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ORIGINAL ARTICLE

Preoperative Fasting C-Peptide Predicts Type 2 Diabetes Mellitus Remission in Low-BMI Chinese Patients After Roux-en-Y Gastric Bypass

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Abstract

Objective This study investigated the role of preoperative fasting C-peptide (FCP) levels in predicting diabetic outcomes in low-BMI Chinese patients following Roux-en-Y gastric bypass (RYGB) by comparing the metabolic outcomes of patients with FCP > 1 ng/ml versus FCP ≤ 1 ng/ml.

Methods The study sample included 78 type 2 diabetes mellitus patients with an average BMI < 30 kg/m^2 at baseline. Patients' parameters were analyzed before and after surgery, with a 2-year follow-up. A univariate logistic regression analysis and multivariate analysis of variance between the remission and improvement group were performed to determine factors that were associated with type 2 diabetes remission after RYGB. Linear correlation analyses between FCP and metabolic parameters were performed. Patients were divided into two groups: FCP > 1 ng/ml and FCP ≤ 1 ng/ml, with measured parameters compared between the groups.

Results Patients' fasting plasma glucose, 2-h postprandial plasma glucose, FCP, and HbA1c improved significantly after surgery ($p < 0.05$). Factors associated with type 2 diabetes remission were BMI, 2hINS, and FCP at the univariate logistic regression analysis ($p < 0.05$). Multivariate logistic regression analysis was performed then showed the results were more related to FCP (OR = 2.39). FCP showed a significant linear correlation with fasting insulin and BMI ($p < 0.05$). There was a significant difference in remission rate between the FCP > 1 ng/ml and FCP ≤ 1 ng/ml groups ($p = 0.01$). The parameters of patients with FCP > 1 ng/ml, including BMI, plasma glucose, HbA1c, and plasma insulin, decreased markedly after surgery ($p < 0.05$).

Conclusion FCP level is a significant predictor of diabetes outcomes after RYGB in low-BMI Chinese patients. An FCP level of 1 ng/ml may be a useful threshold for predicting surgical prognosis, with FCP > 1 ng/ml predicting better clinical outcomes following RYGB.

Keywords Roux-en-Y gastric bypass · Low BMI · Type 2 diabetes mellitus · Fasting C-peptide · Chinese patients

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in the Chinese population has been increasing annually, representing one of the most challenging public health problems.[1,2] Patients with obesity and T2DM can achieve sustainable weight loss and diabetes remission after metabolic surgery.[3] Compared with conventional medical therapy, metabolic surgery can also significantly improve glycemic control in obese patients with T2DM.[4,5] Other investigations have shown that metabolic surgery leads to greater weight loss and better glycemic control and quality of life over a 3-year follow-up period.[6,7] Furthermore, compared to conventional medical therapy, metabolic surgery has superior utility in improving T2DM complications, such as macrovascular and microvascular events.[8,9] Additionally, T2DM patients with nonmorbid obesity or overweight show better weight loss and glycemic control after metabolic surgery.[7] Laparoscopic Roux-en-Y gastric bypass (LRYGB) has been proven a safe and effective surgical procedure.[10] Gastric bypass, combined with medical and lifestyle management, is now recommended for T2DM

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patients to improve diabetes control and metabolic dysregulation.[11,12]

Most T2DM Chinese patients have mild obesity or are classified as overweight. LRYGB is effective for the regulation of weight and glycemic control in Chinese T2DM patients with a body mass index (BMI) < 35 kg/m^2.[13] Notably, pancreatic beta-cell function declines in the Chinese T2DM population at an early stage, leading to a progressive reduction in insulin secretion. Preoperative beta-cell function is important for T2DM remission. Therefore, indices of preoperative beta-cell function may be used to better estimate remission rates of T2DM with metabolic surgery. Unlike insulin, C-peptide is not degraded or cleared by the liver, and the peripheral C-peptide concentration is a better index of insulin secretion than peripheral insulin concentration.[14] As a result, bariatric surgery is recommended for obese and T2DM patients with elevated C-peptide levels.[15]

One important factor associated with higher rates of T2D remission with metabolic surgery is the fasting C-peptide (FCP) level. The Chinese Society for Metabolic and Bariatric Surgery (CSMBS) recommends surgery for patients with levels of half the normal FCP range (1.1–4.4 ng/ml).[16] There is an important effect of bariatric surgery in the treatment of T2DM in low-BMI patients with C-peptide levels above 1.0 ng/ml,[17–19] but we need more data to support the FCP level criteria.

Consequently, this study investigated whether a preoperative FCP level of 1 ng/ml could be used as a single cutoff point for predicting postoperative diabetic outcomes following LRYGB by comparing metabolic outcomes between FCP > 1 ng/ml and FCP ≤ 1 ng/ml groups.

Materials and Methods

Patients

This investigation was a cohort study including 78 T2DM patients who underwent LRYGB and were enrolled from October 2010 through October 2012 at Third Xiangya Hospital of Central South University in China. No patients were lost to follow-up at any time point. The diagnosis and classification of T2DM were determined using the criteria of the American Diabetes Association.[20] The study was reviewed and approved by the human ethics committee of the Third Xiangya Hospital of Central South University and was guided by the principles of the Helsinki Declaration. All patients provided written informed consent before surgical procedures were performed. The inclusion criteria were as follows: BMI greater than or equal to 32.5 kg/m^2; BMI lower than 32.5 kg/m^2 with T2DM poorly controlled by standard medical therapy and lifestyle management, combined with at least 2 additional metabolic syndrome criteria, including elevated fasting triglycerides (TG), decreased fasting high-density lipoprotein (HDL); and hypertension or presentation with other diabetic complications, including abnormal glucose metabolism with insulin resistance, obstructive sleep apnea syndrome, nonalcoholic steatohepatitis, hyperuricemia, polycystic ovary syndrome. Central obesity was determined as an increased waist circumference (WC) ≥ 90 cm for males and WC ≥ 85 cm for females.

The exclusion criteria were as follows: a history of type 1 diabetes, gestational diabetes, or another special type of diabetes mellitus; dysgnosia; intellectual immaturity; severe psychiatric conditions; drug abuse or alcohol addiction; other severe medical conditions; or incompatibility with changes in diet and living habits.

The latest Chinese metabolic surgery outcome classifications are as follows: complete remission, partial remission, improvement, and inefficacy. Complete remission is defined as a glycated hemoglobin A1c (HbA1c) level of less than 6.5%, a fasting glucose level of less than 5.6 mmol/L, and a 2-h postprandial glucose level of less than 7.8 mmol/L for at least 1 year without active pharmaceutical therapy and with effective management of glucose achieved by lifestyle regulation. Partial remission is defined as an HbA1c level of 6.5 to 7.0%, a fasting plasma glucose (FPG) level of 5.6 to 6.9 mmol/L, and 2-h postprandial glucose (2hPG) of 7.8 to 11.0 mmol/L for at least 1 year without active pharmaceutical therapy and with effective management of glucose achieved by lifestyle regulation. Improvement is defined as an HbA1c level of less than 7.5%, with a significant reduction in the subtypes and doses of hyperglycemic medications after surgery. Inefficacy is defined as no significant postoperative change in glucose level, HbA1c species, or dose of hyperglycemic agents. In this study, patients with complete remission were included in the remission group, and those with partial remission and improvement were included in the improvement group. No patients exhibited inefficacy.

Treatments

Metabolic procedures (LRYGB)[21] were all performed laparoscopically by the same surgeon. There was no conversion to laparotomy. The volume of the gastric pouch was 15 to 30 ml, and the sum of the length of the Roux limb and the biliopancreatic limb was expected to exceed 200 cm.

Patients undergoing metabolic surgery were evaluated by a multidisciplinary team, which included a surgeon, a diabetologist, a cardiovascular physician, a respiratory physician, a psychiatrist, an anesthesiologist, a dietitian, and a project manager. Evaluations were conducted at baseline and at 1 week, 3, 6, 12, and 24 months after surgery. Nutritional supplements after LRYGB included a multivitamin, vitamin B12, iron, folic acid, and calcium citrate with vitamin D.

End points

The primary end point was the remission rate of T2DM between patients with FCP > 1 ng/ml and those with FCP ≤ 1 ng/ml after LRYGB.

Secondary end points were the results of univariate logistic regression analysis between remission and improvement groups (part remission and improvement) on clinical factors at baseline, including gender, age, duration, BMI, TG, plasma cholesterol (CHOL), HDL, fasting insulin (FINS), 2hINS, FCP, 2-h postprandial C-peptide (2hCP), and homeostatic model assessment of insulin resistance (HOMA-IR). Then, a multivariate logistic regression analysis was built with the clinical factors which are significant differences at univariate logistic regression analysis and linear correlations between FCP and the metabolic-related parameters BMI, TG, CHOL, HDL, FPG, 2hPG, FINS, and HOMA-IR. The comparison between and within FCP > 1 ng/ml and FCP ≤ 1 ng/ml group in FPG, 2hPG, HbA1c, BMI, waist-to-hip ratio (WHR), FINS, FCP, 2hCP, HOMA-IR, CHOL, and TG were performed at baseline and postoperative 2 years.

Statistical Analysis

All analyses were performed with SPSS software (version 21, SPSS Inc., Chicago, IL). Continuous variables with a normal distribution are reported as the mean ± SD. Categorical variables are summarized as frequencies. Non-numerical data were evaluated by the χ^2 test, and numerical data were evaluated using Student's *t* test (paired *t* test for before versus after surgery and two-sample *t* tests for the two groups). The univariate and multivariate logistic regression analysis was performed on the related predictive indices and the postoperative curative effect. Pearson's correlation analysis was used to study the relationship between FCP and metabolic-related parameters. A result of $p < 0.05$ was considered statistically significant.

Results

General Outcomes

Of the 78 patients undergoing LRYGB, 52 were males and 26 were females, with a BMI of 28.2 ± 5.8 kg/m^2(range 19.3–35.0 kg/m^2), a mean age of 46.8 ± 9.8 years (range 19–68 years). The mean duration of T2DM was 6.4 ± 4.2 years (range 2–20 years). The mean HbA1c level was 8.1 ± 1.6% (range 5.7–13%). The WHR ranged from 0.8 to 1.3 (mean value 1.0 ± 0.1). Common comorbidities included fatty liver (61.5%) and hypertension (38.5%). The patients' diabetes status of preoperative medication was as follows: oral hypoglycemic agents alone 25.8%, insulin only 21.2%, both oral agents and insulin 46.9%, without diabetes medications 6.1%. The comparison of pre- and post-operative data showed substantial decreases in BMI, WHR, HbA1c, 2hPG, FCP, HOMA-IR, TG, and CHOL ($p < 0.05$).

Primary End points

At 2 years postoperatively, diabetes remission was achieved in 26 of 47 patients (55.3%) in the FCP > 1 ng/ml group and in 8 of 31 patients (25.8%) in the FCP < 1 ng/ml group. The difference was significant between the two groups ($p = 0.01$), indicating the greater therapeutic efficacy of LRYGB in the FCP > 1 ng/ml group. Significant differences were also observed between the two groups in BMI, WHR, and 2hCP/FCP at baseline ($p < 0.05$), but TG, CHOL, FPG, 2hPG, FINS, HOMA-IR, and HbA1c showed no significant differences between the groups at baseline. At the 2-year follow-up, significant differences between the two groups were observed in BMI, 2hPG, 2hCP/FCP, and HbA1c ($p < 0.05$) (Table 4). An impressive reduction was observed in BMI and TG in both FCP > 1 ng/ml and FCP ≤ 1 ng/ml groups ($p < 0.05$) (Table 4). Patients with FCP > 1 ng/ml achieved notable improvements in BMI, TG, 2hPG, 2hCP/FCP, HOMA-IR, and WHR ($p < 0.05$) (Table 4, Fig. 1).

Secondary End points

Factors associated with type 2 diabetes remission were BMI, 2hINS, and FCP at the univariate logistic regression analysis ($p < 0.05$) (Table 1). Multivariate logistic regression analysis was performed then showed the results were more related to FCP (OR = 2.39, $p = 0.10$) (Table 2). FCP showed a significant linear correlation with FINS and BMI ($p < 0.05$) (Tables 3 and 4).

Discussion

The results of the current study show that LRYGB can result in the remission of obesity and T2DM in low-BMI Chinese patients. T2DM patients undergoing LRYGB can achieve notable decreases in weight and levels of blood lipids and blood glucose. Moreover, our cohort study revealed impressive improvements in pancreatic beta-cell function (as indicated by FCP and FINS) and insulin resistance (HOMA-IR) in diabetic patients with mild obesity after RYGB. These data support previous research. Ikramuddin and colleagues[22] found that outcomes related to diabetes control after RYGB compared to conventional treatments were satisfactory, with RYGB resulting in greater weight loss and lower risks of adjustable gastric band surgery.[23,24] Furthermore, gastric bypass with lifestyle and medical management may be superior for the

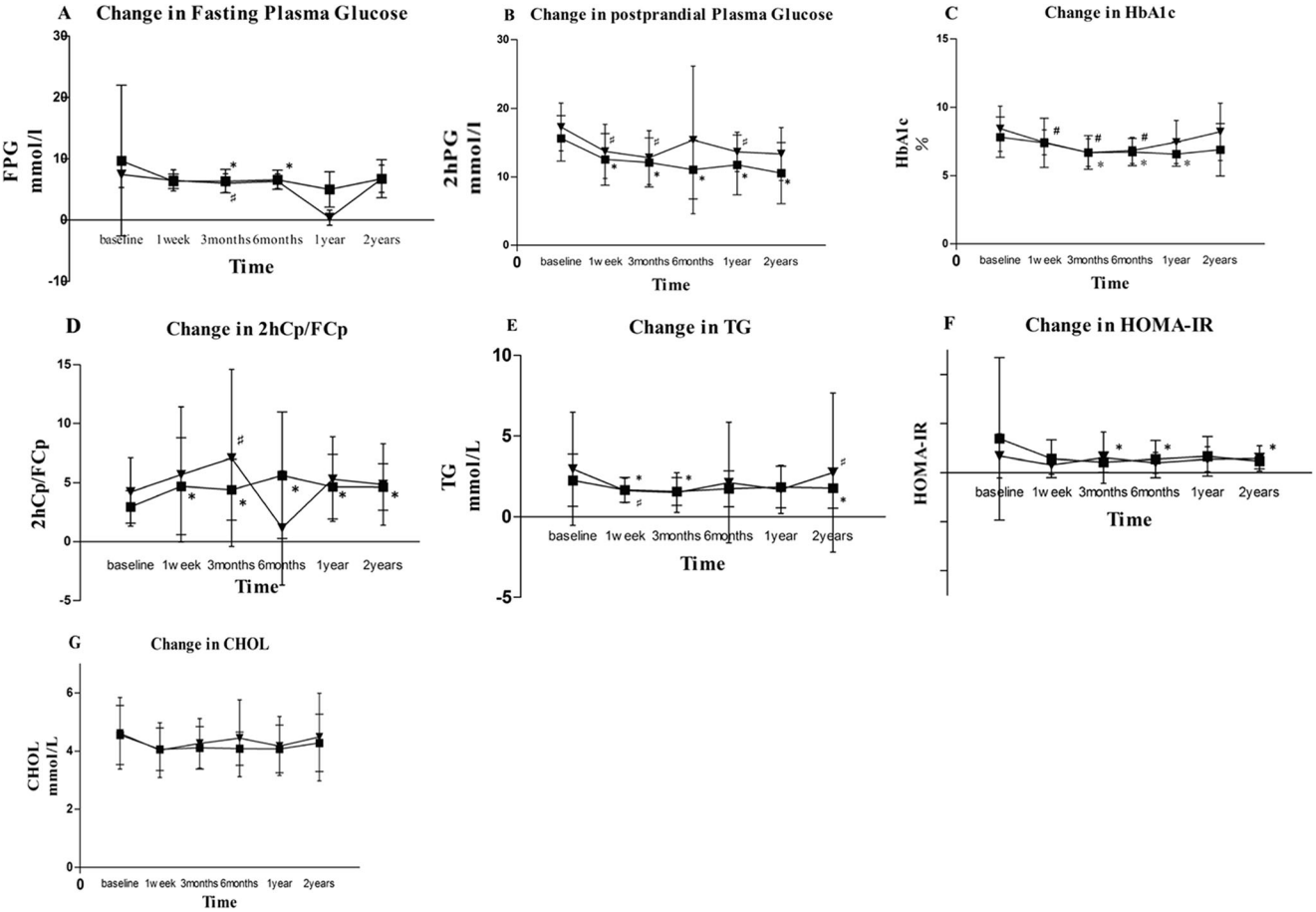

Fig. 1 Changes in diabetes control within FCP > 1 ng/ml and FCP ≤ 1 ng/ml group from baseline through 2 years. * indicates comparison of preoperative and postoperative in FCP > 1 mmol/l group, $p < 0.05$. # indicates comparison of preoperative and postoperative in FCP ≤ 1 mmol/l group, $p < 0.05$. ■ indicates FCP > 1 ng/ml group. ▼ indicates FCP ≤ 1 ng/ml group

Table 1 The univariate logistic regression analysis to investigate factors associated with remission of T2DM

	Wals	OR	95% CI		
			Lower limit	Upper limit	*p*
Gender	0.96	1.02	0.98	1.07	0.33
Age	0.03	0.93	0.36	2.39	0.87
Duration	3.10	1.11	0.99	1.25	0.08
BMI	5.34	0.88	0.78	0.98	0.02*
TG	2.77	1.27	0.96	1.69	0.10
CHOL	0.07	0.95	0.63	1.42	0.79
HDL	1.49	0.36	0.07	1.87	0.22
FINS	0.12	1.00	0.97	1.02	0.73
2hINS	4.03	0.99	0.97	1.00	0.04*
FCP	6.33	3.56	1.32	9.57	0.01*
2hCP	2.02	0.91	0.79	1.04	0.16
HOMA-IR	0.55	1.02	0.97	1.08	0.46

Wals WaldChiSq, *OR* dominance ratio, *95% CI* 95% of confidence interval. *Correlation is significant at the 0.05 level (two-tailed)

treatment of associated complex diseases, such as T2DM, hyperlipidemia, and hypertension.[25]

In the USA, RYGB is usually recommended for patients with morbid obesity (BMI > 35 kg/m^2). However, most Chinese patients with T2DM are overweight or have mild obesity (BMI of 25 to 32.5 kg/m^2). RYGB also protects Chinese patients with mild obesity against wider metabolic dysregulation, including diabetes and related comorbidities.[26] In our study, T2DM patients with a mean BMI of 28.18 kg/m^2 showed notable improvements in weight and glycemic control after RYGB, supporting previous findings.[2] Moreover, gastric

Table 2 The multivariable logistic regression analysis to investigate factors associated with remission of T2DM

	Wals	OR	95% CI		
			Lower limit	Upper limit	*p*
BMI	2.23	0.92	0.82	1.03	0.14
2hINS	1.73	0.99	0.98	1.01	0.19
FCP	2.66	2.39	0.84	6.83	0.10

Table 3 Linear correlation of FCP and metabolic-related parameters

		HbA1c	HOMA-IR	FINS	FPG	2hPG	BMI	TG	CHOL	HDL
FCP	*r*	− 0.214	0.204	0.224*	0.052	− 0.130	0.285*	0.037	0.066	− 0.141
	sig	0.060	0.074	0.049	0.653	0.255	0.012	0.747	0.565	0.219

*Correlation is significant at the 0.05 level (two-tailed)

bypass resulted in better pancreatic beta-cell function and more effectively reduced truncal fat in patients with moderate obesity compared with sleeve gastrectomy.[27]

BMI is the major preoperative selection criterion for metabolic surgery. In the latest guidelines in a joint statement from international diabetes organizations, metabolic surgery is recommended for patients with mild obesity (BMI 30.0–34.9 kg/m^2), with the BMI selection criterion reduced to 27.5 kg/m^2 for the Asian population.[28] However, preoperative BMI as the sole surgical indication has been questioned because it cannot comprehensively predict diabetes outcomes.[7] Therefore, more effective indicators and measurement parameters are needed.

From the univariate logistic regression analysis, BMI, 2hINS, and FCP are prognostic factors. Multivariate analysis showed the FCP odds ratio was 2.39, higher than BMI and 2hINS. Even the *p* value was 0.10 ($p > 0.05$), we can consider this as a marginal significance. Based on the results of univariate and multivariable analysis, FCP can be considered as an important predictor of clinical remission of T2DM. In addition, FCP has a significant linear correlation with FINS and BMI.

The major finding of the present study is the utility of preoperative FCP for predicting diabetes outcomes in Chinese patients with mild obesity. Notably, diabetes remission after LRYGB improved significantly at the 2-year follow-up for T2DM patients with preoperative FCP > 1 ng/ml compared to patients with FCP ≤ 1 ng/ml (55.3 versus 25.8%, $p = 0.01$). The levels of 2hPG and HbA1c showed significant differences between the groups at 2 years, while the follow-up data on FINS, 2hINS, 2hCP/FCP, and HOMA-IR from patients with FCP > 1 ng/ml, reflecting pancreatic beta-cell function and insulin resistance, also showed marked improvements.

Previous research has shown that the function of the pancreatic islets is closely associated with T2DM remission,[29] with impairment of pancreatic islet function emerging at an early stage of T2DM in the Chinese population. Therefore, it is important to assess preoperative pancreatic beta-cell function, especially in the Chinese population.[30] In a cohort study of European T2DM patients with morbid obesity (BMI ≥ 50 kg/m^2), a preoperative FCP level of less than 1.0 nmol/l resulted in poor diabetes outcomes after RYGB.[31] In addition, Lee and colleagues[15] found that T2DM remission after gastric bypass was high for patients with elevated FCP levels. This result is supported by the findings in the present study, in which an improved remission rate of T2DM in patients with mild obesity (BMI < 30 kg/m^2) was evident in those with FCP > 1 ng/ml versus those with FCP ≤ 1 ng/ml. The present data also show marked improvements in lipid metabolism, insulin-secreting function, and fat distribution in the FCP > 1 ng/ml group.

It should be noted that there are limitations in using FCP as a parameter of pancreatic beta-cell function. FCP should not be considered the only relevant preoperative variable, as levels of postprandial C-peptide may also be helpful in predicting diabetes remission.[32] Android fat distribution has also been proposed to be a good indicator of diabetes remission for T2DM following LRYGB.[21] The Diabetes Surgery Score includes a variety of variables indicative of metabolic surgery utility, such as BMI, C-peptide levels, T2DM duration, and patient age.[17] Overall, it seems reasonable to conclude that,

Table 4 Comparison between and within FCP > 1 ng/ml and FCP ≤ 1 ng/ml group on clinical factors at baseline and postoperative 2 years

Index	FCP > 1 (*n* = 47)	FCP ≤ 1 (*n* = 31)	*t* test	*p* values
Preoperative				
BMI	29.5 ± 6.8	26.2 ± 3.0	− 2.969	0.004**
WHR	1.0 ± 0.1	0.9 ± 0.1	− 2.028	0.046*
TG	2.1 ± 1.5	3.0 ± 3.4	1.380	0.176
CHOL	4.6 ± 1.0	4.7 ± 1.2	0.488	0.627
FPG	9.0 ± 9.4	7.5 ± 2.1	− 0.890	0.376
2hPG	15.9 ± 4.4	17.2 ± 3.9	1.415	0.161
FINS	13.7 ± 16.1	12.9 ± 15.5	− 0.235	0.815
2hCP/FCP	2.9 ± 1.3	4.2 ± 2.7	2.445	0.019*
HOMA-IR	6.4 ± 13.4	3.8 ± 4.2	− 1.044	0.300
HbA1c	7.8 ± 1.5	8.4 ± 1.7	1.657	0.102
Postoperative				
BMI	26.0 ± 2.4$^{\#}$	24.3 ± 2.5$^{\#}$	− 2.245	0.030*
WHR	0.93 ± 0.1$^{\#}$	0.9 ± 0.1	− 0.237	0.814
TG	1.8 ± 1.3$^{\#}$	2.7 ± 4.9$^{\#}$	0.832	0.415
CHOL	4.3 ± 1.0	4.5 ± 1.5	0.548	0.586
FPG	6.8 ± 3.1	6.8 ± 2.2	0.009	0.993
2hPG	10.6 ± 4.5$^{\#}$	13.4 ± 3.9	2.183	0.035*
FINS	7.9 ± 4.6$^{\#}$	9.6 ± 7.8	0.898	0.374
2hCP/FCP	4.7 ± 2.0$^{\#}$	4.9 ± 3.4	0.231	0.819*
HOMA-IR	2.4 ± 1.6$^{\#}$	2.9 ± 2.6	0.869	0.390
HbA1c	6.9 ± 1.9	8.2 ± 2.1	2.168	0.036*

t test for FCP > 1 ng/ml group vs. FCP ≤ 1 ng/ml group, **p* values < 0.05; ***p* values < 0.01; Paired *t* test for preoperative vs. postoperative; $^{\#}p$ values < 0.05

although many other factors may also enhance the prediction of diabetes remission, the FCP level is an important indicator. Study limitations should also be noted, including the short follow-up period and the relatively small sample size. Future investigations should employ a longer follow-up period and multicenter sampling, thereby increasing the sample size and the corresponding generalizability of the findings.

Conclusion

In conclusion, RYGB is effective in treating Chinese T2DM patients with mild obesity, and the preoperative FCP level is an important contributor to the prediction of the efficacy of LRYGB. The presented data support the use of FCP levels with a threshold of 1 ng/ml for predicting surgical efficacy. Chinese patients with mild obesity and T2DM with a preoperative FCP > 1 ng/ml showed marked improvements after LRYGB versus patients with FCP ≤ 1 ng/ml. An FCP level of 1 ng/ml is a useful threshold for predicting surgical prognosis for Chinese patients with mild obesity and T2DM.

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Compliance with Ethical Standards

The study was reviewed and approved by the human ethics committee of the Third Xiangya Hospital of Central South University and was guided by the principles of the Helsinki Declaration. All patients provided written informed consent before surgical procedures were performed.

Conflict of Interest The authors declare that they have no conflict of interest.

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