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Original Article

Influence of GLP-1 receptor agonist on insulin dosage and blood glucose control of patients with type 2 diabetes mellitus

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Abstract: Objective: To determine the effect of glucagon-like peptide-1 receptor agonist (GLP-1RA) on cases with type 2 diabetes mellitus (T2DM) in terms of insulin dosage and blood glucose (BG) control. Methods: A total of 180 patients with T2DM admitted to our hospital between March 2016 and March 2019 were selected and assigned to a GLP-1RA group (GLP-1 group, n=100) and a control group (control group, n=80). Patients in the GLP-1 group were treated with GLP-1RA combined with insulin, while those in the other group were treated with insulin alone. The following items of each patient were determined: Body weight, body mass index (BMI), waist circumference, blood pressure (BP), BG-related indexes, insulin dosage, insulin resistance index, cardiovascular function, serum lipid-related indexes, adverse reactions, total effective rate, and treatment satisfaction. Results: Compared with the control group, the GLP-1 group showed a decrease in weight, BMI, waist circumference, BP, BG-related indexes, and insulin resistance index, consumed less insulin dosage, and also showed a decline in cardiovascular function, serum lipid-related indexes (total cholesterol (TC), triacylglycerol (TG), and low density lipoprotein cholesterol (LDL-C)), an increase in high density lipoprotein cholesterol (HDL-C), less adverse reactions, and higher total effective rate and treatment satisfaction. Conclusion: GLP-1RA contributes to better BG control of patients with T2DM, and it reduces the insulin dosage required during operation for its stimulation to the production of insulin.

Keywords: GLP-1RA, type 2 diabetes mellitus, insulin, BMI

Introduction

Diabetes mellitus (TM) is a common malady [1]. It is estimated that more than 415 million adults are affected by TM worldwide. The prevalence rate of this disease is still on the rise, and the number of patients with the disease is expected to increase to 640 million in the next 20-30 years [2, 3]. Type 2 diabetes mellitus (T2DM), a kind of TM, is related to atherosclerotic cardiovascular disease, which is the main risk factor for lesions of great vessels and micro-vessels, and is prone to cause kidney diseases and even increase mortality in severe cases [4, 5]. For the purpose of reducing the risk of vascular complications caused by TM, it is necessary to control blood glucose (BG). However, the benefits of BG control to great vessels are uncertain, and the safety of regulating BG concentration raises people's concern [6, 7]. Here, we decided to investigate a regulator, glucagon-like peptide-1 receptor agonist (GLP-1RA).

GLP-1RA is a drug which is able to effectively change BG concentration [8]. This hypoglycemic agent, which acts on incretin hormone GLP-1, is widely used in the treatment of T2DM. GLP-1 is an endocrine cell-secreted intestinal hormone in the gastrointestinal tract. It stimulates insulin secretion and regulates appetite by affecting the appetite-regulating areas of the cerebral center after food intake. GLP-1RA can ameliorate BG by inhibiting the secretion of glucagon and stimulating the production of insulin by regulation on GLP-1 [9-11]. In addition, GLP-

1RA can protect the kidney to a certain extent, because it can reduce the risk of cardiovascular diseases by regulating BG [12, 13]. Therefore, for patients with cardiovascular or kidney diseases, it is a favorable choice to adopt GLP-1RA for treatment, and in fact, GLP-1RA is often adopted with oral therapy and basic insulin [14, 15]. In the present study, we studied the effect of GLP-1RA on patients with T2DM by evaluating the insulin dosage and BG concentration of the patients.

Methods and materials

General materials

(1) General materials: A total of 180 patients with T2DM admitted to Haian Hospital Affiliated to Nantong University between March 2016 and March 2019 were selected and assigned to a GLP-1RA group (GLP-1 group, n=100) and a control group (control group, n=80). Patients in the GLP-1 group were treated with GLP-1RA combined with insulin, while those in the control group were treated with insulin alone. There was no notable difference between the two groups in the above general information (all $P>0.05$), so the two groups were comparable. This study was carried out with permission from the Ethics Committee of our hospital, and patients and their families voluntarily signed written informed consents after understanding the study.

(2) Inclusion and exclusion criteria: The inclusion criteria of the study: Patients meeting the diagnostic criteria for T2DM and meeting relevant treatment indications in the 2019 *Guidance for Prevention and Treatment of Type II Diabetes Mellitus in China* [16], patients with comparatively complete clinical data, patients whose fasting BG (FBG) was still higher than 7.0 mmol/L after 7 days of diet control and 2 hour postprandial BG (2hPG) was still higher than 11.1 mmol/L after the 7 days. The exclusion criteria of the study: Patients between 18 and 75 years old, patients without T2DM, patients during pregnancy, patients with other comorbid autoimmune diseases, patients with severe organic diseases, blood coagulation dysfunction, hepatic or kidney function obstacle, or malignant tumor, patients with mental disease or consciousness disorder, patients unwilling to cooperate with treatment, and those with relevant treatment contraindications.

Treatment methods

Each patient in the two groups received basic treatment after admission as follows: Each patient orally took metformin hydrochloride tablets (trade name: Glucophage, Sino-American Shanghai Squibb Pharmaceutical Co., Ltd., SFDA approval number: H20023370) at 1.0-1.5 g/d during meals.

Patients in the control group were treated with insulin aspart 30 as follows: Each patient was subcutaneously injected with 16U insulin aspart 30 (manufacturer: Novo Nordisk A/S; specification: 100 U/mL and 3 ml/piece; SFDA approval number: S20133006) at 10 min before breakfast and 8 U insulin aspart 30 at 10 min before supper. The specific dosage was adjusted according to the BG level of the patient. Each patient was treated for 6 consecutive months, and then the efficacy on the patient was evaluated.

Patients in the other group were treated with GLP-1RA based on the treatment to the control group. The administration plan and dosage of insulin aspart 30 for patients in the GLP-1 group were the same as those for patients in the control group. On this basis, each patient was subcutaneously injected with GLP-1RA, liraglutide (manufacturer: Novo Nordisk (China) Pharmaceutical Co., Ltd.; specification: 3 ml: 18 mg; SFDA approval number: J20110026) at an initial dose of 0.6 mg/d, once before sleep each day. The dosage was increased to 1.2 mg/d within 7-14 days based on the BG level of the patient. Each patient was also treated for 6 consecutive months, and then the efficacy on the patient was evaluated.

Detection indexes

(1) Body weight, body mass index (BMI), waist circumference, and blood pressure (BP): The changes of body weight, BMI, waist circumference, and BP of the two groups before treatment and after 6 months of treatment were compared.

(2) BG-related indexes: BG-related indexes of the two groups before treatment and after 6 months of treatment were evaluated and compared. BG-related indexes included FBG, 2hPG, and glycosylated hemoglobin (HbA1c).

(3) Insulin dosage and insulin resistance index (IRI): The IRI (Homa IR) of the two groups before and after 6 months of treatment was compared. The IRI (Homa IR) = FPG × FINS/22.5. A lower index indicated better situation of the patient. In addition, the average insulin dosage (FINS) used for each patient before treatment and after 3 months of treatment were calculated.

(4) Cardiovascular function: The cardiovascular function indicators such as left ventricular ejection fraction (LVEF) and diastolic rate of brachial artery blood vessel of the two groups before treatment and after 6 months of treatment were compared. Diastolic rate of brachial artery blood vessel = (maximum diastolic diameter of vessel-vessel diameter in basic state) × vessel diameter in basic state × 100%.

(5) Level of serum lipid-related indexes: The levels of serum lipid-related indexes of the two groups before therapy and after 6 months of treatment were analyzed and compared. The indexes included total cholesterol (TC), triacylglycerol (TG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C).

(6) Adverse reactions: Adverse reactions including nausea, diarrhea, vomiting, abdominal pain, and hypoglycemia of the two groups were counted and compared.

(7) Total effective rate: The total effective rates of both groups were calculated. The criteria for evaluation of the rate were as follows: Markedly effective: FPG<7.1 mmol/L and 2hPPG<8.3 mmol/L or FPG and 2hPPG were reduced by more than 30% after treatment. Effective: The clinical symptoms were ameliorated and FPG< 8.3 mmol/L and 2hPPG<10.0 mmol/L, or FPG and 2hPPG were reduced by more than 10%-29%; ineffective: No significant change was seen in symptoms and BG. Total effective rate = (the rate of markedly effective treatment + the rate of effective treatment).

(8) Satisfaction: When the patients were discharged from the hospital, the satisfaction degree of the patients was investigated using a self-made questionnaire, which used a score of 90-100 points for satisfaction, a score of 70-90 points for moderate satisfaction, and a score less than 70 points for dissatisfaction.

Statistical analyses

The data were analyzed comprehensively and statistically using SPSS19.0 (Asia Analytics Formerly SPSS, China). Enumeration data were analyzed using the X^2 test, and measurement data were presented by the (X±S), and analyzed by the t test. P<0.05 indicates a notable difference.

Results

General materials

There was no significant difference between the two groups in general information including sex, age, smoking history, drinking history, hypertension history, and hyperlipidemia history (all *P*>0.05) (**Table 1**).

Changes of body weight, BMI, waist circumference, and BP

Investigation on the changes of body weight, BMI, waist circumference, and BP of the two groups revealed that after treatment, both groups presented notable changes in these indexes, and these indexes of the GLP-1 group were all significantly lower than those of the control group (all P<0.05) (**Figure 1**).

BG-related indexes

FBG, 2hPG, and HbA1c in the two groups were investigated, and it was found that after treatment, the levels of them in both groups changed significantly, and levels of them in the GLP-1 group were greatly lower than those in the control group (all *P*<0.05) (**Figure 2**).

Insulin dosage and IRI

Homa IR and insulin dosage of the two group were investigated, and it was found that after treatment, the levels of Homa IR and insulin dosage of both groups changed significantly, while the level of Homa IR in the GLP-1 group was greatly lower than that in the control group (*P*<0.05), and the insulin dosage used for the GLP-1 group was also greatly less than that used for the control group (*P*<0.05) (**Figure 3**).

Cardiovascular function

The LVEF and diastolic rate of brachial artery blood vessel of the two groups were evaluated,

Table 1. General information of the two groups

Item	The GLP-1 group (n=100)	The control group (n=80)	t/X^2	P
Sex			1.82	0.177
Male	53 (53.00)	48 (60.00)		
Female	47 (47.00)	32 (40.00)		
Age (Y)	53.75±4.49	54.13±4.78	0.55	0.584
Course of disease (Y)	8.21±3.56	8.45±3.74	0.44	0.661
Smoking			0.16	0.689
Yes	48 (48.00)	36 (45.00)		
No	52 (52.00)	44 (55.00)		
Drinking			0.36	0.549
Yes	71 (71.00)	60 (75.00)		
No	29 (29.00)	20 (25.00)		
Hyperlipidemia			0.64	0.424
Yes	89 (89.00)	68 (85.00)		
No	11 (11.00)	12 (15.00)		
Hypertension			0.12	0.733
Yes	82 (82.00)	64 (80.00)		
No	18 (18.00)	16 (20.00)		

and it was found that after treatment, the LVEF and diastolic rate of brachial artery blood vessel of both group changed significantly, and the levels of the two in the GLP-1 group were greatly higher than those in the control group (both $P<0.05$) (**Figure 4**).

Levels of serum lipid-related indexes

TG, TC, LDL-C, and HDL-C in the two groups were quantified, and it was found that after treatment, the levels of them in the two groups changed significantly, and the levels of TG, TC, and LDL-C in the GLP-1 group were greatly lower than those in the control group, while the HDL-C level in the GLP-1 group was greatly higher than that in the control group ($P<0.05$) (**Figure 5**).

Evaluation of adverse reactions

According to investigation on the incidence of adverse reactions in the two groups, the incidence in the GLP-1 group was greatly lower than that in the control group ($P<0.05$) (**Table 2**).

Total effective rate

According to investigation on the total effective rate of the two groups, the rate of the GLP-1 group was greatly higher than that of the control group, implying that the GLP-1 group experienced better recovery than the control group ($P<0.05$) (**Table 3**).

Treatment satisfaction

According to comparison of treatment satisfaction between the two groups, the GLP-1 group showed significantly higher satisfaction than the control group ($P<0.05$) (**Table 4**).

Discussion

In order to achieve successful treatment of T2DM, it usually requires controlling of both BG and overweight and obesity, which increases the risk of cardiovascular diseases [17]. This study analyzed the influence of GLP-1 RA on insulin dosage and BG control of patients with T2DM, particularly focusing on a discussion about BG control and solution of cardiovascular problems.

In terms of solving cardiovascular problems, according to general data about body weight, waist circumference and BMI, patients enrolled in this study were basically obese. Obese is prone to induce cardiovascular problems. In addition, many of the patients suffered from hypertension and hyperlipidemia. Compared with the control group, the GLP-1 group performed better in the control of obesity, changes of serum lipid-related indexes, and recovery of

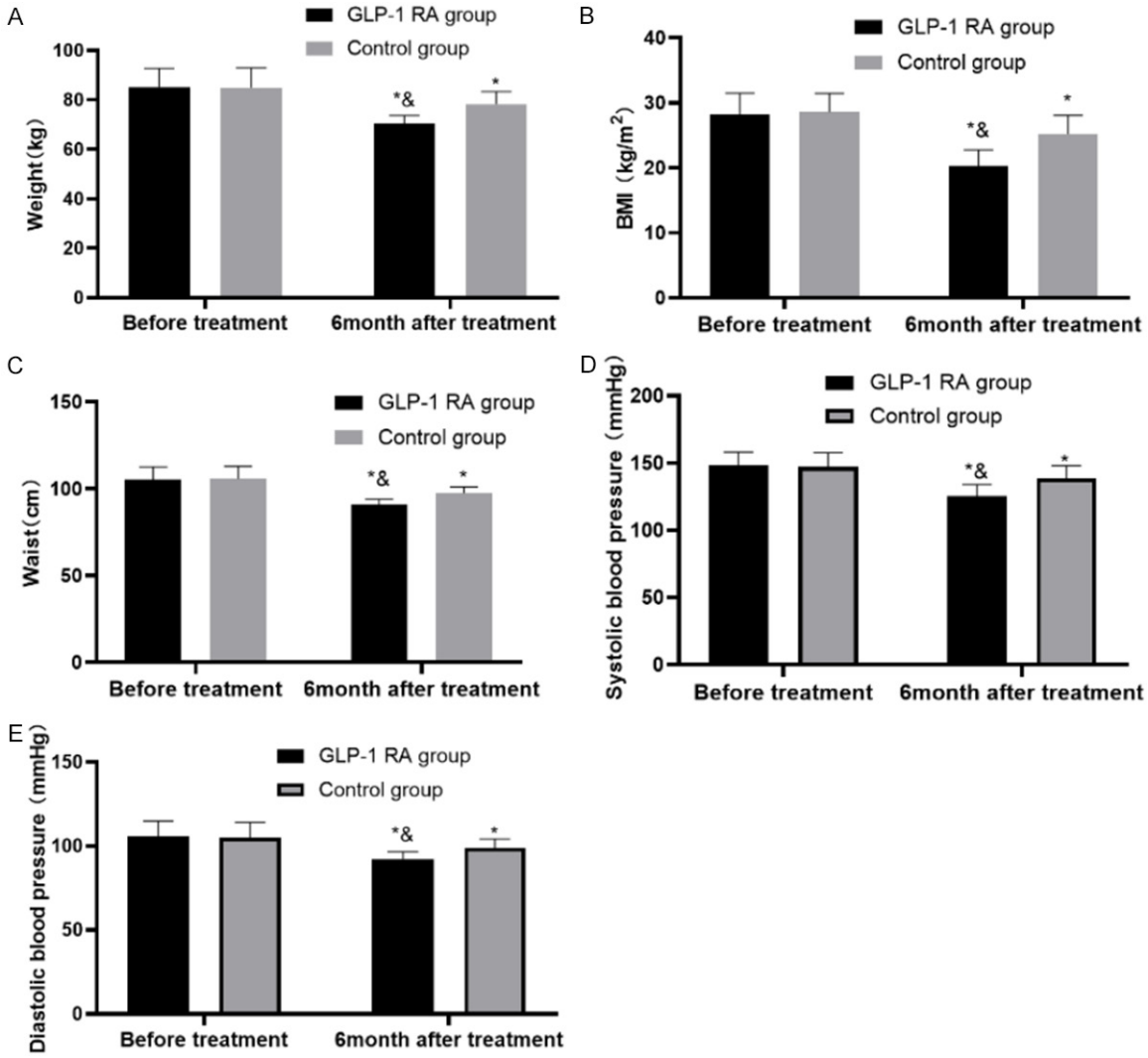

Figure 1. Changes of body weight, BMI, waist circumference, as well as BP. A. Body weight: After treatment, both groups presented notable changes in body weight, and the body weight of the GLP-1 group was greatly lower than that of the control group ($P<0.05$). B. BMI: After treatment, both groups presented notable changes in BMI, and the BMI of the GLP-1 group was greatly lower than that of the control group ($P<0.05$). C. Waist circumference: After treatment, both groups presented notable changes in waist circumference, and the waist circumference of the GLP-1 group was greatly lower than that of the control group ($P<0.05$). D. Systolic blood pressure: After treatment, both groups presented notable changes in systolic blood pressure, and the pressure of the GLP-1 group was greatly lower than that of the control group ($P<0.05$). E. Diastolic blood pressure: After treatment, both groups presented notable changes in diastolic blood pressure, and the pressure of the GLP-1 group was greatly lower than that of the control group ($P<0.05$). Notes: * indicates $P<0.05$ *vs.* the situation before treatment; & indicates $P<0.05$ *vs.* the control group.

cardiovascular function. Compared with normal individuals, patients with DM face higher risks of death and danger when suffering from cardiovascular disease [18]. Obesity, hypertension, and dyslipidemia are known risk factors of cardiovascular diseases, and patients with TM are more likely to develop cardiovascular disease than those without TM [19-21]. Moreover, patients with T2DM face a risk of death when suffering from cardiovascular disease [22]. Lipid abnormality is a crucial physiological mechanism in T2DM, which is closely related to the levels of serum lipid-related indexes such as TG and HDL-C. TG and HDL-C are closely linked in patients with T2DM. Increase in TG will trigger the catabolism of HDL. In addition, T2DM can easily induce low-grade chronic inflammation, and may affect the level of plasma

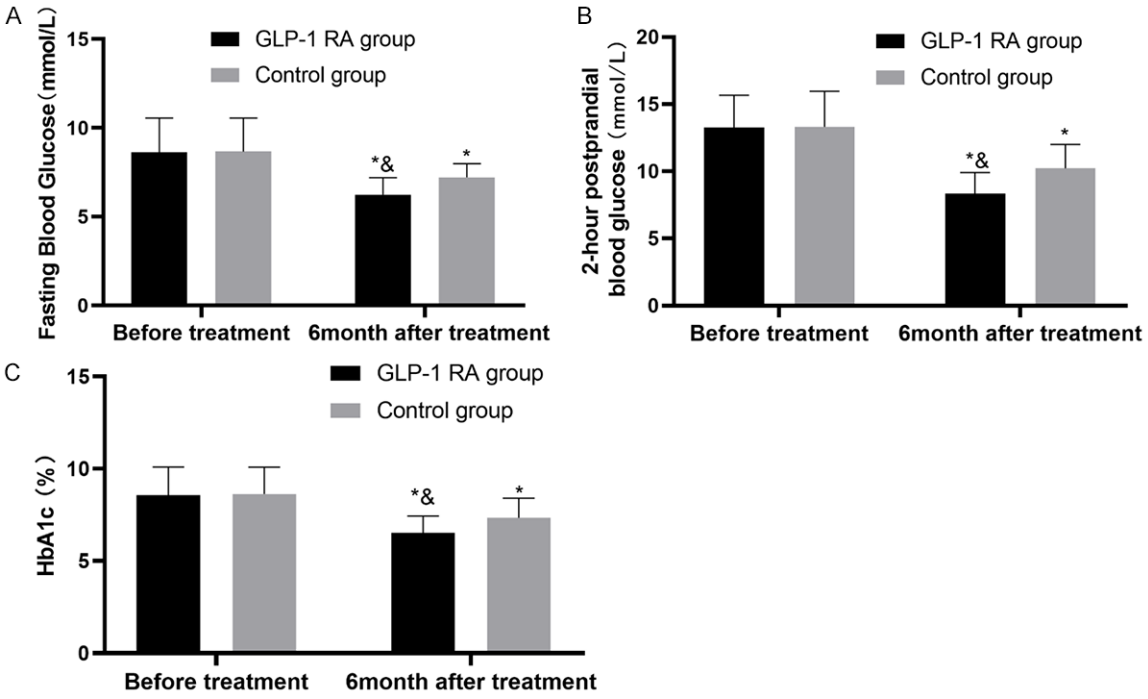

Figure 2. Changes of BG-related indexes of the two groups. A. FBG: After treatment, the level of FBG in both groups changed significantly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). B. 2hPG: After treatment, the level of 2hPG in both groups changed greatly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). C. HbA1c: After treatment, level of HbA1c in both groups changed significantly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). Notes: * indicates P<0.05 *vs.* the situation before treatment; & indicates P<0.05 *vs.* the control group.

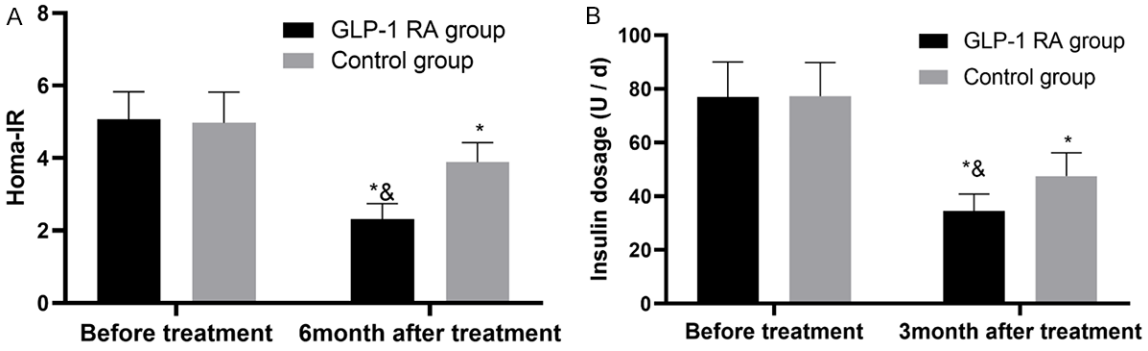

Figure 3. Changes of Homa IR and insulin dosage of the two groups. A. Homa IR: After treatment, the level of Homa IR in both groups changed significantly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). B. Insulin dosage: After treatment, the insulin dosage used for both groups was changed significantly, and the insulin dosage used for the GLP-1 group was greatly less than that used for the control group (P<0.05). Notes: * indicates P<0.05 *vs.* the situation before treatment; & indicates P<0.05 *vs.* the control group.

lipid, and inflammation stimulates the secretion of TG in the liver, degrades HDL, and lowers its level [23]. Lipid abnormality in patients with T2DM is characterized by an increase in blood lipids such as TG and a decrease in HDL-C, which leads to an elevation in insulin resistance and in the levels of BG-related indexes [24]. GLP-1 can strongly stimulate insulin secretion, so GLP-1RA can be used to treat TM. In addition to the ability of treating TM, GLP-1RA has a good therapeutic effect on obesity by regulating the appetite of hypothalamus, and its regulation on LDL-C, TC, and HDL-C can ameliorate the content of blood lipids, so it can lower risks

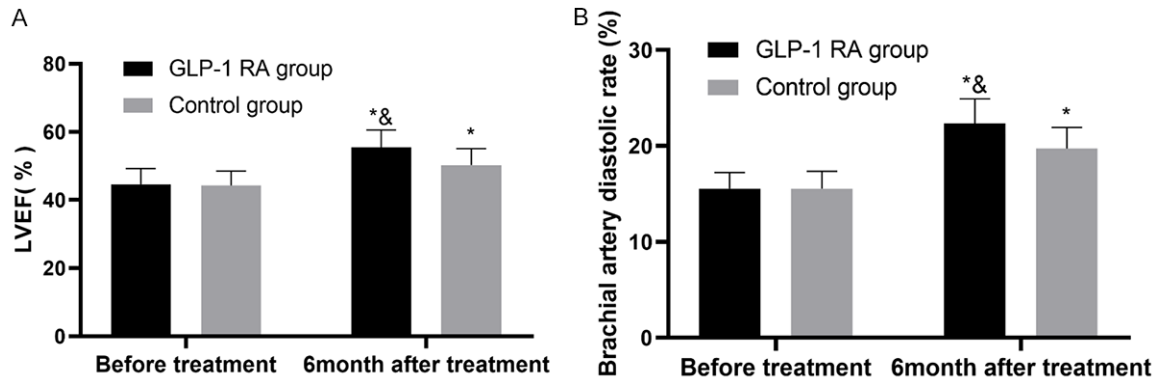

Figure 4. Cardiovascular function of the two groups. A. LVEF: After treatment, LVEF of both groups changed significantly, and the LVEF level in the GLP-1 group was greatly higher than that in the control group (P<0.05). B. Diastolic rate of brachial artery blood vessel: After treatment, the diastolic rate of brachial artery blood vessel of both groups changed significantly, and the rate of the GLP-1 group was greatly higher than that of the control group (P<0.05). Notes: * indicates P<0.05 *vs.* the situation before treatment; & indicates P<0.05 *vs.* the control group.

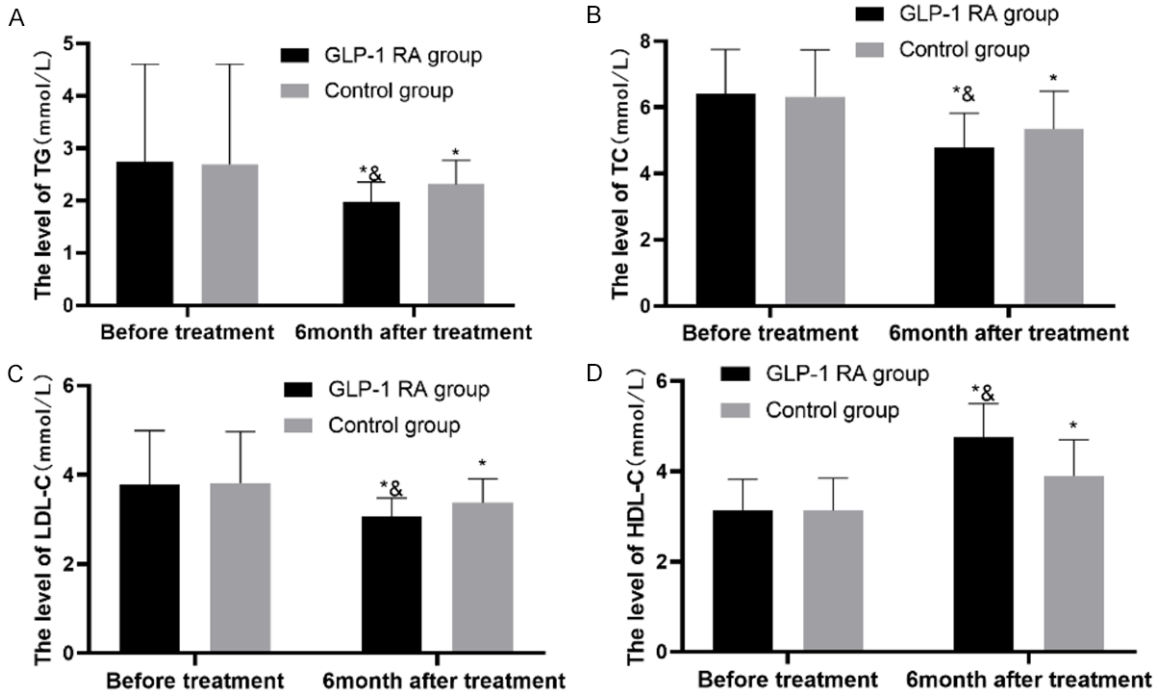

Figure 5. Changes in serum lipid-related indexes of the two groups. A. TG: After treatment, the level of TG in both groups changed significantly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). B. TC: After treatment, the level of TC in both groups changed significantly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). C. LDL-C: After treatment, the level of LDL-C in both groups changed greatly, and the level in the GLP-1 group was greatly lower than that in the control group (P<0.05). D. HDL-C: After treatment, the level of HDL-C in both groups changed significantly, and the level in the GLP-1 group was greatly higher than that in the control group (P<0.05). Notes: * indicates P<0.05 *vs.* the situation before treatment; & indicates P<0.05 *vs.* the control group.

associated with cardiovascular and cerebrovascular diseases faced by patients [25, 26]. The above can explain why the GLP-1 group performed better than the control group treated with insulin alone in terms of obesity, blood lipid, cardiovascular function, and other indexes. The results of this study were good evidences for the ability of GLP-1RA in solving a series of cardiovascular problems caused by obesity.

Table 2. Comparison of complication rate between the two groups

Item	The GLP-1 group (n=100)	The control group (n=80)	X^2	*P*-value
Nausea	2 (2.00)	4 (5.00)	-	-
Diarrhea	1 (1.00)	2 (2.50)	-	-
Vomiting	0 (0.00)	2 (2.50)		
Abdominal pain	1 (0.00)	2 (2.50)		
Hypoglycemia	0 (0.00)	4 (5.00)	-	-
Incidence of adverse reactions (%)	4 (4.00)	14 (17.50)	9.00	0.003

Table 3. Total effective rates of the two groups

Item	The GLP-1 group (n=100)	The control group (n= 80)	X^2	*P*-value
Markedly effective	72 (72.00)	36 (45.00)	-	-
Effective	26 (26.00)	34 (42.50)	-	-
Ineffective	2 (2.00)	10 (12.50)	-	-
Total effective rate (%)	98 (98.00)	70 (87.05)	7.88	0.005

Table 4. Satisfaction of the two groups

Item	The GLP-1 group (n=100)	The control group (n=80)	X^2	*P*-value
Satisfaction	79 (79.00)	42 (52.50)	-	-
Moderate satisfaction	17 (16.00)	24 (30.00)	-	-
Dissatisfaction	4 (4.00)	14 (17.50)	-	-
Satisfaction (%)	96 (93.75)	59 (81.94)	10.43	0.001

In term of BG control, BG control of the GLP-1 group was better than that of the control group. The levels of BG-related indexes in the GLP-1 group were superior to those in the control group. In addition, after 3 months of treatment, the insulin dosage used for the GLP-1 group was less, and after 6 months of treatment, the IRI of the GLP-1 group was lower. GLP-1 can suppress appetite and energy intake, and its function of promoting the secretion of insulin can effectively reduce insulin resistance. High IRI can not only easily lead to weigh gain of patients, but also easily make the glucose in blood hard to decompose by insulin because of the antagonistic effect on insulin, which will give rise to an increase in glucose content [27]. Therefore, GLP-1RA can lower the BG level by reducing insulin resistance. Moreover, GLP-1RA can also help control BG through other mechanisms. In addition to stimulating insulin secretion, GLP-1RA can also reduce BG by inhibiting glucagon level, and its inhibition on appetite can inhibit the increase of BG. Furthermore, GLP-1RA is relatively safe, because it brings about few adverse reactions such as hypoglycemia [28]. GLP-1RA can lower BG level by stimulating the production of insulin, so therapy with GLP-1RA requires much less insulin. The insulin aspart used in the control group can also lower BG, but if insulin aspart is used too much during treatment, hypoglycemia will easily occur, and insulin alone is not beneficial to the treatment of cardiovascular diseases [29]. Moreira et al. have found that adoption of GLP-1RA based on insulin is safe for patients, and can also lower the weight of patients and the frequency of hypoglycemia [30]. Similar to our study, one study by Yaribeygi et al. [31] has found that with a good antihyperglycaemic effect, GLP-1RA can promote insulin secretion while inhibiting glucagon secretion and can show down gastric emptying. As comparison of the two studies shows, GLP-1RA can control blood glucose by stimulating insulin production, so treatment combined with GLP-1RA can reduce the requirement of insulin. Such a combined treatment can not only achieve a better effect, stimulate patient's own insulin secretion to return to normal, but also avoid negative effects of insulin therapy, so its safety can be guaranteed.

This study also has limitations. We have not analyzed the degree of cooperation of patients

during surgery. Additionally, due to the limitations of various conditions, we have not studied the deeper molecular mechanism triggered by GLP-1RA. Therefore, we will understand the patient's emotions and the degree of cooperation in order to better improve the treatment plan in future studies. In future studies, it is also necessary to determine the effect of GLP-1RA on inflammatory factors in other molecular mechanisms, so as to further understand the specific mechanism of GLP-1RA on diabetes mellitus and its safety to patients. To sum up, GLP-1RA contributes to better BG control of patients with T2DM, and it reduces the insulin dosage required during operation because of its stimulation to the production of insulin. In addition, GLP-1RA is safe, and can ameliorate obesity, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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