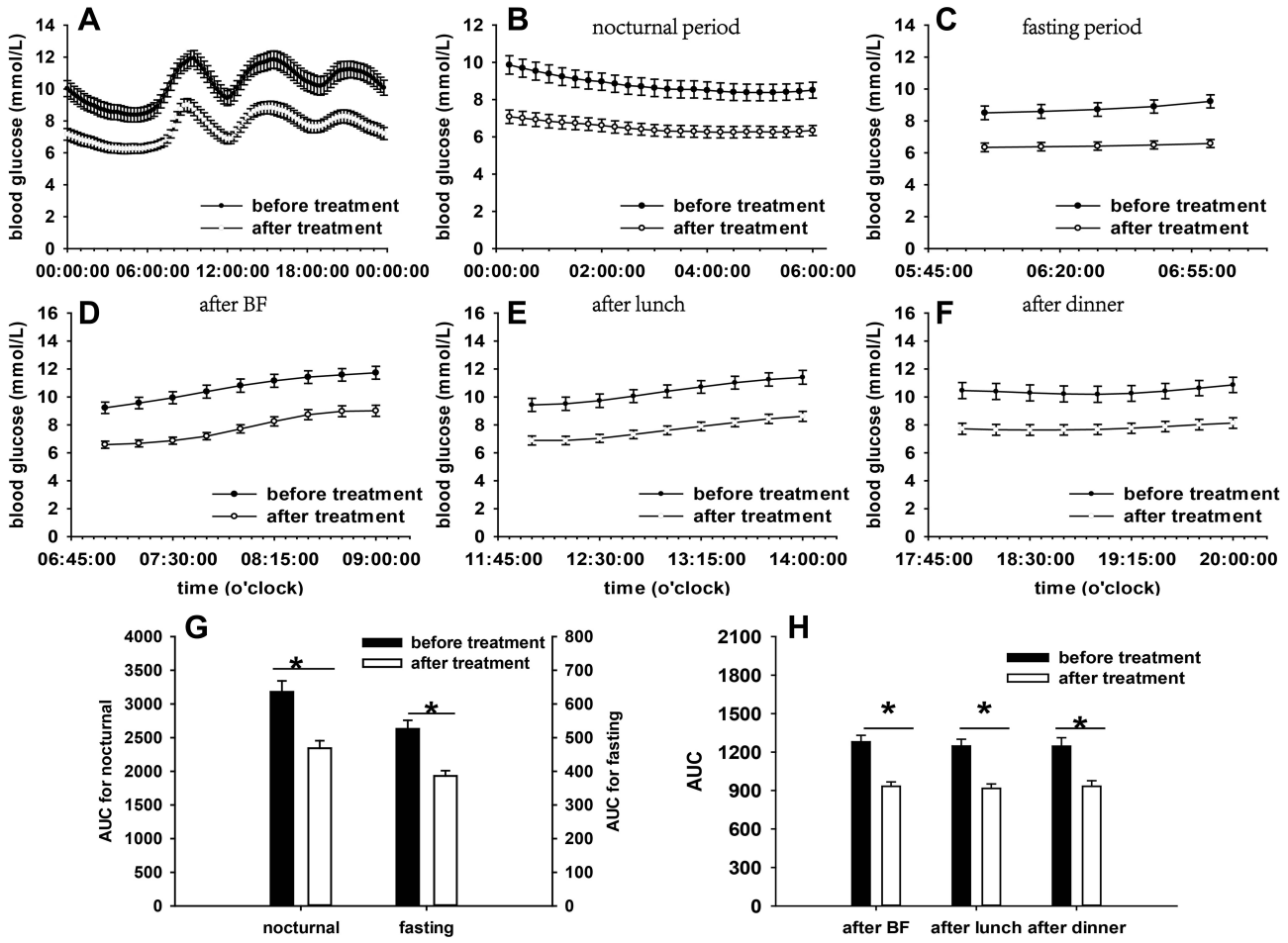

Figure 3 Comparisons of mean blood glucose levels and AUCs before and after liraglutide add-on treatment. Mean blood glucose levels: (**A**) during the day; (**B**) at nocturnal period; (**C**) at fasting period; (**D**) after BF; (**E**) after lunch; (**F**) after dinner. AUC: (**G**) at nocturnal and fasting periods; (**H**) at postprandial periods. The values are presented as mean±SEM. *Represents statistically different AUC in this time period (P<0.05).

Abbreviations: AUC, area under curve; BF, breakfast; SEM, standard error of mean.

advanced glycation end products, for example.[19,20] Furthermore, studies investigating the relationship between TIR and diabetic macro- or micro-angiopathy have highlighted negative correlations.[21–24] The increment of TIR is proportional to vascular lesion occurrence, such as, retinopathy and microalbuminuria, and mortality hazard reduction. This study observed significantly decreased GV, specifically, the TIR increased by 57% after liraglutide treatment compared to that before. Therefore, liraglutide treatment improved GV in the recruited patients, which further decreased the risks of diabetic complications along the course of the disease. Long-term observational studies are required to prove this conclusion.

Table 2 The Incidence of Hypoglycaemia Before and After Treatment

			Before Treatment	After Treatment	P value
Hypoglycaemia incidence (%)	Hypoglycaemia cutoff: 3.9 mmol/L	The whole day	0 (0, 0)	0 (0, 1.09)	0.123
		Daytime	0 (0, 0)	0 (0, 0.537)	0.076
		Night-time	0 (0, 0)	0 (0, 0.272)	0.12
Hypoglycaemia incidence (%)	Hypoglycaemia cutoff: 3.0 mmol/L	The whole day	0 (0, 0)	0 (0, 0)	0.24
		Daytime	0 (0, 0)	0 (0, 0)	0.988
		Night-time	0 (0, 0)	0 (0, 0)	0.189

Notes: The data were shown as median (first quartile, third quartile). The whole day (0:00–24:00), daytime (6:00–24:00), and night-time (0:00–6:00).

Table 3 Comparison of Metabolic Indicators Before and After Treatment

Variables	Before Treatment	After Treatment	P value
Body mass index (kg/m^2)	27.509±0.759	26.893±0.784	0.261
HbA1c (%)	7.876±0.211	6.221±0.235	0.001
FBG (mmol/L)	9.821±0.331	6.289±0.198	0.003
FINS (μIU/mL)	17.942±1.496	18.426±1.847	0.934
HOMA-IR	8.016±0.759	5.344±0.569	0.003
QUICKI	0.472±0.0137	0.522±0.0179	0.024
G/I	0.771±0.0926	0.469±0.0447	0.012
HOMA-β	58.847±5.35	136.757±13.317	0.001

Note: The data were denoted as mean±standard error of mean.
Abbreviations: HbA1c, glycosylated hemoglobin A1c; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance; QUICKI, quantitative insulin sensitivity check index; G/I, fasting glucose-to-insulin ratio.

Blood glucose levels during nocturnal, fasting, and postprandial periods significantly decreased after add-on treatment compared to those before. In addition, the incidence of hypoglycaemia was comparable during the whole day, daytime, and night-time with both the cutoffs before and after add-on treatment. These results indicate that liraglutide treatment in patients with can produce a positive therapeutic effect in diabetic management without increasing the incidence of hypoglycemia. These results add to the existing body of evidence on the effectiveness of liraglutide in the glycaemic control and its safety. The landmark Phase III clinical trials reported significantly decreased fasting and postprandial blood glucose levels without an increased risk of hypoglycaemia.[25–27] Consistent with the previously established conclusion, our study provided convincing proof at time periods perspective, showing significantly decreased blood glucose levels on the whole, and at nocturnal, fasting, and postprandial periods.

It is well established that liraglutide, a GLP-1 receptor agonist, is akin to human endogenous GLP-1 with 97% structure homology, exhibiting similar pharmacodynamics effects, longer half-life, and refractory to degradation compared to that of human GLP-1.[1] Classified as incretin mimetics, liraglutide promotes glucose-dependent insulin secretion and suppresses glucagon secretion, leading to postprandial glycaemic control. Further, the effect of liraglutide on gastric emptying and satiety also plays a critical role in decreasing postprandial blood glucose levels, except for the weight-loss effect. In addition, reduced hepatic glucose output may be relevant to the fasting glycaemic control.[28,29]

Data on the other metabolic parameters indicated significant differences in HbA1c level, FBG level, HOMA-IR, QUICKI, G/I, and HOMA-β before and after add-on treatment. According to these results, one can speculate that liraglutide treatment significantly improved glycaemic control, IR, and β-cell function. However, no significance was found in body mass index before and after treatment. This study did not observe a significant weight loss effect, which is inconsistent with the findings of previous research.[4] Long-term follow-up for weight monitoring was arranged to evaluate the weight loss efficacy of liraglutide.

Consistent with the results of this study, several converging lines of data have suggested the superiority of liraglutide in terms of β-cell preservations. The underlying evidence is based on observations of liraglutide's protective effect in β-cell along with suppressing effect in their apoptosis.[30,31] Previous studies have struggled to prove the insulin sensitivity restoration with liraglutide intervention in a diabetic animal model, illuminating the involvement of reversely increased gene expression of glucose transporter 4 and counteraction of endoplasmic reticulum stress.[32,33] However, clinical studies evaluating the effect of liraglutide treatment on IR in the Asian population have yielded to negative outcomes.[34,35] In the current study, significantly improved IR was noted after liraglutide add-on treatment, lending support to the established conclusion in the animal experiments. Notably, further studies will be necessary to elucidate the therapeutic effect of liraglutide on IR with large samples.

In summary, the management of patients with T2DM with poor glycaemic control is a long and arduous journey, among which lifestyle adaptation is acknowledged as a key component. On the basis of diet and exercise modification, the use of liraglutide combined with oral hypoglycaemic therapy can achieve early and long-term protection of islet

β cells and improve IR, effectively manage GV and hyperglycaemia without increasing the incidence of hypoglycaemia, further suspending the development of diabetic complications. As a new clinical drug, liraglutide's efficacy has been proven by previous reliable studies. The results of this study illustrated its therapeutic effect from a dynamic blood glucose monitoring perspective. However, it is expected that the larger sample sizes and even multi-center clinical observations will verify our results in the future.

Conclusion

This study showed the therapeutic effect of liraglutide from a dynamic glucose monitoring perspective. Using FGMS, this study demonstrated that liraglutide add-on treatment achieved desired outcomes in terms of GV, period glucose levels, and incidence of hypoglycemia. In addition, β-cell function and IR also significantly improved after treatment. Notably, large-scale or multicentre researches are needed to confirm these results. Owing to the ever-growing attention on the adverse effect of GV, it is of paramount importance to exploit FGMS to monitor glucose levels in T2DM to make medication adjustments to reduce GV and increase TIR, further mitigating the progression of diabetic complications.

Abbreviations

GLP-1, glucagon-like peptide-1; FGMS, flash glucose monitoring system; T2DM, type 2 diabetes mellitus; GV, glucose variability; IR, insulin resistance; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin A1c; FINS, fasting insulin; HOMA, homeostasis model assessment; QUICKI, quantitative insulin sensitivity check index; G/I, fasting glucose-to-insulin ratio; 24hMBG, 24-hour mean blood glucose; CV, coefficient variable; SDBG, standard deviation of blood glucose; MAGE, mean amplitude of glycaemic excursions; LAGE, large amplitude of glycaemic excursions; MODD, mean of daily differences; IQR, interquartile range; IDR, interdecile range; PT, percentile time; TIR, time in range; TOR, time out of range.

Consent for Publication

All authors provided written consent to publish this study.

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Author Contributions

All authors contributed to data analysis, and drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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