Changes in bile acid profile after laparoscopic sleeve gastrectomy

Ahmad Abd Al-Aziz

Department of General and Laparoscopic Surgery, Faculty of Medicine, Cairo University, Giza, Egypt

Correspondence to Ahmad Abd Al-Aziz, MD, Department of General and Laparoscopic Surgery, Faculty of Medicine, Cairo University, Giza, Egypt; Tel: 01001907892; e-mail: zizoo_81@hotmail.com

Received 18 January 2018
Accepted 26 January 2018

The Egyptian Journal of Surgery
2018, 37:326–329

Introduction
Bile acids (BAs) have an effect on lipid and metabolic profile, as they are mediators of different regulatory functions in glucose and cholesterol homeostasis and energy expenditure. After sleeve gastrectomy, many changes occur in many biomarkers and in the metabolic profile.
Objective
The aim of this study was to evaluate the effect of laparoscopic sleeve gastrectomy (LSG) on BA profile.
Patients and methods
A total of 93 obese patients were evaluated before and after LSG (1, 6, and 12 months). BA profile was evaluated through the serum marker, 7α-hydroxy-4-cholesten-3-one (C4). Primary and secondary BA and C4 were determined by high-performance liquid chromatography coupled with tandem mass spectrometry detection, and then the data were collected and interpreted.
Results
From May 2015 to January 2017, 93 patients (age 44.6±10.4 years; BMI 42.7 ±9.3 kg/m^2; 62.4% female) were included in this study. Mean weight loss at 1, 6, and 12 months was 14.1, 22.1, and 26.3 kg, respectively ($P<0.0001$). Serum C4 levels at baseline and at 1, 6, and 12 months were 22.4±11.1, 4.4±7.1, 14.8±12.9, and 18.8±16.8 ng/ml, respectively ($P<0.0001$).
Conclusion
Serum BA levels decrease after LSG as the fasting serum levels of C4 decrease after LSG, but then these levels increase gradually.

Keywords:
bariatric surgery, bile acids, obesity, sleeve gastrectomy

Egyptian J Surgery 37:326–329

1110-1121

Introduction

Obesity is accompanied by numerous metabolic abnormalities including insulin resistance, dyslipidemia, subclinical inflammation, and endocrine dysregulations that could contribute to its etiopathogenesis and the development of complications [1]. Obesity is the most common cause for hepatic steatosis, and the rise in obesity has resulted in sharply increasing rates of NAFLD [2]. Bile acids (BAs) are end products of cholesterol metabolism and are also signaling molecules, stimulating production of fibroblast growth factor-19 in the terminal ileum. Fibroblast growth factor-19 acts in the liver in a negative feedback loop by regulating cholesterol 7α-hydroxylase (CYP7A1) activity via the nuclear RXR farnesoid X receptor-α [3]. BAs also act via transmembrane G-protein-coupled receptor [4]. Oral administration of BA reduces weight gain and insulin resistance and increases energy expenditure in animal models [5]. BA may be one of the potential mediators of the benefits of bariatric surgery in terms of weight loss and improvement of associated diseases. The understanding of the effects of bariatric surgery on BA homeostasis may be important in understanding the role of BAs in obesity and its potential role as target in bariatric surgery [6].

Bechmann *et al.* [7] investigated BA profiles in obese patients with NAFLD/NASH and found that serum BA was higher in NASH than that in the simple steatosis, as was CK-18 M30. Recently, Myronovych *et al.* [8] have shown that sleeve gastrectomy (SG) in a high-fat diet mouse model leads to reduction in hepatic steatosis, independent of weight loss, associated with changes in cholic acid (CA) and glycine-conjugated ursodeoxycholic acid.

The aim of this study was to evaluate the effect of laparoscopic sleeve gastrectomy (LSG) on BA profile and synthesis.

Patients and methods

A total of 93 patients underwent LSG in El Kasr Alainy, Faculty of Medicine, Cairo University from May 2015 to January 2017. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee. All study participants provided written informed consent.

The patients' BMI was recorded along with weight loss at 1 month, 6 months, and 1 year.

The serum BA level and the serum levels of C4 were measured preoperatively as baseline and after 1 month, 6 months, and 1 year.

Exclusion criteria included previous bariatric surgery, small bowel or colon resection, previous cholecystectomy, presence of gallbladder stones at baseline, and/or the use of the following drugs: cholestyramine, colesevelam, colestilan, colestimide, colestipol, insulin, exenatide, thiazolidinedione, or dipeptidyl peptidase IV inhibitors, or selective serotonin reuptake inhibitor antidepressants.

The age of the study population ranged from 20 to 64 years, with average of 44.6±10.4 years. There were 35 male and 58 female patients. The BMI of the study population ranged from 30 to 72 kg/m^2, with average of 42.7±9.3 kg/m^2.

Technique

Laparoscopic sleeve gastrectomy

Surgical intervention LSG was performed under general anesthesia. A five-port technique was used in all patients: the first 10-mm midline trocar was inserted under direct optical control (Visiport; Covidien, Minneapolis, MN, USA). A 15-mm trocar inserted into the right hypochondrium served to introduce the endostapler (4.8-mm staples) required for the first transections of the gastric antrum and was useful for extracting the resected stomach. Dissection of the greater gastric curvature was then conducted, separating it from the gastroepiploic arcade of the greater omentum. For this procedure, instruments for sealing and sectioning the tissues (LigaSure; Covidien) were used. Dissection was continued to the angle of His; freeing the posterior fundal region is extremely important to avoid leaving a residual pocket. In all cases, the gastric transection was performed under the guidance of a 38-Fr Faucher bougie. A subhepatic drain was placed along the suture. A methylene blue leak test was performed in all patients before the end of the surgery.

Assays

X7α-hydroxy-4-cholesten-3-one assay

7α-hydroxy-4-cholesten-3-one (C4) serum concentrations were measured by high-performance liquid chromatography coupled with HPLC-MS/MS. C4 was used as the reference compound and its deuterated analogue, C4-d7 (Medical Isotopes Inc., Pelham, New Hampshire, USA), as the internal standard (IS). Sample preparation was performed using liquid–liquid extraction. Overall, 200 ml of the serum sample along with 40 ml of IS solution (1 mg/ml in methanol) was extracted with 500 ml of hexane/chloroform (95 : 5).

The lower limits of detection and quantification were 0.5 and 1.0 ng/ml, respectively.

Bile acids assay

BA serum concentrations were measured by high-performance liquid chromatography coupled with HPLC-MS/MS. CA, deoxycholic acid (DCA), lithocholic acid (LCA), chenodeoxycholic acid (CDCA), and ursodeoxycholic acid (UDCA) were used as the reference compounds, and their deuterated analogues CA-d4, DCA-d4, LCA-d5, CDCA-d4, and UDCA-d4 (Sigma-Aldrich, St Louis, Missouri, USA) were used as the IS.

Mass spectrometry detection was carried out with a 4500 QTrap (Sciex @, The Francis Crick Institute, UK) using turbospray ionization in negative mode and multiple reaction monitoring. Quantitation was based on peak area ratios of BA and its corresponding IS, using Analyst 1.6.1 software for data collection and analysis. The lower limits of detection and quantification for all BA were 0.1 and 1.0 ng/ml, respectively.

Results

From May 2015 to January 2017, 93 patients (age 44.6±10.4 years; BMI 42.7±9.3 kg/m^2) were included in this study. There were 58 (62%) females and 35 (37.6%) males as shown in Table 1.

Mean weight loss at 1, 6, and 12 months was 14.1, 22.1, and 26.3 kg, respectively (P<0.0001).

Serum C4 levels decreased from 22.4±11.1 ng/ml at baseline to 4.4±7.1, 14.8±12.9, and 18.8±16.8 ng/ml at 1, 6, and 12 months, respectively (P=0.0001) (Fig. 1 and

Table 1 Patients' demographics

Variables	Minimum	Maximum	Mean
Age	20	64	44.6
BMI	30	72	42.7

Table 2), suggesting a significant reduction in BA synthesis after LSG. There were no significant differences in C4 levels at baseline compared with 12 months.

Serum levels of BA increased at 1, 6, and 12 months after LSG; however, these changes were significant only for LCA, DCA, and secondary BA (Table 2).

Discussion

BAs are synthesized in the liver from cholesterol and excreted to the bile tract as one of the main components of bile [9].

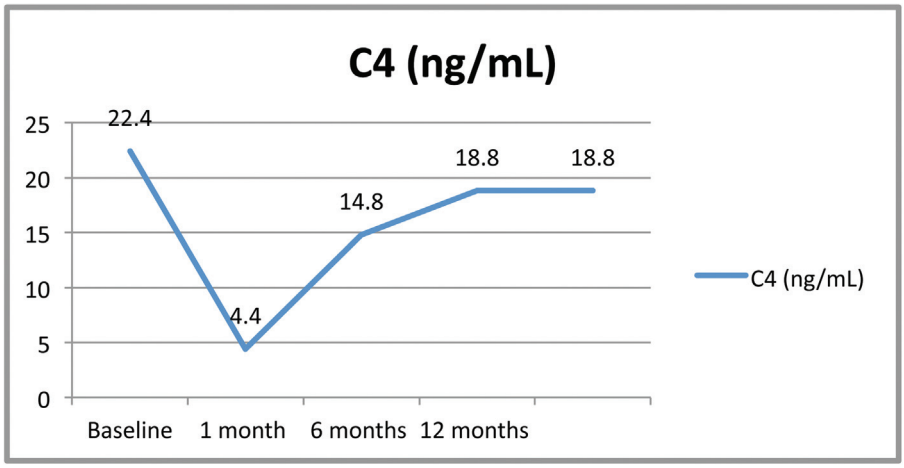
BAs are distributed in different compartments of the so-called enterohepatic circulation that is composed of the liver, bile tract, gallbladder, intestine, and portal circulation [10]. BAs are now recognized as mediators of different regulatory functions in glucose and cholesterol homeostasis and also in control of energy expenditure [11]. In rodents, oral administration of BAs reduces weight gain and insulin resistance and increases energy expenditure [5].

Changes in BA are associated with alterations in gut microbiota, lipopolysaccharides, and consequently, inflammation. These microbiota-induced changes may be due to alterations in circulating bacterial endotoxins, lipopolysaccharides, which produce an immune response [12].

Many bariatric procedures appear to disrupt the enterohepatic circulation and cause changes to BA homoeostasis. Total serum BA concentrations increased more than two-fold 2–4 years after RYGB compared with overweight and obese controls patients without bariatric surgery [13].

In Escalona *et al.* [6] found that fasting and postprandial levels of plasma BAs were elevated relative to low preoperative levels and weight-matched controls. In addition, vertical SG results in elevated plasma BA levels. This change is statistically

Figure 1



Fasting serum levels of 7a-hydroxy-4-cholesten-3-one (C4) before (baseline) and at 1, 6, and 12 months after laparoscopic sleeve gastrectomy.

Table 2 Metabolic changes after laparoscopic sleeve gastrectomy

Variables	Baseline	1 month	6 months	12 months
BMI (kg/m^2; SD)	42.7±9.3	38 + or - 4	36.4±3.5	28.7±2.6
Weight (kg)	99.2±15.1	85.1±14.2	77.1±6.8	72.9±4.7
C4 (ng/ml; SD)	22.4±11.1	4.4±7.1	14.8±12.9	18.8±16.8
CA (ng/ml)	25.3±33.1	22.1±27.1	26±33.4	21±22.9
LCA (ng/ml)	5.3±3.1	3.9±4.1	7.4±5	12.6±15.5
DCA (ng/ml)	74.7±72.2	50.9±48.8	135.7±90	124.9±102
CDCA (ng/ml)	27.2±35.1	23.2±45.1	36.7±48.8	46.8±101.9
UDCA (ng/ml)	8.3±12.8	5.4±5.1	30.2±120.7	14±16.2
Primary BAs (ng/ml)	50.7±71	42.1±64.1	62.9±82.3	69.7±120.2
Secondary BAs (ng/ml)	87.2±70.1	48.1±67.2	175.8±166.5	152.1±100.3
Total unconjugated BAs (ng/ml)	140.1±99.1	105±93.4	234.1±200.1	209.2±166.1

BAs, bile acids; C4, 7α-hydroxy-4-cholesten-3-one; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid.

significant for taurine and glycine subfractions of conjugated BA. Preliminary human data after gastric bypass suggest that this postprandial BA response is increased going back to the normal biphasic pattern. This change in postprandial BA levels after RYGB is mostly a result of glycine-conjugated BA.

Nakatani *et al.* [14] also reported a higher serum BA concentration in patients after restrictive procedures in 15 patients (including nine patients with SG and six with laparoscopic adjustable gastric banding).

A recent study also reported higher serum BA levels after RYGB and BPD, but with opposite effects on BA synthesis [15].

The aim of this study was to evaluate BA synthesis after LSG using C4 as a marker of synthesis.

Our data found that fasting serum levels of C4 decrease after SG, indicating a reduction in the synthesis of BA, as preoperatively (baseline level), it was 22.4±11.1 (ng/ml; SD), and then the levels became 4.4±7.1, 14.8±12.9, and 18.8±16.8 at 1, 6, and 12 months, respectively.

In our study, serum BA levels at fasting decreased after 1 month of LSG and then increased at 6 and 12 months after the procedure. This difference was statistically significant for secondary BAs (LCA and DCA), as baseline LCA level was 5.3±3.1 ng/ml, and then at 1 month was 3.9±4.1, at 6 months was 7.4±5, and after 12 months was 12.6±15.5, whereas baseline DCA level was 74.7±72.2 ng/ml, and at 1 month was 50.9±48.8, at 6 months was 135.7±90, and by the end of 12 months was 124.9±102.

During enterohepatic circulation, BAs advance to the colon where they are substrates of bacteria biotransformation. DCA and LCA are secondary BAs produced only by bacteria dihydroxylation of CA and CDCA acid in the large bowel. Secondary BAs are passively absorbed from the colon returning to the liver via the portal vein. Therefore, portal flow includes primary and secondary BAs to return to the liver during each enterohepatic cycle. These BAs are actively transported into the hepatocytes, then biotransformed, conjugated (glycine or taurine), and again actively transported into the bile. Gut microbiota participates in the development of obesity and other metabolic diseases [16].

Obese individuals had increased levels of firmicutes bacteria and decreased levels of Bacteroidetes compared with nonobese patients. There are reports describing changes in intestinal microbiota after bariatric surgery. Because BAs are substrates of bacteria deconjugation during the enterohepatic circulation, potential mechanisms to change BA homeostasis may include changes on bacterial deconjugation that are induced by changes in microbiota composition [17].

Conclusion

Serum BA levels decrease after LSG as the fasting serum levels of C4 decrease after LSG, but then these levels increase gradually.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Reaven G, Abbasi F, McLaughlin T. Obesity, insulin resistance, and cardiovascular disease. Recent Prog Horm Res 2004; 59:207–224.

2 Sturm R, Hattori A. Morbid obesity rates continue to rise rapidly in the United States. Int J Obes 2013; 37:889–891.

3 Modica S, Gadaleta RM, Moschetta A. Deciphering the nuclear bile acid receptor FXR paradigm. Nucl Recept Signal 2010; 8:e005.

4 Chen X, Lou G, Meng Z, Huang W. TGR5: a novel target for weight maintenance and glucose metabolism. Exp Diabetes Res 2011:2011:5.

5 Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, *et al.* Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature 2006; 439:484–489.

6 Escalona A, Muñoz R, Irribarra V, Solari S, Allende F, Miquel JF. Bile acids synthesis decreases after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis 2016; 12:763–769.

7 Bechmann LP, Kocabayoglu P, Sowa J-P, Sydor S, Best J, Schlattjan M, *et al.* Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. Hepatology 2013; 57:1394–1406.

8 Myronovych A, Kirby M, Ryan KK, Zhang W, Jha P, Setchell KDR, *et al.* Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. Obesity (Silver Spring) 2014; 22:390–400.

9 Hofmann AF, Hagey LR. Bile acids: chemistry, pathochemistry, biology, pathobiology, and therapeutics. Cell Mol Life Sci 2008; 65:2461–2483.

10 Dawson PA. Bile formation and the enterohepatic circulation. In: Johnson LR, editor. Physiology of the gastrointestinal tract. 6th ed. Waltham, MA: Elsevier Academic Press; 2018. pp. 931–956.

11 Nguyen A, Bouscarel B. Bile acids and signal transduction: role in glucose homeostasis. Cell Signal 2008; 20:2180–2197.

12 Belgaumkar AP, Vincent RP, Carswell KA, Hughes RD, Alaghband-Zadeh J, Mitry RR. Changes in bile acid profile after laparoscopic sleeve gastrectomy are associated with improvements in metabolic profile and fatty liver disease. Obes Surg 2016; 26:1195–1202.

13 Patti ME, Houten SM, Bianco AC, Bernier R, Larsen PR, Holst JJ, *et al.* Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity (Silver Spring) 2009; 17:1671–1677.

14 Nakatani H, Kasama K, Takashi O, Mitsuhiro W, Hiroshi H, Hiroshi I. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. Metabolism 2009; 58:1400–1407.

15 Ferrannini E, Camastra S, Astiarraga B, Nannipieri M, Castro-Perez J, Xie D, *et al.* Increased bile acid synthesis and deconjugation after biliopancreatic diversion. Diabetes 2015; 64:3377–3385.

16 Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, *et al.* A core gut microbiome in obese and lean twins. Nature 2009; 457:480–484.

17 Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, *et al.* Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci USA 2009; 106:2365–2370.