Original Article

Uric acid level changes after bariatric surgery in obese subjects with type 2 diabetes mellitus

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Background: The purpose of the study was to investigate the incidence of hyperuricemia (HU) in obese subjects with type 2 diabetes mellitus (T2DM) before and after Roux-en-Y gastric bypass (RYGB), to describe the impact of this therapy in reducing uric acid levels, and its possible mechanism. This study was performed by cooperation with the First affiliated hospital of Soochow University and the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, department of general surgery.

Methods: A retrospective study was performed. From February 2015 to December 2017, we evaluated 147 obese patients with T2DM. Blood samples and other clinical data were drawn before and postoperative (1, 3, 6, 12 months after RYGB). All obese patients with T2DM underwent laparoscopic Roux-en-Y gastric bypass surgery (LRYGB). Different gender with HU were compared before and after surgery.

Results: A total of 147 patients received LRYGB (75 were female, 72 were male), and 48 patients with HU (22 were female, 26 were male). Four women and 2 men were lost to follow-up, they were excepted from this study. No patients with HU lost to follow-up. There's an intuitive downward trend about uric acid levels both in men and women, with men from 497.9 μmol/L before surgery to 371.5 μmol/L 1 year after surgery, P=0.000; women from 432.3 to 354.1 μmol/L, P=0.002. The proportion of HU changed with men from 37.1% (26/70) before surgery to 12.9% (9/70) one year after surgery, women from 31.0% (22/71) to 14.1% (10/71). The results of binary logistic regression analysis confirmed that triglycerides were clinical predictors for HU remission (P=0.004). No major late surgical complications were reported.

Conclusions: Our data showed that, bariatric surgery was effective to decrease the levels of serum uric acid (SUA) in obese patients with T2DM. Compared with traditional drug treatment, this shows a possible treatment of HU by RYGB. The remission of HU was associated with the decreased triglyceride levels in obese patients with T2DM, independent of BMI. The potential role of triglycerides in the remission of HU merits further study.

Keywords: Hyperuricemia (HU); bariatric surgery; obese; type 2 diabetes mellitus (T2DM)

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Introduction

Serum uric acid (SUA) is the end-product of endogenous and dietary purine metabolism in humans. It has been demonstrated that SUA is important to disease and clinical prognosis. For example, obesity is independently associated with SUA (1); there is also a positive relationship between Body Mass Index (BMI) and SUA (2); SUA may imply an increased risk of vascular disease and T2DM (3); SUA may

predict future declines in insulin action (4). In addition, independent association between SUA and cardiovascular disease has also been found in multiple studies (5-8). Even evidences show that SUA may be a true risk factor for cancer incidence and mortality (6,9). In the past decades, the prevalence of hyperuricemia (HU) has varied greatly, and appeared to be increasing (10). Moreover, 18.8% of the patients with HU developed into gout in a 5-year follow-up (11).

Since HU is an important signal of many human diseases (12), prevention and control of SUA level become a critical clinical solution. However, HU is a result of interactions among multiple factors including gender, age, and genetic variances. Elucidating the complicated incidence of HU is a non-trivial work. Note that HU is often diagnosed as SUA not less than 360 μmol/L in women or not less than 420 μmol/L in men (13).

Laparoscopic Roux-en-Y gastric bypass surgery (LRYGB) has been wildly used in the world for weight control or blood glucose control. Our previous studies have confirmed that, LRYGB could improve pulmonary function (14) and LRYGB may be an effective therapeutic intervention in the management of obstructive sleep apnea (15). The research also showed the improvement of Diabetic Nephropathy (16) and the relief of erectile dysfunction after LRYGB (17).

By comparing the patient record data before and after the LRYGB surgery, we found that uric acid levels decreased significantly in patients with HU. Based on the observation, we hypothesize that RYGB is a potential treatment for HU. As the first step to verify the hypothesis, this study aimed to investigate whether RYGB is appropriate for HU in obese patients with type 2 diabetes mellitus (T2DM).

Methods

Study design

This study has been performed by the First affiliated hospital of Soochow University and the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, department of general surgery, completed this study collaboratively. All the preoperative assessment and operations were performed by the Sixth People's Hospital, and the postoperative follow-up were performed by the First affiliated hospital of Soochow University. Patients with HU (preoperative) were divided into two groups by gender.

Inclusion and exclusion criteria

Eligibility criteria included: (I) age ranges from 18 to 65 years old, (II) BMI is over 27.5 kg/m^2, (III) a diagnosis of abnormal glucose tolerance or T2DM (based on the criteria of the American Diabetes Association, course of disease less than 15 years), and (IV) a fasting C-peptide by the oral glucose tolerance test >1 ng/mL and a ratio of peak to fasting value >2 ng/mL.

Patients with established diagnoses of type 1 diabetes mellitus, latent autoimmune diabetes in adulthood, malignancy, debilitating disease, unresolved psychiatric illness, unable to follow-up or substance abuse were excluded from the study.

Follow-up

Age, weight, BMI, waistline, hipline, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded before and after bypass surgery. Biochemical parameters were evaluated by obtaining blood samples after an overnight fast, included blood urea nitrogen (BUN), serum creatinine (SCr), SUA, free fatty acid (FFA) and hemoglobin A1c (HbA1c).

According to recommendation for gouty arthritis, patients were encouraged to reduce high purine food intake, keep a diet, stop smoking and refrain from drinking before and after surgery (18). Colchicine and non-steroid anti-inflammatory drugs (NSAIDs) were not used to decrease the GI irritation and side effect after surgery.

Patients followed-up at one month postoperative, three months postoperative, six months postoperative, one year postoperative. The wound recovery follow-up was performed only once at one month postoperative.

Statistical analysis

All data were analyzed using SPSS statistical software for Windows, version 22.0, data expressed as means ± SD or as the median (interquartile range). Comparisons of continuous data between two groups were performed using an independent sample *t*-test/pair *t* test or the Mann-Whitney U-test where appropriate. Correlations between clinical parameters and HU were identified by using partial correlation analysis. Binary logistic regression analysis was performed to assess the independent predictive effects of

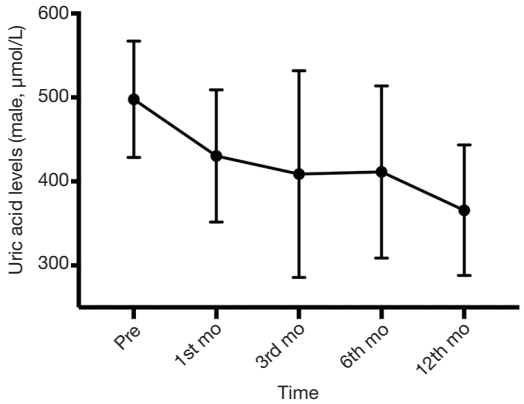

Figure 1 Variation about uric acid levels (men, μmol/L).

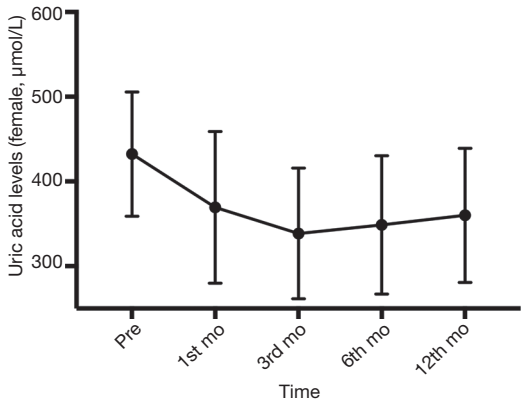

Figure 2 Variation about uric acid levels (women, μmol/L).

the variables on remission of HU. A P value less than 0.05 was considered significance.

Results

Patients

A total of 147 patients received RYGB, six patients (4 female and 2 male) lost follow-up were excluded. There were 141 patients involved in this study, 71 (50.3%) were female, 70 (49.6%) were male. Among them 48 patients (22 female and 26 male) with HU. Each of the surgery was performed as a laparoscopy without mortality or major complications. No severe malnutrition or vitamin or mineral deficiencies were observed during follow-up. In the 147 patients, 38 (52.7%) male and 14 (18.7%) female had history of alcohol intake, among those with HU, 12 (46.2%) male and 2 (9.1%) female were observed before surgery. No alcohol

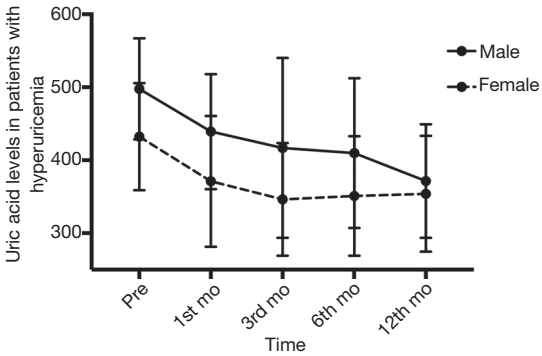

Figure 3 Uric acid levels with hyperuricemia. Patients with hyperuricemia showed higher uric acid level in men than in women before surgery (P=0.000), but 12 months after Roux-en-Y gastric bypass (RYGB), there was no significant difference.

consumption patients included in this study. After surgery, according the dietary instruction, patients were forbidden alcohol intake at least 1 year after surgery.

Changes about Uric acid level

In our study, the ratio of HU is 34.0% (48/141). All the patients with HU (preoperative) were divided into two groups by gender. The two groups were compared before and after surgery.

In *Figures 1*,*2*, there is an intuitive downward trend on the percentage of HU (with male from 37.1% before surgery to 12.7% one-year after surgery, and with female from 31.0% to 14.1%). We also learned that, on the proportion of HU, such downward trend is flattens out with the time after surgery (*Figure 3*). For instance, comparing to the variations between half-year and one-year follow-up, the variations between pre-surgery and one-month after surgery follow-up is clearly more obvious.

In *Figure 1* and *Figure 2*, the SUA levels has an intuitive downward trend too, with male from 497.9 μmol/L before surgery to 371.5 μmol/L 1 year after surgery, P=0.000; female from 432.3 μmol/L before surgery to 354.1 μmol/L 1 year after surgery, P=0.002. Through there is a downward trend about the proportion of HU after half year from the surgery in female (*Table 1*), the SUA levels in female showed a tendency of increase at the same time (*Figure 2*).

The two groups also had a significant remission in BMI (male, P=0.000; female, P=0.000), Waistline (male, P=0.000; female, P=0.000) , Hipline (male, P=0.000; female, P=0.000), waist-to-hip ratio (male, P=0.000; female, P=0.068), SUA

Table 1 Incidence of hyperuricemia

Gender	Pre-surgery	1st month after surgery	3rd month after surgery	6th month after surgery	12th month after surgery
Male (%)	37.1	25.7	18.6	14.3	12.7
Female (%)	31.0	26.8	18.3	15.5	14.1

(male, P=0.000; female, P=0.003), triglycerides (male, P=0.000; female, P=0.004), HbA1c (male, P=0.001; female, P=0.000) and FFA (male, P=0.016; female, P=0.002) (*Table 2*) 1-year after surgery. There is no significant difference in HR (male, P=0.134; female, P=0.294), BUN (male, P=0.658; female, P=0.426); SCr (female, P=0.511) 1-year after surgery.

Factors predictive of HU remission

According to the correlation test for SUA in patients with baseline (*Table 3*), analysis showed that in HU patients, BMI, waistline, hipline, triglycerides and HbA1c level have relationship with the remission of HU. The diabetes duration as well as triglyceride levels differed between remission and no-remission group in HU patients 1 year after surgery (*Table 4*).

The results of Binary logistic regression analysis confirmed that triglycerides were clinical predictors for HU remission [P=0.004, Exp(B)=0.206, *Table 5*].

Discussion

The incidence of HUA

Epidemiological studies indicate that HUA is relatively prevalent in the general population. The prevalence of HUA in Shandong, China, reached 16.7% in a 2009 survey, approaching the levels of Western developed countries (19). While in our study, the percentage of HUA is 34.0% (48/141), men 37.1% (26/70), women 31.0% (22/71), almost twice that of general population. Studies have shown an important association between SUA and obesity with T2DM, SUA levels were higher in T2DM patients than those without T2DM, and higher BMI further accentuates this risk (20). We found that obese patients had significantly higher SUA levels compared to normal subjects. Studies have also identified other risk factors such as alcohol intake, diet and genetic (1).

In this study, we hypothesized that the incidence of HU and SUA levels would be markedly elevated at baseline after bariatric surgery in obesity with T2DM, and that the incidence of HU and SUA levels would decrease postoperatively. Furthermore, we hypothesized that this decrease in the incidence of HU would correlate with change in weight and other important clinical parameters postoperatively. The present study showed that the incidence of HU has a significant decline after RYGB. It's obvious that RYGB can reduce the incidence of HU, there has a significant decline just one month after RYGB. Men showed a greater decline than woman. So as to the SUA level. With men from 37.1% before surgery to 12.7% 1 year after surgery, women from 31.0% before surgery to 14.1% 1 year after surgery.

Therapeutic effect about drugs and surgery

Many drugs have therapeutic effect on HU, such as xanthine oxidase inhibitors, probenecid, benzbromarone. These drugs can reduce the generation of uric acid or can promote the excretion of uric acid. But as a chronic disease, patients who have a diagnosis of HU or gout may need long-term medication or even for life long, medication adherence and drug side effects are big problems.

Studies show that (21), the number of patients taking benzbromarone alone whose SUA values fell within normal range [men <7 mg/dL (420 μmol/L) and women <6 mg/dL (360 μmol/L)] was 75% and for the group taking allopurinol alone this number was 51.8% , the number of patients taking both drugs was 85.7%, and The entire patient group experienced a significant drop in serum urate levels, from 8.5±1.8 to 6.7±2.1 mg/dL (P<0.001), regardless of the prescribed medication. The mean drop in serum urate levels was 1.8mg/dL. While in our study, the number of patients whose SUA values fell within normal range was 60.4% (29/48). In men, the SUA levels have dropped from 497.9±69.3 to 371.5±82.0 μmol/L. In women, the SUA levels have dropped from 432.3±73.4 to 354.1±80.9 μmol/L. In men, the mean drop in serum urate levels was 126.4 μmol/L (2.1 mg/dL), In women, was 78.2 μmol/L (1.3 mg/dL), better than drug therapy mentioned above.

Table 2 Characteristic of the study population according to hyperuricemia status

Variables	Male (n=26)					Female (n=22)				
	Pre	1 month after surgery	3 months after surgery	6 months after surgery	12 months after surgery	Pre	1 month after surgery	3 months after surgery	6 months after surgery	12 months after surgery
BMI (kg/m^2)	33.3±3.4	28.9±2.7*	27.0±2.4**	25.5±2.5**	24.4±2.5**	31.3±3.1	27.7±3.1**	25.5±2.6**	23.7±2.2**	23.5±2.2**
Waistline (cm)	112.2±11.1	100.1±8.2*	95.2±8.9**	89.1±7.4**	87.5±6.7**	103.2±9.2	94.5±10.2**	89.7±7.5**	85.5±7.0**	86.9±8.0**
Hipline (cm)	110.7±8.4	101.8±5.9*	98.4±6.2**	94.9±5.3**	95.6±5.8**	108.3±9.3	101.4±7.0**	97.1±6.3**	94.0±6.4**	94.3±3.9**
WHR	1.0±0.1	1.0±0.0**	1.0±0.1**	0.9±0.0**	0.9±0.0**	1.0±0.1	0.9±0.1	0.9±0.0	0.9±0.0**	0.9±0.1
HR (bpm)	78.5±8.0	80.6±13.3	78.0±6.0	74.9±7.0	75.3±7.1	76.2±6.0	79.4±15.6	74.5±7.3	73.4±6.9	73.8±8.8
SBP (mmHg)	133.7±12.9	128.0±12.6	124.1±11.5**	121.0±13.8**	120.8±13.4**	128.5±17.2	123.7±16.4	118.1±11.0*	116.5±15.9*	116.1±11.8**
DBP (mmHg)	84.9±13.0	80.9±11.7	79.9±8.8	77.3±8.4*	77.3±8.3*	81.0±11.0	78.3±8.6	76.2±8.3	71.9±8.7*	70.8±9.7**
BUN (mmol/L)	5.1±1.4	3.6±1.0**	3.8±0.8	4.6±0.9	4.9±1.1	4.6±1.9	3.7±1.4	4.0±0.9	4.6±1.3	5.1±1.6
Cr (μmol/L)	74.0±15.3	73.4±14.2	72.5±15.3	69.5±10.9	71.9±13.6**	58.1±15.0	57.5±11.4	56.4±13.5	56.1±13.4	55.6±9.4
UA (μmol/L)	497.9±69.3	439.2±80.1	416.9±124.4**	409.8±102.5**	371.5±82.0**	432.3±73.4	371.1±89.3*	346.4±77.4*	351.0±82.0**	354.1±80.9**
TG (mmol/L)	3.6±1.2	1.7±0.7**	1.5±0.4**	1.3±0.4**	1.3±0.7**	2.1±1.3	1.7±0.7	1.3±0.5**	1.1±0.3**	1.2±0.4**
HbA1c (%)	7.9±1.9	6.7±0.9**	5.9±0.6**	5.6±0.5**	6.3±1.4**	7.9±2.0	7.0±1.3	6.1±0.9*	5.9±0.7**	5.9±0.5**
FFA (μEq/L)	516.1±196.7	711.5±236.3**	506.3±188.8	379.7±131.7**	369.1±227.2*	534.1±238.6	713.4±332.6*	615.5±301.2	416.8±148.2	338.3±149.0**

Data expressed as mean ± SD or as the median (interquartile range). Hyperuricemia defined as uric acid >360 μmol/L (women) and 420 μmol/L (men). BMI, body mass index; WHR, waist-to-hip ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; SCr, serum creatinine; SUA, serum uric acid; TG, triglycerides; HbA1c, Hemoglobin A1C; FFA, free fatty acid. *P<0.05, **P<0.01: compared to baseline.

Table 3 The correlation test for UA in patients with hyperuricemia

Variables	UA (male)		UA (female)	
	r	P	r	P
BMI (kg/ m^2)	0.283	0.001	0.303	0.001
Waistline (cm)	0.255	0.003	0.274	0.004
Hipline (cm)	0.244	0.005	0.272	0.004
WHR	0.183	0.037	0.117	0.224
SBP (mmHg)	0.032	0.722	–0.089	0.355
DBP (mmHg)	0.063	0.478	–0.023	0.811
TG (mmol/L)	0.349	0.000	0.340	0.000
HbA1c (%)	0.189	0.032	0.202	0.035
FFA (μEq/L)	0.059	0.507	–0.022	0.820

Hyperuricemia defined as uric acid >360 μmol/L (women) and 420 μmol/L (men). BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HbA1c, hemoglobin A1C; FFA, free fatty acid.

Table 4 Variables for remission of hyperuricemia after LRYGB

Variables	Remission (N=29)	No remission (N=19)	P
Age (years)	44.1±13.6	40.1±14.2	0.334
T2D duration (years)	5.6±2.5	3.7±2.9	0.046
BMI (kg/m^2)	32.5±3.7	32.2±2.9	0.785
Waistline (cm)	109.3±11.9	106.3±9.9	0.366
Hipline (cm)	110.9±9.0	107.6±8.4	0.219
WHR	1.0±0.1	1.0±0.1	0.892
BUN (mmol/L)	5.0±1.8	4.6±1.4	0.438
SBP (mmHg)	132.3±18.7	129.8±6.7	0.584
DBP (mmHg)	82.9±14.4	83.4±8.2	0.905
TG (mmol/L)	2.7±1.0	3.2±1.1	0.028
HbA1c (%)	7.9±1.8	7.8±2.2	0.885
FFA (μEq/L)	501.6±216.4	559.2±213.1	0.369

LRYGB, laparoscopic Roux-en-Y gastric bypass surgery; T2D, type 2 diabetes mellitus; BMI, body mass index; WHR, waist-to-hip ratio; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HbA1c, Hemoglobin A1C; FFA, free fatty acid.

Table 5 Multiple logistic regression analysis of variables about hyperuricemia

Variables	B	S.E.	P	Exp(B)
TG (mmol/L)	32.919	11.378	0.004	0.206

Predicted probability is of membership for none remission. B, coefficient of regression; SE, standard error; Exp(B), odd ration; TG, triglycerides.

The benefits of RYGB for treatment of morbid obesity and its glycemic control are well documented. As is shown in a recent study with 3-year follow-up versus intensive medical therapy, among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery resulted in glycemic control in significantly more patients than did medical therapy alone. Reports about the effects of bariatric surgery in obese patients with T2DM are increasing, there are also studies try to find physiologic mechanisms to explain this phenomenon, these factors including FFA, GLP-1, bile acid, intestinal flora. But the exact mechanism is still unknown.

Factors associated with SUA

Levels of SUA post-operation seem to be related to factors associated with obesity: waistline and triglycerides. The correlation test for SUA in patients with baseline has shown that triglycerides have a correlation with SUA. A high triglycerides level before surgery may has a significant decline in SUA levels, suggesting a possible biological link between improvement in SUA and improvement in factors associated with obesity.

As this article written before, Studies have shown an important association between SUA and T2DM, SUA levels were higher in T2DM patients than those without T2DM, and higher BMI further accentuates this risk (20). We found that obese patients had significantly higher SUA levels compared to normal subjects (1), which was also seen in other studies that SUA levels were higher compared to normal subjects (22).

Possible mechanisms

There are studies to find physiologic mechanisms between triglyceride and SUA, studies explain this in terms of free fatty acid metabolism. The increase of blood triglyceride will produce more free fatty acids, thus accelerate the decomposition of ATP, then, increased the production of uric acid (23).

Some animal experiment (24) results suggest that high uric acid could inhibit the enzyme who catalytic decomposition of triglycerides, so it can reduce blood triglyceride decomposition, causing elevated blood triglycerides. Enhancement of phosphopentose metabolism can promote the synthesis of fat, lead to blood triglyceride rising, it can promote the synthesis of purine bases, and the increased purine base will also further promote the formation of uric acid, leading to the increasing of blood uric acid.

In our trial, SUA is associated with triglycerides. Further, other studies (7,13,25) have shown a link between SUA and triglycerides-related disorders especially cardiovascular disease. For instance, recent evidence (26) supports that increased SUA levels are independently and significantly associated with risk of cardiovascular events in a population of mainly elderly patients affected by peripheral vasculopathy. The study showed that hypertriglyceridemia was a risk factor for HU, and the reduction of triglycerides level plays an important role in the remission of HU.

Body mass index has been demonstrated to be associated with SUA level in many developed countries (26,27), one study showed a positive relationship between BMI and SUA among healthy subjects (2). They find that SUA change was related with for BMI change (7). In our trial, there is no evidence to suggest that SUA has a relationship with BMI, but it shows that waistline have a correlation with SUA (P=0.007). According to Tsushima's report (28), uric acid secretion in adipose tissue was increased in obese patients. Among obese subjects, excessive fat accumulation could produce and secrete uric acid and is relatively associated with overproduction-type HU. This may be a possible mechanism for the relationship between obese related factors and SUA.

There is a relationship between SUA and gender. Study shows that (29) hyperuricemic prevalence was 12.2%, with male significantly higher than female. In our study, Incidence of HU was higher in men than women, after surgery, men have a more Obvious downward trend. Uric acid levels have a slightly rise in women 3 months after surgery, but in men, Uric acid levels is declining among all the follow-up period. The current study (30) indicated that the genetic factors in our study showed a relatively effect. This may contribute to the difference about the incidence of HU and the decline of uric acid levels.

SUA is considered a risk marker of cardiovascular morbidity (31). In patients with T2DM, high SUA levels have been linked with many aspects, such as macrovascular disease (32), peripheral neuropathy (33). In our study, all the participants involved have a diagnosis of T2DM, so, diabetes related factors are not included in this article.

Existing problems

Our dates were from a clinical study, compared with the animal testing, it has higher clinical reference value. The

study was completed by different departments, Follow-up doctors and the surgeon was separated, this can reduce the bias of the results.

However, our sample size is not very big, it's a retrospective design and almost all the patients were under follow-up now. May we will have a follow-up report next, with a larger size and longer follow-up period.

Conclusions

The beneficial results observed in our study suggest that gastric bypass can reduce the incidence of HU and decline uric acid levels in Chinese obese patients with T2DM. This shows a possible treatment of HU by RYGB. Our study may also come up with an idea that, Surgical indications of RYGB can be moderately enlarged to cure some patients with HU, but further more studies are necessary before make this decision.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committee of Shanghai Sixth People's Hospital (2016-123) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Due to the retrospective nature of this study, the need for informed consent was waived.

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