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Original Article

Early improvement in obese patients with polycystic ovary syndrome after metabolic surgery may be independent of the benefits of weight loss

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Abstract: Objective: This study was designed to investigate the clinical curative effect of laparoscopic sleeve gastrectomy (LSG) for polycystic ovary syndrome (PCOS) patients. Methods: A retrospective analysis was performed on 21 obese PCOS patients who underwent LSG. Data on demographic characteristics, anthropometry, glucose metabolic parameters, lipid metabolic parameters, and sex hormone index were documented and analyzed at baseline and 6 months after LSG. The changes of PCOS-related symptoms, including menstruation disorders, lack of ovulation and conception, hirsutism, and acanthosis nigricans, were documented after LSG. Results: 90% of the patients recovered their normal menstrual cycle and ovulation within 3 months post-surgery. At 6 months after LSG, fasting blood glucose, glycosylated hemoglobin, fasting insulin, and homeostasis model assessment of insulin resistance were significantly decreased ($P < 0.001$). Conversely, the insulin sensitivity index was significantly increased ($P < 0.001$). Triglyceride and uric acid levels were significantly decreased ($P < 0.01$), whereas high-density lipoprotein was significantly increased ($P < 0.001$). The testosterone level was also significantly decreased ($P < 0.001$). Body weight and body mass index were significantly decreased at 6 months after LSG ($P < 0.001$). Conclusion: LSG can significantly improve the clinical symptoms of PCOS patients in the early period, which may be independent of long-term weight loss.

Keywords: Polycystic ovarian syndrome, laparoscopic sleeve gastrectomy, obesity

Introduction

Polycystic ovary syndrome (PCOS) is a complex, multisystem endocrine and metabolic disorder with variable clinical features that characterized by high androgen levels, lack of ovulation, and the presence of ovarian cysts. Its prevalence varies with different diagnostic criteria, regions and ethnicities. The reported prevalence rate was about 6-10% [1]. The prevalence rate in Han nationality women aged about 19-45 years was reported to be 5.6% [2]. However, the etiology is still unknown. Studies have shown that about 50% PCOS patients are obese [3], and obesity aggravates the clinical symptoms of PCOS. At present, there is no definite therapy and effective clinical treatment. In recent years, it has been reported that metabolic surgery can significantly improve the symptoms of PCOS patients. Despite the unclear mechanisms, weight loss is considered to be related to improvement of PCOS. In this study, the clinical symptoms and laboratory indexes were evaluated in obese PCOS patients, who underwent laparoscopic sleeve gastrectomy (LSG), aiming at exploring the potential mechanisms. Deciphering the role of LSG in obese PCOS patients as well as the mecha-

nisms will help us better understand the effect of LSG on patients and provide scientific basis for the usage of LSG in other diseases.

Methods

A total of 21 obese PCOS patients who underwent LSG at the Tenth People's Hospital Affiliated to Tongji University from May 2013 to July 2017 were enrolled in this study. The average age was 27.27 ± 5.98 years, and the body mass index (BMI) was 39.55 ± 5.79 kg/m^2.

The general inclusion criteria were applied as follows: (1) All enrolled patients were selected according to the Asian guidelines for the surgical treatment of obesity (BMI ≥ 32 kg/m^2). (2) All patients met the PCOS international diagnostic criteria established in Rotterdam in 2003 [4]: oligo-ovulation and/or anovulation, excess androgen activity, and polycystic ovaries (confirmed with gynecological ultrasound). Further, polycystic ovarian changes were confirmed using B-ultrasonography, that is, ≥ 12 small follicles of 2-9 mm diameter were found in each ovary and/or the ovarian volume increased (ovarian volume [> 10 mL on each side] = 0.5 × length [cm] × width [cm] × thickness [cm]). Ultrasound examination was performed 3-5 days after the menstrual cycle or progesterone withdrawal bleeding. If any two of the three criteria were met, PCOS was diagnosed. (3) All patients were treated with the metabolic surgery and agreed to undergo regular follow-up after surgery.

The exclusion criteria were as follows: (1) congenital adrenocortical hyperplasia, Cushing syndrome, atypical 21-hydroxylase deficiency adrenocortical hyperplasia, hyperprolactinemia and thyroid diseases, androgen-secreting tumors, exogenous androgen use, or other diseases; (2) severe heart failure, renal dysfunction, respiratory dysfunction, and other sever organ diseases; (3) a history of drug and/or alcohol abuse; (4) serious diseases of the blood system; (5) presence of a malignant tumor; (6) cognitive dysfunction and impaired ability in judgment; and (7) inability to complete the examinations, or refusal to sign the informed consent forms.

All patients were enrolled at the Department of Endocrinology and Metabolism of Shanghai Tenth People's Hospital. Informed consents were obtained from all individual participants. Electronic gastroscopy was applied to exclude any contraindication. Standard LSG was performed [5]. Clinical evaluation was performed at baseline and 6 months after surgery.

All patients underwent physical examination, including measurements of height, weight, waist circumference, hip circumference, and neck circumference. The BMI and waist-to-hip ratio were calculated. The details of menstrual cycle, duration, volume, and color were obtained pre- and post-operation, and the results of gynecological B-ultrasound were recorded. The ages and medical history of enrolled patients, including acanthosis nigricans, hirsutism, acne, hypertension, and diabetes mellitus, were also documented.

Data on laboratory values were obtained after the patients' admission. (1) All patients underwent a 75-g oral glucose tolerance test. Blood glucose, C-peptide, and insulin levels were measured at 0, 30, 60, 120, and 180 mins after a meal, respectively. Fasting plasma glucose, glycosylated hemoglobin A1c (HbA1c) and fasting insulin (FINS) were evaluated. Further, the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity index (IAI) were calculated. The insulin resistance index (HOMA-IR) was calculated using the state model equation: FINS (mU/mL) × fasting blood glucose (FBG; mmol/L)/22.5 [6]. The IAI was calculated as follows: 1/FBG (mmol/L) × FINS (mmol/L). (2) Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and uric acid (UA) levels were measured. (3) Sex hormone indexes, including serum testosterone (T), estradiol (E2), progesterone (P), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and pituitary prolactin (PRL), were measured. All patients were evaluated at admission and 6 months post-operation.

Statistical analysis

Statistical analyses were performed using the SPSS 20.0 software package (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was performed to analyze the distribution of data. Normally distributed data were expressed as mean ± standard deviation and compared using the unpaired t-test. Other data were expressed as median and range and compared using non-parametric tests (Wilcoxon test). The χ^2 test and Fisher's exact test were used to determine the associations between the cate-

Table 1. Changes in anthropometric indices ($\bar{x}$ ± sd)

	Weight (kg)	BMI (kg/m^2)	Neck circumference (cm)	Waist circumference (cm)	Hip circumference (cm)	Waist-to-hip ratio
Baseline	107.81 ± 18.82	39.55 ± 5.79	40.32 ± 3.59	114.84 ± 15.03	122.38 ± 11.30	0.93 ± 0.07
6 months after LSG	79.45 ± 15.03	29.15 ± 5.16	35.77 ± 3.58	93.81 ± 14.55	105.27 ± 12.24	0.89 ± 0.08
t	13.581	14.937	5.047	11.228	13.884	4.200
P	0.000	0.000	0.001	0.000	0.000	0.001

Table 2. Changes in glycolipid metabolism indices ($\bar{x}$ ± sd)

	FBG (mmoL/L)	HbA1c (%)	TC (mmoL/L)	TG (mmoL/L)	HDL (mmoL/L)	LDL (mmoL/L)
Baseline	5.56 ± 0.31	5.93 ± 0.85	4.62 ± 0.86	2.12 ± 0.73	1.02 ± 0.17	2.87 ± 0.77
6 months after LSG	4.45 ± 0.46	5.10 ± 0.29	4.73±0.92	1.01 ± 0.33	1.17 ± 0.25	2.78 ± 0.81
t	4.687	4.833	-0.042	2.926	-4.076	0.467
P	0.000	0.000	0.967	0.009	0.001	0.646

Table 3. Insulin resistance and uric acid change

	FINS (mmoL/L)	HOMA-IR	IAI	UA (mg/dL)
Baseline	32.19 ± 16.55	8.44 ± 5.12	0.008 ± 0.006	419.48 ± 66.57
6 months after LSG	10.78 ± 4.61	1.97 ± 0.98	0.028 ± 0.015	351.17 ± 56.10
t	6.901	5.603	-6.722	6.385
P	0.000	0.000	0.000	0.000

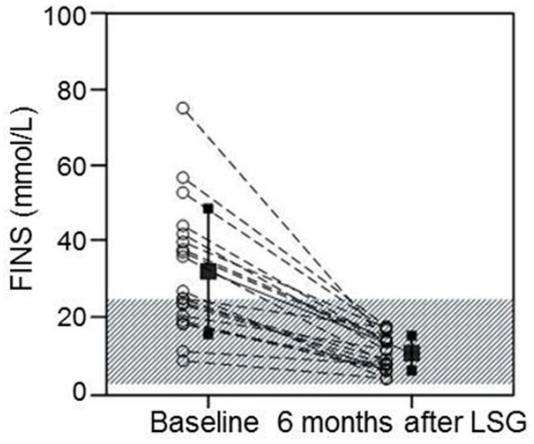

Figure 1. The changes in FINS levels at baseline and 6 months after LSG. P < 0.001.

gorized variables. A *P* value of < 0.05 was considered statistically significant.

Results

Changes in anthropometric indices

Compared with the baseline values, the body weight and BMI of obese PCOS patients were significantly decreased at 6 months after LSG (*P* < 0.001). The neck circumference, waist circumference, hip circumference, and waist-hip ratio were all significantly reduced (*P* < 0.001) (**Table 1**).

Changes in glycolipid metabolism indices

At 6 months after LSG, the levels of FBG, HbA1c and TG were significantly reduced (*P* < 0.01), whereas HDL was significantly increased (*P* < 0.001). The differences in TC and LDL after LSG were not obvious (*P* > 0.05) compared with the baseline (**Table 2**).

Insulin secretion, insulin resistance, and UA level

Among the 21 PCOS cases, 14 cases of hyperinsulinemia were cured after LSG. At 6 months after LSG, the average FINS and HOMA-IR, and UA levels were significantly decreased (*P* < 0.001) (see **Table 3** and **Figure 1**). In contrast, IAI was significantly increased (*P* < 0.001) (**Table 3**).

Changes of the hypothalamus-pituitary-gonadal axis

Six months after LSG, the T level was significantly decreased (*P* < 0.001) (**Table 4** and

Table 4. Changes of the hypothalamus-pituitary-gonadal axis

	T (nmol/L)	E2 (pmol/L)	P (nmol/L)	LH/FSH	PRL (mIU/L)
Baseline	1.58 ± 0.83	231.74 ± 218.02	4.24 ± 5.91	1.46 ± 1.07	465.91 ± 255.27
6 months after LSG	1.00 ± 0.67	265.99 ± 128.74	8.23 ± 11.54	1.55 ± 1.23	509.16 ± 300.57
t	4.810	-0.618	-1.460	-0.356	-0.783
P	0.000	0.545	0.163	0.726	0.444

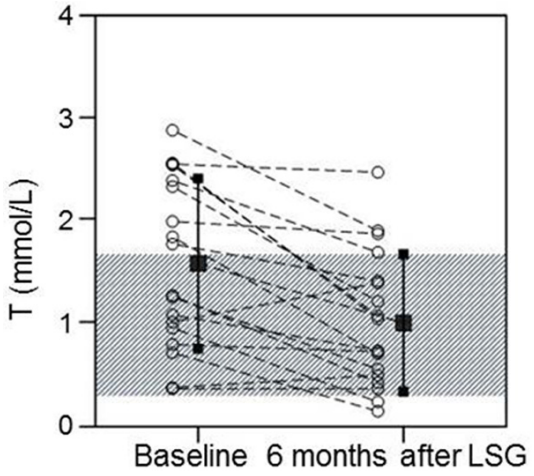

Figure 2. Trend of changes in serum testosterone (T) levels at baseline and 6 months after laparoscopic sleeve gastrectomy (LSG).

Figure 2). The E2, P, LH/FSH, and PRL levels were not significantly different ($P > 0.05$) (see **Table 4**).

Changes in menstrual cycle and symptoms

All 21 patients with PCOS had abnormal menstruation before surgery, including 7 with rare menstruation, 9 with amenorrhea for > 2 years, and 5 with irregular uterine bleeding.

Interestingly, 3 patients had menstruation on days 2, 3, and 7 after LSG. Moreover, about 90% (19/21) of the patients had menstruation within 3 months (average, 1.89 ± 1.286 months). One patient achieved natural pregnancy 1 year after LSG and delivered a baby girl through a caesarean section. In addition to the improvement of abnormal menstrual symptoms, 21 patients showed varying degrees of improvement in ovarian polycystic morphology, hirsutism, acne, acanthosis nigricans, and other aspects, as detailed in **Table 5**.

Discussion

PCOS is one of the most complex and common metabolic disorders among women between the ages of 20 and 55 years. The etiology of PCOS is still unclear. The common symptoms of PCOS include menstrual disorders, infertility, high levels of masculinizing hormones, hirsutism, and other clinical manifestations. It is often associated with metabolic syndrome (MetS), including hypertension, type 2 diabetes, insulin resistance, hyperlipidemia, and apnea syndrome. Approximately 50% of PCOS patients are accompanied by obesity, which in turn aggravates ovulation disorders, irregular menstruation, low pregnancy rate, hirsutism, infertility, and other clinical symptoms.

PCOS patients often exhibit symptoms related to endocrine and metabolic disorders, such as abnormal blood glucose levels and dyslipidemia. Epidemiological surveys showed that the prevalence of type 2 diabetes mellitus in PCOS patients was 7.5-10% and the impaired glucose tolerance rate was 31-35%, which were much higher than that in normal subjects. The progression of obese PCOS patients from normal glucose metabolism to impaired glucose tolerance or diabetes mellitus was significantly faster than that of non-PCOS patients. The insulin and serum total testosterone secretions were increased in obese prepubertal and adolescent patients. Insulin resistance is further exacerbated by hyperandrogenism. It has been reported that insulin resistance exists in 50-70% of PCOS patients [8-10], and insulin resistance and compensatory hyperinsulinemia further aggravate obesity by enhancing appetite, which is another important factor in the pathogenesis of PCOS. HOMA-IR is associated with the severity of PCOS. It has been reported that even normal-weight PCOS patients can have a certain extent of hyperinsulinemia, and obesity exacerbates the symptoms [8-10]. Obese PCOS patients are more likely to develop lipid metabolism disorders, including decreased HDL cholesterol and increased TC and TG, independent of age and BMI. In addition, obese PCOS patients are more likely to develop metabolic disorders including insulin resistance, diabetes

Table 5. Comparison of PCOS symptoms at baseline and 6 months after LSG

	Abnormal menstruation			Polycystic ovary	Hirsutism	Acne	Acanthosis nigricans
	Dilute menstruation	Amenorrhea	Irregular uterine bleeding				
Baseline (no. of cases)	7	9	5	12	7	2	10
6 months after LSG (no. of cases)	0	1	0	1	1	1	0
χ^2		38.182		13.48	5.559	0.359	13.125
P		0.000		0.000	0.018	0.547	0.000

Note: Menstrual abnormalities and ovarian polycysts were assessed using the Rotterdam standard in 2003 [4]. Hirsutism was evaluated using the Ferriman-Gallwey scoring system, in which a score of > 4 points suggests hirsutism. Acanthosis nigricans was also scored, with the neck as the standard (the scores were all > 2).

mellitus, and dyslipidemia, which increase the risk of cardiovascular diseases such as atherosclerosis and organic cardiac diseases.

The 2013 American Endocrinological Society guidelines [11] recommend non-surgical treatments for PCOS, including weight loss, menstrual regulation, and metabolic improvement; however, the long-term outcomes are not satisfactory. Weight loss through dieting and exercising is limited [12-14]. Other studies have demonstrated that only 5-10% of body weight can be lost by lifestyle adjustments (exercise and diet), which is difficult to maintain for a long time [12-14], despite the long-term effective improvement of MetS in PCOS patients [15]. The support for obese children and adolescents from family members has a significant impact on the success of lifestyle changes. Drug treatment often has a limited effect.

Metabolic surgery has been applied in the clinical setting for decades. With the development of minimally invasive techniques and the optimization of surgical methods, most metabolic operations are performed by laparoscopy, which is safer with a lower operative mortality and fewer postoperative complications. With minimally invasive surgery, the patients recover quickly [17, 18]. Metabolic surgery has a significant effect on obese patients, as it can not only effectively cause weight loss but also rapidly improve combined MetS, including hypertension, type 2 diabetes, insulin resistance, hyperlipidemia, and apnea (sleep apnea syndrome). LSG can greatly decrease the secretion of hunger-related hormones in the gastric fundus and inhibit hunger by resecting most of the stomach, which in turn contributes to weight loss [19, 20]. As LSG does not change the normal physiological structure of the digestive tract itself, it has recently become the preferred method of metabolic surgery.

In recent years, metabolic surgery exhibits effective control of blood glucose, improvement of insulin resistance and sensitivity in patients with severe obesity and type 2 diabetes [21-24], and has been widely accepted and recommended in the guidelines [25, 26]. Researchers gradually realized that metabolic surgery has promising effects on obese PCOS patients, including weight loss and endocrine changes, indicating the advantages in the treatment of PCOS [25, 26]. Eid et al. [28] reported that all patients recovered normal menstrual cycles after an average of 3.4 ± 2.1 months in their study in 24 obese PCOS patients. Brancatisano et al. [29] found that in 48% of patients, PCOS-related symptoms such as amenorrhea, hirsutism, and infertility disappeared after 13 months follow-up. Another study demonstrated that 71.4% of patients recovered their menstrual after surgery [30]. Escobar-Morreale et al. [31] showed that sex hormones were significantly improved and the alleviation rate of PCOS was 96% in a meta-analysis of obesity-related reproductive disorders after weight loss.

It is generally believed that weight loss can cause changes in menstruation. However, with the accumulation of research findings, the effectiveness of metabolic surgery for PCOS treatment may not only be due to the weight loss effect. LSG surgery may have an influence on the regulation of endocrine hormones and can ameliorate insulin resistance and the corresponding inflammatory responses. In our current study, 21 PCOS patients had abnormal menstruation before surgery. Interestingly, three patients had menstruation on days 2, 3, and 7 after LSG. Importantly, menstrual recovery occurred much earlier than the change in body weight or BMI. Furthermore, 90% (19/21) of patients had menstruation within 3 months, with an average time of menstrual recovery of

1.89 ± 1.28 months. Only one patient had no menstruation even at 6 months after the operation. This patient had been amenorrheic for 10 years. Therefore, compared with body weight or BMI changes at 6 months after LSG, menstrual recovery occurred earlier. One patient achieved natural pregnancy 1 year after LSG and delivered a baby through a caesarean section. Similar findings were also reported in previous studies. Some PCOS patients with long-term amenorrhea had menstruation in a short period or even within a week after surgery while no changes or improvements in body weight and BMI have occurred yet.

Several potential mechanisms may account for the early improvement after gastric volume reduction surgery in PCOS patients. First, metabolic surgery may alleviate the clinical symptoms of PCOS patients by mediating endocrine hormones, especially the androgen level. An elevated androgen level is one of the key pathophysiological mechanisms of PCOS [32]. In our current study, we also found that LSG can significantly reduce the serum testosterone T levels, as T returned to the normal level in 11 patients. Thus, the changes in serum testosterone T levels may account for the role of LSG in PCOS patients. Second, existing research and clinical evidence show that metabolic surgery can change some gastrointestinal endocrine hormones, such as glucagon-like peptide 1 and ghrelin [19, 33, 34]. Although the pathogenesis of PCOS is still unclear, the gastrointestinal hormones and other yet-undiscovered hormone changes after metabolic surgery may also be among the mechanisms of improving MetS and reproductive endocrine disorders in patients with PCOS. Third, chronic low-grade inflammation has emerged as a key contributor to the pathogenesis of PCOS [7], whereas, metabolic surgery can alleviate systemic inflammation in obesity [35]. Previous report also indicated that some patients had a greater decrease in CRP after gastric bypass, independent of the change in body weight [36]. Therefore, the inflammation changes after LSG may also contribute to the symptom's improvement in PCOS patients. The intervention mechanism of gastric volume reduction in PCOS may be independent of weight loss and may be closely related to changes in endocrine hormones, metabolism, and inflammation. The hormone changes may also be the main cause of earlier menstruation recovery. Our study also demonstrated that with the improvement of hormone levels, clinical symptoms such as hirsutism, acne, and acanthosis nigricans were significantly improved in the short term.

An elevated androgen level is one of the key pathophysiological mechanisms of PCOS. An animal model experiment [37, 38] revealed that when LSG-treated rats were exposed to high androgen levels, the menstrual cycle could not return to normal. While the menstrual cycle returned to normal until the androgen level has decreased to normal level. This indicates that the improvement of menstrual cycles by LSG in PCOS patients depends on the decrease of androgen levels. In our current study, we find that LSG can significantly reduce the serum testosterone T levels, as T returned to the normal level in 11 patients. The long-term effects still need further follow-up.

Basic research and clinical evidence show that the role of metabolic surgery in the treatment of type 2 diabetes is exerted by mediating gastrointestinal hormones, such as glucagon-like peptide 1 and ghrelin. Although the pathogenesis of PCOS is still unclear, we speculate that gastrointestinal hormones and other unidentified hormone changes after metabolic surgery may also be among the mechanisms of improving MetS and reproductive endocrine disorders in PCOS patients, rather than through weight loss alone. Thereby, whether metabolic surgery can be used in non-obese PCOS patients is not clear. Studies have found that non-obese PCOS patients also have some manifestations of hyperinsulinemia, irregular menstruation, and MetS. More clinical evidence is needed to further elucidate the mechanism of metabolic surgery in PCOS patients.

We believe that LSG is one of the optimal choices for weight loss and treatment of type 2 diabetes mellitus, as its effect on weight loss is remarkable with fewer complications and no changes in physiological structure. Further, studies have reported that LSG can effectively alleviate PCOS-related amenorrhea or menstrual sparse, hyperandrogenism, and MetS symptoms. The mechanism of these effects may not be simply related to weight loss. Compared with the traditional PCOS treatments, LSG has the advantages of a definite effect, reliable results, long-term efficacy, and

fewer adverse effects. Multidisciplinary methods include metabolic surgery in the treatment of obese PCOS patients should be considered in the clinical decision-making. The potential suitability of gastric surgery for normal-weight PCOS patients should also be considered when conventional treatments fail. The intervention mechanism of gastric volume reduction in PCOS may be independent of weight loss and may be closely related to changes in endocrine hormones, metabolism, and inflammation. Further studies are needed to investigate the underlying mechanisms. Our study had some limitations, including the small number of enrolled patients, short follow-up time, and lack of non-surgical treatment in control group. Thus, further prospective studies with a large sample size are required to confirm the conclusions of this study and to further elucidate the potential mechanisms.

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Disclosure of conflict of interest

None.

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