Original Article
Effect of liraglutide combined with metformin or acarbose on glucose control in type 2 diabetes mellitus and risk factors of gastrointestinal adverse reactions

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Abstract: Objective: To investigate the effect of liraglutide combined with metformin or acarbose on glucose control in patients with type 2 diabetes mellitus (T2DM) and to analyze the risk factors of gastrointestinal adverse reactions. Methods: This retrospective study was conducted on 88 T2DM patients who were treated in our hospital from February 2019 to August 2021. The patients were divided into Group A (n=40) and Group B (n=48) according to different treatment methods. Group A was treated with liraglutide and metformin, while Group B was given liraglutide and acarbose. The effects of glucose control (FPG, 2hPG, HbA1c), inflammatory indexes (IL-6, CRP, SAA), fasting C-peptide, 2-h postprandial C-peptide levels and adverse reactions were compared. Afterwards, The risk factors of gastrointestinal adverse reactions were assessed via logistics regression. Results: It was found that the FPG, 2hPG and HbA1c levels after treatment were lower than those before treatment (P<0.05), and the levels in group A were lower than those in group B (P<0.05). The serum IL-6, CRP and SAA levels after treatment were lower than those before treatment (P<0.05), but there was no marked difference between the two groups after treatment (P>0.05). The fasting C-peptide and 2-h postprandial C-peptide levels in group A after treatment were higher than those in group B (P<0.05). Logistics regression analysis revealed that complicated digestive system diseases and combined use of acarbose were independent risk factors. Conclusion: Compared with liraglutide and acarbose, liraglutide and metformin has better glucose control effect in T2DM. Although there is no obvious difference in eliminating inflammation, liraglutide combined with acarbose will increase the incidence of gastrointestinal adverse reactions in patients. So, liraglutide combined with metformin is recommended for T2DM treatment.

Keywords: Liraglutide, metformin, acarbose, type 2 diabetes mellitus, gastrointestinal adverse reactions, risk factors analysis

Introduction

Type 2 diabetes mellitus (T2DM) is a kind of chronic metabolic disorder, which has increased exponentially in many third world countries [1]. It will not only cause pathological hyperglycemia in patients, but also reduce the secretion of insulin, leading to multiple complications, affecting the functions of various organs, and ultimately causing great harm to their quality of life and prognosis [2, 3]. Overweight, obesity, and unbalanced life and rest can easily lead to type 2 diabetes and aggravate the illness [4]. The aggravation of T2DM usually brings a heavy burden to limited medical resources, and it is still a challenge to the treatment and prognosis of diabetes [5, 6].

Drug therapy is the first choice for clinical treatment of T2DM, in which liraglutide is widely used in various trials on diabetes [7-9]. Liraglutide is one of the long-acting analogues of glucagon-like peptide-1 and can cross the blood-brain barrier and play an essential role in diabetes and its oxidative stress and apoptosis [10]. However, liraglutide can cause a variety of cardiovascular-related adverse reactions, while reducing patients' appetite and causing gastrointestinal adverse reactions [11, 12]. Metformin, which can effectively control the glycosylated

blood glucose and blood glucose level of patients, so as to avoid complications, is widely used in treating diabetes [13]. Metformin has been used clinically for 60 years. It can effectively improve the cardiovascular function caused by diabetes [14]. Acarbose is a kind of α-glycosidase inhibitor, which can effectively inhibit the synthesis of sucrase, pancreatic amylase and small intestinal epithelial glucoamylase, hinder the degradation of intestinal carbohydrates and reduce plasma insulin secretion [15].

Liraglutide in combination with metformin or acarbose has been proved to be effective in T2DM treatment. But it is vague whether there is a difference in the efficacy of the two schemes. Early studies have shown that combination of drugs can reduce the incidence of adverse reactions in patients. Whether the two regimen can reduce the incidence of gastrointestinal adverse reactions needs further analysis.

The purpose of this research was to analyze the efficacy of liraglutide combined with metformin or acarbose in T2DM patients and to explore the risk factors of gastrointestinal adverse reactions.

Methods

General data

A retrospective analysis was conducted on 88 T2DM patients who were treated in our hospital from February 2019 to August 2021. The patients were divided into group A (n=40) and group B (n=48) according to different treatment methods. The research was approved by the Ethics Committee of our hospital, and the subjects and their guardians were informed and signed a fully informed consent form. Ethics code: 2019A041LL (trial).

Inclusion criteria: ① Patients met the World Health Organization diagnostic criteria for diabetes [16] and were diagnosed as T2DM; ② Patients with complete clinical data; ③ Patients who could cooperate in the study. Exclusion criteria: ① Patients who were allergic to insulin; ② Patients with severe hypoglycemia; ③ Patients with acute complications of diabetes in the last 6 months; ④ Patients with hypertension nephropathy and nephritis hematuria;

⑤ Patients with irregular life pattern; ⑥ Patients who were transferred to the hospital midway, switched to other treatment schemes, lost follow-up or dropped out of the experiment; ⑦ Patients with poor compliance and could not complete the test as required.

Treatment methods

Group A was treated with liraglutide and metformin. The patients were given subcutaneous injection of liraglutide [Novo Nordisk (China) Pharmaceutical Co., Ltd. SFDA Approval No. J20160037] 0.6 mg each time, once a day for 15 weeks. On this basis, 0.85 g metformin hydrochloridetablets(Sino-AmericanShanghaiSquibb Pharmaceuticals Co., Ltd., SFDA Approval No. H20023370) were given orally once a day.

Group B: Patients were given subcutaneous injection of liraglutide [Novo Nordisk (China) Pharmaceutical Co., Ltd. SFDA Approval No. J20160037] 0.6 mg each time, once a day for 15 weeks. Additionally, acarbose tablets (Bayer Healthcare Co., Ltd., SFDA Approval No. H20023370) were given 50 mg each time, three times a day.

During this period, the diet of both groups was controlled. The patients were required to reduce the intake of sugar and have more exercies.

Serum collection

The venous blood 5 mL of patients was collected and placed at room temperature for 30 min, then centrifuged at 4°C, 1500× g for 10 min, and stored in a refrigerator at -70°C.

Outcome measures

Main outcome measures

Glucose control effect: The levels of blood glucose and insulin in both groups were evaluated before and after treatment (1 day after treatment). Fasting blood glucose (FBG) and 2-hour postprandial blood glucose (2hPBG) were measured by blood glucose analyzer. Patients' glycated hemoglobin (HbAlc) was measured by an automatic biochemical analyzer.

Determination of C-peptide: C-peptide was detected before and 1 day after treatment in two groups of patients. It was then determined

Table 1. General data of two groups of patients [n (%) (Means ± SD)]

Factor	Group A (n=40)	Group B (n=48)	t/χ² value	P value
Average age (years)	50.53±6.96	51.21±6.53	0.47	0.638
BMI (kg/m²)	23.26±2.12	22.98±2.57	0.55	0.584
Average course of disease (years)	3.54±0.32	3.61±0.29	1.08	0.285
Gender			0.01	0.907
Man	18 (45.00)	21 (43.75)		
Woman	22 (55.00)	27 (56.25)		
Residence			0.04	0.851
Villages	14 (35.00)	17 (35.42)		
Cities and towns	26 (65.00)	29 (64.58)		
Working condition			0.23	0.633
Lay-off/retirement	23 (57.50)	30 (62.50)		
Incumbent	17 (42.50)	18 (37.50)		
Drinking			0.05	0.815
Yes	21 (52.50)	24 (50.00)		
No	19 (47.50)	24 (50.00)		
Smoking			1.52	0.218
Yes	28 (70.00)	39 (81.25)		
No	13 (30.00)	9 (18.75)		
Past medical history				
Hypertension	18	27	1.105	0.293
Hyperlipidemia	10	11	0.052	0.819
Chronic obstructive pulmonary disease	6	8	0.045	0.831
Complicated by digestive system diseases	12	15	0.016	0.899

by radioimmunoassay kit of Depp (Tianjin). The inter- and intra-assay coefficients of variation (CVs) were 4.4% and 9.8%, respectively. The levels of fasting C-peptide and postprandial 2h C-peptide in venous blood of patients were measured.

Inflammation index: Inflammation indexes of patients were detected before and 1 day after treatment. Enzyme-linked immunosorbent assay (ELISA) was applied to detect C-reactive protein (CRP, Shanghai, China, mlbio, ml05-7570), interleukin-6 (IL-6, Shanghai, China, mlbio, ml058097) and serum amyloid A (SAA, Shanghai, China, mlbio, ml060332).

Efficacy evaluation: The efficacy evaluation of two groups of patients was tested. Markedly effective: After treatment, the symptoms of patients basically disappeared (FBG<7.2 mmol/L, 2hPBG<8.3 mmol/L). Effective: After treatment, the symptoms of patients were obviously improved (FGB<8.3 mmol/L and 2hPBG<10.0 mmol/L). Ineffective: After treatment, the symptoms of patients was not improved, and the blood glucose did not meet

the above standards. Total effective rate = (markedly effective + effective)/total cases ×100%.

Secondary outcome measures

Adverse reactions: A series of adverse reactions during the treatment was observed, including edema, nausea, gastrointestinal discomfort and hypoglycemia. Logistic regression was used to assess the risk factors of gastrointestinal adverse reactions.

Statistical methods

SPSS22.0 statistical software (Easybio, China) was used for data analysis. The counting data were tested by χ² test. The measured data, expressed as (mean ± standard deviation), were assessed via independent sample t-test. While those within groups were evaluated via paired t-test. Logistic regression method was used to evaluate the risk factors for gastrointestinal adverse reactions in T2DM patients. GraphPadPrism8 software was used to for figure rendering. P<0.05 was regarded as statistically significant.
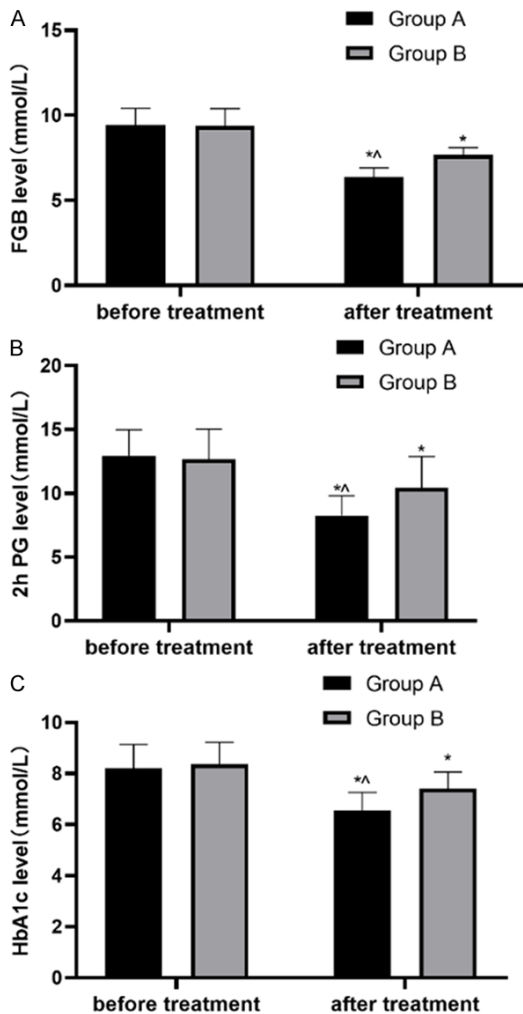
Figure 1. Changes of blood glucose in both groups. A. FGB level in patients before and after treatment; B. 2hPG level before and after treatment in both groups; C. HbA1c level before and after treatment. Note: *P<0.05, compared with before treatment; ^P<0.05, compared with group B after treatment.

Results

General data

According to the baseline data of both groups, there was no obvious difference in average age, gender, body mass index (BMI), and drinking or smoking history (P>0.05), indicating the two groups were comparable (**Table 1**).

Effect on Glucose control (FPG, 2hPG, HbA1c)

It was found that before treatment, there was no difference in the FPG, 2hPG and HbA1c levels between group A and B (P>0.05); But after
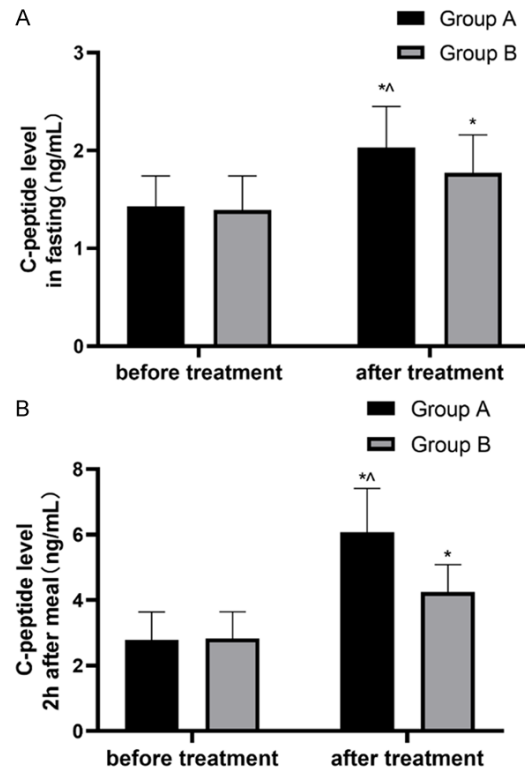

Figure 2. Changes of C-peptide levels in both groups of patients. A. C-peptide level in patients before and after treatment; B. 2h C-peptide level in patients before and after treatment. Note: *P <0.05, compared with before treatment; ^P<0.05, compared with group B after treatment.

one day of treatment, those levels in both groups reduced, and the levels in group A were even lower than those in group B (P<0.05) (**Figure 1**).

C-peptide determination

It was found that there was no difference in fasting C-peptide and postprandial 2h C-peptide levels between two groups before treatment (P>0.05). After treatment, the levels in both groups were higher than those before treatment (all P<0.05), and the levels in group A were significantly higher than those in group B (both P<0.05) (**Figure 2**).

Inflammatory indicators

It was found that the IL-6, CRP and SAA levels in both groups were not different before treatment (P>0.05), but after treatment, the levels were lower than those before treatment (P<0.05). However, there was no difference in
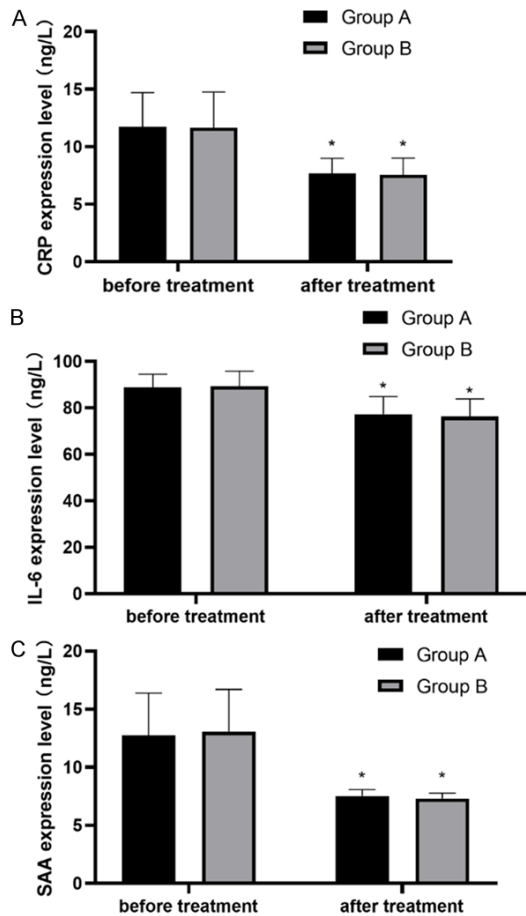
Figure 3. Changes of inflammatory indexes in both groups before and after treatment. A. IL-6 level in patients before and after treatment; B. CRP level in patients before and after treatment; C. SAA level in patients before and after treatment. Note: *P<0.05, compared with before treatment.

inflammatory indexes between groups (P>0.05) (**Figure 3**).

Efficacy

It was found that the total effective rate in patients of Group A was higher than that in group B (P<0.05) (**Table 2**).

Adverse reactions

There was no marked difference in the incidence of adverse reactions between Groups A and B (P<0.05) (**Table 3**).

Analysis of risk factors of gastrointestinal adverse reactions

The adverse reactions of two groups of patients were counted and analyzed. The results mani-

fested that there were 16 cases of gastrointestinal reaction in group A and 35 in group B. There was marked difference in gastrointestinal adverse reactions between two groups through chi-square test (P<0.05) (**Table 4**). Then patients were divided into groups based on the occurrence of gastrointestinal tract, and the clinical data were collected (**Table 5**). Through univariate and multivariate analysis, it was found that digestive system diseases and treatment were independent factors of gastrointestinal reaction (**Table 6**).

Discussion

As the fifth leading cause of death worldwide, the number of people with diabetes is rising sharply [17, 18]. T2DM is the most common type of diabetes, accounting for almost 90% of the patients. It causes many complications, thus bringing about great damage to the quality of life and organ function of patients [19]. Hence, the treatment plan, the inhibition of inflammation caused by various complications of diabetes, and the prognosis have become research hotspots [20].

2hPG, FPG and HbA1c play an essential role in the detection and prognosis of diabetes, and these three indexes are independent of each other [21]. HbA1c is widely used as a diagnostic marker for T2DM, which reflects the average plasma glucose level in the first 2-3 months [22]. Although the measurements of FPG and 2hPG can reflect patients' blood glucose levels to some extent, additional detection of HbA1c can provides more accurate result and can predict the risk of future diabetic complications such as cardiovascular disease. Meanwhile higher HbA1c is associated with higher CVD risk and total mortality [23]. As shown in this study, the 2hPG, FPG and HbA1c levels in group A after treatment were markedly lower than those in group B. After all, acarbose is still a kind of oligosaccharide containing pseudosaccharides, and its inhibitory effect on various intestinal maltase, sucrase, dextrinase and glucosamylase is very limited. It can only inhibit or postpone the absorption of various carbohydrates [24]. As a natural product used in herbs, metformin can directly or indirectly act on the liver to reduce glucose production and play a role in the intestinal part to increase glucose utilization, and most importantly, it can enhance insulin sensitivity [25]. Thus, in group A, combined use of liraglutide and metformin

Table 2. Comparison of efficacy between two groups after treatment [n (%)]

	Group A (n=40)	Group B (n=48)	χ^2	P
Markedly effective	26 (65.00)	21 (43.75)	-	-
Effective	12 (30.00)	15 (31.25)	-	-
Ineffective	2 (5.00)	12 (25.00)	-	-
Total effective rate	38 (95.00)	36 (75.00)	6.52	0.011

Table 3. Comparison of efficacy between two groups after treatment [n (%)]

	Group A (n=40)	Group B (n=48)	χ^2	P
Edema	0 (0.00)	1 (2.08)	-	-
Nausea	1 (2.50)	1 (2.08)	-	-
Hypoglycemia	0 (0.00)	1 (2.08)	-	-
Incidence of adverse reactions	2 (5.00)	3 (20.83)	0.064	0.801

Table 4. Comparison of incidence of gastrointestinal reactions

Groups	Occurred	Not occurred	χ^2 value	P value
Group A (n=40)	16	24	9.702	0.002
Group B (n=48)	35	13		

has a better effect on glucose control in patients with diabetes.

From the level of C-peptide determination, the two indexes of C-peptide in group A were higher than those in group B after treatment. C-peptide and insulin are secreted from islet cells in an equal molecular way. Compared with insulin, C-peptide is higher and more stable, so it is generally used to evaluate islet cell function [26]. In view of the results of this study, the efficacy of liraglutide combined with metformin in group A was better.

As for inflammatory factors, the postoperative inflammatory factors of both groups decreased, but there was no obvious difference between two groups. Metformin can not only improve blood glucose control, but also increase the autophagy of CD4+ T cells, and the enhanced function of mitochondrial bioenergy can effectively reduce oxidation and inflammation [27]. However, acarbose also reduced the levels of inflammatory factors in T2DM patients [28]. Although both the two regimens reduced inflammatory factors, it is still vague which one was more effective. As to the adverse reactions, it was found that the incidence of inflammatory reactions, especially gastrointestinal adverse reactions, in group A was less than that in group B, indicating that liraglutide combined with metformin is safer and more friendly to patients' gastrointestinal function.

To better determine the occurrence of gastrointestinal adverse reactions in patients, we carried out regression analysis. We found that the complicated with digestive system diseases and the treatment regimen were independently tied to gastrointestinal adverse reactions. As the most representative drug of α-glycosidase inhibitor, acarbose can delay the absorption of carbohydrates in the small intestine, and a large quantity of undigested carbohydrates reaches the large intestine. It is further decomposed under the action of intestinal bacteria, resulting in excessive gas production in the intestine [29]. The use of acarbose should start from a low dose, and the dosage can be gradually increased without gastrointestinal adverse reactions. If patients have gastrointestinal adverse reactions, it is necessary to change the drug treatment. The doctors should comprehensively evaluate patients' gastrointestinal system and formulate a gradually increased drug administration and slow feeding program, so as to avoid poor tolerance and compliance. Digestive tract disease is not a contraindication of liraglutide, but GLP-1 receptor agonists can delay gastric emptying and may aggravate the disease. It is suggested that the patients with digestive tract disease should switch to other hypoglycemic drugs with less gastrointestinal stimulation, such as insulin, sulfonylurea or glinide, etc. If it is necessary to use liraglutide, a low initial dose with gradual increase is recommended.

This research still has some shortcomings. First of all, there is no long-term follow-up of patients. Diabetes is a lifelong disease; The long-term use of the two drugs may cause drug resistance, whether the efficacy would be impaired needs further study. Secondly, the regression study has sample bias. Although we

Table 5. Assignment table

Factor	Assignment
Age (X)	<50=0; ≥50=1
BMI (X)	<23 kg/m² =0; ≥23 kg/m² =1
Course of disease (X)	<3.5 years =0; ≥3.5 years =1
Gender (X)	Male =0; Female =1
History of alcoholism (X)	Yes =0; No =1
History of smoking (X)	Yes =0; No =1
Hypertension (X)	Yes =0; No =1
Diabetes (X)	Yes =0; No =1
Obstructive pulmonary emphysema (X)	Yes =0; No =1
Complicated with digestive system diseases (X)	Yes =0; No =1
Treatment plans (X)	Liraglutide combined with metformin =0; Liraglutide combined with acarbose =1
Gastrointestinal adverse reactions (Y)	Yes =1; No =0

Table 6. Logistics regression analysis

Factor	Univariate analysis			Multivariate analysis		
	P value	OR value	95 CI%	P value	OR value	95 CI%
Age	0.871	0.924	0.353-2.414			
BMI	0.259	0.611	0.260-1.438			
Course of disease	0.956	0.975	0.407-2.337			
Gender	0.259	1.636	0.696-3.848			
History of alcoholism	0.370	1.477	0.630-3.460			
History of smoking	0.554	0.743	0.277-1.990			
Hypertension	0.209	0.578	0.246-1.358	0.021	3.217	1.196-8.652
Diabetes	0.274	1.735	0.646-4.656			
Obstructive pulmonary emphysema	0.218	2.069	0.651-6.579			
Complicated with digestive system diseases	0.002	4.038	1.646-9.908	0.003	4.536	1.698-12.122
Treatment plans	0.015	0.276	0.098-0.780	0.013	0.236	0.075-0.740

have compared the baseline data, the bias of the results cannot be avoided. Thus, we hope to conduct long-term follow-up and randomized controlled trials to improve the conclusions.

To sum up, compared with liraglutide and acarbose, liraglutide combined with metformin is more effective in controlling glucose during T2DM treatment. Although there is no remarkable difference in eliminating inflammation, liraglutide combined with acarbose can increase the incidence of gastrointestinal adverse reactions in T2DM patients. It is recommended to use liraglutide combined with metformin.

Disclosure of conflict of interest

None.

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