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*Observational Study*

**Effect of glucagon-like peptide-1 receptor agonists on glucose excursion and inflammation in overweight or obese type 2 diabetic patients**

Huang XM *et al.* GLP-1RA controlled glucose excursion and inflammation

## **Abstract**

### **BACKGROUND**

Currently, the lack of comparative studies between weekly and daily formulations of glucagon-like peptide-1 receptor agonists (GLP-1RA) for glucose excursion is worthy of investigation.

### **AIM**

To investigate the effects of weekly and daily formulations of GLP-1RA on glucose excursion and inflammation in overweight and obese patients with type 2 diabetes.

### **METHODS**

Seventy patients with type 2 diabetes mellitus who were treated at our hospital between January 2019 and January 2022 were enrolled in this retrospective analysis. All patients were treated with metformin. We evaluated changes in blood glucose levels and a series of important indicators in patients before and after treatment with either a weekly or daily preparation of GLP-1RA (group A;  $n = 33$  and group B;  $n = 37$ , respectively).

### **RESULTS**

The degree of decrease in the levels of fasting blood glucose, mean blood glucose, mean amplitude of glycemic excursions, total cholesterol, triglycerides, tumor necrosis factor- $\alpha$ , interleukin-6, and high-sensitivity C-reactive protein after treatment in group A was higher than that in group B ( $P < 0.05$ ), whereas the 2 h postprandial blood glucose levels decreased more so in group B than in group A ( $P < 0.001$ ). However, there were no statistically significant differences in the levels of glycated hemoglobin, standard deviation of blood glucose, coefficient of variation, absolute mean of daily differences, percentage of time with  $3.9 \text{ mmol/L} < \text{glucose} < 10 \text{ mmol/L}$ , and high- and low-density lipoproteins between the two groups ( $P > 0.05$ ). The incidence of adverse reactions was significantly lower in group A than in group B ( $P < 0.05$ ).

## CONCLUSION

The effect of the weekly preparation of GLP-1RA in controlling blood glucose levels in the patients, suppressing inflammation, and reducing adverse reactions was significantly higher than that of the daily preparations, which is worthy of clinical promotion.

**Key Words:** Glucagon-like peptide-1 receptor agonists; Weekly preparation; Daily preparation; Overweight or obese; Type 2 diabetes mellitus; Glucose excursion; Inflammation

Huang XM, Zhong X, Du YJ, Guo YY, Pan TR. Effect of glucagon-like peptide-1 receptor agonists on glucose excursion and inflammation in overweight or obese type 2 diabetic patients. *World J Diabetes* 2023; In press

## INTRODUCTION

The prevalence of diabetes is increasing worldwide, with nearly 500 million people living with diabetes and is expected to increase by 25% by 2030 and 51% by 2045<sup>[1]</sup>. Currently, the prevalence of diabetes in China is as high as 11.2% and patients with type 2 diabetes mellitus (T2DM) account for > 90% of the population. However, the awareness rate (36.5%), treatment rate (32.2%), and control rate (49.2%) of diabetes are low, and the prevalence of diabetes in obese and overweight individuals has increased dramatically; therefore, standardized diagnosis and treatment of the disease is vital<sup>[2]</sup>. Glucose excursion has become a new and important indicator for assessing glycemic control in treating diabetes. Numerous studies have confirmed that the occurrence and development of chronic complications of diabetes are not only related to overall blood glucose levels but also more closely associated with glycemic fluctuations, which are independent risk factors for chronic complications of diabetes<sup>[3]</sup>. Continuous glucose monitoring systems can monitor blood glucose fluctuations continuously for 24 h, detect nocturnal asymptomatic hypoglycemia and postprandial hyperglycemic states

that are easily overlooked by self-glucose monitoring, and accurately assess fluctuating changes in blood glucose in diabetic patients<sup>[4]</sup>.

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have received much attention because of their unique glucose-lowering mechanisms, which mainly include a glucose concentration-dependent approach to promote insulin release, inhibit glucagon secretion, protect  $\beta$ -cells to increase their numbers, reduce hepatic glucose output, suppress appetite to increase satiety, and delay gastric emptying and gastrointestinal motility to lower blood glucose levels and reduce body weight<sup>[5-7]</sup>. In addition to these mechanisms, the role of GLP-1RA in suppressing inflammation is currently receiving widespread attention. Diabetes mellitus is a complex chronic metabolic disease that requires continuous medical management with glycemic control along with multifactorial risk reduction strategies (*e.g.*, blood pressure, lipid, and weight control)<sup>[8,9]</sup>.

GLP-1RA is another injectable agent other than insulin in the treatment of T2DM, which is divided into two categories: Daily and long-acting weekly agents according to the duration of action, among which the clinical use of weekly agents greatly reduces the number of injections and increases patient compliance, which is one of the important factors for long-term glycemic control in diabetic patients<sup>[10]</sup>. The weekly formulation has good prospects for clinical application as a once-weekly injection regimen. The current lack of comparative studies between weekly and daily formulations of GLP-1RA on glucose excursion is worthy of in-depth exploration, especially for providing a new avenue for improving patient compliance and glycemic control in clinical treatment.

## **MATERIALS AND METHODS**

### ***Clinical data***

Seventy patients with T2DM who were treated at our hospital between January 2019 and January 2022 were enrolled in this retrospective analysis. All patients were treated with metformin. Specifically, patients were treated with either a weekly or daily

preparation of GLP-1RA (group A;  $n = 33$  and group B;  $n = 37$ , respectively). This study was approved by our Medical Ethics Committee.

### ***Inclusion and exclusion criteria***

The inclusion criteria were as follows: (1) Patients with symptoms that met the latest World Health Organization diagnostic criteria for diabetes mellitus<sup>[11]</sup>; (2) 18-60 years old; (3) Metformin monotherapy of up to 1500 mg in the last three months for substandard glucose control; (4) 7.5%-10.0% glycated hemoglobin (HbA1c); and (5)  $24 \text{ kg/m}^2 \leq \text{body mass index (BMI)} \leq 35 \text{ kg/m}^2$ .

Exclusion criteria: (1) Type 1 diabetes or other specific types of diabetes; (2) T2DM combined with acute complications of diabetes, infection, or stress; (3) Severe liver, kidney, and gastrointestinal diseases (alanine aminotransferase and aspartate aminotransferase 2.5 times higher than the upper limit of normal, bilirubin 1.5 times higher than the upper limit of normal, and blood creatinine  $> 106 \text{ } \mu\text{mol/L}$ ); (4) Myocardial infarction and chronic cardiac insufficiency (NYHA classes III-IV); (5) History of acute or chronic pancreatitis; (6) Patients with thyroid disease or serum calcitonin levels  $> 20 \text{ pg/mL}$ ; and (7) Pregnancy, lactation, or planning a pregnancy in the near future.

### ***Treatment options***

All patients received an education on diabetes knowledge from dedicated staff, followed by the diet and appropriate amount of post-meal exercise as specified by a physician; they could skillfully apply the blood glucose meter for self-measurement, and all blood glucose meters were calibrated before use. This was combined with 500 mg of metformin three times daily. Patients in group A were started with dulaglutide (Eli Lilly Nederland B.V., S20190021, the Netherlands) 0.75 mg subcutaneously once a week and increased to 1.5 mg once per week after one week if formamidopyrimidine DNA glycosylase (FPG)  $> 7.0 \text{ mmol/L}$  or 2-h plasma glucose (2hPG)  $> 11.0 \text{ mmol/L}$  was measured. Patients in group B started with 0.6 mg of liraglutide subcutaneously

once daily and increased to 1.2 mg twice daily if FPG > 7.0 mmol/L or 2hPG > 11.0 mmol/L was measured after one week and increased to 1.8 mg once daily if FPG > 7.0 mmol/L or 2hPG > 11.0 mmol/L was measured after one week. Patients who were originally taking oral antihypertensive and lipid-regulating drugs continued the original regimen.

#### ***Ambulatory glucose monitoring indicators***

Patients wore a 72-h ambulatory continuous glucose monitor (CGM; MMT-7745; Medtronic, Minneapolis, MN, United States) before and after 12 wk of treatment, and monitored three times a day before meals and before bedtime as well as fasting fingertip glucose to calibrate ambulatory glucose values. The software analysis system was used to process the blood glucose data to derive the following parameters: 24-h mean blood glucose (MBG), 24-h standard deviation of blood glucose (SDBG), coefficient of variation (CV%), mean amplitude of glycemic excursions (MAGE), absolute mean of daily differences (MODD), and percentage of time with 3.9 mmol/L < glucose < 10 mmol/L (TIR).

#### ***Outcome measures***

The main outcome measures were as follows: Blood glucose levels [plasma fasting blood glucose (FBG), 2 h postprandial blood glucose (2h PBG), and HbA1c] were compared before and after treatment between the two groups. The changes in ambulatory glucose monitoring indices, including MBG, SDBG, CV%, MAGE, MODD, and TIR, were compared between the two groups.

The secondary outcome measures were as follows: The baseline clinical data of the two groups were compared. The incidence of adverse reactions and changes in lipid indices (total cholesterol and triglyceride levels) were compared between the two groups. The levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) were compared between the two groups before

and after treatment using an enzyme-linked immunosorbent assay, and the changes in BMI were compared before and after treatment.

Before and after 12 wk of treatment, the patient was equipped with a 72-h ambulatory CGM (medtronic), which monitored fasting fingertip blood glucose three times a day before meals and before bedtime. A software analysis system was used to process blood glucose data to obtain the following parameters: MBG, SDBG, CV%, MAGE, MODD, and TIR.

### *Statistical analysis*

The counting data were expressed as rates and counted by chi-square test. The measurement data were expressed as (mean  $\pm$  SD), and the paired sample *t*-test was used for intra-group comparison before and after treatment, and the independent sample *t*-test was used for inter-group comparison.  $P < 0.05$  indicates that the difference is statistically remarkable. All statistical analyses were performed using SPSS 20.0 software.

## **RESULTS**

### *Clinical baseline data*

The clinical data of the two groups were compared. And there was no statistical difference in age, gender, course of disease, BMI, and history of hypertension and smoking between patients in group A and group B ( $P > 0.05$ , Table 1).

### *Changes in blood glucose levels*

Comparison of the changes in blood glucose levels and islet cell function between the two groups revealed that FBG, 2h PBG and HbA1c decreased significantly in both groups after treatment ( $P < 0.05$ ). Among them, FBG decreased more in group A than in group B after treatment, and 2h PBG decreased more in group B than in group A ( $P < 0.001$ , Figure 1). There was no difference in HbA1c between the two groups after treatment ( $P > 0.05$ ).

### *Changes in dynamic indicators of patients' blood glucose*

The dynamic indicators of blood glucose before and after treatment in the two groups were found to be statistically non-different in MBG, SDBG, CV%, MAGE, MODD, and TIR before treatment in the two groups ( $P > 0.05$ , Figure 2). Patients were treated with a significant decrease in MBG, SDBG, CV%, MAGE, and MODD in both groups compared to pre-treatment, while TIR increased dramatically ( $P < 0.001$ , Figure 2). Further comparison revealed that MBG and MAGE were significantly lower in group A than in group B ( $P < 0.01$ , Figure 2), but there was no statistical difference in SDBG, CV%, MODD, and TIR between both groups ( $P > 0.05$ , Figure 2).

### *Changes in patients' blood lipid indexes*

In this study, we also examined the changes in the lipid indexes of patients. Total cholesterol, triglyceride and low-density lipoprotein (LDL) levels were significantly lower and high-density lipoprotein (HDL) levels were significantly higher ( $P < 0.01$ ) in both groups after treatment compared to those before treatment. Among them, total cholesterol and triglyceride levels decreased more in group A than in group B after treatment ( $P < 0.05$ , Figure 3), but there was no difference between HDL and LDL ( $P > 0.05$ ).

### *Changes in inflammatory factor levels in patients*

In this study, we also detected changes in inflammatory factors in patients. <sup>2</sup> The levels of TNF- $\alpha$ , IL-6 and hs-CRP were significantly lower in both groups after treatment compared with those before treatment ( $P < 0.01$ ). Among them, the level of TNF- $\alpha$ , IL-6 and hs-CRP decreased to a greater extent in group A than in group B after treatment ( $P < 0.05$ , Figure 4).

### *Analysis of adverse reactions*

Comparison of the adverse reactions between the two groups revealed that the incidence of adverse reactions was significantly lower in group A than in group B. There was a statistical difference ( $P < 0.05$ , Table 2).

#### *Changes in BMI after treatment*

In this study, we also examined the changes in BMI before and after treatment in both groups. Patients in both groups showed a significant decrease in BMI through treatment ( $P < 0.05$ ), with patients in group A showing a higher decrease in BMI after treatment than those in group B ( $P < 0.001$ , Table 3).

### **DISCUSSION**

Studying the causes of T2DM has expanded from the well-known deficiency of islet  $\beta$ -cell secretion, increased hepatic glycogen output, and decreased muscle glucose uptake to lipid metabolic disorder, weakening of the effect of intestinal glucagon, inappropriate secretion of glucagon in islet  $\alpha$ -cells, increase of glucose reabsorption by renal tubules, and hypothalamic regulatory disorder of blood glucose<sup>[12-14]</sup>.

Numerous types of drugs are available for the treatment of T2DM, including insulin promoters, insulin sensitizers,  $\alpha$ -glucosidase inhibitors, insulin or insulin analogs, dipeptidyl peptidase 4 inhibitors, and sodium-glucose co-transporter 2 inhibitors<sup>[15-17]</sup>. However, most of these drugs are not only ineffective in maintaining blood glucose in the long term, but also have side effects such as weight gain, progressive pancreatic  $\beta$ -cell failure, liver and renal impairment, gastrointestinal reactions, and an increased risk of hypoglycemia<sup>[18,19]</sup>. GLP-1RA corrects the multiple pathophysiological mechanisms of T2DM and exert their biological effects by binding to GLP-1 receptors *in vivo*<sup>[20]</sup>. GLP-1 receptors are widely distributed in several organs or tissues throughout the body, including the central nervous system, gastrointestinal tract, cardiovascular system, liver, adipose tissue, muscle, and pancreas. There is a current lack of domestic and foreign research on the effects of weekly and daily formulations of GLP-1RA on blood glucose fluctuation; weekly formulations have good clinical application prospects to

improve patient treatment compliance, and more clinical experience and safety data need to be obtained in future clinical practice.

In the present study, we compared the blood glucose control effects of weekly GLP-1RA administration with that of daily GLP-1RA administration and analyzed glucose excursion and inflammation in overweight or obese patients with T2DM. After treatment, FBG, MBG, MAGE, total cholesterol, triglyceride, and TNF- $\alpha$  levels were measured in patients in group A. The decrease in IL-6 and hs-CRP levels was greater in group A than in group B. We also found through glucose dynamic tests that the MBG, SDBG, CV%, MAGE, and MODD of patients in the two groups decreased significantly after treatment compared to those before treatment, whereas TIR increased in both groups. This indicates that both treatment schemes can improve blood glucose drift in patients. However, we found that the MBG and MAGE levels in group A were significantly lower than those in group B. Previously, in a meta-analysis performed by Yang *et al*<sup>[21]</sup>, it was found that the use of a GLP-1RA weekly formula was superior to the daily formula in improving HbA1c and FBG levels in patients with T2DM, which is consistent with our findings. This is because weekly preparations can effectively control FBG levels by stimulating insulin secretion and inhibiting glucagon secretion, whereas daily preparations mainly rely on delaying gastric emptying and slowing glucose absorption in the duodenum, mainly to lower PBG levels. In addition, weekly preparations have a half-life of several days and can continuously agitate GLP-1R to produce hypoglycemic effects; therefore, the hypoglycemic efficacy of weekly preparations, especially for FBG control, is better than that of daily preparations<sup>[22]</sup>. Most of the initially diagnosed obese patients with T2DM have inflammation, and inflammatory factors such as TNF- $\alpha$ , IL-6, and hs-CRP are abnormally elevated, and this inflammation leads to insulin resistance and increases the risk of cardiovascular disease, so it is significant to control inflammation in the body<sup>[23]</sup>. The results of the current study showed that after treatment, the <sup>1</sup> levels of TNF- $\alpha$  and IL-6 in group A were lower than those in group B, indicating that the use of weekly preparations of

GLP-1RA for treating obese patients with T2DM is more effective, facilitates the reduction of inflammatory factors, and has a higher safety for clinical application.

GLP-1 receptors are expressed on cardiomyocytes, vascular smooth muscle cells, and vascular endothelial cells. GLP-1RA can inhibit smooth muscle cell proliferation and high glucose-induced apoptosis in endothelial cells, promote endothelial cell proliferation, stabilize the endothelial environment, and reduce injury, which directly affects the cardiovascular system and ultimately the outcome of patients with T2DM<sup>[24]</sup>. GLP-1RA acts on the hypothalamic feeding center to delay the emptying of food into the stomach, suppressing the appetite of patients with a significant weight loss effect, and thus reducing the risk of cardiovascular disease<sup>[25]</sup>. In addition, GLP-1RA inhibitors directly participate in lipid metabolism and accelerate fat mobilization. The present study showed that the levels of total cholesterol and triglycerides post-treatment were lower in patients treated with the weekly formulation of GLP-1RA than in those treated with the daily formulation, suggesting that both drugs are suitable for obese patients with high lipid levels, but that the weekly formulation is the most effective.

This study has some limitations. First, we did not conduct patient follow-up sessions. Second, this study was retrospective, which may have introduced a recall bias in the analysis of the results. Finally, only the short-term treatment effects of the two drugs were analyzed, and it remains unclear whether there are differences in the long-term. Future studies should address these limitations through extensive clinical trials to refine our conclusions.

## **CONCLUSION**

In conclusion, the effect of weekly preparations of GLP-1RA in controlling the blood glucose levels in obese patients with T2DM, inhibiting inflammation, and reducing adverse reactions was significantly higher than that of daily preparations, which is worthy of clinical promotion.

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