

Changes in fasting bile acid profiles after Roux-en-Y gastric bypass and sleeve gastrectomy

Chunlan Zhang, MSc, Jingjing Zhang, MD^{*}, Zhiguang Zhou, MD

Abstract

Background: Bile acid is an essential factor that plays a role in metabolic regulation, but how bile acid is regulated after Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) remains unclear. This meta-analysis aimed to investigate changes in the levels of fasting bile acids following RYGB and SG.

Methods: A systematic literature search of the PubMed, EMBASE, Cochrane Library and Web of Science databases through July 2020 was performed in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The concentrations of bile acids were evaluated.

Results: Thirteen studies with 289 patients were included. Our results showed that patients who underwent RYGB had increased levels of fasting total bile acids, primary bile acids, secondary bile acids, conjugated bile acids, and unconjugated bile acids, but no significant differences in all these bile acid levels were observed in patients who underwent SG. Furthermore, 12a-hydroxylated bile acid levels and the 12a-hydroxylated/non-12a-hydroxylated bile acid ratio also increased following RYGB.

Conclusion: In this study, we found that fasting bile acid levels, especially 12a-hydroxylated bile acids levels, were increased after RYGB. However, no differences in fasting bile acid levels were observed following SG.

Abbreviations: BMI = body mass index, BPD/DS = biliopancreatic diversion with duodenal switch, CA = cholic acid, CDCA = chenodeoxycholic acid, CIs = confidence intervals, DCA = deoxycholic acid, FGF19 = fibroblast growth factor 19, FXR = farnesoid X receptor, GCDCA = glycochenodeoxycholic acid, GDCA = glycodeoxycholic acid, HOMA-IR = homeostatic model assessment for insulin resistance, NOS = Newcastle-Ottawa scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RYGB = Roux-en-Y gastric bypass, SG = sleeve gastrectomy, SMDs = standard mean differences, T2D = type 2 diabetes, TCDCa = taurochenodeoxycholic acid, TGR5 = G protein-coupled receptor 5.

Keywords: bile acids, Roux-en-Y gastric bypass, sleeve gastrectomy

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

The prevalence of obesity has continued to increase over the past 30 years and is associated with an increased risk of numerous comorbid medical conditions, including insulin resistance, type 2 diabetes (T2D), and cardiovascular diseases.^[1,2] Bariatric surgery is the most effective and sustainable treatment for obesity with or without diabetes. Currently, the 2 most popular bariatric procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), are effective in promoting weight loss and metabolic benefits. Although many of these metabolic improvements are undoubtedly attributable to long-term weight loss, additional data support a weight-independent role of other hormonal or metabolic mediators involved in driving metabolic improvements after bariatric procedures.

Bile acids are cholesterol-derived metabolites that facilitate the intestinal absorption and transport of dietary nutrients and lipids. In recent years, bile acids have emerged as signaling molecules by binding to the farnesoid X receptor (FXR) and the G protein-coupled receptor 5 (TGR5) in multiple organs, leading to regulation of intestinal incretin secretion, hepatic gluconeogenesis, glycogen synthesis, and energy expenditure, and have been implicated as potential mediators of weight-independent effects of bariatric surgery.^[3,4] Obese FXR- or TGR5-knockout mice that underwent bariatric surgery exhibited impaired weight loss and glucose tolerance improvement, suggesting that bile acid-FXR/TGR5 signaling may positively affect glucose metabolism

after bariatric surgery.^[5,6] Studies have also shown a relationship between significant improvement in the glycemic response and changes in bile acid profiles and signaling in morbidly patients with obesity following bariatric surgery.^[7]

However, the effects of SG on bile acid levels are inconsistent, with some studies reporting increased plasma concentrations,^[8,9] some reporting no change,^[10–12] and some even reporting decreased concentrations.^[13] Most studies have reported increases in circulating bile acid concentrations following RYGB.^[7,14–16] However, some studies reported no change in serum bile acid levels after RYGB.^[17,18] One study also found that serum bile acids were decreased at 1 month after RYGB but increased to levels higher than those before surgery at 2 years after surgery.^[19] Thus, conducting a meta-analysis to settle this dispute is urgent. The mechanisms leading to these effects are currently of great interest, and it is important to understand how bile acid metabolism and enterohepatic circulation may be affected by bariatric operations. We performed this systematic review and meta-analysis to determine the relationship between bile acid levels and bariatric surgery.

2. Methods

As this study is a meta-analysis based on previously published studies, the ethical approval and patient consent are not required.

2.1. Literature search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[20] The electronic databases PubMed, EMBASE, Cochrane Library, and Web of Science were thoroughly searched through July 2020. The following relevant MESH terms and free text for all field research were used: “Surgeries, Bariatric” OR “Surgery, Bariatric” OR “Metabolic Surgery” OR “Metabolic Surgeries” OR “Surgeries, Metabolic” OR “Surgery, Metabolic” OR “Bariatric Surgical Procedures” OR “Bariatric Surgical Procedure” OR “Procedure, Bariatric Surgical” OR “Procedures, Bariatric Surgical” OR “Surgical Procedure, Bariatric” OR “Surgical Procedures, Bariatric” OR “Bariatric Surgeries” OR “Stomach Stapling” OR “Stapling, Stomach” OR “Sleeve Gastrectomy” OR “Gastric Bypass” OR “Bypass, Gastric” OR “Roux-en-Y Gastric Bypass” OR “Bypass, Roux-en-Y Gastric” OR “Gastric Bypass”, “Roux-en-Y” OR “Roux en Y Gastric Bypass” OR “Greenville Gastric Bypass” OR “Gastric Bypass, Greenville” OR “Gastroileal Bypass” OR “Bypass, Gastroileal” OR “Gastrojejunostomy” OR “Gastrojejunostomies” AND “Bile Acids and Salts” OR “Bile Acids” OR “Acids, Bile” OR “Bile Salts” OR “Salts, Bile.”^[21] We also manually searched for additional papers concerning bariatric surgery and bile acid in the reference lists of identified articles.

2.2. Selection criteria

The inclusion criteria were as follows: original comparative reports with > 5 patients; studies published in English; studies conducted in human subjects; studies reporting fasting bile acid levels pre- and post-RYGB or SG; and studies in which bile acids were assessed by ultra-high-performance liquid chromatography coupled with a triple quadrupole mass spectrometer.

The exclusion criteria were as follows: nonhuman studies; studies with non-RYGB or SG interventions; or letters and comments, reviews, and meta-analyses.

2.3. Data extraction

Two authors (CZ and JZ) independently extracted the following parameters: study type, first author (publication year), country, age range/year, participants, intervention, duration of intervention, measurements of bile acid, outcome measures, authors' conclusions, and quality score. Two authors independently performed data extraction, and disagreements were resolved by consensus or by referring to a third author (ZZ).

2.4. Quality assessment and risk of bias

Since there is no assessment method suitable for various study types (i.e., randomized controlled trials [RCTs] and cross-sectional studies and cohort studies), the risk of bias was assessed using the RoB 2.0 tool from the new Cochrane handbook and Newcastle–Ottawa scale (NOS), respectively.^[22] The included RCTs were assessed for randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (see Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/F466>, which demonstrates the risk bias of the included RCTs). Each criterion was judged as a high or low risk of bias, or some concerns. We used the NOS to assess the quality of nonrandomized studies. A study with a score of 6 or higher was defined as high quality. The prospective cohort studies included in our study were all considered to be of high quality. Two independent reviewers (CZ and JZ) performed the quality assessments, and disagreements regarding scores were resolved through discussion.

2.5. Statistical analysis

We calculated the standard mean differences (SMDs) in bile acid levels pre- and post-RYGB or SG with 95% confidence intervals (95% CIs). A random effects model was used because of the clinical heterogeneity of the studies. Cochran Q (Chi-square) test was used to quantify the heterogeneity, and the I^2 statistic was used to assess the extent of inconsistency: low >25%, moderate >50%, and high >75%. A funnel plot was constructed to assess potential publication bias. All statistical analyses were conducted using Review Manager (RevMan V5.3, Cochrane Collaboration, UK) statistical software. Two-sided $P < .05$ was defined as statistically significant.

3. Results

3.1. Study characteristics

Figure 1 shows the details of the studies included in this meta-analysis. Searches using the index words produced a total of 2164 publications. After checking for duplicates and reviewing the titles and abstracts, 2108 publications were eliminated; thus, 56 publications remained for further assessment. During full-text screening, 43 studies were excluded for various reasons. A final total of 13 studies evaluating the role of bile acid in 289 surgery patients were included in the current meta-analysis. Table 1 lists the major characteristics of the studies. The collected information consisted of first author (publication year), study type, sample size, age, body mass index (BMI), outcome measures, duration of intervention, and surgery type.

3.2. Changes in total bile acids after RYGB or SG

RYGB was evaluated in 11 studies, and SG was evaluated in 4. As demonstrated in Figure 2, the results of our meta-analysis

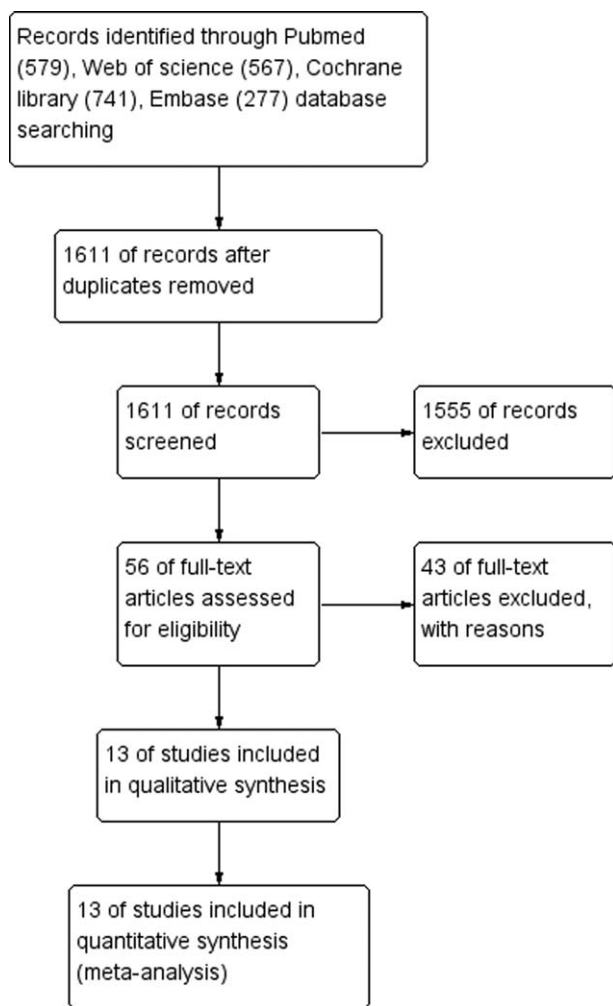


Figure 1. Flowchart showing the literature search and study selection processes.

revealed a significant increase in fasting total bile acid levels [SMD=0.60; 95% CI (0.33 and 0.86), $P < .001$] in patients after RYGB. In addition, after SG, there were no significant differences between total fasting bile acid levels before and after the operation [SMD=0.29; 95% CI (-0.13 and 0.7), $P = .17$].

3.3. Changes in primary and secondary bile acids after RYGB or SG

As shown in Figures 3 and 4, the primary bile acid levels [SMD=0.78; 95% CI (0.34 and 1.21), $P = .0005$] and secondary bile acid levels [SMD=0.6; 95% CI (0.24 and 0.96), $P = .001$] were increased significantly at 12 months after RYGB. However, no significant changes were found in the levels of primary and secondary bile acids in patients who underwent SG.

3.4. Changes in conjugated and unconjugated bile acids after RYGB or SG

The conjugated bile acid levels [SMD=0.50; 95% CI (0.16 and 0.84), $P = .004$] and unconjugated bile acid levels [SMD=0.48; 95% CI (0.29 and 0.67), $P < .001$] were increased in patients after RYGB, while they were not significantly changed in patients following SG (Figs. 5 and 6).

3.5. Other changes in different fractions of bile acids

As summarized in Table 2, fasting cholic acid (CA), deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), chenodeoxycholic acid (CDCA), glycochenodeoxycholic acid (GCDCA), and taurochenodeoxycholic acid (TCDCA) levels were all increased in patients with obesity after RYGB. Moreover, 12a-hydroxylated bile acids and the 12a-hydroxylated/non-12a-hydroxylated bile acids ratio also increased post-RYGB.

Table 1
Characteristics of the included studies.

References	Study type	Sample size	Age, yr	BMI, kg/m ²	Initial total bile acids, μmol/L	Initial primary bile acids, μmol/L	Initial secondary bile acids, μmol/L	Initial conjugated bile acids, μmol/L	Initial unconjugated bile acids, μmol/L	Follow-up	Surgery type
Ahlin et al ^[23]	control	6	43.7±9.4	45.3±5.7	1.7±0.6	0.8±0.3	0.9±0.5	0.8±0.2	0.9±0.4	185 d	RYGB
Ahmad et al ^[18]	longitudinal study	5	44.8±12.9	47.7±7.4	1.1±0.7	—	—	0.6±0.4	0.5±0.3	40 weeks	RYGB
Belgaumkar et al ^[10]	longitudinal study	18	46.3±2.9	60.1±2.6	2.5±1.8	1.2±0.9	0.9±0.3	1.5±0.9	0.6±0.3	6 mo	LSG
Chen et al ^[9]	longitudinal study	8	42.9±9.6	43.0±4.7	6.3±1.0	4.0±0.6	2.2±0.4	4.9±0.8	1.3±0.2	3 mo	RYGB
		11	43.9±6.7	43.4±6.1	6.5±1.2	4.2±0.6	2.3±0.5	5.1±0.7	1.4±0.6	3 mo	LSG
Dutia et al ^[19]	longitudinal study	13	49.5±8.5	43.3±4.9	4.3±3.6	2.9±3.3	1.5±0.6	3.2±3.8	1.2±0.5	2 yr	RYGB
Jorgensen et al ^[15]	longitudinal study	25	—	—	1.9±1.4	0.6±0.5	0.6±0.2	0.7±0.3	0.4±0.3	1 yr	RYGB
Mika et al ^[29]	control	9	—	41.0±1.0	10.0±0.9	6.7±0.9	3.4±0.4	5.5±0.8	4.5±0.4	3 mo	RYGB
		7	—	41.0±1.6	7.6±0.9	5.5±0.8	2.1±0.4	3.4±0.7	4.2±0.5	3 mo	LSG
Risstad et al ^[14]	RCT	31	35.2±7.0	54.8±3.2	2.3±6.5	1.6±5.2	0.7±2.0	1.3±4.1	0.9±4.1	5 yr	RYGB
Sachdev et al ^[7]	RCT	15	46.9±2.2	36.2±0.7	1.7±1.6	—	—	—	—	1 yr	RYGB
Shimizu et al ^[11]	longitudinal study	10	48.8±2.7	40.9±3.2	2.8±0.7	—	—	—	—	6 mo	LSG
Simonen et al ^[40]	longitudinal study	30	45.2±7.9	46.1±5.9	6.1±6.5	3.6±2.7	2.6±5.9	4.5±6.7	1.8±2.3	12 mo	RYGB
Werling et al ^[16]	longitudinal study	63	43 (36–56)	43.7 (39.3–49.2)	1.7±1.4	—	—	1.4±1.1	0.5±0.3	15 mo	RYGB
Yu et al ^[17]	longitudinal study	38	45.0±12.6	32.2±3.8	3.8±2.3	2.7±2.1	1.1±0.7	2.0±1.8	1.8±1.5	1 yr	RYGB

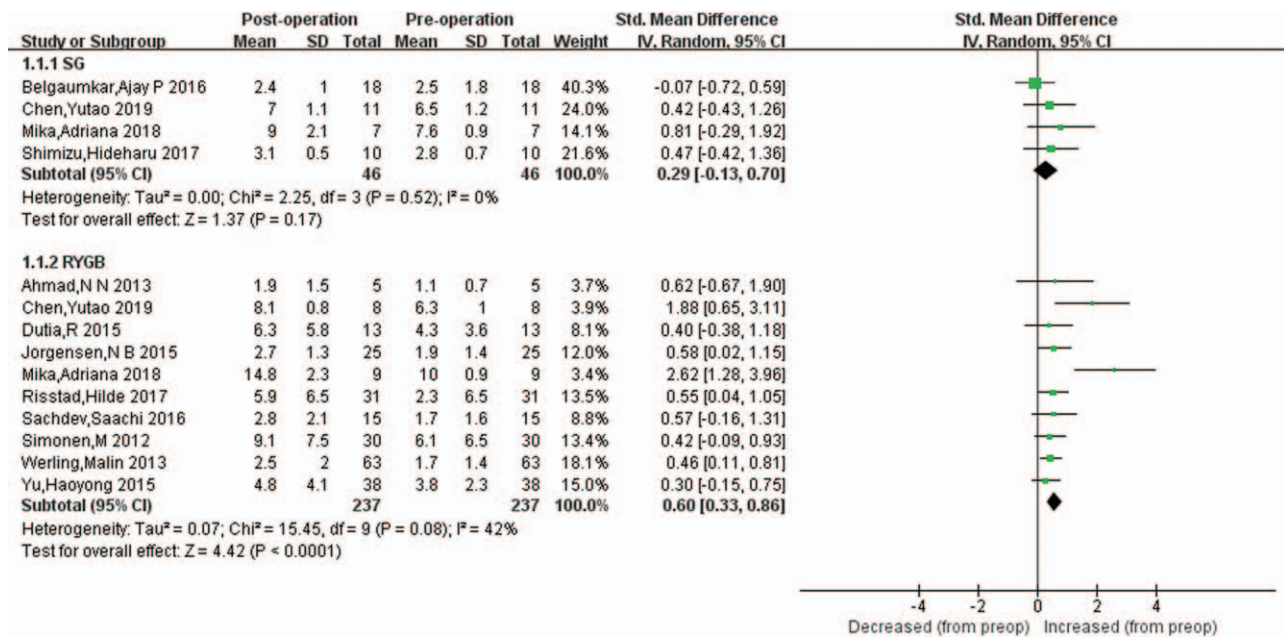


Figure 2. Forest plot of fasting total bile acid levels before and after SG and RYGB.

3.6. Publication bias

Publication bias was analyzed using funnel plots. All 5 funnel plots were relatively symmetric and did not suggest the presence of publication bias (see Figure S2, Supplemental Digital Content, <http://links.lww.com/MD/F467>, which shows the publication bias).

4. Discussion

In our meta-analysis, we found that fasting bile acid levels increased after bariatric surgery, and this increase was associated

with the type of procedure. To the best of our knowledge, this was the first systematic review and meta-analysis to use statistical methods to summarize and analyze clinical trials to detect fasting bile acid changes.

Bile acids are known to play key roles in lipid metabolism. The discovery that bile acids activate FXR and TGR5 confirmed bile acid as hormones that alter glucose metabolism, inflammation pathways and energy metabolism in different tissues.^[3,4,23] Furthermore, emerging evidence indicates that circulating bile acids may play an important role in glucose metabolism and weight loss following bariatric surgery.^[8,10,24] On the basis of the

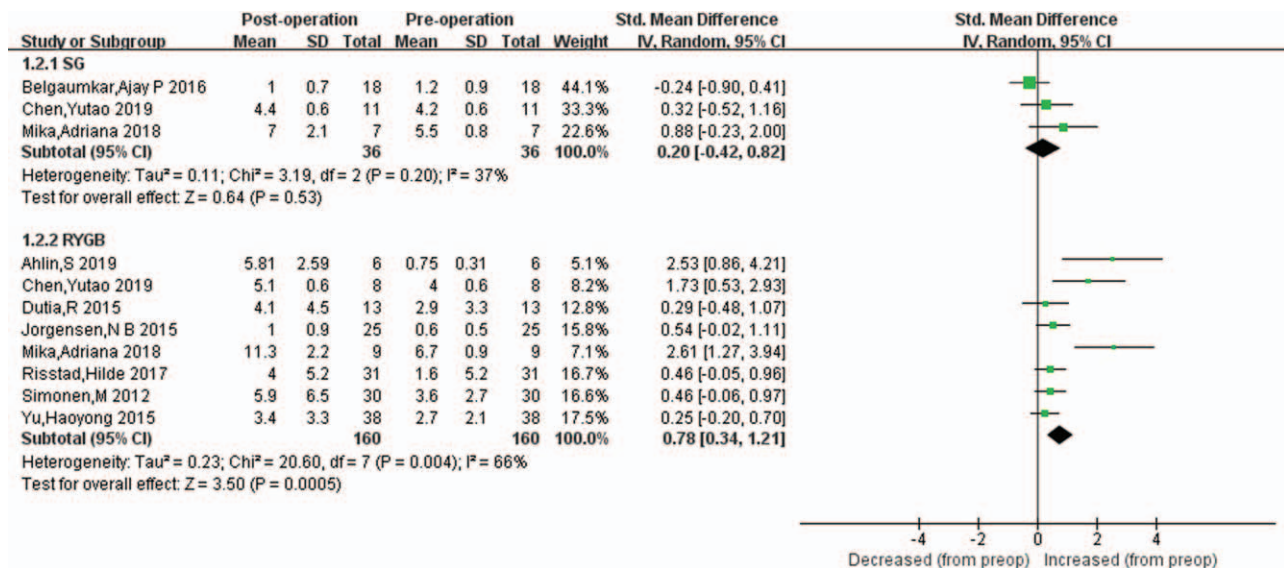


Figure 3. Forest plot of fasting primary bile acid levels before and after SG and RYGB.

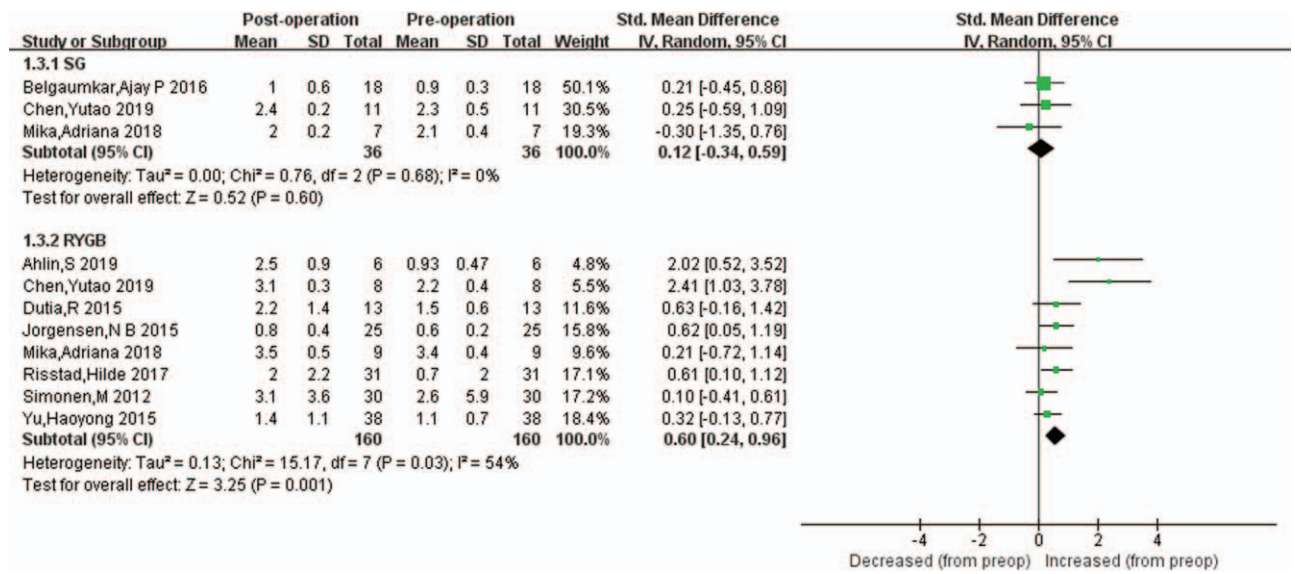


Figure 4. Forest plot of fasting secondary bile acid levels before and after SG and RYGB.

data reported in published articles,^[16,19,25–27] researchers calculated that circulating bile acid concentrations were inversely correlated with homeostatic model assessment for insulin resistance (HOMA-IR) scores and insulin concentrations in groups of patients before and after RYGB.^[28] This confirms, at least in part, that elevated circulating concentrations of bile acids contribute to improved glucose metabolism in patients who have undergone bariatric surgery.

The results of this meta-analysis support that the levels of fasting bile acids increase after RYGB but not SG. Although the underlying mechanisms for the different alterations in bile acid levels following RYGB and SG are not fully clear, based on several studies, the bile loop and intestinal microbiota may play

key roles in that process. First, a previous study found that bariatric procedures involving the transport of concentrated bile by a section of the small intestine (bile loop) excluded from the food passage led to the increased absorption of bile acids by ileocytes and subsequent increases in bile acid blood concentrations.^[29] One difference between the 2 bariatric procedures analyzed in this study is the existence of a bile loop, which is formed during RYGB but not during SG. The different effects of bariatric surgery on bile acids may be directly related to the length of the bile loop. This hypothesis seems to be supported by a significant positive correlation between bile loop length and serum concentrations of bile acids at 3 months after RYGB^[30]; moreover, the increase in total serum bile acids was greater in

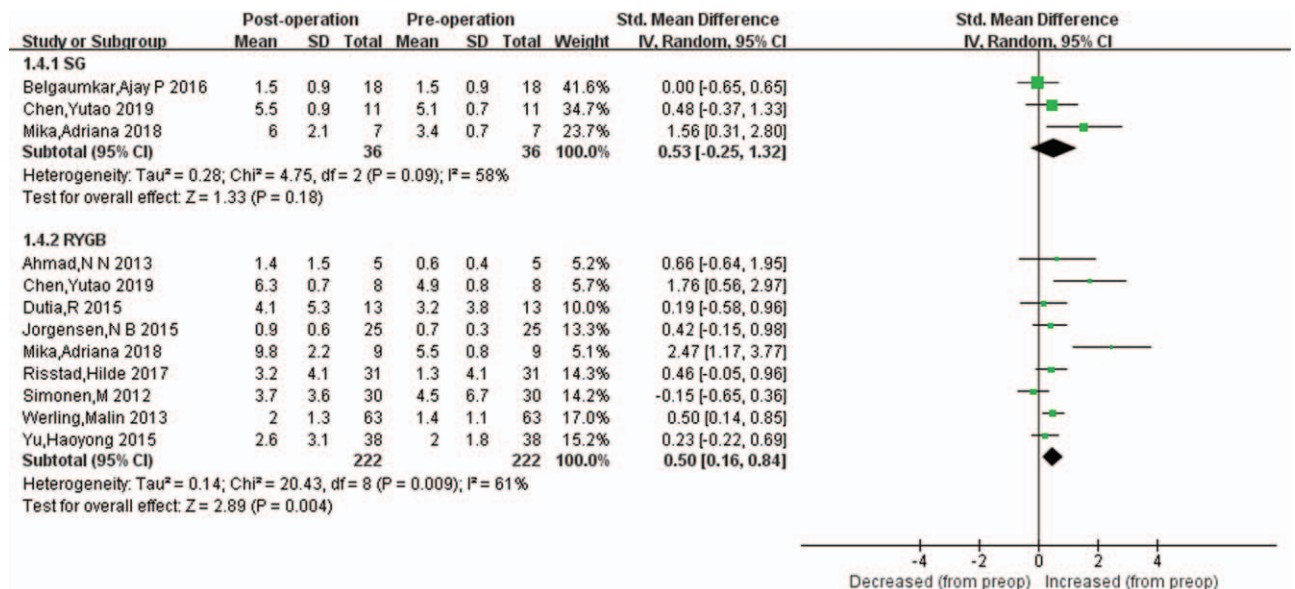


Figure 5. Forest plot of fasting conjugated bile acid levels before and after SG and RYGB.

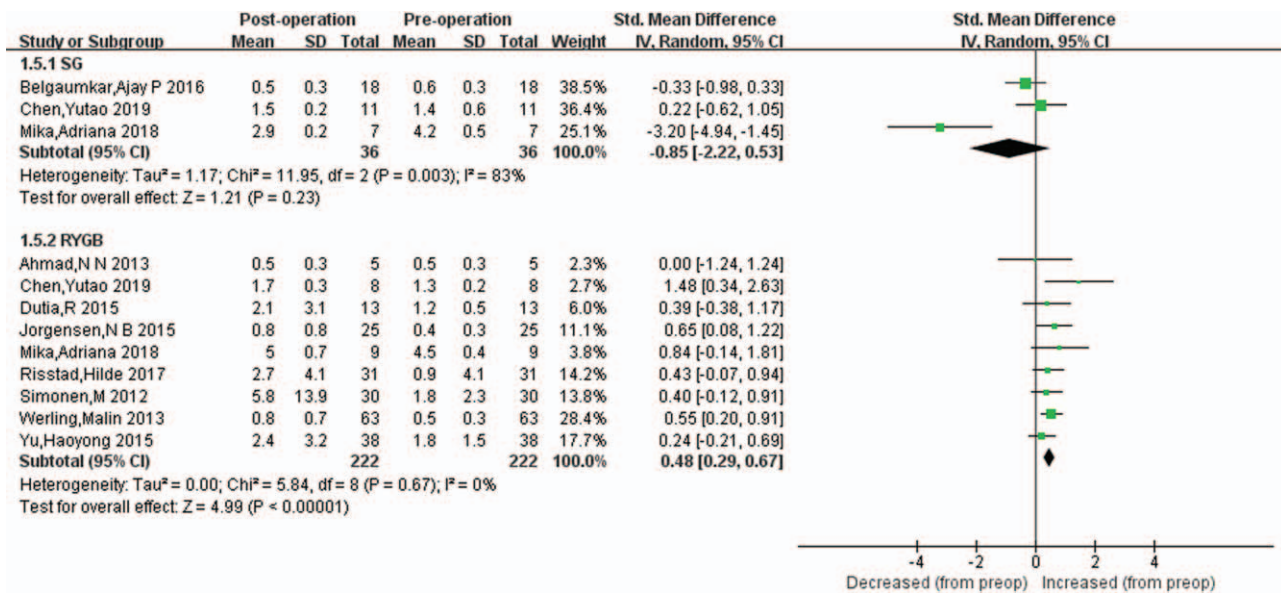


Figure 6. Forest plot of fasting unconjugated bile acid levels before and after SG and RYGB.

patients subjected to biliopancreatic diversion with duodenal switch (BPD/DS) than in those subjected to RYGB^[14] (BPD/DS results in a longer concentrated bile passage than RYGB). Second, the intestinal microbiota is involved in the biotransformation of bile acids.^[31] As a result of their antimicrobial activity, bile acids can affect the abundance and composition of the gut microbiota.^[31,32] An association between increased circulating bile acid concentrations and changes in gut microbial composition has been reported.^[5] This means that bile acids and the gut microbiota are closely integrated and affect each other—bile affects the growth and colonization of bacteria in the intestine, while bacteria contribute to the biotransformation of bile acid. Taken together, these results imply that the gut microbiota plays a role in regulating bile acids. Patients who undergo RYGB and SG have significantly different gut microbiota profiles due to different operation characteristics.^[33,34]

Our results show that 6 different fractions of bile acids (CDCA, GCDCA, TCDCA, CA, DCA, and GDCA) are significantly increased after RYGB. The different chemical properties of bile acids alter their biological functions. CDCA and its conjugated derivatives are the predominant stimulators of the FXR,^[35] and DCA is a partial antagonist of FXR activation.^[36] Fibroblast growth factor 19 (FGF19) secretion is stimulated by bile acids binding to the FXR on mucosal cells of the terminal ileum. The positive metabolic effects of FGF19 include decreased gluconeogenesis and adiposity and increased glycogen and protein synthesis.^[37,38] The other main finding of our work is the increase in 12- α hydroxylated bile acid (CA, DCA, and GDCA) concentrations and the 12- α hydroxylated/non-12- α hydroxylated ratio. Haeusler et al^[39] found that insulin resistance correlates with a higher ratio of fasting plasma 12- α hydroxylated bile acids in healthy subjects; however, this increase was not found in T2D subjects. Further studies are needed to identify whether the increases in 12- α hydroxylated bile acid concentrations and the 12- α hydroxylated/non-12- α hydroxylated ratio have positive metabolic effects on weight loss and glucose homeostasis improvement following RYGB.

Another issue regarding bile acids after SG is the discrepancy between animal models and human studies. Animal models have confirmed the important role of bile acids and their signal pathways in weight loss and glucose homeostasis improvement after SG.^[5] This meta-analysis demonstrates that fasting bile acid profiles are unchanged after SG. In fact, mice and humans are inherently different in many aspects related to bile acid biology. For example, mice and humans have different bile acid compositions, potentially leading to different physiological effects and interventional outcomes in related studies.^[40] Therefore, whether the mechanisms of bile acid actions identified in mice apply to humans is unclear.

Collectively, the overall analysis suggested that patients with obesity who underwent RYGB had higher levels of bile acids after surgery than those who underwent SG. Moreover, bile acids may influence glucose metabolism and subsequently contribute to the remission of T2D following RYGB when circulating bile acid concentrations are elevated.

4.1. Limitations of our study

Limitations should be considered when interpreting our meta-analysis. First, the total number of included studies was only 13, and only 289 patients had usable data. Second, there were many factors that may have influenced the heterogeneity and the results of this meta-analysis, such as the age range of participants, comorbidities, visit duration, and other factors. Third, our work does not address post-prandial changes in bile acids. Future studies should focus on the causal relationship between long-term post-RYGB weight changes and diabetes remission and bile acid levels to further explore the mechanisms of bile acids after bariatric surgery.

5. Conclusion

The results of this meta-analysis showed that fasting bile acid levels were increased after RYGB, while there were no differences

Table 2**The summary of changes in bile acid profiles.**

Bile acids	Surgery type	Number of studies	Random effects SMD (95% CI)	I ² (%)	P
CA	SG	1	-0.51 [-1.18 to 0.15]	N/A	.13
	RYGB	7	0.74 [0.37 to 1.11]	61	.0001
CDCA	SG	1	-0.35 [-1.01 to 0.31]	N/A	.3
	RYGB	7	0.45 [0.25-0.65]	0	.0001
DCA	SG	1	-0.7 [-1.38 to -0.02]	N/A	.04
	RYGB	7	0.71 [0.42-1.00]	43	.00001
UDCA	SG	1	0.48 [-0.18 to 1.14]	N/A	.16
	RYGB	6	-0.41 [-0.83 to 0.02]	75	.06
LCA	SG	1	0.00 [-0.65 to 0.65]	N/A	1.00
	RYGB	4	-0.17 [-1.13 to 0.79]	90	.73
GCA	SG	1	-0.60 [-1.27 to 0.07]	N/A	.08
	RYGB	7	0.26 [-0.05 to 0.57]	50	.1
TCA	SG	1	-0.44 [-1.10 to 0.22]	N/A	.20
	RYGB	6	0.22 [-0.25 to 0.69]	65	.36
GCDCA	SG	1	-0.01 [-0.67, to0.64]	N/A	.97
	RYGB	6	0.43 [0.21-0.65]	0	.0001
TCDCa	SG	1	-0.31 [-0.97 to 0.35]	N/A	.36
	RYGB	7	0.47 [0.18-0.77]	45	.002
GDCA	SG	1	-0.10 [-0.75 to 0.55]	N/A	.76
	RYGB	7	0.71 [0.45-0.97]	28	.00001
TDCA	SG	1	-0.26 [-0.91 to 0.40]	N/A	.44
	RYGB	7	0.58 [-0.09 to 1.25]	89	.09
GUDCA	SG	1	0.65 [-0.02 to 1.32]	N/A	.06
	RYGB	5	-0.28 [-0.92 to 0.36]	83	.39
TUDCA	SG	N/A	N/A	N/A	N/A
	RYGB	2	-0.50 [-1.47 to 0.47]	87	.31
GLCA	SG	1	0.00 [-0.65 to 0.65]	N/A	1
	RYGB	6	-0.73 [-3.10 to 1.64]	99	.55
TLCA	SG	1	0.00 [-0.65 to 0.65]	N/A	1
	RYGB	5	-0.04 [-0.29 to 0.21]	0	.75
12a-hydroxylated	SG	1	1.78 [0.77-2.80]	N/A	.0006
	RYGB	3	0.72 [0.29-1.14]	0	.0009
Non-12a-hydroxylated	SG	1	0.95 [0.06-1.84]	N/A	.04
	RYGB	2	0.17 [-0.44 to 0.78]	0	.58
12a-hydroxylated/non-12a-hydroxylated ratio	SG	2	-0.59 [-2.16 to 0.98]	87	.46
	RYGB	4	0.47 [0.01-0.92]	32	.04

12a-hydroxylated BAs include CA, GCA, TCA, DCA, GDCA, and TDCA; non-12a-hydroxylated BAs include CDCA, GCDCA, TCDCa, UDCA, GUDCA, TUDCA, LCA, GLCA, and TLCA.

CA = cholic acid, CDCA = chenodeoxycholic acid, DCA = deoxycholic acid, GCA = glycocholic acid, GCDCA = glycochenodeoxycholic acid, GDCA = glycodeoxycholic acid, GLCA = glycolithocholic acid, GUDCA = glyoursodeoxycholic acid, LCA = lithocholic acid, TCA = taurocholic acid, TCDCa = taurochenodeoxycholic acid, TDCA = taurodeoxycholic acid, TLCA = tauroolithocholic, TUDCA = taoursodeoxycholic acid, UDCA = ursodeoxycholic acid.

following SG. The potential mechanism may be the creation of a bile loop and changes in intestinal microbiota after RYGB and SG due to different operation characteristics. Recent evidence suggests that circulating bile acids represent a promising target for the management of metabolic disorders and may also contribute to the metabolic improvement observed after RYGB.

Author contributions

Data curation: Chunlan Zhang.

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Funding acquisition: Jingjing Zhang, Zhiguang Zhou.

Resources: Zhiguang Zhou.

Supervision: Jingjing Zhang, Zhiguang Zhou.

Writing – original draft: Chunlan Zhang.

Writing – review & editing: Jingjing Zhang, Zhiguang Zhou.

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