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EFFECTS OF GASTRIC BYPASS ON NON-OBESE TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To assess the therapeutic effect of gastric bypass on non-obese type 2 diabetes mellitus (T2DM). **Methods:** Databases including PubMed, Web of Science, CNKI and Wan fang database were searched from 1985 to November 2016, and references of articles were also searched to collect randomized controlled trails or before-after self-controlled trails on gastric bypass in treating T2DM. We screened articles according to the predefined inclusion and exclusion criteria, extracted data, and evaluated quality of the included studies. Then meta-analyses were performed using RevcMan 5.2. **Results:** A total of 7 before-after self-controlled trials involving 230 patients were finally included. All these trials were graded as low quality, and all is three scores by Jadad scale. The results of meta-analysis showed that the therapeutic effect of gastric bypass on non-obese T2DM after twelve months treatment was good, There were significant reductions in both glycosylated hemoglobin[MD=-2.76, 95%CI (-3.55,-1.97), P<0.00001] and fasting plasma glucose[MD=- 4.13,95%CI (-5.70,-2.56), P<0.00001], And the level of glycosylated hemoglobin to reduce postoperative twelve months after six months significantly[MD=0.27, 95% CI(0.05,0.49), P=0.02] the therapeutic effect of gastric bypass on non-obese T2DM after six months treatment was good. There were significant reductions in both glycosylated hemoglobin [MD=-2.78, 95%CI (-3.48,-2.08), P<0.00001] and fasting plasma glucose [MD=-4.62, 95% CI (-5.86,- 3.38), P<0.00001], the same time, the differences were statistically significant. Sensitivity analysis indicated that these results were stable, but funnel-plots indicated possible publication bias existed. **Conclusion:** The short-term therapeutic effect of gastric bypass on non-obese type 2 diabetes mellitus is better, medium-term curative effect is stable, but because of the small sample size into literature, methodological quality defects, still need to high quality, large sample and long-term follow-up studies to further verify the therapeutic effect.

KEYWORDS: Type 2 diabetes mellitus; Gastric bypass; Non-obese; Systematic review; Meta- analysis.

INTRODUCTION

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, nonketotic hyperosmolar coma, or death. Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.

Diabetes is a serious human health problem and metabolic diseases, according to the latest statistics of the International Diabetes Federation, there were 382 million diabetics worldwide, type 2 diabetes accounts for more than 90%, while China has become the first biggest country of diabetes.[1] The treatment for diabetes has become a global problem.

In recent years, bariatric surgery has become the current treatment of type 2 diabetes, the most popular surgical approach, especially gastric bypass, is widely used for the treatment of type 2 diabetes, obesity, and the effect is obvious[2]; but for the non-obese type 2 diabetic patients, How is the efficacy of gastric bypass surgery, the lack of sufficient clinical evidence still need further study.

This study is a systematic review using gastric bypass surgical as treatment of non-obese type 2 diabetes effect; it provides more evidence for the treatment of gastric bypass surgery in non-obese type 2 diabetes for clinicians to improve the non-obese type 2 clinical manifestations and quality of life of diabetic patients to provide a reliable basis for selection.

METHODS

1. Inclusion and exclusion criteria

(1) Type of Study: Randomized controlled trials and self-controlledtrials;

(2) Research object: Inclusion criteria ① according to the T2DM diagnostic standards published by WHO in

1999[fasting plasma glucose (FPG)> 7.1mmol / L and (or) postprandial blood glucose> 11.1mmol / L]; ②WHO published non-obese criteria [BMI <30Kg / m2]; ③ patients with gastric bypass surgery. ④ follow-up time ≥ 12 months ⑤ race, age, sex, Unlimited duration.

Exclusion criteria ① patients with a medical history of type 1 diabetes, impaired glucose tolerance, autoimmune antibodies positive, Cardiopulmonary and other organ failure; ② combined with other operations; ③ mini-gastric bypass surgery; ④ duplicate publication

(3) Intervention: gastric bypass surgery.
(4) Outcomes: ① main indicators: glycosylated hemoglobin; ② Secondary outcomes: Fasting plasma glucose

2. Document Retrieval

We searched on PubMed, Web of Science, CNKI, Wan fang database and retrospective including some references, from 1985 to November 2016. We tried to e-mail some authors and wished to get experimental data relevant, but we did not receive replies. Chinese search terms include: type 2 diabetes, obesity and non-gastric bypass surgery; English search terms include: Type 2 Diabetes Mellitus, Non-obese and Gastric Bypass.

3. Document data extraction and Included studies Method of Quality Assessment

For Data extraction we used self-made table data to extract contents such as title, author, publication time, test type, case number, age, gender, BMI, duration, detect targets and follow- up time. Referring to the modified Jadad scale.[3] Evaluation includes the Methods of Quality Assessment.

4. Statistical analysis

A Meta- analysis of data was made using RevMan5.2 software. The included studies between Heterogeneity using Chi-square test, test level of $\alpha = 0.1$, I2 was used to assess the heterogeneity size $I2 \leq 25\%$ indicate heterogeneity is smaller, $25\% < I2 \leq 50\%$ for moderate heterogeneity, $I2 > 50\%$ shows that there is a high degree of heterogeneity among results. If there is not heterogeneity in studies, we can use a fixed effect model combined to precede the analysis; if there is heterogeneity, we should examine the heterogeneity sources, such as included studies with only clinical homogeneity, we can immediately use the effect model to precede the Meta-analysis. in order to test the stability ,sensitivity analysis of the results using a fixed effects model and random effects models respectively carry out the meta- analysis then compare to other result for consistency.[4]

RESULTS

1. Document Retrieval results

We Checked articles in English and Chinese, after reading the documents again 8 articles where selected 4 in Chinese and 4 in English, A total of 290 cases. The literature screening process and results are shown in Figure 1. The studies at most 60 cases, at least 16 cases were more than 10 cases. The basic characteristics of each included studies are shown in Table 1.

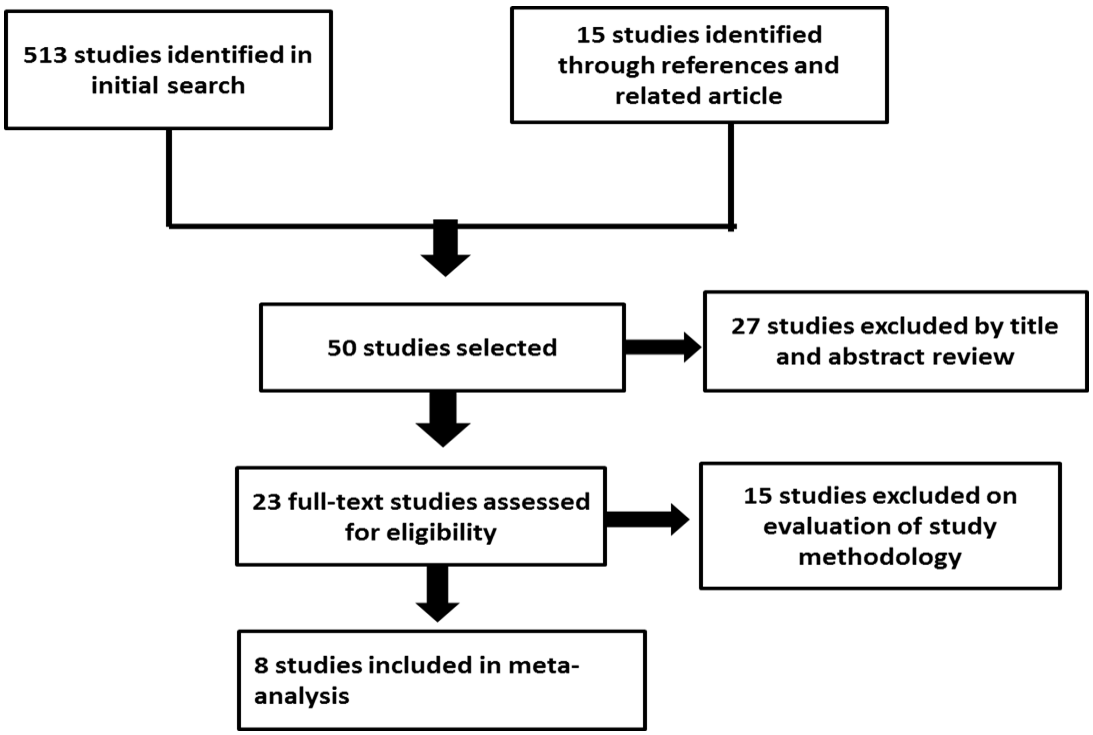

Fig. 1: Chart flow of study identification and study selection process.

2. General Characteristics of included studies and methods of included studies Quality Assessment

Table 1

3. Efficacy analysis

3.1 Glycosylated hemoglobin

(1) 6 month after surgery: There were six studies[5,8-12] comparing the differences in Glycosylated hemoglobin levels before the surgery and 6 month after the surgery. A total of 239 cases, 1 case lost, The results showed that gastric bypass surgery in non-obese T2DM patients 6 months after the surgery, Glycosylated hemoglobin levels were significantly lower than the preoperative [MD = -2.64,95% CI (-3.28, -1.99), P <0.00001] (Figure 2).

(2) 12 months after surgery: There were eight studies [5-12] comparing the differences in Glycosylated hemoglobin levels before the surgery and 12 month after the surgery. A total of 290 cases, 9 cases lost. The results showed that gastric bypass surgery in non-obese T2DM patients, 12 months after the surgery, Glycosylated hemoglobin levels were significantly lower than the preoperative [MD = -2.69,95% CI (-3.39, -2.00), P <0.00001] (Figure 3) and Glycosylated hemoglobin levels decrease were significantly better than six months after the surgery[MD = 0.27,95% CI (0.09,0.44), P = 0.003] (Fig. 4).

3.2 Fasting plasma glucose

(1) 6 months after surgery: There were six studies comparing the differences in fasting plasma glucose levels before the surgery and 6 month after the surgery. A total of 239 cases, 1 case lost, The results showed that gastric bypass surgery in non-obese T2DM patients, 6 months after the surgery, the fasting plasma glucose levels were significantly lower than the preoperative [MD = - 4.67,95% CI (-5.71, -3.63), P <0.00001] (Fig. 5);

(2) 12 months after surgery: There were seven studies comparing the differences in fasting plasma glucose levels before the surgery and 6 month after the surgery. A total of 261 cases, The results showed that gastric bypass surgery in non-obese T2DM patients, 12 months after the surgery the fasting plasma glucose levels were significantly lower than the preoperative [MD=-4.27, 95%CI (-5.64,-2.90), P<0.00001] (Fig.6), but comparing with the fasting plasma glucose levels 6 months after surgery there were not significant differences [MD = 0.12, 95% CI (-0.07,0.31), P = 0.23] (Fig. 7).

3.3 Statistical analysis

Except the comparison study of fasting plasma glucose levels in non-obese T2DM patients between 6 months and 12 months after gastric bypass surgery, other studies with different degree of statistical heterogeneity（I2≠0%), thus we use effects model immediately to carry out the Meta – analysis. Sensitivity analysis showed that using fixed effects model results with a random effects model are consistent. Suggesting that the results of this combined analysis study are stable and reliable.

Table 1: Basic characteristics and quality evaluation.

included studies	Test type	case(male /female)	age	History(years)	BMI(Kg/㎡)	outcome measures	Follow-up time	Quality Evaluation
Jun yin 2014	Retrospective analysis	28 (5/23)	27-22	1-28	18-27.5	HbA1c	16 months	3
Kirubakaran 2014	Retrospective analysis	29 (13/16)	32-66	2-26	20.9-26.9	HbA1c	12 months	3
Dawei zhang2013	Retrospective analysis	22 (15/7)	35-65	＜10	20-29-9	HbA1c	12 months	3
Juntao yang 2010	Retrospective analysis	21 (15/6)	45-69	0.5-11	18.2-29.9	HbA1c	26 months	3
Tang lijun2011	Retrospective analysis	58 (6/22)	32-56	＜14	MD-23.9	HbA1c	12 months	3
Hu shitao 2014	Retrospective analysis	56 (34/22)	24-68	＜15	＜29.9	HbA1c	12months	3
Zhang xiangwen2014	Retrospective analysis	16(9/7)	21-55	1.2-12	22.3-27.8	HbA1c	12months	3
Chen yafeng 2012	Retrospective analysis	60(9/21)	22-69	＜10	18.69-29.99	HbA1c	12months	3

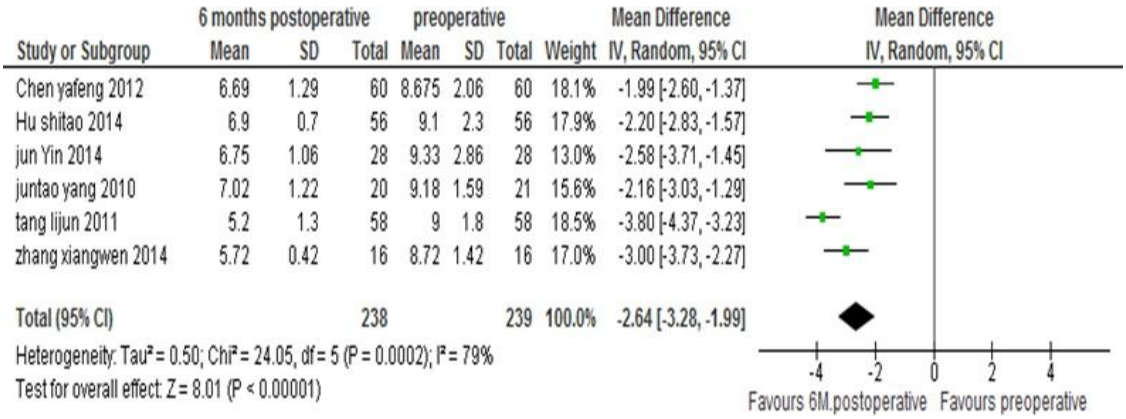

Fig. 2: Forest plot of glycosylated hemoglobin on non-obese T2DM patients before and after 6 months of gastric bypass surgery.

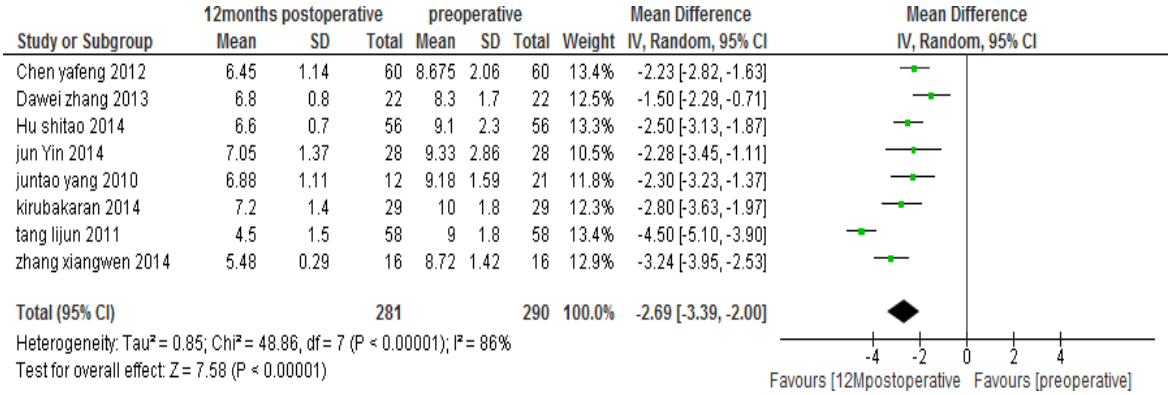

Fig. 3: Forest plot of glycosylated hemoglobin on non-obese T2DM patients before and after 12 month of gastric bypass surgery.

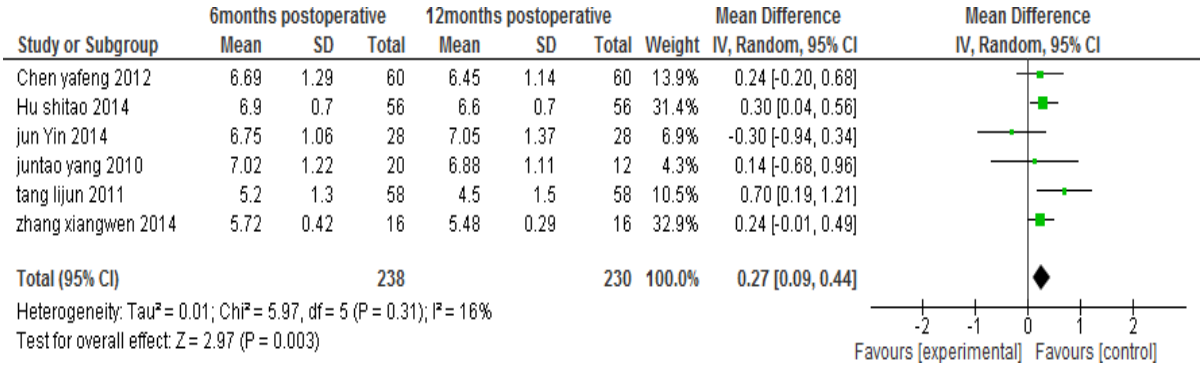

Fig. 4: Forest plot of glycosylated hemoglobin on non-obese T2DM patients after gastric bypass surgery for 6 months and 12 months postoperative.

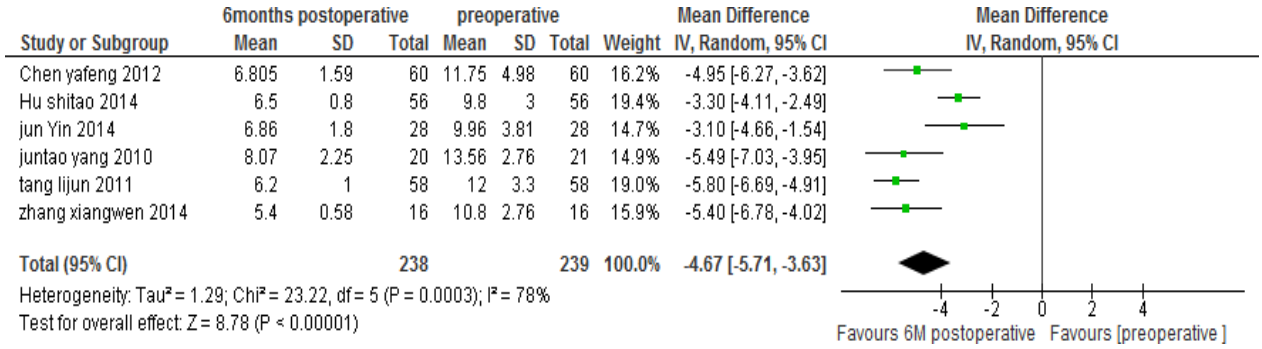

Fig. 5: Forest plot of fasting blood glucose on non-obese T2DM patients before and after 6 months of gastric bypass surgery.

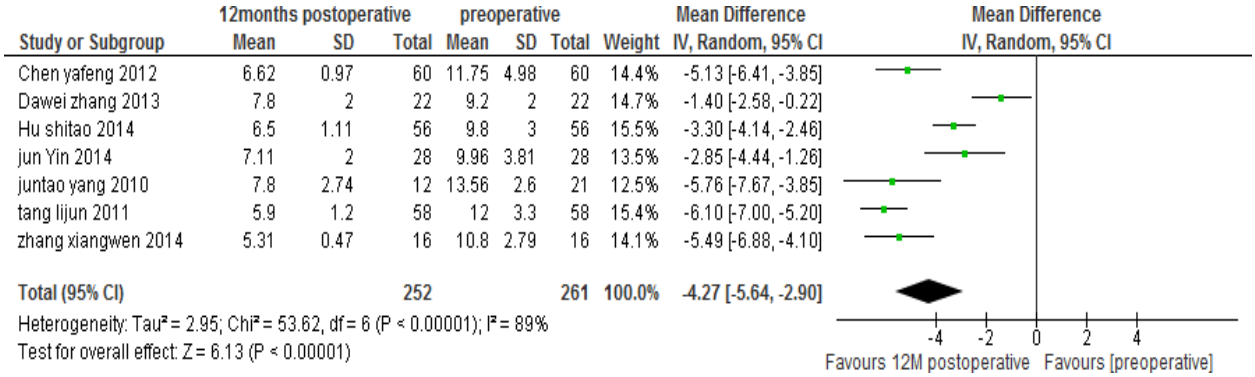

Fig. 6: Forest plot of fasting blood glucose on non-obese T2DM patients before and after 12 months of gastric bypass surgery.

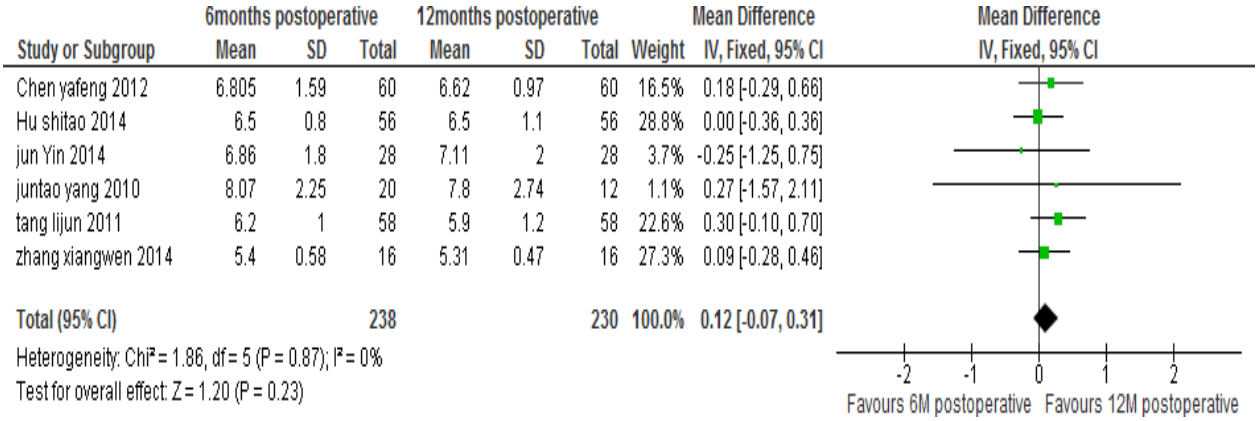

Fig. 7: Forest plot of fasting blood glucose on non-obese T2DM patients after gastric bypass surgery for 6 months and 12 months postoperative.

DISCUSSIONS

In recent years, the incidence of diabetes showed a gradual upward trend, has become one of the current threat to global human health, the most important noninfectious diseases, mostly in T2DM.

T2DM patients with an average life expectancy compare to non-diabetic patients is at least 5 to 10 years. The main hazards are from complications, such as coronary artery disease, diabetic nephropathy, and retinopathy. The Current main method of treatment for patients with T2DM is medical treatment including diabetes education, diet, exercise, oral hypoglycemic agents, insulin injections, etc. However, these treatments because life needs are still persisting, resulting in poor patient compliance, cannot fundamentally cure diabetes, nor prevent the occurrence of diabetic complications, development Therefore, T2DM patients need a long-term blood sugar control treatment and its complication.

Gastric bypass surgery began in the 1980s, the bariatric surgery fast development has become an important creation, in recent years it was found that the effect was not only reducing the patient's weight, but the most important was the improve of postoperative disorders in patients with the metabolic syndrome.

Gastric bypass surgery for obese T2DM diabetes treatment has been widely recognized by the International Diabetes Federation, the American Diabetes Association and the Chinese Diabetes Association, and was included in the obese T2DM treatment guidelines.

Karal, considered that gastric bypass surgery is only suitable for obesity complications BMI> 35kg/ m2, but a large number of clinical research and evidence-based medicine in recent years suggested that gastric bypass surgery for MBI <35 kg / m2 also has a good effect in non- pathological obese T2DM. Although obesity is a factor in the high incidence of T2DM, but a considerable part of T2DM is not associated with obesity, for example Chinas diabetic patients have an average BMI of about 25 kg / m2, but the non-obese T2DM patients surgery treatment is not unified and standardized, its effect and mechanism are still unclear, thus the research t of gastric bypass surgery efficacy in non-obese patients with T2DM is especially meaningful.

The Meta-analysis results of non-obese T2DM patients after gastric bypass surgery have showed a significant decrease of fasting plasma glucose and Glycosylated hemoglobin levels, 12 months and 6 months after surgery fasting plasma glucose levels decreases have no significant differences, but 12 months after surgery decreased fasting plasma glucose level is significantly better than that 6 months preoperative. Glycosylated hemoglobin is an important index to evaluate diabetes

blood glucose control situation and to predict vascular complications.

The Meta-analysis results showed that gastric bypass surgery in non-obese T2DM also has good antidiabetic effect, and good stability. But the results are also subject to certain restrictions, such as to determine the effect of a single indicator, inadequate period of observation.

Kirubakaran Malapan[6-8] after Clinical studies have found non-obese T2DM postoperative insulin function had been improved. Li Han[24-25] found that non-obese T2DM postoperative glucagon-like peptide -1 (GLP-1) significantly increased, GLP-1 is secreted by the terminal ileum L cells, it can promote glycogen synthesis and lipolysis, inhibition of gastric emptying, inhibition of glucagon secretion, increases insulin sensitivity, GLP-I in the "gut - islet axis" is considered as a major factor in controlling T2DM and thus likely to play an import role in gastric bypass surgery for treating diabetes.

These presents gastric bypass surgery treatment of non-obese T2DM possible mechanism of action, although the mechanism is not fully understood, but it is widely thought that it is related to the transformation of the gastrointestinal tract and gastrointestinal hormonal changes, the implementation of gastric bypass surgery reduces duodenal stimulation by food, thereby reducing gastric inhibitory peptide (GIP) and other "insulin resistance factor" generation, improve blood sugar, and premature entry of food into the jejunum is stimulates GLP-1 production, which can improve insulin resistance.[26]

This paper uses comprehensive gastric bypass treatment reports of non-obese T2DM patients, increased sample size; improved statistical power provides objective evidence for the treatment of gastric bypass surgery to determine the efficacy of non-obese patients with T2DM. the paper includes 8 documents in the design of self-controlled, lack of clinically randomized controlled trials reported, this suggests that there is need to conduct multicenter clinically randomized control trials of gastric bypass treatment of non-obese T2DM patients.

Self -controlled intervention studies designed to compare test subjects before and after the study, the subject is its own control, eliminating the individual differences, reducing the sample volume, saving time and cost, and also reduces volunteer and researchers bias; self-controlled study design Is susceptible to interference factors such as time, thus it cannot be controlled and randomized simultaneously, so the quality of the literature is low, it will affect the efficacy of extrapolation. The purpose of the systematic review is to obtain the best available evidence, based on existing research status, efficacy evaluation of self -controlled study was acceptable.[27-28]

In summary, the use of gastric bypass surgery treatment of non-obese T2DM has good effect, and is more stable, but the long-term efficacy remains to be further followed-up and verified. This provides an extensive theoretical basis of gastric bypass treatment of non-obese T2DM provides, and may change the basic principles of non-obese T2DM treatment, but the specific mechanism of surgery and its roles have not been completely elucidated, it still needs a large sample of high- quality long-term follow-up study and further exploration.

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