Lipopolysaccharide and inflammatory cytokines levels decreased after sleeve gastrectomy in Chinese adults with obesity

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Abstract. Obesity is linked to a low-grade systemic inflammation and lipopolysaccharide (LPS) is a key factor. Sleeve gastrectomy (SG) can significantly cause weight loss, but few reports have looked into the changes of LPS and inflammatory cytokines after surgery. To explore the potential short-term impact of SG on LPS and inflammatory cytokines and their relationship to early metabolic changes in obesity. 30 Chinese adults with obesity (BMI 39.37 ± 8.22 kg/m², 25 female) receiving SG were included in this study. Fasting blood samples were collected at baseline and 30 days after SG. Serum LPS markedly reduced from 336.50 (73.54, 500) pg/mL to 5.00 (5.00, 5.24) pg/mL at 1 month after SG (p < 0.05). There was a significant decrease in plasma IL-6, IL-8, and serum CRP after SG (all p < 0.05). Insulin resistance improved remarkably after surgery as displayed by reductions in fasting insulin level (FINS, p < 0.001), and HOMA-IR (p < 0.001). In addition, visceral fat area (VFA) decreased from 209.70 ± 39.96 cm² to 193.28 ± 43.68 cm² after SG (p < 0.001). LPS was positively correlated with FINS (r = 0.391, p = 0.033) and HOMA-IR (r = 0.38, p = 0.038) before SG. Meanwhile, VFA was positively associated with CRP (r = 0.388, p = 0.034) before surgery. When assessing 30-days postoperative changes, a positive correlation was found between the variations of LPS, IL-8 and the reduction of VFA. After multivariate analyses, only the reduced IL-8 level was independently associated with the reduction of VFA (p = 0.015). In conclusion, SG can significantly relieve the inflammation in obesity in the short term and LPS might be an earlier predictor of inflammatory changes after surgery.

Key words: Lipopolysaccharide, Sleeve gastrectomy, Bariatric surgery, Inflammatory cytokines, Obesity

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OBESITY is rapidly emerging as a major public health problem worldwide, expecting more than one billion people with obesity by 2030. The prevalence of obesity among Chinese adults has increased from 3.8% to 11.3% over the past two decades [1]. Obesity is highly associated with an increased risk in the comorbidities of type 2 diabetes mellitus (T2DM), insulin resistance (IR), dyslipidemia, cardiovascular diseases, and certain cancers. These metabolic disorders are potentially linked to a low-grade chronic inflammatory state, characterized by increased levels of inflammatory cytokines, such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) [2, 3]. However, the triggering factors of inflammation, obesity, and T2DM remain to be further clarified.

NF-κB is a multi-unit transcription factor which plays an important role in the regulation of a variety of target genes associated with inflammation. Lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, has been known as an inducer of NF-κB activity and an underlying factor of obesity-driven low-grade inflammation [4]. LPS acts on target tissues such as adipose, skeletal muscle, and liver. These tissues have specific receptors which interact with LPS and induce the secretion of inflammatory cytokines and negatively regulate insulin signaling [5, 6]. Two LPS-pathway proteins, including cluster of differentiation 14 (CD14) and LPS-binding protein (LBP), are widely used as indirect measures of response to the LPS endotoxin in numerous
experimental studies [7]. Increased circulating LPS and LBP concentrations have been found in patients with obesity [2, 8].

Bariatric surgery is an effective treatment for obesity and results in substantial and long-term weight loss. Laparoscopic sleeve gastrectomy (SG) is one of the most commonly performed bariatric surgical procedures in the world. Bariatric surgery leads to major improvements in many obesity-related morbidities and mortalities. Interestingly, the improvement in metabolic alterations such as glycemic control occurs even before significant weight reduction could intervene [9, 10]. Thus, other mechanisms may be participating. Bariatric surgery causes the changes of gut microbiota and increases bacterial diversity, influencing circulating LPS levels. Previous studies have found a significant reduction in LPS and inflammatory cytokines after bariatric surgery in patients with obesity and T2DM at 6 month [11] and at 1 year [4] together with an improvement in glycemic control and weight reduction. A recent study showed similar weight reduction and improvement of metabolic disorders in prediabetic and diabetic subjects with obesity at 90 days after SG [12]. However, few human researches have been performed on the effect of bariatric surgery on LPS and inflammatory cytokines and its association with the early metabolic improvements, which occur less than 60 days after surgery, especially earlier in one month. Therefore, the aim of this study is to examine the potential short-term impact of SG on the LPS and inflammatory cytokines levels such as IL-6, IL-8, and CRP as well as the earlier changes of them 30 days after SG and their relationship to early metabolic improvement in Chinese adults with obesity.

Methods

Study design and subjects

30 Chinese adults with obesity (age 29.50 ± 8.43 years, 25 female) receiving SG at Department of Bariatric and Metabolic Surgery, The First Affiliated Hospital with Nanjing Medical University were included to this study between Nov 2017 and May 2018. Eligible subjects were 18 to 55 years old with a body mass index (BMI) >32.5 kg/m², with or without T2DM, or a BMI >27.5 kg/m² with associated T2DM but failed medical control and combined with at least two metabolic diseases or co-morbidities. Meanwhile, the following criteria were also required: duration of T2DM <15 years with fasting C-peptide >50% of normal limit for subjects with T2DM. Waist circumference: male >90 cm, female >85 cm. The weight of subjects was stable for at least 3 months prior to surgery [13]. Subjects were excluded if they had cardiovascular disease, arthritis, acute inflammatory disease, infectious disease, gastrointestinal surgery previously or were receiving drugs that could alter the lipid profile or the metabolic parameters at inclusion in the study [13].

The study was reviewed and approved by the institutional human ethics committee in accordance with national guidelines and the provisions of the Helsinki Declaration. All subjects provided written informed consent to participate in the study, and additional written informed consent was obtained before any surgical procedure. The study was approved by the Ethical Committee of the First Affiliated Hospital of Nanjing Medical University (2016-SR-220). All operations were performed by two experienced surgeons. Surgical operation procedures and requirements refer to our published articles [13].

Blood sample collection and laboratory measurements

Data were collected before (0 month) and 1 month after surgery. At the clinic visit, weight and height were measured by a trained physician. BMI (weight in kilograms divided by height in meters squared), weight loss (WL) and percentage of excess weight loss (%EWL) were also measured and calculated before surgery and during postoperative follow-up.

Participants also provided a 12 h fasting blood sample at the clinic visit. Complete blood cell count, fasting plasma glucose (FPG), fasting insulin (FINS), fasting C-peptide (FCP), total cholesterol (TC), total triglycerides (TG), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), alanine transaminase (ALT), aspartate aminotransferase (AST), glutamyl transpeptidase (GGT), and serum bilirubin were assessed with a standard clinical automatic analyzer. Insulin sensitivity index (ISI) and homeostasis model assessment of insulin resistance index (HOMA-IR) were counted after procedure. The HOMA-IR was calculated as FPG (mmol/L) × FINS (mIU/L)/22.5. ISI was calculated as 22.5/FPG (mmol/L) × FINS (mIU/L). Serum LPS was analyzed by limulus amebocyte lysate colorimetric assay (EKT205, Beijing, China) according to the manufacturer’s instructions. Plasma IL-6 and IL-8 levels were measured using an enzyme-linked immunosorbent assay kit (Jiancheng, Nanjing, China) according to the manufacturer’s protocols. Serum CRP was measured using immunoturbidimetry on a Roche Cobas Mira chemistry analyzer (Germany, Roche Cobas 8000) and read at 570 nm.

Body composition analysis

Body composition was measured using Inbody770 (Korea Biospace) at frequencies of 5, 50, 250, 500, and
1,000 kHz. With the 4-electrode 8-point contact electrode bioelectrical impedance analysis (BIA) method, Inbody770 comprehensively analyzed body composition. The test was carried out in a suitable temperature and humidity environment (10–40°C, 30–75%RH, 70–106 kPa). All subjects fasted for at least 8 hours before the test, wore minimal clothing without any metallic materials, and stood barefoot on the corresponding position of the foot electrodes, with their hands holding the hand electrodes naturally falling apart from the body. The testing time was 30s–60s. All subjects were tested by the same well trained physician before and 1 month after surgery. Data output based on the manufacturer’s algorithm, including body fat and visceral fat area.

**Statistical analysis**

All results were analyzed by SPSS, version 19.0 (SPSS Inc., Chicago, IL, USA). The continuous variables are presented as means ± standard deviations (SD) or median (25th, 75th percentiles), categorical variables are presented as numbers (%). When evaluating the changes of the results from pre- to post-SG, the differences were assessed using the paired sample t test for normally distributed variables or Wilcoxon signed-rank test for variables with skewed distribution. The correlation between the changes of LPS, IL-6, IL-8, and CRP concentrations and the changes of the indicated variables with bariatric surgery were performed using Spearman r correlation and multiple linear regression analysis. The results were considered statistically significant at the p < 0.05, and extremely significant at the p < 0.01 (two-tailed significance).

**Results**

**Clinical parameters**

Basic characteristics of the subjects were summarized in Table 1. Neither conversion to open surgery nor postoperative complications occurred in the subjects.

One month after SG, mean total body weight (BW) decreased from 108.44 ± 26.49 kg at baseline to 93.39 ± 23.75 kg (p < 0.001, Table 2). The subjects showed a marked weight loss (13.90 ± 4.39 kg), accompanied by significantly lower BMI values (33.60 ± 7.36 kg/m², p < 0.001) after SG (Table 2). Mean %EWL was 34.06 ± 15.85%. The visceral fat area (VFA) decreased significantly from 209.70 ± 39.96 cm² at baseline to 193.28 ± 43.68 cm² (p < 0.001), and body fat decreased from 50.40 ± 17.37 kg to 42.61 ± 15.70 kg 30 days after SG (Table 2). Anthropometric measurements including waist circumference, hip circumference, and waist to hip ratio (WHR) decreased significantly (p < 0.001, Table 2), suggesting a significant reduction in body fat composition after SG.

| Characteristic      | before SG          |
|---------------------|--------------------|
| Age (years)         | 29.50 ± 8.43       |
| Sex (female/male)   | 25/5 (83.33%, 16.67%) |
| Weight (kg)         | 108.44 ± 26.49     |
| BMI (kg/m²)         | 39.37 ± 8.22       |
| Co-morbidities      |                    |
| Hypertension        | 17 (56.67%)        |
| Dyslipidemia        | 23 (76.67%)        |
| Type 2 diabetes     | 6 (20%)            |
| Insulin resistance (IR) | 25 (83.33%)        |
| HbA1c (%)           | 6.17 ± 1.19        |

Systolic and diastolic blood pressure reduced markedly in the subjects postoperatively (p < 0.001, Table 2).

**Blood levels of glucose metabolism, lipid metabolism and liver function at baseline and effect of laparoscopic sleeve gastrectomy**

There was a significant decrease in FPG, FCP and FINS levels one month after surgery (Table 2, all p < 0.001). HOMA-IR level dramatically dropped from 8.60 (5.26, 11.59) to 2.82 (1.86, 4.45) with SG (p < 0.001, Table 2). On the other hand, the ISI concentration increased in the first 30 days after surgery compared with baseline (p = 0.001), indicating an improvement of insulin sensitivity after surgery.

Additionally, changes in serum lipid profile were characterized by the reduction of TC, TG and LDL-c after surgery (all p < 0.05, Table 2). The serum HDL-c level decreased slightly after SG, but there was no significant difference compared with basal level (Table 2). The levels of serum total bilirubin, direct bilirubin and serum albumin improved at one month after SG compared with preoperation. A significant reduction in GGT level was observed post-surgery (p = 0.001). However, ALT, AST and indirect bilirubin concentrations did not change significantly at one month after surgery (Table 2).

**Variations of serum LPS, serum CRP, plasma IL-6 and IL-8 after laparoscopic sleeve gastrectomy at days 30**

At baseline, fasting serum level of LPS was significantly elevated in the subjects (336.50 (73.54, 500) pg/mL, normal reference value: 0–20 pg/mL). There was a significant difference in LPS level at one month after SG compared with preoperation (Table 2 and Fig. 1). Meanwhile, there was a significant decrease in plasma IL-6 level (pre-SG to post-SG, 445.35 ± 204.99 ng/L vs. 209.70 ± 39.96 cm² at baseline to 193.28 ± 43.68 cm² (p < 0.001), and body fat decreased from 50.40 ± 17.37 kg to 42.61 ± 15.70 kg 30 days after SG (Table 2). Anthropometric measurements including waist circumference, hip circumference, and waist to hip ratio (WHR) decreased significantly (p < 0.001, Table 2), suggesting a significant reduction in body fat composition after SG.
362.60 ± 172.48 ng/L, $p < 0.05$, Table 2 and Fig. 2), as well as in plasma IL-8 level (101.02 ± 52.63 ng/L vs. 69.63 ± 48.92 ng/L, $p < 0.05$, Table 2 and Fig. 3) after SG. Furthermore, serum CRP significantly decreased from basal 4.51 (2.59, 14.02) mg/L to 1.01 (0.62, 3.28) mg/L at one month postoperatively (Table 2 and Fig. 4, $p < 0.001$).

Taken together, these data confirm that after SG the acute loss of body weight is associated with a significant improvement of the metabolic situation, including glucose and lipid metabolism, and an attenuated overall inflammatory state.
We examined the associations between LPS, IL-6, IL-8, and CRP levels and metabolic variables before SG. At baseline, serum LPS was positively correlated with FINS ($r = 0.391$, $p = 0.033$) and HOMA-IR ($r = 0.38$, $p = 0.038$), whereas the correlation with ISI was moderate ($r = –0.369$, $p = 0.045$, Table 3). The basal IL-8 level was positively correlated with TG ($r = 0.491$, $p = 0.006$, Table 3). Additionally, a close correlation between CRP and VFA was also found before SG ($r = 0.388$, $p = 0.034$, Table 3). Meanwhile, CRP was positively correlated with TC ($r = 0.379$, $p = 0.039$, Table 3) and LDL-c ($r = 0.431$, $p = 0.017$, Table 3). However, there was no correlation between IL-6, IL-8, and CRP levels and FPG, FINS, HOMA-IR, and ISI.
sis, the reduction of FPG was the only variable that was independently associated with the change in FPG level after SG (Table 4). There was no association between reduced LPS level and %EWL (r = 0.188, p = 0.321), BW (r = 0.317, p = 0.088) or other metabolic variables. None of the variables were independently associated with the change in IL-6 level after SG in the multiple linear regression analysis (Table 4). In addition, we found no significant correlation between sex hormone levels and LPS, IL-6, IL-8 and CRP levels before SG (Supplemental Table 1).

**Table 3** Correlation between LPS, IL-6, IL-8, and CRP concentrations and metabolic variables before laparoscopic sleeve gastrectomy

|                  | LPS       |         | IL-6       |         | IL-8       |         | CRP       |         |
|------------------|-----------|---------|------------|---------|------------|---------|-----------|---------|
| BW (kg)          | 0.151     | 0.427   | 0.126      | 0.506   | 0.092      | 0.629   | 0.213     | 0.259   |
| BMI (kg/m²)      | 0.002     | 0.991   | 0.255      | 0.173   | 0.183      | 0.033   | 0.268     | 0.152   |
| WC (cm)          | 0.12      | 0.529   | 0.231      | 0.219   | 0.147      | 0.439   | 0.263     | 0.161   |
| VFA (cm²)        | 0.044     | 0.816   | 0.184      | 0.331   | 0.021      | 0.912   | 0.388     | 0.034   |
| FPG (mmol/L)     | 0.174     | 0.357   | 0.192      | 0.308   | 0.089      | 0.638   | 0.144     | 0.449   |
| FINS (mIU/mL)    | 0.391     | 0.033*  | 0.155      | 0.414   | 0.047      | 0.805   | 0.184     | 0.332   |
| HOMA-IR          | 0.38      | 0.038*  | 0.177      | 0.349   | 0.071      | 0.711   | 0.173     | 0.36    |
| ISI              | -0.369    | 0.045*  | -0.183     | 0.332   | -0.081     | 0.671   | -0.178    | 0.345   |
| TG (mmol/L)      | 0.122     | 0.519   | -0.042     | 0.825   | **0.491**  | **0.006** | -0.263    | 0.159   |
| TC (mmol/L)      | 0.031     | 0.872   | 0.096      | 0.612   | 0.174      | 0.357   | **0.379** | **0.039** |
| HDL-c (mmol/L)   | -0.293    | 0.116   | 0.26       | 0.166   | -0.306     | 0.1     | 0.138     | 0.468   |
| LDL-c (mmol/L)   | 0.038     | 0.841   | 0.09       | 0.636   | 0.167      | 0.378   | **0.431** | **0.017** |

BW, body weight; BMI, body mass index; WC, waist circumference; VFA, visceral fat area; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance index; ISI, insulin sensitivity index; TG, total triglycerides; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol

Spearman r correlation, *p < 0.05

Statistically significant values are indicated in bold.

**Association between variations of LPS, IL-6, IL-8, and CRP levels and changes of metabolic variables after SG**

When comparing the change in LPS level from baseline to 1-month follow-up after SG, reduced serum LPS level was closely correlated with reduced VFA level (r = 0.392, p = 0.032, Table 4). There was no association between reduced LPS level and %EWL (r = 0.188, p = 0.321), BW (r = 0.317, p = 0.088) or other metabolic variables. None of the variables were independently associated with the change in LPS after SG in the multiple linear regression analysis (Table 4).

The change in IL-6 level was significantly associated with the change in waist circumference (r = 0.391, p = 0.033, Table 4), and FPG (r = 0.431, p = 0.017, Table 4) 30 days after SG. In the multiple linear regression analysis, the reduction of FPG was the only variable that remained significantly and independently associated with the change in IL-6 level after SG (r = 0.398, p = 0.036, Table 4).

After SG, reduced plasma IL-8 level was positively correlated with reduced VFA (r = 0.4, p = 0.029, Table 4). After multivariate analyses, the change of IL-8 with surgery was independently associated with reduced FVA (r = 0.483, p = 0.015, Table 4). None of the other variables was independently associated with the change in IL-8 levels after SG (Table 4).

However, no correlation was found between reduced CRP level and changes of metabolic variables one month after SG (Table 4). In addition, we found no significant correlation between sex hormone levels and LPS, IL-6, IL-8 and CRP levels before SG (Supplemental Table 1).

**Discussion**

In this study, the analysis of the short-term changes in subjects with obesity post-SG provided important information regarding potential associations between metabolic adaptations and inflammation. Our study indicated that SG was effective in BMI decrease and significant weight loss even in the short term, as well as improvement of body composition (including fat mass and VFA) and other anthropometric parameters. Furthermore, the present study found significant differences in the expression levels of LPS, IL-6, IL-8, and CRP in short term after SG. Moreover, a positive correlation was observed between the changes of LPS, IL-8 and the reduction of VFA.

Bariatric surgery promotes remission of diabetes mellitus and improves insulin resistance compared with medical intervention, but the mechanism is not very clear. It has been proposed that some potential mechanisms may be involved in the carbohydrate metabolism, including intestinal microflora metabolism [14], bile acid physiology [15] and a reduction in LPS level after surgery [5, 6].
LPS, a component of the outer membrane of gram-negative bacteria, is formed by a phosphoglycolipid or lipid A that is covalently linked to a hydrophilic heteropolysaccharide [16]. Increasing evidence shows that LPS could be a key factor in the low-grade inflammation seen at baseline. Moreover, a significant reduction in LPS 180 days after Roux-en-Y gastric bypass (RYGB), compared to controls, and reduced significantly one year after RYGB. Studies assessing LPS level after bariatric surgery is still not very clear, and gut microbiota might be one of the possible causes. Gut microbiota can affect numerous aspects of host metabolism, including energy synthesis, biosynthesis of steroid hormones and bile acid metabolism [20]. In addition, gut microbiota plays an important role in the development of the immune system and the maintenance of intestinal epithelial integrity [21]. The proportion of LPS in the gut microbiota has been found to be higher in obese individuals than in lean individuals [14]. Experimental data has shown that an oral infusion of gut microbiota from lean donors to mice with metabolic syndrome could temporarily improve insulin sensitivity [22]. Bariatric surgery has also caused important changes in the composition of the gut microbiota, including increases in Proteobacteria (E. coli, Enterobacter spp.), and decreases in Clostridium, Bacteroides and Prevotella [21]. Akkermansia muciniphila has significant ability to degrade mucin, and has been proved to be able to prevent inflammation and adipose tissue alterations [23]. Clinical studies have shown an increase in the abundance of this species after RYGB [24], or SG [21] in subjects with obesity. SG is a restrictive procedure, which removes a significant portion of

Table 4 Correlation (*) and multiple linear regression analysis (#) between the changes of LPS, IL-6, IL-8 and CRP concentrations and the changes of the indicated variables with laparoscopic sleeve gastrectomy.

|                      | ΔLPS | ΔIL-6 | ΔIL-8 | ΔCRP |
|----------------------|------|-------|-------|------|
|                      | r*   | p*    | B*    | p*   |
| ΔBW (kg)             | 0.317| 0.088| 0.472| 0.016|
| ΔBMI (kg/m²)         | 0.247| 0.189| 0.119| 0.54 |
| ΔWC (cm)             | 0.123| 0.516| 0.116| 0.561|
| ΔVFA (cm²)           | 0.392| 0.032| 0.249| 0.194|
| ΔFPG (mmol/L)        | 0.158| 0.404| 0.08 | 0.664|
| ΔHOMA-IR             | 0.4   | 0.029| 0.483| 0.015|
| ΔTC (mmol/L)         | -0.097| 0.609| -0.091| 0.573|
| ΔDVL (mmol/L)        | 0.219| 0.245| 0.116| 0.564|
| ΔHDL-c (mmol/L)      | 0.281| 0.132| 0.137| 0.648|
| ΔIL-6 (mg/L)         | 0.038| 0.842| 0.159| 0.417|
| ΔIL-8 (mg/L)         | 0.108| 0.75  | 0.092| 0.644|
| ΔCRP (mg/L)          | 0.229| 0.224| 0.008| 0.834|

BW, body weight; BMI, body mass index; WC, waist circumference; VFA, visceral fat area; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance index; TG, total triglycerides; TC, total cholesterol; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol

*: Spearman r correlation, p < 0.05

#: multiple linear regression analysis, p < 0.05

Statistically significant values are indicated in bold.
the stomach and reduces its volume, leading to a significant reduction in the amount of food consumed. This procedure results in anatomical rearrangements, which directly changes gastrointestinal anatomy and function, accelerating food transit and altering hormonal regulation [21]. Consequently, changes in the composition of gut microbiota might modify endotoxemia directly by reducing LPS production or indirectly by affecting the gut function.

Another possible explanation for the decrease in LPS after bariatric surgery may be associated with changes in gut permeability caused by surgery. Cani et al. [25] found that increased gut permeability in obesity enhanced LPS translocation, which leads to a rise in plasma LPS level and the subsequent increase in the low-grade inflammation state. Moreover, dietary components affect the endotoxin absorption process and a high-fat diet may contribute to the change of gut permeability [26]. It has been found that fatty acid olate promotes absorption of bioactive LPS through the induction of chylomicron formation. However, Butyrate, on the other hand, enters circulation without chylomicron formation and does not increase endotoxemia [27].

Previous researches showed LPS increased the activity of CD14 and TLR-4 signaling and was a potent activator for macrophages and various downstream signaling pathways, including MAPKs, Akt and NF-κB [28, 29]. The activation of these typical pathways is associated with elevated levels of various inflammatory factors, such as IL-1β, IL-6, and TNF-α. IL-6 is the strongest activator of liver in acute phase reaction, and has important pro-inflammatory and chemotactic activities in many infectious and inflammatory diseases [30]. IL-8 is a cysteine-amino acid chemokine that is considered to be a powerful effector of neutrophil functions and attracts several cell types involved in inflammation [31]. Previous studies demonstrated levels of IL-6, IL-8, and TNF-α were significantly elevated in participants with obesity [32, 33]. Cheng et al. [34] found that secretion of IL-1β, IL-6, and TNF-α was increased in LPS-treated murine macrophage cells in vitro through the activation of NF-κB pathway. Circulating levels of IL-6 were significantly higher in diet-induced obese mice than in Lean mice. Moreover, plasma TNF-α and leptin were significantly elevated in response to LPS and were differentially affected by IL-6 deficiency [35]. CRP is a useful predictor for early postoperative complications. The increase of CRP level in obesity has been reported and thought to be due to the increase in adipose tissue and accumulation of free fatty acids, thus promoting the release of proinflammatory cytokines and the CRP synthesis in the liver [36]. The postoperative day (POD) on which CRP measurement is at the optimal time to predict outcome varies from POD 1 to POD 5 [37]. Yang et al. [38] found that serum CRP level was higher in individuals with obesity than normal controls, and significantly decreased 1 year after RYGB. In addition, other clinical studies also found a significant decrease in CRP level at 3 months after SG and RYGB [12], and at 6 months after RYGB [11]. However, studies assessing IL-6 and IL-8 levels after bariatric surgery are limited. In the present study, the levels of IL-6, IL-8 and CRP reduced markedly in short term after SG. These observations suggest that LPS-induced inflammatory responses in obesity may be significantly inhibited with bariatric surgery.

The present study showed no significant correlation between the variation of LPS and the changes of BW and BMI. Moreover, the variation of LPS had no correlation with %EWL, suggesting factors beyond weight loss may be involved after SG. Adipose tissue is an important endocrine tissue that secretes some cytokines and chemokines [39]. Low grade chronic inflammation in the adipose tissue is associated with obesity. Adipose inflammation has been found to be an important contributor to systemic insulin resistance and multiple metabolic rearrangement [39]. Previous studies found that adipose tissue was highly reduced within the first few months after surgery. Longer post-operative follow-up studies demonstrate further declines in visceral adipose tissue but not subcutaneous adipose tissue [40]. Computed tomography (CT) and dual-energy X-ray absorptiometry (DEXA) have been confirmed to be precise and reliable measurements for estimating abdominal fat distribution [41]. However, certain factors including cost, accessibility, and radiation exposure limit the use of whole-body imaging. By contrast, bioelectrical impedance analysis (BIA), which is relatively simple, quick (takes only a few minutes), and noninvasive, provides reliable measurements of body composition in healthy subjects and in obesity or T2DM [42]. Our study found that VFA measured by BIA decreased significantly one month after SG. Furthermore, the changes in LPS and plasma IL-8 level were positively correlated with the reduction of VFA, suggesting that bariatric surgery is capable of improving adipose tissue function. However, the relationship between LPS and visceral fat remains uncertain: does LPS promote body fat accumulation; or does fat mass influence LPS production, catabolism or release?

In addition, our study found that total and direct bilirubin concentrations increased significantly one month after SG. The specific mechanism may be related to bile acid metabolism. Bile acids can directly inhibit gluconeogenesis, promote glycogen synthesis and reduce blood glucose level by binding to the ligand-activated transcription factor farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) [43]. Previ-
ous studies have found that plasma bile acids increased remarkably in obesity with or without T2DM after bariatric surgery [43, 44]. These effects of bile acids are not restricted to the gastrointestinal tract, but can affect different tissues throughout the organism.

The present study has some limitations such as lack of non-obesity group, stool specimens, biopsy specimens and quantification of adipose tissue volumes during post-operative evaluation, and the imbalance between male and female participants which limit our exploration of relevance between a reduction in VFA or inflammatory cytokines and a reduction in LPS. However, since our study was mostly exploratory and designed to evaluate short-term benefits of bariatric surgery, it had enough power to detect the earlier changes of LPS, inflammatory cytokines and metabolic variables in obesity with sleeve gastrectomy.

Conclusions

In summary, apart from improvements in BMI and glycemic control, the levels of LPS and inflammatory cytokines (IL-6, IL-8, and CRP) significantly decreased in subjects with obesity in the short term after SG. Moreover, LPS level was closely correlated with insulin resistance, and the short-term variations of LPS and IL-8 after SG were strongly associated with the reduction of VFA. Our findings support a hypothesis of low-grade endotoxemia as a potential trigger of obesity, and LPS may be an earlier indicator of inflammatory changes after bariatric surgery. Furthermore, our results suggest that the antidiabetic effects of bariatric surgery might be mechanistically linked to, and may even be a result of, a reduction in systemic LPS level. Further studies are required to better evaluate the potential role of LPS-induced inflammatory response in the mechanism of bariatric surgery, including how those assessments can be applied to clinical practice.

Conflict of Interest Statement

The authors declare no conflict of interest and are responsible for the content and writing of this paper.

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Ethics Approval

This work was conducted with the approval of the Ethical Committee of the First Affiliated Hospital of Nanjing Medical University (2016-SR-220).

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