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SHORT REPORT

Metabolic alterations in plasma after laparoscopic sleeve gastrectomy

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ABSTRACT

Laparoscopic sleeve gastrectomy (LSG) is an important therapeutic option for morbidly obese patients. Although LSG promotes sufficient weight loss, how LSG changes plasma metabolites remains unclear. We assessed changes in plasma metabolite levels after LSG. We collected plasma samples from 15 morbidly obese Japanese patients before and 3 months after LSG. A total of 48 metabolites were quantified using capillary electrophoresis time-of-flight mass spectrometry-based metabolomic profiling. Branched chain amino acids, several essential amino acids, choline, 2-hydroxybutyric acid, 2-oxoisovaleric acid and hypoxanthine were significantly decreased after LSG. Tricarboxylic acid cycle metabolites, including citric acid, succinic acid and malic acid, were significantly elevated after LSG. This is the first report to show dynamic alterations in plasma metabolite concentrations, as assessed using capillary electrophoresis time-of-flight mass spectrometry, in morbidly obese patients after LSG. Our results might show how LSG helps improve obesity, in part through metabolic status changes, and propose novel therapeutic targets to ameliorate obesity.

INTRODUCTION

The prevalence of obesity has increased to pandemic levels over the past 50 years[1]. Obesity represents one of the most important chronic diseases worldwide, and is associated with adverse health consequences throughout an individual's life[1–3]. Given its dramatically escalating prevalence, therapeutic interventions are increasingly being considered for treating obesity and its associated metabolic diseases[2].

In particular, surgical interventions have rapidly gained popularity[4,5]. A recent systematic review and meta-analysis showed surgery substantially reduces long-term (>10 years) bodyweight[6]. Furthermore, bariatric surgery reduces long-term mortality[7]. Laparoscopic sleeve gastrectomy (LSG), which is a simple procedure and has a lower complication rate than other bariatric operations, results in stable and adequate weight loss, and improves comorbidities in morbidly obese patients[8–10]. In Japan, LSG is the only procedure covered by insurance; thus, it has garnered significant attention. Although a substantial body of evidence shows that LSG is beneficial for reducing bodyweight and ameliorating metabolic disorders, little is known about systemic metabolic changes after LSG. Consequently, the present study aimed to compare plasma metabolite concentrations from before and 3 months after LSG using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS), which relatively and absolutely evaluates 916 and 110 ionic metabolites, respectively, to evaluate changes in obesity pathogenesis.

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METHODS

Study participants

Between May 2019 and October 2019, morbidly obese patients scheduled to undergo LSG at Chibune General Hospital were consequently recruited for this study. All included patients provided oral and written informed consent; the study was carried out according to the principles of the Declaration of Helsinki. This study was approved by the ethics committees of Kobe University (No. 180355) and Chibune General Hospital (No.

20190422A), and was registered with the UMIN Clinical Trials Registry (UMIN000035635). LSG procedure was carried out following the guidelines of the Japanese Society for Treatment of Obesity: patients whose body mass index (BMI) ≥35 kg/m^2 or BMI ≥32 kg/m^2 with comorbidities. All patients received a dietary intervention for approximately 6 months before LSG. The definition of remission of diabetes was as follows: fasting plasma glucose <126 mg/dL and glycohemoglobin <6.5% with the absence of treatment.

Plasma metabolite extraction and CE-TOFMS analysis

Blood samples, taken in a fasting state, were collected in tubes containing ethylenediaminetetraacetic acid disodium salt. CE-TOFMS analysis was carried out using an Agilent capillary electrophoresis system (Agilent Technologies, Waldbronn, Germany) by Human Metabolome Technologies[11]. The systems were connected by a fused silica capillary (50 μm i.d. × 80 cm total length) with a commercial electrophoresis buffer as the electrolyte. Spectrometry analysis was carried out over a range from 50 to 1,000 m/z. Peaks were extracted using MasterHands automatic integration software version 2.17.1.11 (Keio University, Yamagata, Japan), and analyzed to determine their m/z, peak area and migration time[12]. The areas of annotated peaks were subsequently normalized based on internal standard levels and sample amounts, and used to calculate absolute metabolite concentrations. The list of

Table 1 | Changes in clinical parameters for 15 patients after laparoscopic sleeve gastrectomy

Variables	Before LSG	After LSG	*P*-value
Age (years)	52.2 ± 6.5		–
Sex (female), *n* (%)	12 (80)		–
Body mass index (kg/m^2)	40.8 ± 6.6	33.5 ± 6.1	<0.0001
Comorbidities, *n* (%)			
Diabetes mellitus	10 (67)	5 (33)	0.14
Hypertension	11 (73)	9 (60)	0.70
Dyslipidemia	13 (87)	12 (80)	>0.99
Sleep apnea syndrome	4 (27)	4 (27)	>0.99
Medication, *n* (%)			
ACE-I/ARB	9 (60)	5 (33)	0.27
Calcium channel blocker	7 (47)	6 (40)	0.99
Antiplatelet/anticoagulant	2 (13)	2 (13)	0.99
PPI/H2 blocker	6 (40)	10 (67)	0.27
Statin/fibrate	12 (80)	5 (33)	0.025
Insulin analogs	4 (27)	1 (7)	0.33
DPP4 inhibitor	2 (13)	0 (0)	0.48
SGLT2 inhibitor	7 (47)	2 (13)	0.11
GLP-1 analogs	3 (20)	1 (7)	0.60
Metformin	6 (40)	0 (0)	0.017
α-Glucosidase inhibitors	2 (13)	0 (0)	0.48
Laboratory data			
Aspartate transaminase (U/L)	31.5 ± 15.8	20.6 ± 4.8	0.013
Alanine transaminase (U/L)	32.2 ± 14.7	19.3 ± 6.0	0.0032
γ-Glutamyl transpeptidase (U/L)	30.7 ± 17.0	19.1 ± 8.9	0.011
Lactate dehydrogenase (U/L)	192.1 ± 58.6	164.7 ± 33.1	<0.0001
Alkaline phosphatase (U/L)	214.4 ± 43.7	246.3 ± 58.6	0.0033
Blood urea nitrogen (mg/dL)	14.2 ± 4.2	14.4 ± 5.6	0.84
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.87
Fasting plasma glucose (mg/dL)	119.2 ± 20.4	118.7 ± 32.3	0.95
Glycohemoglobin (%)	6.6 ± 0.8	6.1 ± 0.9	0.021
Total cholesterol (mg/dL)	176.9 ± 35.3	205.4 ± 45.7	0.048
HDL-C (mg/dL)	48.8 ± 15.1	56.9 ± 15.0	<0.0001
LDL-C (mg/dL)	103.8 ± 33.9	127.7 ± 42.7	0.056
Triglycerides (mg/dL)	168.1 ± 101.2	131.3 ± 73.8	0.069
C-reactive protein (mg/dL)	1.0 ± 1.9	0.44 ± 0.7	0.27

Data are shown as mean ± standard deviation for normally distributed data, or *n* (%). Analysis was carried out using the paired *t*-test or Fisher's exact test, as appropriate. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LSG, laparoscopic sleeve gastrectomy; PPI, proton pump inhibitor; SGLT2, sodium–glucose cotransporter 2.

metabolites we evaluated is listed online (https://humanmetabolome.com/jp/services/annotation-en).

Statistical analysis

Results are expressed as the mean ± standard deviation for normally distributed data. Postoperative results were compared with preoperative baseline data using a paired *t*-test. The Fisher's exact test was used to compare categorical variables. Spearman's rank correlation coefficient was calculated to discover a link between two parameters. For all tests, *P*-values <0.05 were considered statistically significant. Principal coordinate analysis and z-scores were calculated using JMP version 14 (SAS Institute, Cary, NC, USA). All other data supporting the study findings are available from the corresponding author on reasonable request.

RESULTS

Baseline patient characteristics

Baseline patients characteristics, comorbidities, medications and laboratory data before LSG are listed in Table 1. The mean patient age was 52.2 ± 6.5 years, 12 patients were women. The mean BMI before LSG was 40.8 ± 6.6 kg/m^2.

Changes to body composition and metabolic status after laparoscopic sleeve gastrectomy

The mean follow-up period was 92.1 ± 2.2 days. Changes to body composition and other parameters are shown in Table 1 and Figure 1a,b. BMI (40.8 ± 6.6 kg/m^2 vs 33.5 ± 6.1 kg/m^2, $P < 0.0001$), body fat mass (48.1 ± 13.2 kg vs 37.1 ± 13.2 kg, $P < 0.001$) and body muscle mass (51.2 ± 11.1 kg vs 46.2 ± 9.6 kg, $P < 0.001$) decreased significantly after LSG. Post-surgery liver function, as assessed by aspartate transaminase, alanine transaminase, γ-glutamyl transpeptidase, lactate dehydrogenase and alkaline phosphatase, improved significantly. Furthermore, glycohemoglobin levels decreased significantly, despite efforts to wean patients off antidiabetic medications. The remission rate of diabetes was 50% (patients 1, 6, 10, 12 and 15). In contrast, with the high discontinuation rates of statin/fibrate, total cholesterol and low-density lipoprotein were elevated. C-reactive protein levels, an indicator for systemic inflammation, tended to be decreased after LSG (1.0 ± 1.9 mg/dL vs 0.44 ± 0.7 mg/dL, $P = 0.27$).

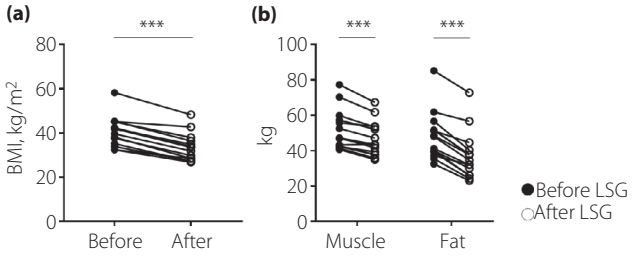

Figure 1 | Alterations in body composition after laparoscopic sleeve gastrectomy (LSG). (a) Changes in body mass index (BMI). (b) Changes in muscle weight and fat weight. ***$P < 0.001$. The paired *t*-test was used.

Changes in plasma metabolites after laparoscopic sleeve gastrectomy

Overall, 185 metabolites were detected, of which 48 could be quantified (Table S1). Principal coordinate analysis showed a dramatic change in the metabolite profile after LSG (Figure 2a). A volcano plot comparing the statistical significance and the post-LSG metabolite fold-change shows that 19 metabolite concentrations significantly changed after LSG. Plasma levels of 14 metabolites, including branched chain amino acids (BCAA; valine, leucine, isoleucine) and other essential amino acids (EAA; tryptophan and phenylalanin), tyrosine, choline, creatine, ornithine, hypoxanthine, 2-oxoisovaleric acid, 2-hydroxybutyric acid, *N,N*-dimethylglycine and uridine decreased significantly after LSG. In contrast, plasma levels of five metabolites, including citric acid, succinic acid, malic acid, arginine and glycine, increased significantly after LSG (Figure 2b). A heatmap of the z-scores for BMI and each metabolite show that LSG altered metabolites related to the tricarboxylic acid cycle and essential amino acids (Figure 2c).

Associations of plasma metabolites with clinical indices

Figure 3 shows the association between BMI and laboratory data and 48 metabolites. Several metabolites concentrations were significantly correlated with liver function, lipid profile, glucose, glycohemoglobin and C-reactive protein.

DISCUSSION

This is the first report of non-targeted plasma metabolomics analysis using CE-TOFMS, and to identify metabolomic changes in morbidly obese patients before and after LSG[13]. In the present study group, 50% of patients showed remission of diabetes, which is consistent with a previous report[14]. Our key findings showed that: (i) LSG decreased plasma BCAA and EAA levels; and (ii) LSG increased plasma tricarboxylic acid cycle intermediates, such as citric acid, succinic acid and malic acid. Furthermore, we identified several metabolites that are significantly associated with clinical indices.

We observed a significant reduction of BCAA and EAA after LSG. There are several studies showing that BCAA and EAA contribute to the development of obesity. Previous reports from other Asian countries showed that Roux-en-Y gastric bypass also significantly decreased blood BCAA levels, as assessed by liquid chromatography-mass spectrometry in obese patients[15,16]. BCAA levels are regulated by BCAA catabolic enzyme activity in adipose tissues, and can be used as predictive biomarkers for obesity and insulin resistance[17,18]; thus, decreased BCAA levels might reflect improved adipose tissue function. Furthermore, EAA and choline, which are predominantly present within eggs, red meat and fish[19], were reduced after LSG. These results might derive from reduced

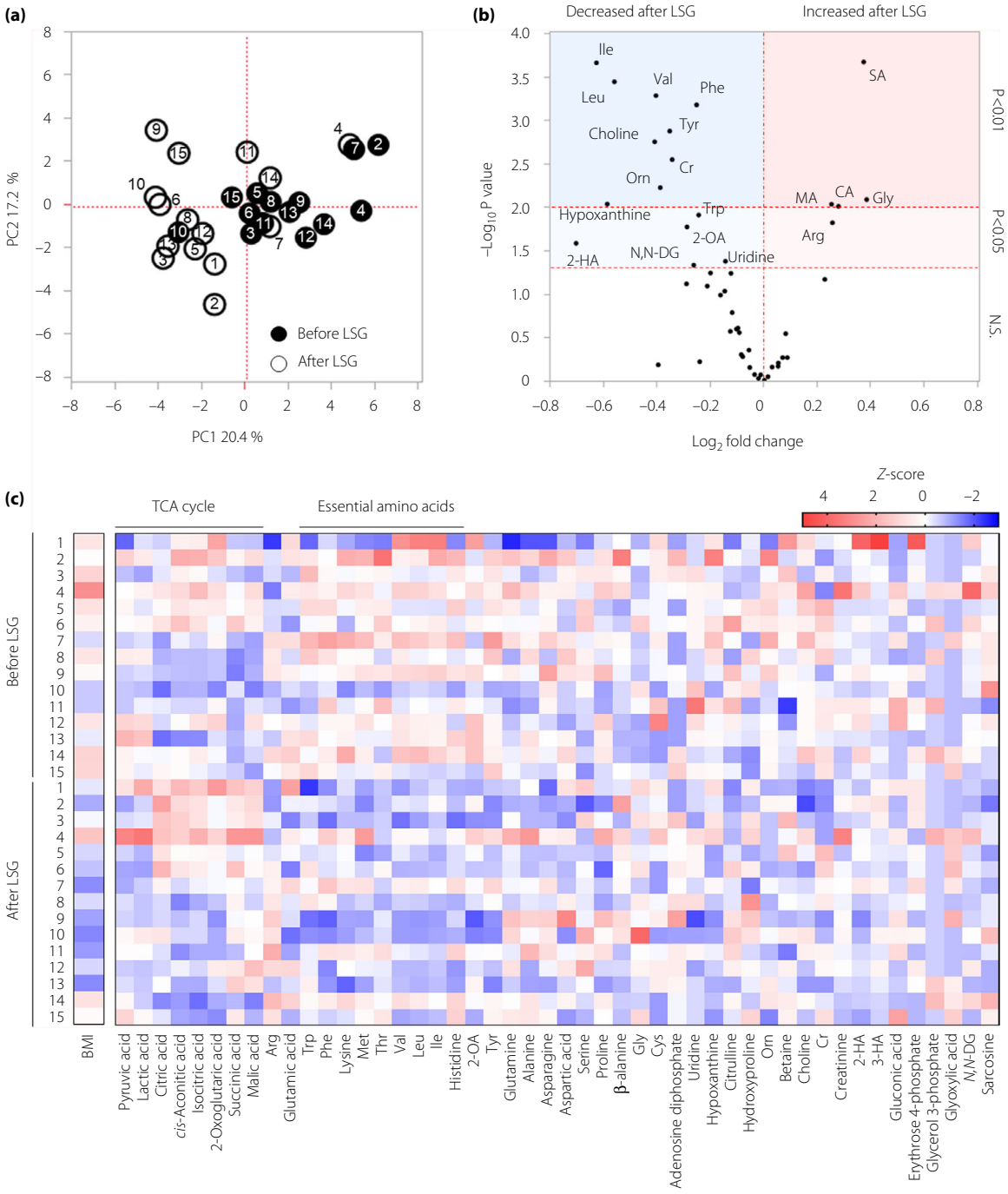

Figure 2 | The alteration of plasma metabolites after laparoscopic sleeve gastrectomy. (a) Principal coordinate analysis was carried out to compare the distribution of metabolites before (dot) and after (circle) laparoscopic sleeve gastrectomy (LSG). (b) A volcano plot of statistical significance compared with the post-LSG fold-change of concentrations. (c) A heatmap of z-scores for body mass index (BMI) and 48 metabolites. Arg, arginine; CA, citric acid; Cr, creatine; DG, dimethylglycine; Gly, glycine; HA, hydroxybutyric acid; Ile, isoleucine; Leu, leucine; MA, malic acid; Met, methionine; N.S., not significant; OA, oxoisovaleric acid; Orn, ornithine; Phe, phenylalanine; SA, succinic acid; TCA, tricarboxylic acid; Trp, tryptophan; Tyr, tyrosine; Val, valine.

food intake after LSG. Otherwise, gut microbiota can metabolize EAA and choline[19–21]; thus, alterations in the gut microbiota after LSG, as has been previously reported[22–24], might help explain the reductions in EAA and choline levels. Given that gut microbiota differ among ethnicities, it might be better to establish evidence in each country.

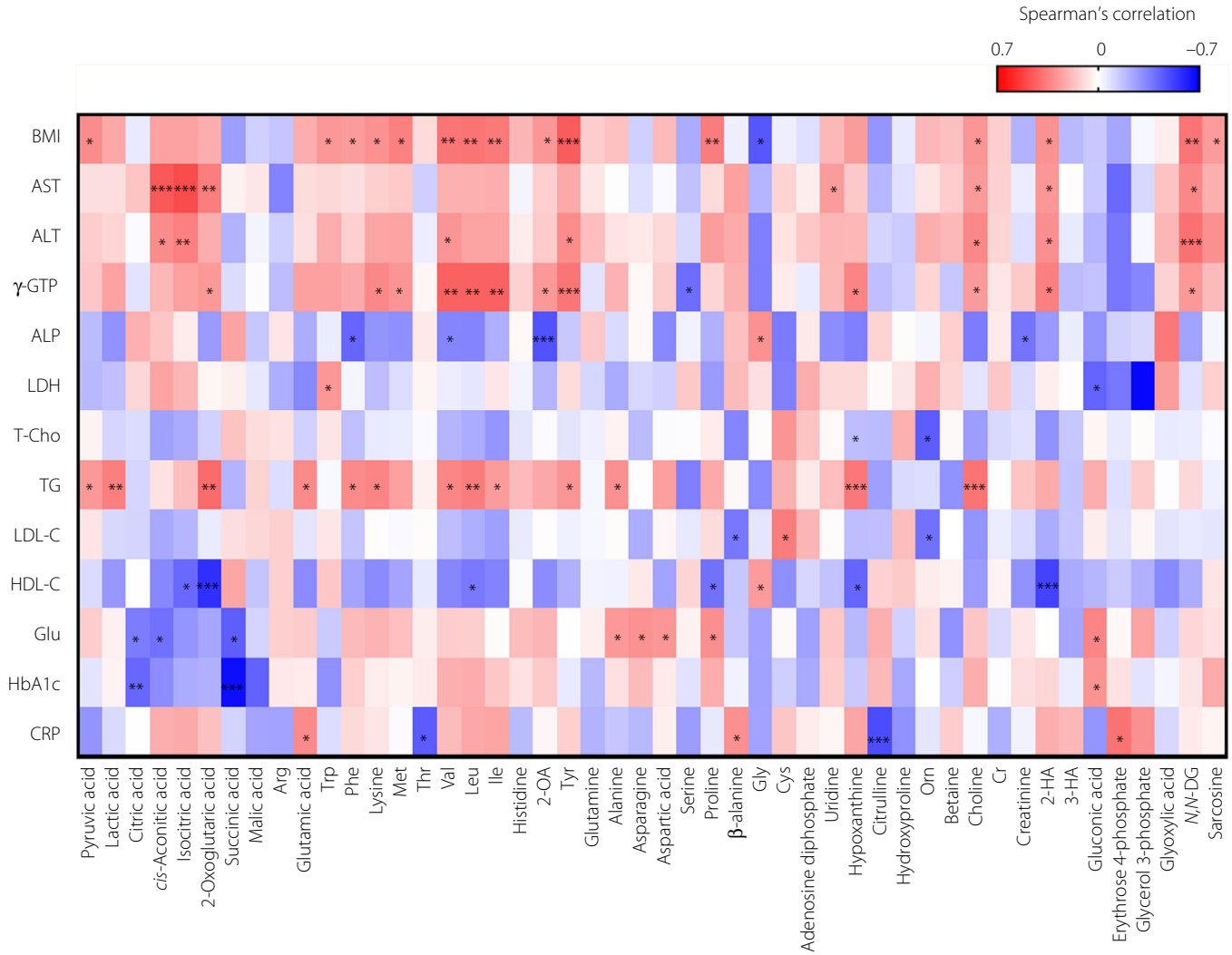

Figure 3 | Associations of plasma metabolites with clinical indices. The Spearman's rank correlation coefficient was used to determine the strength and direction of a link between two parameters. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine transaminase; Arg, arginine; AST, aspartate transaminase; BMI, body mass index; CA, citric acid; Cr, creatine; CRP, C-reactive protein; DG, dimethylglycine; Glu, glucose; Gly, glycine; HA, hydroxybutyric acid; HbA1c, glycohemoglobin; HDL-C, high-density lipoprotein cholesterol; Ile, isoleucine; Leu, leucine; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; MA, malic acid; Met, methionine; OA, oxoisovaleric acid; Orn, ornithine; Phe, phenylalanine; SA, succinic acid; TCA, tricarboxylic acid; T-Cho, total cholesterol; TG, triglycerides; Trp, tryptophan; Tyr, tyrosine; Val, valine.

Interestingly, levels of metabolites related to the tricarboxylic acid cycle were significantly elevated after LSG. Previous human trials also showed increased serum citric acid levels, as assessed by liquid or gas chromatography-mass spectrometry after LSG and Roux-en-Y gastric bypass[25,26]. Furthermore, a study in mice showed that compared with a normal chow-fed diet, a high-fat diet depressed levels of tricarboxylic acid cycle intermediates in the blood and liver[27]. Collectively, these indicate that LSG and its associated weight loss might improve mitochondrial function.

In summary, we identified dynamic alterations in plasma metabolite concentrations 3 months after LSG in 15 morbidly obese Japanese patients. Although food intake and the changes of medication might affect the plasma metabolite concentrations[28,29], the present results support LSG as an effective therapeutic strategy for treating obesity not only as a weight loss surgery, but also as a metabolomic intervention[30]. The present findings have the potential to show how LSG ameliorates obesity and present novel therapeutic targets for treating obesity.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Alteration of plasma metabolites after laparoscopic sleeve gastrectomy. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. LSG, laparoscopic sleeve gastrectomy.