

# Effect of polyethylene Glycol Loxenatide (long-acting GLP-1RA) on lipid, glucose levels and weight in type 2 diabetes mellitus patients with obesity

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**Abstract. – OBJECTIVE:** To explore the effect of polyethylene glycol loxenatide (long-acting GLP-1R agonist) on the lipid, glucose levels, and weight in type 2 diabetes mellitus patients with obesity.

**PATIENTS AND METHODS:** A total of 40 obese patients with type 2 diabetes mellitus in our hospital from July 2019 to June 2020 were randomly divided into a control group and a study group. The study group was treated with metformin and polyethylene glycol loxenatide injection, while the control group was treated with metformin.

**RESULTS:** Before treatment, there was no significant difference in FPG (Fasting Blood Glucose) and PPG (Post Prandial Glycaemia) levels between the study group and the control group ( $p>0.05$ ). After a treatment period, the FPG and PPG levels in the study group were significantly lower than those in the control group ( $p<0.05$ ). With the longer treatment time, the patient's weight and BMI were lower ( $p<0.05$ ). The weight and BMI of patients changed the least after one month of treatment, and the weight and BMI changed the most after more than seven months of treatment. After a period of treatment, the levels of FPG and PPG in the blood of male patients in the study group were significantly lower than those of female patients ( $p<0.05$ ). After treatment, the TG level of the study group was significantly lower than that of the control group ( $p<0.05$ ). In comparison, the HDL-C level was significantly higher than that of the control group ( $p<0.05$ ).

**CONCLUSIONS:** Lipid and glucose levels of type 2 diabetes mellitus patients with obesity

have decreased after 12 weeks of polyethylene glycol loxenatide use. The weight of type 2 diabetes mellitus patients with obesity has changed after using polyethylene glycol loxenatide for a period of treatment. Among them, there is a certain relationship between body weight and treatment time, gender, and original body weight, which is worthy of further research and promotion in clinical practice.

*Key Words:*

Type 2 diabetes mellitus with obesity, Polyethylene glycol loxenatide, Weight change, Influencing factors.

## Introduction

With the continuous improvement of people's living standards, there are more and more patients with obesity and diabetes, which seriously affects the quality of life of patients<sup>1-5</sup>. In diabetic patients with long-term glomerular hyperfiltration, high perfusion caused more significant damage to the kidney, prone to early renal arteriosclerosis, and a large amount of proteinuria. If we cannot get better treatment in the early stage, it will further damage the function of the kidney<sup>6</sup>.

GLP-1R agonists are widely used in treating type 2 diabetes mellitus with obesity, which can reduce body weight and control the blood glucose in patients to maintain normal levels<sup>7</sup>. Based on its exceptional technology and process,

the weekly injection of polyethylene glycol loxenate, (produced by Jiangsu Haosen Pharmaceutical Co., Ltd., China), makes it possible to inject diabetes intervention drugs once a week, which is a progress in the technological revolution and dramatically improves the compliance of patients with the use of drugs<sup>8,9</sup>. The half-life of polyethylene glycol loxenate is 5.5-5.8 days. The long-term mechanism is mainly the change of amino acids at four sites and the modification of polyethylene glycol, which changes the amino acids at positions 2, 14, 28 and 39 of exendin-4, thus avoiding its rapid degradation by the DPP-IV enzyme and enhancing the stability of the peptide. In addition, by forming an umbrella-like protective layer on the surface of the modified sites of drug molecules, better protection of drug molecules can be achieved, the immunogenicity of drugs can be reduced, and the activity of drug molecules can be better maintained. Glycine at position two is replaced by alanine, the cleavage site of DPP4. Amino acid replacement at this site is a standard method to increase the half-life of GLP-1 drugs; methionine at position 14 is easy to be oxidized, resulting in decreased

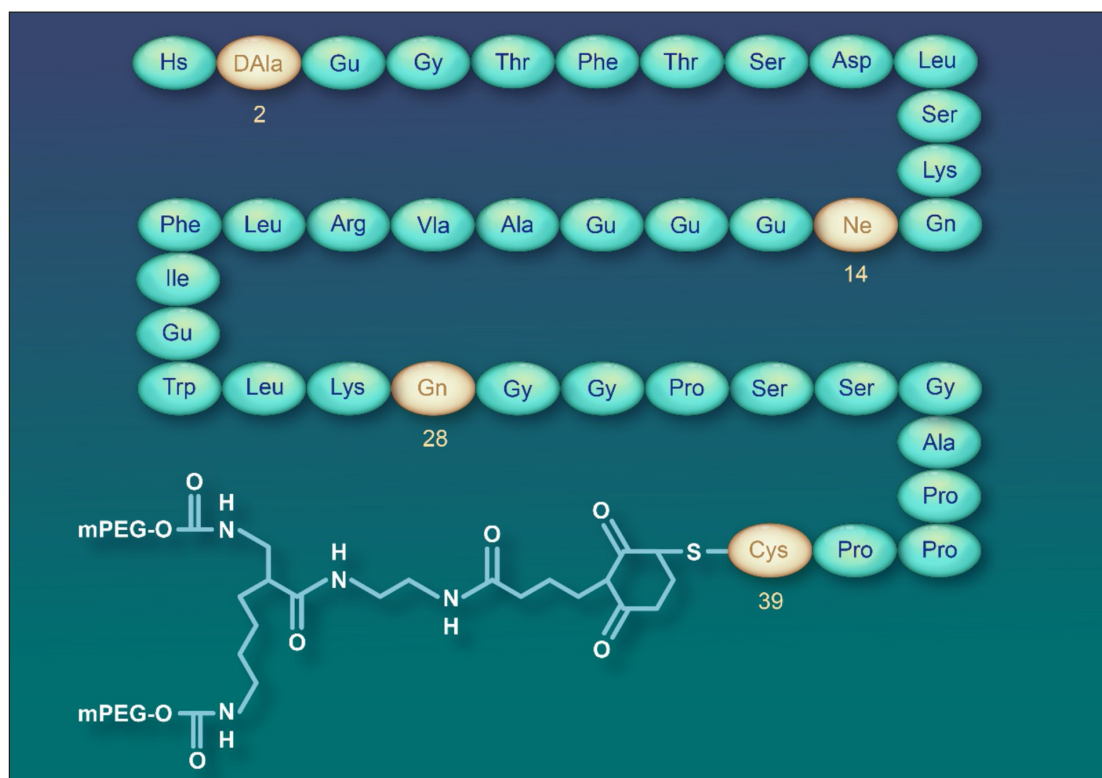
protein activity; the isoelectric point of n-leucine and methionine is close, but it does not contain sulfur group, so it will not be oxidized, making the whole protein more stable; position 28 Asparagine is easy to hydrolyze and deamination, resulting in protein hydrolysis or inactivation. Glutamine was replaced to increase the stability of the protein; the 39<sup>th</sup> C-terminal was replaced with cystine to connect polyethylene glycol<sup>1,8-10</sup> (Figure 1).

In this study, a total of 40 patients with type 2 diabetes mellitus and obesity in our hospital were randomly divided into a control group and a study group to explore the effect of polyethylene glycol loxenate on weight, blood lipid, BMI and other changes in patients with type 2 diabetes mellitus and obesity.

## Patients and Methods

### General Information

A total of 40 patients with type 2 diabetes mellitus and obesity treated in our hospital from July 2019 to June 2020 were randomly selected



**Figure 1.** The long-term mechanism is mainly the change of amino acids at four sites and the modification of polyethylene glycol, which changes the amino acids at positions 2, 14, 28 and 39 of exendin-4.

and divided into the control group and study group. In the study group, there were 10 males and 10 females, aged from 44 to 78 years, with an average age of  $63.29 \pm 1.27$  years. The disease course was 4 to 19 years, with an intermediate duration of  $8.9 \pm 1.7$  years. In the control group, there were 20 patients, including 10 males and 10 females, aged 47-81 years, with an average age of  $64.23 \pm 1.31$  years. The disease course was 4-20 years, with an intermediate period of  $9.9 \pm 1.9$  years.

Inclusion criteria: patients diagnosed with type 2 diabetes mellitus and obesity voluntarily participated in this study and agreed to follow up. Exclusion criteria: patients with a history of mental illness, rheumatism and rheumatoid arthritis; patients with abnormal liver function; patients with a history of infection within one month; patients with pregnancy, complicated with other diseases and more profound; patients with a severe understanding disorder or poor compliance; patients with interruption of treatment due to different reasons are considered invalid<sup>1,4,5</sup>. The age, gender, course of the disease and other general information of the two groups were comparable ( $p > 0.05$ ). The hospital ethics committee approved this study, and all patients agreed and signed the informed consent.

### Methods

Eligible patients were randomly randomized to the control and study groups in a 1:1 ratio. The patients in the control group received metformin (Glucophage®, MET), while the patients in the study group received MET and polyethylene glycol loxenate injection (Fulaimei®, PEX168). The control group was daily administered MET 1,500-2,000 mg orally. The study group daily received MET 1,500-2,000 mg orally plus weekly 100 µg injections of PEX168.

After 12 weeks of continuous intervention, the physical changes of patients in the two groups were recorded by telephone, e-mail, or outpatient follow-up. During the treatment week, the patients were given the subcutaneous injection once a week, 0.2 mg/time, and the injection dose was adjusted according to the blood glucose level of the patients<sup>7,9-13</sup>. GLP-1 has multiple functions of GLP-1 and GLP-2 secreted by intestinal L cells under the action of nutrients, bacterial metabolites, inflammatory toxins and cytokines, and its effectiveness has been confirmed in many clinical studies, but the mechanism has not been fully explored<sup>10,14,15</sup> (Figures 2-3 for details).

### Observation Indexes

After a period of treatment, the levels of FPG and PPG in the blood of the two groups were observed, and the changes of body weight and BMI after one month, two months, three months, four to six months and more than seven months of treatment were recorded, as well as the changes of blood glucose in different genders, and the changes of TG and HDL-C in the study group and the control group.

### Statistical Analysis

SPSS 24.0 (IBM Corp., Armonk, NY, USA) analyzed the data. The count was tested by  $\chi^2$ -test, and the measurement was tested by  $t$ -test ( $\chi^2$ ).  $p < 0.05$  was considered statistically significant.

## Results

### Comparison of Blood Glucose Levels Between the Two Groups Before and After Treatment

Before treatment, the levels of FPG and PPG in the blood of the study group were not significantly different from those of the control group ( $p > 0.05$ ). After a period of treatment, the levels of FPG and PPG in the study group treated with polyethylene glycol loxenate were significantly lower than those in the control group treated with conventional therapy ( $p < 0.05$ ). The specific data are shown in Table I.

### Comparison of Body Weight and BMI Between the Two Groups at Different Time Points of Treatment

Before treatment, there was no significant change in body weight and BMI at different time points ( $p > 0.05$ ). After treatment of 12 weeks, the weight and BMI of patients treated with pegylated loxenate gradually decreased with the treatment time ( $p < 0.05$ ). The weight and BMI of patients changed the least after one month of treatment, and the weight and BMI of patients after more than seven months of treatment changed the most. The specific data are shown in Table II.

### Comparison of Blood Glucose Levels of Different Genders Before and After Treatment in the Study Group

Before treatment, there was no significant difference in FPG and PPG levels between male and female patients in the study group treated with polyethylene glycol loxenate ( $p > 0.05$ ).

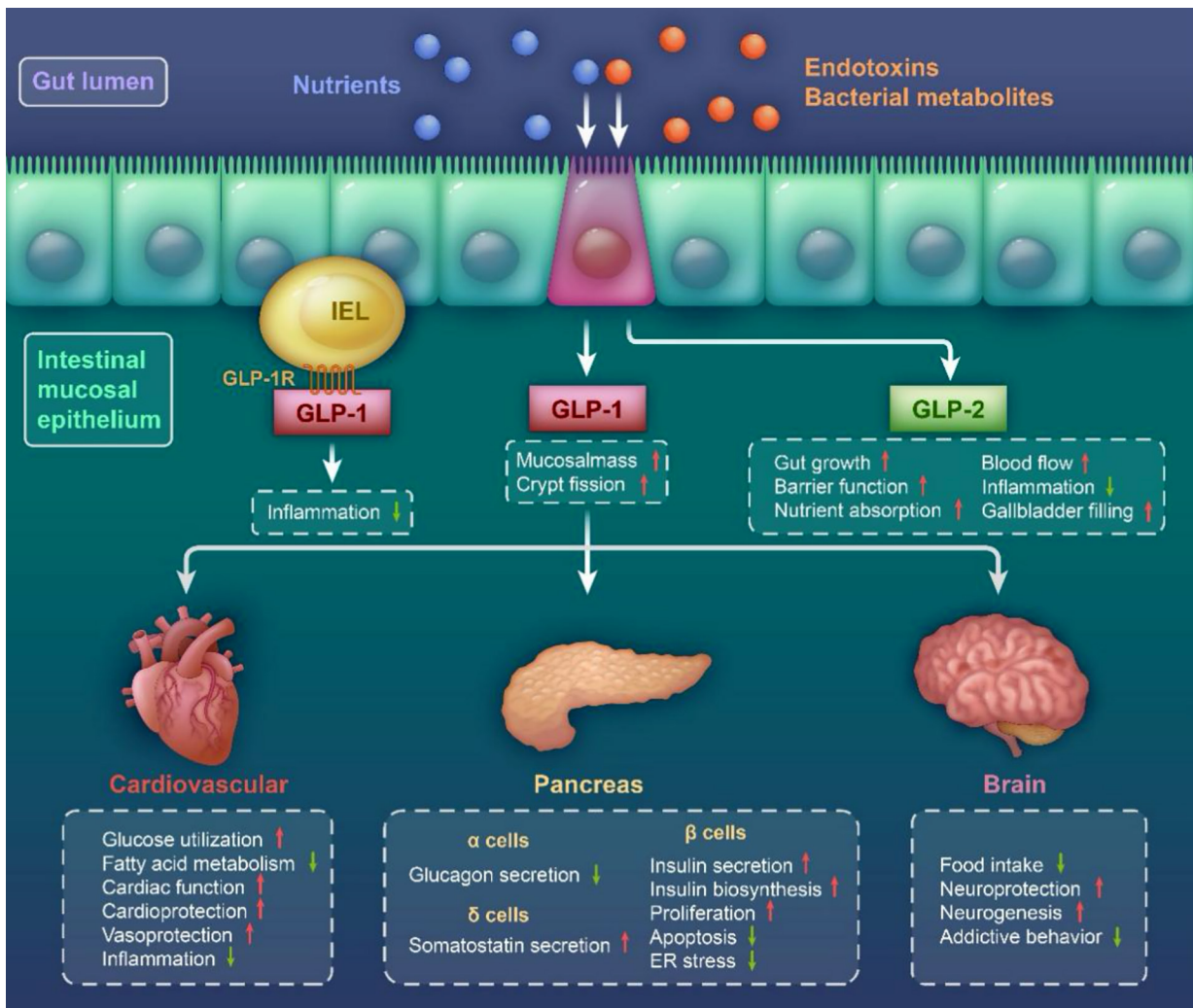


Figure 2. Cardiovascular, pancreas and brain effects of GLP-1.

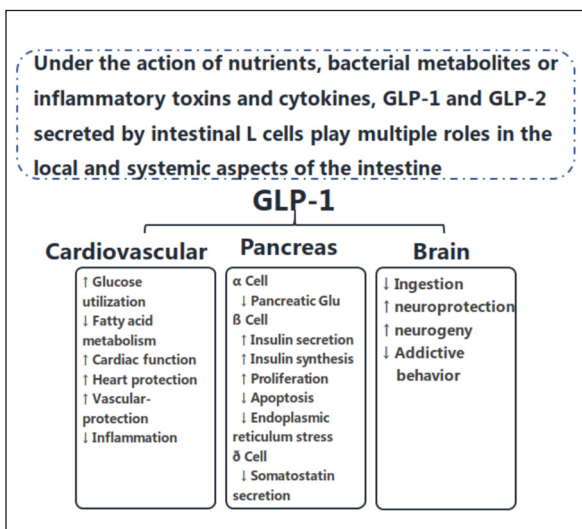


Figure 3. GLP-1 multiple physiological effects.

After a period of treatment, the levels of FPG and PPG in the blood of male patients in the study group treated with polyethylene glycol loxenate were significantly lower than those of female patients ( $p < 0.05$ ). The specific data are shown in Table III.

### Comparison of Lipid Levels Between the Two Groups After Treatment

Before treatment, there was no significant difference in TG and HDL-C levels between the study and control groups ( $p > 0.05$ ). After a period of treatment, the TG level of the study group treated with polyethylene glycol loxenate was significantly lower than that of the control group ( $p < 0.05$ ). In comparison, the HDL-C level was considerably higher than that of the control group ( $p < 0.05$ ). The specific data are shown in Table IV.

**Table I.** Comparison of blood glucose levels between the two groups before and after treatment ( $n \bar{x} \pm s$ ).

Subjects	N	Before treatment		After treatment	
		FPG	PPG	FPG	PPG
Control group	20	6.4 ± 1.5	7.2 ± 0.5	5.9 ± 0.8	6.8 ± 0.8
Study group	20	6.2 ± 1.8	7.3 ± 0.6	4.4 ± 0.7	5.4 ± 0.5
T		0.148	-0.222	1.039	0.721
p		0.890	0.835	0.037	0.012

**Table II.** Comparison of body weight and BMI after different times of treatment with polyethylene glycol Loxenatide ( $n, \bar{x} \pm s$ ).

Gender	N	Control group		Study group		Comparison	
		Weight (kg, $\bar{x} \pm s$ )	BMI (kg/m <sup>2</sup> , $\bar{x} \pm s$ )	Weight (kg, $\bar{x} \pm s$ )	BMI (kg/m <sup>2</sup> , $\bar{x} \pm s$ )	Weight (kg, $\bar{x} \pm s$ )	BMI (kg/m <sup>2</sup> , $\bar{x} \pm s$ )
Follow-up at one month	20	76.64 ± 5.35	28.26 ± 3.11	76.25 ± 5.47	28.19 ± 3.23		
Follow-up in 2 months	20	75.38 ± 4.97	28.15 ± 2.93	72.54 ± 5.56	26.82 ± 3.10		
Follow-up in 3 months	20	75.28 ± 5.03	28.12 ± 2.99	68.09 ± 5.07	25.16 ± 2.84		
Follow-up in 4-6 months	15	74.00 ± 5.03	27.65 ± 3.02	66.66 ± 5.33	24.63 ± 2.85		
Follow-up > 7 months	13	74.03 ± 5.69	27.66 ± 3.14	58.13 ± 4.08	21.46 ± 2.19		
F		0.213	0.023	12.433	5.744	23.174	10.385
p		0.814	0.977	0.007	0.042	0.000	0.011

## Discussion

Polyethylene glycol loxenatide is a commonly drug used to reduce blood glucose levels in clinical treatment. It can not only reduce blood glucose levels, but also reduce the weight of patients.

However, the agent's weight reduction mechanism is not fully understood, so the agent is not well known among obese patients. Therefore, given this phenomenon, we injected polyethylene glycol loxenatide reagent into type 2 diabetes mellitus patients with obesity. After a period of treatment,

**Table III.** Comparison of blood glucose levels of different genders before and after treatment in the study group ( $n, \bar{x} \pm s$ ).

Gender	N	Before treatment		After treatment	
		FPG	PPG	FPG	PPG
Female	10	6.3 ± 1.6	7.3 ± 0.6	5.4 ± 0.6	6.1 ± 0.4
Male	10	6.2 ± 1.9	7.4 ± 0.7	4.9 ± 0.3	5.9 ± 0.4
T		0.070	-0.188	5.196	5.511
p		0.948	0.860	0.007	0.005

**Table IV.** Comparison of lipid levels between the two groups after treatment ( $n, \bar{x} \pm s$ ).

Gender	N	TG/(mmol/L)		HDL-C/(mmol/L)		LDL-C/(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	20	2.75 ± 0.62	2.09 ± 0.23	1.33 ± 0.30	1.53 ± 0.29	4.52 ± 0.71	2.72 ± 0.51
Control group	20	2.67 ± 0.59	2.35 ± 0.46	1.31 ± 0.29	1.28 ± 0.12	4.51 ± 1.42	2.97 ± 0.93
T	0.162	-0.876	3.048	2.948	10.161	9.74	
p	0.879	0.431	0.038	0.042	0.021	0.005	

we followed up with the patients and recorded the weight changes, adverse reactions and influencing factors of the patients during the injection. In this way, patients can better understand the therapeutic effect of the reagent and its harm to the human body and then use the reagent safely<sup>8,10,16-19</sup>.

This study showed that the main factors influencing the weight change of type 2 diabetes mellitus patients with obesity were gender, treatment time and original weight. The above data show that, before treatment, the FPG and PPG levels in the blood of the study group treated with polyethylene glycol loxenate were not significantly different from those of the control group treated with conventional treatment. After a period of treatment, the FPG and PPG levels in the blood of the study group were significantly lower than those of the control group. Before treatment, there was no significant change in the weight and BMI of the treatment group at different times. After treatment, the longer the treatment time, the lower the weight and BMI of the patients. One month after treatment, the weight and BMI of the patients changed the least, and more than seven months after treatment the weight and BMI of the patients changed the most. The longer the treatment time, the more significant the weight change of patients, which fully proves that the length of treatment time affects the weight change of patients injected with polyethylene glycol loxenate reagent<sup>20,21</sup>.

The primary mechanism of polyethylene glycol loxenate reagent to reduce the weight of patients is to delay the gastric emptying and inhibit the appetite of patients, and then reduce the food intake of patients, and ultimately reduce the weight of patients. The weight change of patients with different gender after injection of polyethylene glycol loxenate reagent is extra, and polyethylene glycol loxenate reagent has more substantial inhibitory effect on men<sup>10,16,17</sup>. The study showed that before treatment, the levels of FPG and PPG in the blood of male patients in the study group were not significantly different from those of female patients. After a period of treatment, the levels of FPG and PPG in the blood of male patients in the study group were significantly lower than those of female patients<sup>22</sup>. Before treatment, the TG and HDL-C levels of the study group had no significant difference with the control group. After a period of treatment, the TG level of the study group was significantly lower than that of the control group, and the HDL-C level of the study group was significantly higher than that of the control group.

This study shows that the biggest factors affecting the weight change of patients are the original weight and the length of treatment. Many type 2 diabetes mellitus patients with obesity have the phenomenon of left atrium enlargement, ascending aorta widening and left ventricular diastolic function weakening. Left atrial enlargement will lead to stroke, heart failure, all-cause death, hypertension, atrial fibrillation and other diseases greatly increased<sup>23,24</sup>. The menstrual cycle and menstrual volume of patients using polyethylene glycol loxenate reagent were significantly normal. At the same time, polyethylene glycol loxenate reagent can reduce body weight, improve hyperinsulinemia, reduce blood pressure, blood glucose and blood lipid<sup>25-27</sup>.

Polyethylene glycol loxenate has significant effect on blood glucose control, excellent therapeutic effect, and is safe and reliable. It can be used alone in patients with type 2 diabetes mellitus and obesity. After the use of polyethylene glycol loxenate reagent, the blood glucose concentration of patients was significantly reduced, and the normal blood glucose level was maintained for a period of time<sup>28,29</sup>. During this period, patients should coordinate their diet, try to use light and less salt food, keep normal work and rest time, and maintain a relaxed and happy mood, so as to ensure that the efficacy of the reagent is more effective.

### **Limitations**

Several limitations existed in this study. First, our sample size was relatively small due to the experimental conditions. Given the small sample size, these results need to be validated with a larger sample size and with samples collected prior to diagnostic and treatment. Second, the conclusions obtained may be biased because the intervention drug was administered subcutaneously, but the corresponding simulated solution was not available as a placebo in our hospitals. Finally, the patients included in this study were overweight patients, so the effect of PEX-168 injection in normal weight patients is yet to be evaluated.

### **Conclusions**

Lipid and glucose levels of type 2 diabetes mellitus patients with obesity has decreased after 12 weeks of polyethylene glycol loxenate use. The weight of type 2 diabetes mellitus patients

with obesity has changed after using polyethylene glycol loxenate for 12 weeks. Among them, there is a certain relationship between body weight and treatment time, gender and original body weight, which is worthy of further research and promotion in clinical practice.

#### Conflict of Interest

The Authors declare that they have no conflict of interests.

#### Acknowledgements

The authors sincerely thank all the participants.

#### Informed Consent

Patients gave their informed consent to participate in the trial and received all necessary information.

#### Authors' Contribution

Xiaoyu Li, Chuping Li, and Chuanyan Zhang contributed conception and design of the study. Dan Zhu, Zezhen Wu, Shuo Zhang, Ducheng Hou, Fengwu Chen, and Chuyan Zheng analyzed and sorted literature materials. Kaijian Hou was the project architect and the person in charge and guides the writing of the paper. Xiaoyu Li edited the article. All authors agreed to be accountable for the content of the work.

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#### Ethics Committee Approval

The clinical ethics has been approved by China Clinical Research Registration Center and the Ethics Committee approval Longhu hospital, The First Affiliated Hospital of Medical College of Shantou University (No. LHLL2021001). Registration No. ChiCTR1900026514 of China Clinical Research Registration Center. Link: <http://www.chictr.org.cn/showprojen.aspx?proj=44112>

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