




Reduction in Thyroid-Stimulating Hormone Correlated with Improved Inflammation Markers in Chinese Patients with Morbid Obesity Undergoing Laparoscopic Sleeve Gastrectomy

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Abstract

Objective Bariatric surgery has a significant impact on levels of thyroid hormones and various inflammatory markers in obesity. The relationship between changes in thyroid hormones and inflammatory markers after bariatric surgery is unknown. We aimed to investigate the changes in thyroid hormones and their relations to inflammatory changes after laparoscopic sleeve gastrectomy (LSG) in Chinese patients with morbid obesity.

Methods Eighty-eight patients with morbid obesity (56.8% female; age 30.9 ± 9.5 years; BMI 39.9 ± 5.7 kg/m²) submitted to LSG were selected. Patients were subdivided into euthyroid group and subclinical hypothyroidism (SH) group. Thyroid-stimulating hormone (TSH), free thyroxine (FT4), inflammatory markers, and related metabolic indexes were analyzed pre- and 12 months post-LSG.

Results SH patients presented significantly higher interleukin (IL)-6, tumor necrosis factor (TNF)- α , and C-reactive protein (CRP) than euthyroid patients. Twelve-month post-surgery, the SH incidence decreased from 31.8 to 2.3% ($P < 0.001$). TSH levels were declined significantly in both groups but were more pronounced in SH group ($P < 0.001$), whereas no change in FT4 in either group. Additionally, we observed marked reduction of IL-6, TNF- α , and CRP in SH group, as well as TNF- α and CRP in euthyroid group. After adjusting for age, baseline BMI, and changes in BMI, decrease in TSH correlated significantly with decreased HOMA-IR and TNF- α in euthyroid group and decreased fasting insulin (FINS), IL-6, TNF- α , and CRP in SH group.

Conclusion LSG promotes TSH reduction in patients with morbid obesity that is more pronounced in patients with SH and correlated with improved inflammatory state after surgery.

Keywords Laparoscopic sleeve gastrectomy · Morbid obesity · Thyroid-stimulating hormone · Inflammatory state

Introduction

Obesity is often accompanied by thyroid dysfunction. Overt hypothyroidism, characterized by elevated thyroid-stimulating hormone (TSH) level (reference range for our laboratory 0.3–4.0 mIU/L) and decreased free thyroxine (FT4) level below 11.0 pmol/L, has been well studied to be associated with weight gain. Of note, there has been an upsurge of interest in the relationship between subclinical hypothyroidism (SH) and morbid obesity recently. SH is defined as an elevated TSH level above 4.0 mIU/L and normal level of FT4 between 11.0 and 25.0 pmol/L. It can be noted in 14.1% of subjects with a mean body mass index (BMI) of greater than 44.8 ± 6.4 kg/m² [1] and 25% with a mean BMI of 53.0 ± 10.4 kg/m² [2]. This rate is significantly higher than that in the general population ranging from 4 to 9% [3]. Recently, SH has been documented to be correlated with a

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low-grade chronic inflammation [4]. In the clinical study by Turemen et al. [5], they showed that SH patients had significantly higher inflammation markers compared to the normal healthy controls, including interleukin (IL)-6, tumor necrosis factor (TNF)- α , and hs-C-reactive protein (CRP). Also, Tuzcu et al. [6] found a positive correlation between CRP and TSH. In addition, Taddai S et al. [7] showed significantly higher CRP and IL-6 levels among patients with SH. These findings indicate that there exists a close relationship between low-grade chronic inflammation and SH.

To date, bariatric surgery is the most effective management method for severe obesity and its complications [8, 9]. Its effects on thyroid function have also been reported with inconsistent results. Abu-Ghanem et al. [10] and Neves et al. [11] demonstrated a significant reduction in TSH but no change in FT4 following sleeve gastrectomy in euthyroid patients with morbid obesity, while MacCuish et al. [12] observed nonsignificant change in TSH but significant increase in FT4 level at 12 months after Roux-en-Y gastric bypass (RYGB) surgery in euthyroid people with morbid obesity. Additionally, the impact of bariatric surgery on inflammatory markers has been recently noted. A systematic review and meta-analysis by Rao et al. [13] concluded significant reductions in inflammatory markers such as IL-6 and CRP but no changes in TNF- α . Recently, laparoscopic sleeve gastrectomy (LSG), as an effective and safe weight-loss surgery, has also been shown to decline the CRP levels [14].

Nevertheless, data regarding the effect of LSG on thyroid hormones in SH patient with morbid obesity and its correlation with changes in inflammatory markers variations after LSG is lacking. Therefore, we conducted the first study to investigate the changes of thyroid hormones and their relations to inflammatory marker variations at 12 months following LSG in Chinese patients with morbid obesity.

Patients and Methods

Study Population

We conducted a retrospective study including 88 patients with morbid obesity aged 30.9 ± 9.5 years who underwent the standard LSG in our institution between July 2012 and January 2019. Inclusion criteria are as follows: subjects with BMI equal or greater than 35 kg/m^2 and age ranging from 18 to 65 years. Patients were excluded if they had a history of overt hypothyroidism or hyperthyroidism, autoimmune thyroid disease, previous thyroidectomy or radioiodine treatment, genetic diseases, previous gastrointestinal surgery, severe liver and renal dysfunction, mental illness, current or previous treatment with drugs that might affect the serum thyroid hormone levels, and unable to understand and comply with the study protocol.

According to different conditions of thyroid function, patients were subdivided into euthyroid group and SH group based on the levels of TSH (reference range 0.3–4.0 mIU/L) and FT4 (reference range 11–25 pmol/L). Euthyroidism was defined as TSH and FT4 levels within the normal reference ranges. SH was considered in the presence of a serum TSH level above 4.0 mIU/L in combination with a normal FT4 level [1].

This study protocol was performed in accordance with Helsinki Declaration and was approved by the ethics committee of Shanghai Tenth People's Hospital. Written informed consent was obtained from all participants prior to enrolment. The Clinical Registration Number was ChiCTR-OCS-12002381.

Anthropometric Measurements

Preoperative and follow-up data were obtained from all the participants. Height, weight, waist circumference (WC), hip circumference (HC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were directly measured by trained physicians. BMI was calculated as weight (kg) divided by the square of height in meters (m^2). The waist/hip ratio (WHR) was calculated as WC in centimeter divided by HC in centimeter. Percentage of total weight loss (%TWL) was calculated by the following formula: $\%TWL = [\text{initial weight (kg)} - \text{current weight (kg)}] / [\text{initial weight (kg)}] \times 100$. Percentage of excess weight loss (%EWL) was determined according to the following equation: $\%EWL = [\text{Initial weight (kg)} - \text{current weight (kg)}] / [\text{initial weight (kg)} - \text{ideal weight (kg)}] \times 100$ based on ideal weight ($\text{kg}) = 25 (\text{kg/m}^2) \times [\text{height (m)}]^2$. Changes in BMI (ΔBMI) = Initial BMI (kg/m^2) – current BMI (kg/m^2).

Biochemical Measurements

Fasting blood samples were drawn from all the participants at baseline and 12 months after LSG to measure fasting plasma glucose (FPG), fasting insulin (FINS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TSH, FT4, and inflammatory markers by the clinical laboratory of our hospital. The levels of TSH and FT4 were measured using the electrochemiluminescence immunoassay method. The reference value for serum TSH and FT4 is 0.3–4.0 mIU/L and 11.0–25.0 pmol/L, respectively. In addition, we measured the inflammatory markers including IL-6, IL-8, TNF- α , and CRP using standard methodologies.

Homeostasis model assessment of insulin resistance (HOMA-IR) was evaluated using the formula [15]: $\text{FPG (mmol/L)} \times \text{FINS (mIU/L)} / 22.5$. Changes in TSH (ΔTSH) were computed by the formula: $\Delta\text{TSH} = [\text{Initial TSH (mIU/L)} - \text{current TSH (mIU/L)}]$. The percentage of TSH variation

(%) was determined as $[\text{Initial TSH (mIU/L)} - \text{current TSH (mIU/L)}] / \text{initial TSH (mIU/L)} \times 100$.

Statistical Analysis

All statistical analyses were performed using SPSS 20.0 software. Data were presented as means \pm standard deviation (SD) for continuous variables or percentages for categorical variables. Abnormally distributed data were logarithmically transformed before analysis when needed. Comparisons of clinical variables between SH group and euthyroid group were tested using independent Student's *t* test or chi-squared test. Paired samples *t* test was used to compare the data before and after surgery. Pearson's correlation analysis was used to evaluate the relationship between changes in TSH and various clinical parameters variations after LSG. Multivariate linear regression analyses were used to identify the possible contributing factors that influence changes in thyroid hormones at 12 months after surgery. A two-sided *P* value of < 0.05 was considered statistically significant.

Results

Clinical Characteristics of Study Participants at Baseline and 12 Months After LSG

We analyzed 88 subjects (50 females and 38 males) with mean age 30.9 ± 9.5 years and mean preoperative BMI 39.9 ± 5.7 kg/m² (Table 1). At baseline, SH was present in 28 out of 88 patients (31.8%). There were no significant differences between euthyroid and SH groups in relation to weight, BMI, WHR, SBP, DBP, FPG, FINS, HOMA-IR, TC, TG, HDL-C, and LDL-C. Twelve months after surgery, participants' weight, BMI, WHR, SBP, and DBP decreased significantly in both groups (all $P < 0.01$). The %TWL and %EWL reached to $32.3 \pm 7.5\%$ and $84.9 \pm 30.2\%$ over 1-year period in SH group, which were similar to $32.0 \pm 5.7\%$ and $86.3 \pm 26.3\%$ observed in euthyroid group. Marked reduction in FPG, FINS, HOMA-IR, and TG as well as increase in HDL-C levels after LSG were observed in both groups (all $P < 0.05$). TC was decreased significantly in euthyroid group, but there was no significant change of LDL-C in either group.

Changes in Thyroid Hormones After LSG

Thyroid hormone levels before and after surgery are presented in Table 1 and Fig. 1. At baseline, patients in SH group presented significantly higher levels of TSH compared with patients in euthyroid group (5.9 ± 2.1 vs 2.4 ± 0.8 mIU/L, $P < 0.001$), whereas the FT4 levels were not statistically different between the two groups (16.1 ± 3.3 vs $16.3 \pm$

2.5 pmol/L, $P = 0.695$). Twelve months after LSG, the TSH levels decreased significantly to 2.3 ± 1.3 mIU/L in SH group ($P < 0.001$) and to 1.8 ± 0.6 mIU/L in euthyroid group ($P < 0.001$), whereas there were no significant changes in FT4 levels in either group ($P = 0.061$, $P = 0.060$, respectively) (Fig. 1a–d). In addition, changes in TSH and percentage of TSH variations were remarkably greater in SH group than in non-SH group (3.6 ± 1.9 vs 0.8 ± 0.8 mIU/L, $P < 0.001$; 60.3 ± 21.3 vs $17.8 \pm 8.9\%$, $P < 0.001$, respectively) (Fig. 1e and f). Furthermore, the incidence of SH among the participants was declined significantly from 31.8% at baseline to 2.3% at 12 months ($P < 0.001$) (Fig. 1g).

Changes in Inflammatory Markers After LSG

As shown in Table 1, SH group had remarkably higher levels of IL-6, TNF- α , and CRP in comparison with euthyroid group ($P = 0.017$, $P = 0.003$, $P = 0.001$, respectively), while there were no significant differences in IL-8 levels between the two groups ($P = 0.141$). Twelve months after surgery, in SH group, there was a significant reduction in IL-6, TNF- α , and CRP levels, changing from 1.8 ± 0.5 to 1.0 ± 0.2 pg/mL ($P < 0.01$), 2.7 ± 0.5 to 2.1 ± 0.3 pg/mL ($P < 0.05$), and 2.4 ± 0.9 to 0.9 ± 0.5 mg/L ($P < 0.01$), whereas IL-8 did not change significantly (3.6 ± 0.8 vs 2.9 ± 1.3 pg/mL, $P = 0.161$). In euthyroid group, there was a significant reduction in TNF- α after surgery (2.3 ± 0.6 vs 1.8 ± 0.5 pg/mL, $P = 0.011$) but changes in IL-6, IL-8, and CRP failed to reach a statistical significance (all $P > 0.05$).

Relationship Between Inflammatory Changes and TSH Reduction After LSG

As shown in Fig. 2, Δ TSH at 12 months after LSG correlated significantly with Δ BMI ($r = 0.338$, $P = 0.008$), Δ FINS ($r = 0.388$, $P = 0.002$), Δ HOMA-IR ($r = 0.407$, $P < 0.001$), and Δ TNF- α ($r = 0.274$, $P < 0.034$) in euthyroid group, whereas no significant associations were observed between Δ TSH and Δ IL-6, Δ IL-8, and Δ CRP. In SH group, Δ TSH correlated significantly with Δ FINS ($r = 0.605$, $P < 0.001$), Δ HOMA-IR ($r = 0.427$, $P = 0.023$), Δ IL-6 ($r = 0.572$, $P = 0.001$), Δ TNF- α ($r = 0.519$, $P = 0.004$), and Δ CRP ($r = 0.588$, $P = 0.001$) but did not correlate with Δ BMI and Δ IL-8 (shown in Fig. 3). In order to identify the contribution of changes in inflammatory markers to TSH variation after LSG, we conducted multivariate linear regression analysis (Table 2). After adjusting age, baseline BMI, and changes in BMI, Δ TSH was correlated significantly with Δ FINS ($\beta = 0.251$, $P = 0.011$), Δ IL-6 ($\beta = 0.447$, $P = 0.017$), Δ TNF- α ($\beta = 0.429$, $P = 0.009$), and Δ CRP ($\beta = 0.385$, $P = 0.035$) in SH group, as well as Δ HOMA-IR ($\beta = 0.231$, $P = 0.018$) and Δ TNF- α ($\beta = 0.310$, $P = 0.002$) in euthyroid group. However, Δ TSH did not correlated with Δ IL-8 in SH group,

Table 1 Baseline clinical characteristics and metabolic changes at 12 months after LSG

Parameters	Euthyroid group (<i>n</i> = 60)		SH group (<i>n</i> = 28)	
	At baseline	12 months after LSG	At baseline	12 months after LSG
Sex (female/male)	33/27	33/27	17/11	17/11
Age (years)	31.4 ± 9.4	–	29.2 ± 9.7	–
Anthropometric data				
Weight (kg)	115.8 ± 22.5	77.7 ± 15.4 ^{###}	117.8 ± 22.0	82.4 ± 24.3 ^{###}
BMI (kg/m ²)	39.7 ± 5.7	26.9 ± 3.5 ^{###}	40.9 ± 5.8	28.1 ± 6.5 ^{###}
Waist/hip ratio	0.99 ± 0.07	0.91 ± 0.06 ^{###}	1.01 ± 0.05	0.92 ± 0.06 ^{###}
SBP (mmHg)	136.0 ± 16.0	121.8 ± 13.9 ^{###}	137.5 ± 10.1	122.5 ± 10.4 ^{##}
DBP (mmHg)	85.8 ± 11.8	76.3 ± 11.6 ^{###}	88.1 ± 8.8	77.6 ± 6.8 ^{##}
%EWL (%)	–	86.3 ± 26.3	–	84.9 ± 30.2
%TWL (%)	–	32.0 ± 5.7	–	32.3 ± 7.5
Glucolipid metabolism				
FPG (mmol/L)	5.8 ± 1.1	4.6 ± 0.9 ^{##}	5.8 ± 2.6	4.5 ± 0.4 ^{##}
Ln FINS (mIU/L)	3.3 ± 0.5	1.9 ± 0.6 ^{###}	3.4 ± 0.5	2.3 ± 0.6 ^{###}
Ln HOMA-IR	2.0 ± 0.6	0.3 ± 0.2 ^{###}	2.1 ± 0.6	0.7 ± 0.7 ^{###}
TC (mmol/L)	4.5 ± 1.0	4.1 ± 0.9 ^{##}	4.7 ± 0.7	4.6 ± 0.6
TG (mmol/L)	1.8 ± 1.1	0.8 ± 0.4 ^{###}	2.6 ± 0.5	1.0 ± 0.3 [#]
HDL-C (mmol/L)	1.1 ± 0.4	1.3 ± 0.3 ^{###}	0.9 ± 0.1	1.2 ± 0.2 ^{##}
LDL-C (mmol/L)	2.7 ± 0.8	2.6 ± 0.8	2.9 ± 0.8	2.5 ± 0.9
Thyroid hormones				
TSH (mIU/L)	2.4 ± 0.8	1.8 ± 0.6 ^{###}	5.9 ± 2.1 ^{***}	2.3 ± 1.3 ^{###}
FT4 (pmol/L)	16.3 ± 2.5	15.8 ± 1.7	16.1 ± 3.3	14.5 ± 1.7
Inflammatory markers				
Ln IL-6 (pg/mL)	1.3 ± 0.8	1.0 ± 0.9	1.8 ± 0.5 [*]	1.0 ± 0.2 ^{##}
Ln IL-8 (pg/mL)	3.3 ± 1.3	2.7 ± 1.6	3.6 ± 0.8	2.9 ± 1.3
Ln TNF-α (pg/mL)	2.3 ± 0.6	1.8 ± 0.5 [#]	2.7 ± 0.5 ^{**}	2.1 ± 0.3 [#]
Ln CRP (mg/L)	1.7 ± 0.7	1.2 ± 0.6	2.4 ± 0.9 ^{**}	0.9 ± 0.5 ^{##}

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *%EWL* percentage excess weight loss, *%TWL* percentage total weight loss, *FPG* fasting plasma glucose, *FINS* fasting insulin, *HOMA-IR* homeostasis model assessment of insulin resistance, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TSH* thyroid-stimulating hormone, *FT4* free thyroxine, *IL-6* interleukin-6, *IL-8* interleukin-8, *TNF-α* tumor necrosis factor-α, *CRP* C-reactive protein, *SH* subclinical hypothyroidism

P* < 0.05, *P* < 0.01, ****P* < 0.001, versus euthyroid group; # *P* < 0.05, ## *P* < 0.01, ### *P* < 0.001 versus baseline values

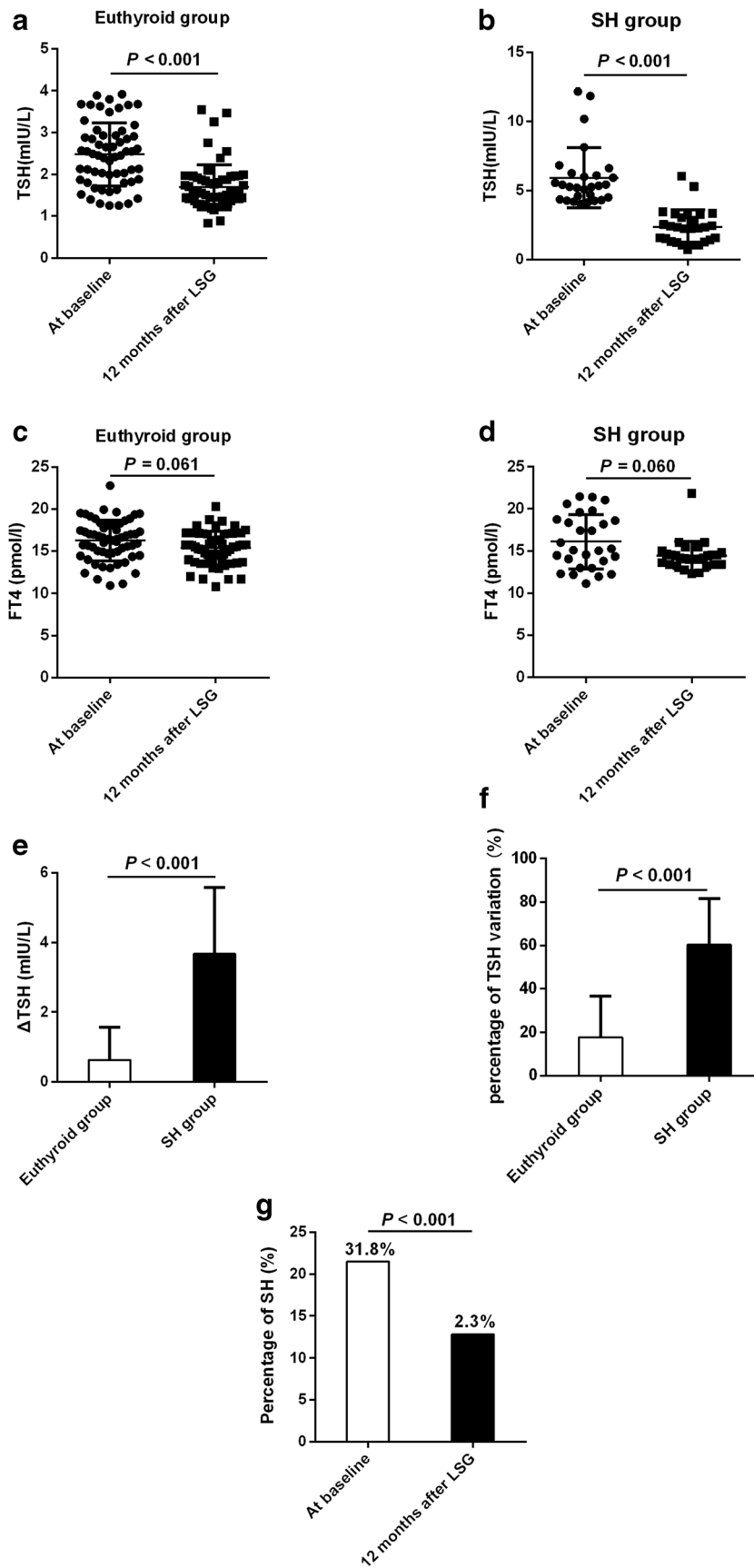
as well as Δ IL-6, Δ IL-8, and Δ CRP in euthyroid group (all *P* > 0.05).

Discussion

Previous studies have evaluated the effects of bariatric surgery on thyroid function and inflammatory state [16–19]. Nevertheless, there is lack of data regarding the associations between changes in thyroid hormones and inflammatory changes after bariatric surgery. To our best knowledge, this is the first study to examine the relationship between changes in serum TSH levels and inflammatory markers variations in Chinese patients with morbid obesity following LSG. The

results showed that there was a significant reduction in serum TSH levels after LSG, which was more pronounced among patients with SH compared with those with normal thyroid

Fig. 1 Variations in thyroid hormones levels before and after LSG and their differences between euthyroid and SH groups. **a–d** TSH levels were significantly decreased in both euthyroid and SH groups (all *P* < 0.001), whereas no significant changes in FT4 in either group. **e, f** Changes in TSH and percentage of TSH changes at 12 months after LSG were significantly greater in SH group than in euthyroid group (all *P* < 0.001). **g** Percentage of SH patients decreased significantly after surgery (*P* < 0.001). TSH thyroid-stimulating hormone, FT4 free thyroxine, Δ TSH changes in TSH before and after surgery. Percentage of TSH variation (%): [Initial TSH (mIU/L) – current TSH (mIU/L)] / initial TSH (mIU/L) × 100. *P* values < 0.05 were accepted as statistically significant



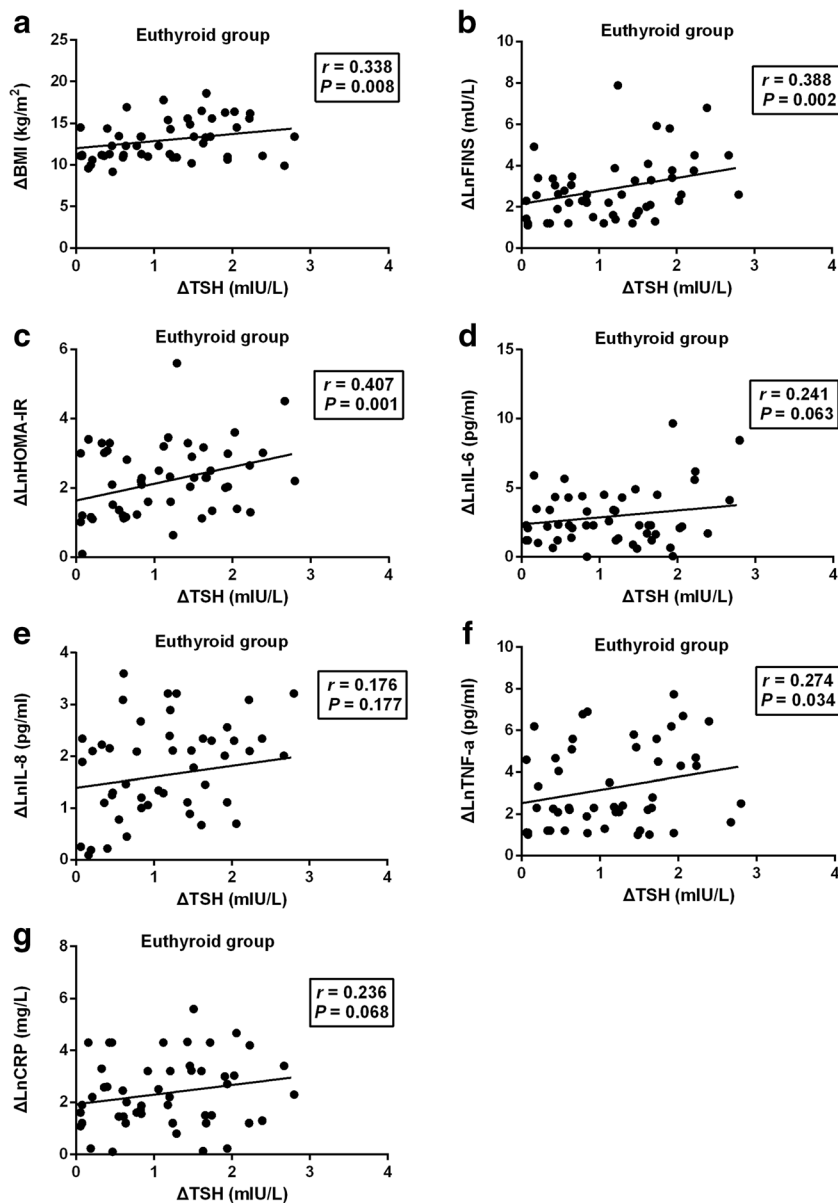


Fig. 2 Correlation of variation in TSH with changes in related metabolic indices after LSG in euthyroid group. TSH variation correlated significantly with changes in BMI, FINS, HOMA-IR, and TNF-α but not with changes in IL-6, IL-8, and CRP. BMI body mass index, FINS

fasting insulin, HOMA-IR homeostasis model assessment of insulin resistance, IL-6 interleukin-6, IL-8 interleukin-8, TNF-α tumor necrosis factor-α, CRP C-reactive protein. *P* values < 0.05 were accepted as statistically significant

function. In addition, the changes of inflammatory markers were correlated with reduction in TSH, indicating that the improved inflammatory state may be associated with the beneficial effects of LSG on thyroid function.

Most studies have demonstrated increased TSH concentrations in patients with morbid obesity. In the study by Rumińska et al. [20], their data showed significantly increased TSH levels in children with obesity compared to healthy controls without obesity. Bétry et al. [21] also found a positive relationship between serum TSH and BMI in individuals with obesity. Even in euthyroid general population, serum TSH has been observed to be correlated with weight gain [22].

Furthermore, weight loss induced by bariatric surgery has been reported significantly correlated with TSH decrease in euthyroid patients with morbid obesity [11, 23]. Even in patients with a clinical diagnosis of hypothyroidism, the normalization of TSH levels have been observed following bariatric surgery [1, 24]. Previous studies have suggested that the TSH increase may represent a compensatory activation of hypothalamus-pituitary-thyroid axis in response to excessive body weight [25]. Therefore, the rise in TSH in most patients with obesity, along with a fall in TSH after weight loss, may reflect the TSH as part of adaptive thermogenesis to excessive weight and metabolic adaptation to weight loss. However, the

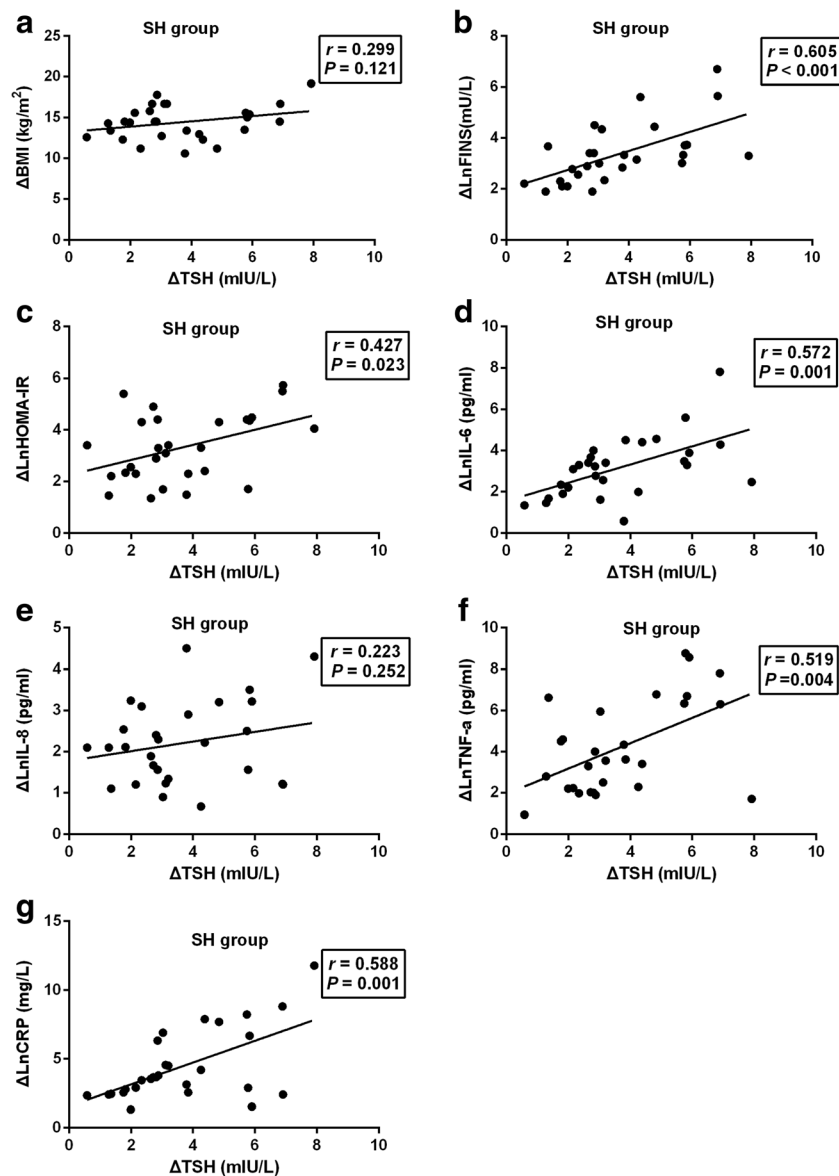


Fig. 3 Correlation of variation in TSH with changes in related metabolic indices after LSG in SH group. TSH variation correlated significantly with changes in FINS, HOMA-IR, IL-6, TNF- α , and CRP but not with change in BMI and IL-8. BMI body mass index, FINS fasting insulin,

HOMA-IR homeostasis model assessment of insulin resistance, IL-6 interleukin-6, IL-8 interleukin-8, TNF- α tumor necrosis factor- α , CRP C-reactive protein. P values < 0.05 were accepted as statistically significant

mechanism and the clinical implications of this alteration remain to be elucidated.

Previous studies have yielded inconsistent conclusions regarding the effect of bariatric surgery on thyroid function. Most [10, 11, 17, 26, 27], but not all [12, 28], studies have shown a significant reduction of TSH and no change in FT4 after the procedure due to different baseline characteristics of study population, types of surgical procedures performed, and follow-up durations. In a clinical study including 86 subjects with obesity who had no previous diagnosis of thyroid disorder, submitted to LRYGB or adjustable gastric banding, the authors observed a statistically significant reduction in TSH

but nonsignificant change in FT4 at 12 months after surgery [26]. In another study of 949 euthyroid patients with morbid obesity submitted to bariatric surgery (laparoscopic adjustable gastric band, LRYGB, or LSG), patients were subdivided in two groups: normal TSH group (TSH < 2.5 mIU/L) and high-normal TSH group (TSH ≥ 2.5 mIU/L) [11]. The results showed that there was a significant decrease of TSH 12 months after surgery that was more marked in the high-normal TSH group, and this significant decrease was only observed in the high-normal TSH group (normal TSH group 1.57 ± 0.49 to 1.53 ± 0.69 mIU/L, $p = 0.063$; high-normal TSH group 3.23 ± 0.59 to 2.38 ± 0.86 mIU/L, $p < 0.001$).

Table 2 Multiple regression analysis showing the relationship between variation in TSH and changes in inflammatory markers after LSG

Parameters	Euthyroid group			SH group		
	β	<i>t</i>	<i>P</i>	β	<i>t</i>	<i>P</i>
Δ Ln FINS (mU/L)	0.181	1.826	0.072	0.251	2.594	0.011*
Δ Ln HOMA-IR	0.231	2.411	0.018*	0.196	1.169	0.254
Δ Ln IL-6 (pg/mL)	0.110	1.099	0.275	0.447	2.584	0.017*
Δ Ln IL-8 (pg/mL)	0.101	1.005	0.318	-0.283	-1.168	0.327
Δ Ln TNF- α (pg/mL)	0.310	3.246	0.002**	0.429	2.850	0.009**
Δ Ln CRP (mg/L)	0.042	0.444	0.658	0.385	2.245	0.035*

Δ was calculated as changes in variables before and 12 month after LSG. Age, baseline BMI, and Δ BMI were adjusted

FINS fasting insulin, HOMA-IR homeostasis model assessment of insulin resistance, IL-6 interleukin-6, IL-8 interleukin-8, TNF- α tumor necrosis factor- α , CRP C-reactive protein

* $P < 0.05$; ** $P < 0.01$

Also, they compared the TSH variation between LSG and LRYGB and found no significant effect was observed between the two groups ($\beta = -0.068$, $p = 0.278$). From a clinical point of view, these findings indicated that patients with morbid obesity and higher TSH levels tend to normalize thyroid function following metabolic surgery. In support of this view, Zendel et al. [27] performed a study including 93 hypothyroid patients who underwent LSG in 77 (82.8%) and LRYGB in 16 (17.2%) patients. The results showed that mean TSH levels were significantly decreased after 6 and 12 months following surgery with no alterations in mean FT4 levels. Similarly, Rudnicki et al. [17] carried out a study in 90 patients with hypothyroidism and 89% patients treated with thyroid hormone replacement therapy (HRT) prior to LSG or LRYGB. After surgery, all patients with deranged TSH prior to surgery (TSH > 4.5 mU/L) had normal TSH levels after surgery in both LSG and LRYGB groups. However, the percentage of patients that stopped HRT completely was significantly higher in the LSG group, indicating that LSG may be a good treatment choice for patients with hypothyroidism, even in those who are treated with thyroid HRT. In contrast, Liu et al. [28] concluded that both TSH and FT4 levels were decreased significantly after RYGB in euthyroid Chinese patients with obesity and T2DM, while MacCuish et al. [12] reported a significant increase in FT4 but no change in TSH after LRYGB in 55 euthyroid patients with morbid obesity. In recent study including 38 euthyroid patients with morbid obesity, Abu-Ghanem et al. [10] revealed a marked decrease in level of TSH but nonsignificant changes in level of FT4 following LSG. However, data regarding thyroid hormone changes after LSG in patients with SH are scarce, especially in China. We therefore performed the first study to evaluate the changes in TSH and FT4 levels after LSG in Chinese patients with SH and compared the TSH variation between SH group and euthyroid group. The results showed a significant decrease in TSH levels with no change in T4 levels after LSG in both

SH and euthyroid groups. In addition, the changes in TSH and percentage of TSH variations were remarkably greater in SH group than in non-SH group. Meanwhile, we found a 92.8% normalization of TSH among the SH patients 1-year after LSG, which was similar to a 90% remission of SH at 1-year after LSG described by Ruiz-Tovar et al. [29]. These findings indicate that LSG may be an effective treatment method for normalizing thyroid hormone levels in SH with morbid obesity.

Lately, bariatric surgery has been demonstrated to alleviate the chronic inflammatory state in obesity. Level of CRP was significantly decreased at 12 months following RYGB [30]. Hakeam et al. [14] supported this study by reporting a statistically significant reduction in CRP during 6-month period after LSG. In addition, significant decreases in CRP, IL-6, soluble TNF- α receptor (sTNF α R) 1, and sTNF α R 2 were observed at 12 months after bariatric surgery [31]. Also, in the clinical study of 41 patients with extreme obesity who underwent RYGB, Netto et al. [32] concluded significant decline in both CRP and TNF- α at 6 months post RYGB. However, the effect of bariatric surgery on inflammatory markers remains controversial. Some reported significantly increased TNF- α 6 months post-surgery [33] while others indicated significant decrease in CRP but nonsignificant alteration in IL-6 and TNF- α [34]. In our study, we found a significant reduced TNF- α in euthyroid group as well as reduced CRP, IL-6, and TNF- α in SH group following LSG. Although the exact mechanism underlying the improved inflammatory state following bariatric surgery is unclear, the accompanied improvement of insulin resistance (IR) may, at least in part, mediate the alleviation of inflammatory state post bariatric surgery. As we know, human adipose tissue is an important source of proinflammatory cytokines and anti-inflammatory cytokine. The low-grade inflammation has been suggested as a link between obesity and IR. On one hand, elevated proinflammatory cytokines, such as IL-6 and TNF- α , could cause

IR by impairing the phosphorylation of insulin receptor and insulin receptor substrate-1 by upregulation of suppressor of cytokine signaling-3 (SOCS-3) proteins and downregulation of peroxisomal proliferator-activated receptor- γ receptors [35, 36]. On the other hand, obesity-induced IR can lead to elevated inflammation state by interfering with the anti-inflammatory effect of insulin [37]. In addition, Illán-Gómez et al. [38] found that there was a significant decrease in levels of IL-6, hs-CRP, insulin, and HOMA-IR and significant post-operative correlations between IL-6 levels and CRP with HOMA-IR. Also, in our study, we found significant reduction in IR and accompanied improved inflammatory markers. Thus, weight reduction induced by bariatric surgery may be an effective intervention for decreasing adipose tissue mass, leading to improved IR and finally causing the decreases in levels of inflammatory markers [34]. However, the mechanism of interaction between the improved inflammatory state and the well-documented improved IR post-bariatric surgery remains to be elucidated.

Considering that increasing studies have reported a close association between SH and elevated inflammatory markers [5, 39], whether there is a significant association between changes in inflammatory markers and alteration in thyroid function after bariatric surgery is unknown. Therefore, we further investigated the correlation between TSH reduction and inflammatory changes after LSG. As expected, the correlation analysis results revealed that TSH reduction was significantly correlated with decreased IL-6, TNF- α , and CRP in SH group and decreased TNF- α in euthyroid group in addition to decreased FINS and HOMA-IR in both group. No significant correlations between changes in IL-8 and TSH after surgery, indicating that the impact of IL-8 on the changes of thyroid function is limited. Considering that the correlation between weight loss and TSH reduction and between weight loss and decline in inflammatory markers has been well studied [1, 34], it is probable that the correlation between decline in TSH and decline in inflammatory markers is mediated by weight loss. To address this issue, we performed a multiple regression analysis to detect the main factors related to the TSH variation following LSG. After adjusting for age, baseline BMI, and changes in BMI post LSG, we observed that the alteration in TSH was still correlated with decreased FINS, IL-6, TNF- α , and CRP in SH group, as well as decreased HOMA-IR and TNF- α in euthyroid group, suggesting that improved inflammatory state may be associated with the beneficial effect of LSG on TSH reduction in addition to alleviated insulin resistance (IR) and substantial weight loss.

However, the underlying mechanism responsible for the alteration in TSH following metabolic surgery is still poorly understood and remains to be investigated. One explanation

for this may be the decreased level of leptin after bariatric surgery, which has been well demonstrated in several studies [40–42]. Leptin, mainly expressed in adipose tissue, exerts a vital role in energy expenditure and regulation of fat mass and body weight [43]. It can also maintain the expression of thyrotropin-releasing hormone (TRH) in the hypothalamic paraventricular nucleus of the hypothalamus via the JAK/STAT pathway and has a stimulatory effect on the production of thyroid hormones [44]. Thus, surgery-induced reduction of leptin would lead to the reduction of TSH [45]. A second explanation may derive from the reduction in the level of ghrelin induced by bariatric surgery. In view of the fact that serum ghrelin level has been demonstrated positively correlated with TSH level [46], we assume that decreased ghrelin level after RYGB and SG could be associated with the reduction in TSH. Another noteworthy explanation may result from the improved inflammatory state after obesity surgery. There is a growing evidence that inflammatory markers, such as IL-6, TNF- α , and CRP, are increased in patients with SH [5, 7], which could be reversed by bariatric surgery [14, 30–32]. Consistently, in our study, we found significantly increased levels of IL-6, TNF- α , and CRP in SH group compared to euthyroid group at baseline, which were decreased significantly at 12 months following LSG. Strikingly, our results revealed a significant correlation between TSH reduction and decrease in IL-6, TNF- α , and CRP in SH group as well as decrease in TNF- α in euthyroid group, indicating that the improvement of inflammatory state may make a contribution to the change of TSH after LSG. However, the causative link between changes in thyroid hormones and changes in inflammatory markers is unclear. On one hand, thyroid hormone levels have been suggested to influence cytokine production. In the study by Antunes et al. [47], IL-6, as a pro-inflammatory cytokine, has been reported to be induced by TSH in preadipocytes through a cAMP protein kinase A pathway. CRP, as a common inflammatory cytokine, has been concluded to be linked to SH [7]. Another inflammatory cytokine, TNF- α , can be induced in bone marrow cells by TSH in the study by Whetsell et al. [48]. In addition, IL-6 level might be correlated with hypothyroidism severity due to that serum IL-6 level has been positively correlated with levothyroxine replacement therapy (LRT) dose and negatively correlated with FT4 level in hypothyroidism due to autoimmune thyroiditis [49]. Moreover, Marchiori et al. [50] found that 1 year of LRT treatment caused significant reduction in pro-inflammatory cytokines including IL-6 and TNF- α . However, there are conflicting results regarding the effects of hypothyroidism treatment on systemic inflammation. In the study by Díez et al. [51], they failed to observe significant reduction in the high levels of TNF- α and TNF- α receptors after normalization of thyroid function in hypothyroid patients. On the other hand, TNF- α and IL-6 have been previously shown to have an inhibitory impact on the

hypothalamic-pituitary-thyroid axis. Pang et al. [52] found significantly reduced serum levels of TSH, T4, free T4, T3, and hypothalamic TRH after single injection of 200 µg TNF- α /kg body weight in male Sprague-Dawley rats in comparison with the corresponding items in saline-treated controls and that serum TSH and hypothalamic TRH were significantly decreased with the increasing daily doses of TNF- α . Similarly, van Haasteren et al. [53] showed that continuous intraperitoneal infusion of 15 µg IL-6 per day for 7 days in rats led to transient reduction in plasma levels of TSH and T4. Taken together, these findings indicate that there may be bidirectional relationship between elevated inflammatory markers and altered thyroid function, which needs to be further investigated. Apart from these factors, we also found significant relationship between TSH reduction and improved IR. In view of that TSH is independently associated with IR [54], significant improvement of IR following LSG may partially explain the changes of thyroid hormones. However, further studies are needed to draw a definitive correlation between changes in TSH and changes in inflammatory markers following LSG.

The authors acknowledge that there are several limitations in this study. Firstly, the relatively small sample size may lead to high variability. Secondly, the short follow-up period is further limitation, which will preclude the definitive conclusions with respect to the long-term predicted outcomes. Thirdly, we did not include all the variables which may involve in the effect of LSG on thyroid function and inflammation state. Future studies with a larger sample size and a longer follow-up period are warranted.

Conclusion

LSG promotes a more pronounced reduction in serum TSH levels in patients with morbid obesity and SH compared to those with normal thyroid function at 12 months. Improvement of inflammatory markers at 12 months after LSG may be associated with the beneficial effect of LSG on the thyroid function. Further studies are needed to confirm our findings and investigate the exact mechanism.

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Authors' Contribution Cuiling Zhu analyzed the data and drafted this manuscript. Jingyang Gao and Fangyun Mei collected the data for the work. Liesheng Lu and Donglei Zhou performed the surgery and involved in the discussion of the study results. Shen Qu designed the study and approved the final manuscript for publication. All authors take responsibility for the content of this study.

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Compliance with Ethical Standards

This study protocol was performed in accordance with Helsinki Declaration and was approved by the ethics committee of Shanghai Tenth People's Hospital. Written informed consent was obtained from all participants prior to enrolment. The Clinical Registration Number was ChiCTR-OCS-12002381.

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

Ethical Approval This study was approved by the ethics committee of the Shanghai Tenth People's Hospital of Tongji University. Informed consent was obtained from all individual participants of the study.

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