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ORIGINAL CONTRIBUTIONS

Serum Glucagon, Bile Acids, and FGF-19: Metabolic Behavior Patterns After Roux-en-Y Gastric Bypass and Vertical Sleeve Gastrectomy

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Abstract

Background Metabolic/bariatric surgery is a highly effective treatment for obesity and metabolic diseases. Serum glucagon, bile acids, and FGF-19 are key effectors of various metabolic processes and may play central roles in bariatric surgical outcomes. It is unclear whether these factors behave similarly after Roux-en-Y gastric bypass (RYGB) vs vertical sleeve gastrectomy (VSG).

Methods Serum glucagon, bile acids (cholic acid [CA], chenodeoxycholic acid [CDCA], deoxycholic acid [DCA]), and FGF-19 were analyzed in samples of fasting blood collected before bariatric surgery, on postoperative days 2 and 10, and at 3- and 6-month follow-up.

Results From September 2016 to July 2017, patients with obesity underwent RYGB or VSG; 42 patients (RYGB $n = 21$; VSG $n = 21$) were included in the analysis. In the RYGB group, glucagon, CA, and CDCA increased continuously after surgery ($p = 0.0003$, $p = 0.0009$, $p = 0.0001$, respectively); after an initial decrease ($p = 0.04$), DCA increased significantly ($p = 0.0386$). Serum FGF-19 was unchanged. In the VSG group, glucagon increased on day 2 ($p = 0.0080$), but decreased over the 6-month study course ($p = 0.0025$). Primary BAs (CA and CDCA) decreased immediately after surgery ($p = 0.0016$, $p = 0.0091$) and then rose ($p = 0.0350$, $p = 0.0350$); DCA followed the curve of the primary BAs until it fell off at 6 months ($p = 0.0005$). VSG group serum FGF-19 trended upward.

Conclusion RYGB and VSG involve different surgical techniques and final anatomical configurations. Between postoperative day 2 and 6-month follow-up, RYGB and VSG resulted in divergent patterns of change in serum glucagon, bile acids, and FGF-19.

Keywords Obesity · Bariatric surgery · Metabolic surgery · Diabetes · Weight loss · RYGB, VSG

Key Points

1. In the RYGB group: Glucagon and the primary bile acids CA and CDCA increased continuously after surgery, while the secondary bile acid DCA decreased initially and later significantly increased.

2. In the VSG group: Glucagon increased initially but later decreased. The primary bile acids CA and CDCA, as well as DCA, decreased immediately and showed no significant change thereafter.

3. RYGB and VSG resulted in divergent patterns of change in serum glucagon, bile acids, and FGF-19. The different alterations in bile acid levels following RYGB and VSG have been confirmed by a recent meta-analysis.

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Introduction

Metabolic/bariatric surgery has been proven to be the most effective and durable therapy for obesity [1]: surgical treatment can achieve permanent weight loss and thus sustained improvement in comorbidities [2, 3]. For example, the metabolic improvement regarding glucose homeostasis and insulin sensitivity can be observed within days after surgery, before substantial weight loss occurs [4, 5].

Hormonal or other metabolic mediators are likely responsible for these early effects. The "hindgut theory" postulates that the rapid transit of nutrients to the distal intestine causes intense stimulation of intestinal L-cells and GLP-1 secretion [6, 7]. Previous studies have described a marked increase in postprandial GLP-1 levels immediately following RYGB that is sustained [8–10] and that coincides with a significant

increase in bile acids (BAs) [11]. Bile acids are synthesized primarily in the liver through the classic and alternate pathways. The classic pathway is responsible for 75% of BA pool size and is regulated by the rate-limiting enzyme, cholesterol 7α-hydroxylase (CYP7A1) [12, 13]. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the most abundant primary BAs and are secreted into the gastrointestinal tract for digestion and absorption of dietary fats. The majority of the BAs are reabsorbed by the enterohepatic circulation in the distal intestine [14]. BAs that escape the enterohepatic circulation are transformed into secondary BAs (e.g., CA is converted to deoxycholic acid [DCA] by gut bacteria) [15]. Fibroblast growth factor 19 (FGF-19) inhibits the expression of CYP7A1 in hepatocytes and, thus, in BA synthesis. In addition, the nuclear BA receptor FXR regulates the expression of FGF-19 in the ileum [16]. Increased levels of BA after RYGB have been shown to affect FGF-19 concentrations, reduce insulin resistance, initiate better glucose metabolism control, and influence weight loss [17].

Another key hormone suspected to be affected by RYGB is glucagon, since hyperglucagonemia is etiologically related to hyperglycemia in patients with diabetes [18, 19]. However, the findings reported in the literature on postoperative glucagon changes are inconsistent, depending on the assays used [20–22].

Results for RYGB and VSG weight loss, comorbidity resolution, and metabolic improvement are comparable and cannot be explained by restriction alone after surgery. In rodents, after VSG, changes have been detected in circulating BA concentrations [23–25]. Also in VSG, another important mechanism seems to be modulation of the abundance and composition of gut microbial communities, with direct or indirect interaction with BAs [26]. Almost all rodent studies unanimously describe an increase of total BAs following VSG that is congruent with the results after RYGB [27, 28]. The limited data in humans remain highly contradictory and often show no significant changes in BA concentrations after VSG [29–33].

Most studies have confirmed that BA concentrations are increased following RYGB, while the effect of VSG on bile acids was inconsistent: Some studies showed a similar tendency [30, 33], while others detected no change [31, 34]. At 6-month follow-up after both RYGB [35, 36] and VSG [37], FGF-19 levels have been reported to increase.

To gain deeper insight into the roles of glucagon, BAs, and FGF-19 in obesity, this study aimed to evaluate their postoperative course in serum after RYGB and VSG.

Methods

Study Design

The study was designed as a prospective, single-center analysis comparing the effects of two bariatric procedures (RYGB, VSG) on the modulation of molecules centrally involved in weight and metabolism. The study was approved by the university faculty ethics committee and institutional review board (#EK 416092015) and was conducted at a university hospital.

Inclusion

Participants were patients with poorly managed obesity (body mass index [BMI] $\geq$ 35 kg/m^2 with one or more comorbidities [e.g., diabetes, arterial hypertension, sleep apnea] or BMI $\geq$ 40 kg/m^2) who presented for bariatric surgery in the outpatient clinic. Patients were completely informed about the procedure options and the study and engaged in discussion with the surgeon.

Generally, RYGB was recommended if gastroesophageal reflux disease (GERD) was diagnosed previously. VSG was recommended particularly to patients with a BMI > 50 kg/m^2 or young female patients who desired to have children in the future. After consultation with the surgeon and depending on the patients' wishes, RYGB or VSG was elected. Participation for all patients was predicated on their written informed consent.

Surgical Technique

The RYGB technique included a small gastric pouch of 30 ml with a 30-mm pouch-jejunostomy. A 150-cm antecolic Roux limb and an exclusion of 60 cm of the biliopancreatic limb were measured. The VSG procedure was performed along the length of a 42-F bougie from the angle of His to approximately 4–5 cm from the pylorus.

Fasting blood samples were collected before surgery, on days 2 and 10 after the surgery, as well as at 3 to 6 months postoperatively. Perioperative care was the same for all patients in the study regardless of operative group.

Assays

Serum glucagon, BAs, and FGF-19 were assayed. In the normal course of our center's bariatric surgery workup, we do not measure BA concentrations; BA measurements taken were especially performed for this prospective study. Every blood sample was frozen and later underwent enzyme-linked immunosorbent assay (ELISA) and chromatography for this trial.

Glucagon levels were assayed using the Quantikine Glucagon Immunoassay (R&D Systems Europe Ltd, Abingdon, UK). CA, DCA, and CDCA were analyzed using high-performance liquid chromatography (JASCO, Portland, OR, USA) and tandem mass spectrometry

(Applied Biosystems, Cheshire, UK). An ELISA Quantikine Human FGF-19 Immunoassay (R&D Systems Europe Ltd, Abingdon, UK) was used to assess FGF-19.

Statistical Analysis

All statistical calculations were performed with the SAS statistical program, release 9.4 (SAS Institute Inc., Cary, NC, USA). For quantitative variables, mean and standard deviations were assessed. For qualitative factors, absolute and relative frequencies were given. For comparing the two treatment groups regarding baseline values, Fisher's exact test or the two-sample t test was applied, as appropriate. In order to investigate if there are changes over time regarding glucagon, BAs, and FGF-19, a Friedman rank sum test was performed. In the case of a significant test result, pairwise comparisons were performed using Wilcoxon tests for paired samples. In general, the result of a statistical test was considered statistically significant for a p value < 0.05.

Results

The study was conducted at our university hospital between September 2016 and July 2017. All operations were performed laparoscopically by two of the co-authors (MO, GV).

Demographics

Patients who presented for bariatric surgery who wished to participate in the study were included. Fifty-seven patients were enrolled, with an average age of 40 years old. Postoperatively, 15 patients were excluded for incomplete blood tests or test failures. The final analysis included 21 patients who underwent RYGB and 21 patients, VSG.

Baseline characteristics are shown in Table 1. Average preoperative weight and BMI were lower in the RYGB group (124.1 ± 16.0 kg; 46.4 ± 4.7 kg/m^2) than in the VSG group (160.0 ± 26.0 kg; 56.3 ± 7.7 kg/m^2). Diabetes mellitus, dyslipidemia, and their treatments did not differ between groups. The weight loss was more pronounced in the RYGB group ($p = 0.014$). However, no correlation was found between the bile acids and weight loss. Serious complication ($>$ grade 2 in the Clavien-Dindo classification) did not occur in all patients.

Glucagon

In the RYGB group, glucagon increased continuously and significantly after surgery: Median increasing percentages were 73% ($p < 0.0001$), 98% ($p = 0.0004$), and 60% (p

Table 1. Baseline patient characteristics

	RYGB	VSG	P value
Number of patients	21	21	
Female (%)	20 (95)	17 (81)	p = 0.3433
Age (years)	43.2 ± 11.4	41.7 ± 12.1	$p = 0.6763$
Weight (kg)	124.1 ± 16.0	160.0 ± 26.1	$p < 0.0001$
Preoperative BMI (kg/m^2)	46.4 ± 4.7	56.3 ± 7.7	$p < 0.0001$
%EWL	54	45	$p = 0.014$
Diabetes mellitus (%)	7 (33)	4 (19)	$p = 0.484$
GLP-1 analogues (%)	1 (5)	0 (0)	$p = 1$
Metformin (%)	6 (28)	1 (5)	$p = 0.093$
Gliptins (%)	1 (5)	0 (0)	$p = 1$
Dyslipidemia (%)	5 (24)	6 (28)	$p = 1$
Statin (%)	1 (5)	1 (5)	$p = 1$
PCSK9 inhibitor (%)	0 (0)	0 (0)	$p = 1$

RYGB Roux-en-Y gastric bypass, *VSG* vertical sleeve gastrectomy, *BMI* body mass index, *%EWL* percent of excess weight loss, *GLP-1* glucagon-like peptide-1, *PCSK9* proprotein convertase subtilisin/kexin type 9. All values are shown as means.

$= 0.0003$) after 2 days, 10 days, and 6 months relative to preoperative values (Fig. 1). In the VSG group, glucagon increased by 52% from preoperative status by the second day after surgery ($p = 0.0080$). However, at 6 months, glucagon had decreased by 47% compared to the second postoperative day ($p = 0.0025$).

Bile Acids

CA

After RYGB, serum CA increased continuously (Table 2). The difference became significant between 3 and 6 months (4.3-fold compared to preoperative values, $p = 0.0132$, and 2-fold compared to postoperative day 2, $p = 0.0009$). In the VSG group, CA decreased by 54% shortly after surgery ($p = 0.0016$ on day 2) and increased by 49% between day 2 and day 10 ($p = 0.0350$) (Fig. 2).

DCA

In both groups, the level of serum DCA dropped until the day 2 ($p = 0.0400$ RYGB, $p = 0.0005$ VSG) and rose again afterwards (Table 2). The difference became significant after 6 months in the RYGB group ($p = 0.0009$, $p < 0.0001$, and $p = 0.0386$ compared to preoperative values and those on day 2 and 10, respectively). In the VSG group, DCA increased significantly from day 2 to day 10 ($p = 0.0001$) and then decreased through the 6-month study course ($p = 0.0005$, compared to day 2) (Fig. 3).

Fig. 1. Serum glucagon in Roux-en-Y gastric bypass (RYGB) group and in vertical sleeve gastrectomy (VSG) group. Pre = preoperatively, 2D post = 2 days postoperatively, 10D post = 10 days postoperatively, 3–6 Mon post = 3–6 months postoperatively. Significant p values between time points are indicated
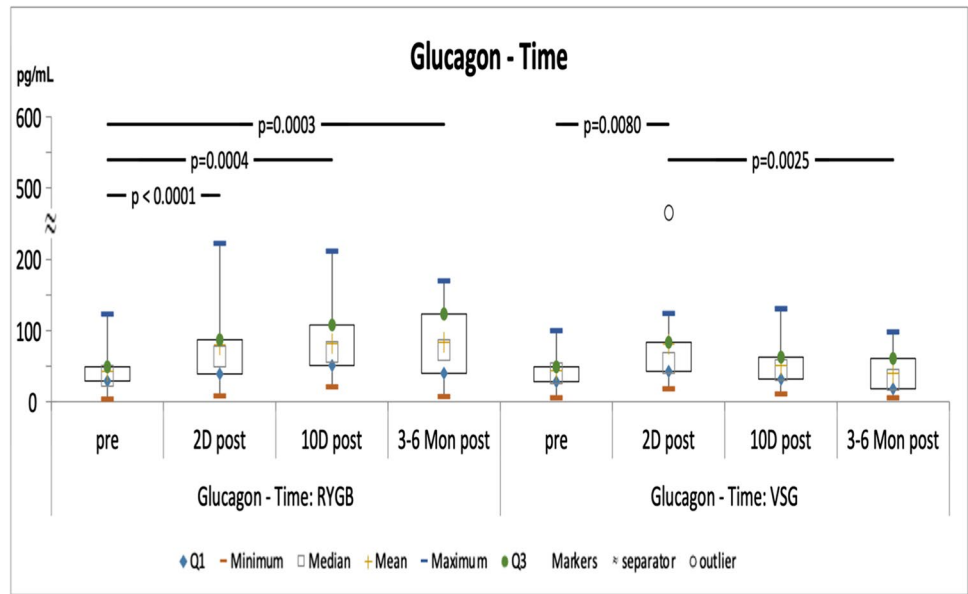
CDCA

A continuous increase of CDCA levels was observed in the RYGB group, reaching its peak after 6 months (Table 2). This was a 4.3-fold increase relative to preoperative CDCA levels ($p =0 .0030$), a 2.8-fold increase compared to day 2 ($p = 0.0001$), and a 1.2-fold increase compared to day 10 ($p = 0.0317$). In the VSG group, the CDCA level dropped immediately after surgery ($p = 0.0091$) and then rose until it reached its original level at 6 months ($p = 0.0425$ on day 10, and $p = 0.0350$ at 6 months compared to day 2) (Fig. 4).

FGF-19

In RYGB and VSG group, the serum level of FGF 19 stayed unchanged after the surgeries ($p = 0.5936$ and $p = 0.6652$ using Friedman test, respectively).

Discussion

As the metabolic effects of BAs have been increasingly recognized, a number of clinical studies have investigated their changes after bariatric surgery to identify the causal connection between BAs and metabolic improvements [38]. Most published studies show that fasting total BA concentrations increased following RYGB [11, 30, 33, 35, 39]. However, only a few studies differentiated individual BAs and their postoperative course, as was done in the current study. Also, early changes in BAs have not been observed since most studies did not begin to track postoperative changes until 1 month after surgery, even though metabolic improvements can be observed within days after surgery. For this reason, the current study was designed to detect longitudinal changes in primary and secondary BAs from as early as 2 days after bariatric surgery.

After RYGB, both primary BAs (CA and CDCA) increased continuously and reached their highest levels at

Table 2. Medians of variables at different time points

Time	RYGB				VSG			
	Pre	2D post	10D post	3–6 Mon post	Pre	2D post	10D post	3–6 Mon post
Glucagon, pg/mL	35.90	63.40	69.47	72.48	39.61	54.44	44.25	30.54
CA, nmol/L	25.37	45.23	56.92	116.61	52.93	36.62	59.92	65.64
DCA, nmol/L	138.50	45.73	210.12	418.56	458.74	74.11	327.98	194.53
CDCA, nmol/L	51.45	81.90	162.15	402.46	256.00	60.29	152.07	252.25
FGF-19, pg/mL	110.76	115.83	137.50	161.66	131.10	129.02	175.08	160.70

RYGB Roux-en-Y gastric bypass, *VSG* vertical sleeve gastrectomy, *CA* cholic acid, *DCA* deoxycholic acid, *CDCA* chenodeoxycholic acid, *FGF-19* fibroblast growth factor 19, *pre* preoperatively, *2D post* 2 days postoperatively, *10D post* 10 days postoperatively, *3–6 Mon post* 3–6 months postoperatively.

Fig. 2. Serum cholic acid (CA) in Roux-en-Y gastric bypass (RYGB) group and in vertical sleeve gastrectomy (VSG) group. Pre = preoperatively, 2D post = 2 days postoperatively, 10D post = 10 days postoperatively, 3–6 Mon post = 3–6 months postoperatively. Significant p values between time points are indicated
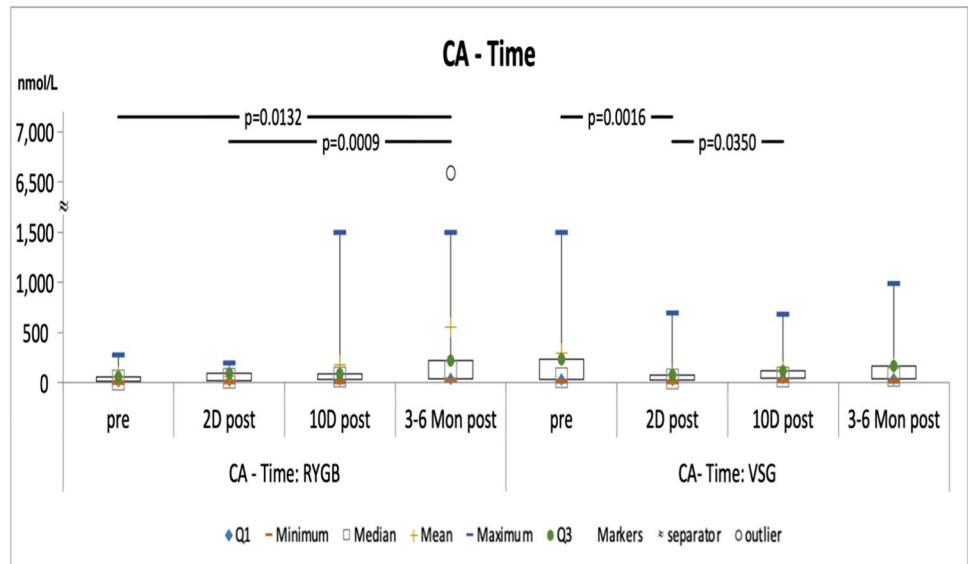
the last points of examination (3–6 months after surgery). The secondary BA (DCA) decreased initially but showed a significant increase after 3–6 months. This observation is in line with findings in the existing literature [11, 17, 30, 35, 36, 39]. After RYGB, the rapid delivery of nutrients to the distal intestine causes stimulation of intestinal L-cells and GLP-1 secretion [6, 20]. Prior studies describe a large increase in postprandial GLP-1 immediately after RYGB that is sustained in the long term [8, 9]. This GLP-1 rise coincided with a significant increase of BAs in the current study.

In comparison, postoperative BA changes in the VSG cohort were less pronounced and did not mirror BA behavior after RYGB. Shortly after VSG, BAs decreased significantly. However, no significant changes were detected after 10 days or at 3–6 months. These findings are consistent with most previous findings [31–34, 40]. VSG accelerates intestinal motility, enabling the transportation of a greater amount of primary BA to the distal ileum and the large intestine [41, 42]. Following the elevated resorption of primary BAs and, thus, reduction of BAs entering the large intestine, it was not surprising

Fig. 3. Serum deoxycholic acid (DCA) in Roux-en-Y gastric bypass (RYGB) group and in vertical sleeve gastrectomy (VSG) group. Pre = preoperatively, 2D post = 2 days postoperatively, 10D post = 10 days postoperatively, 3–6 Mon post = 3–6 months postoperatively. Significant p values between time points are indicated
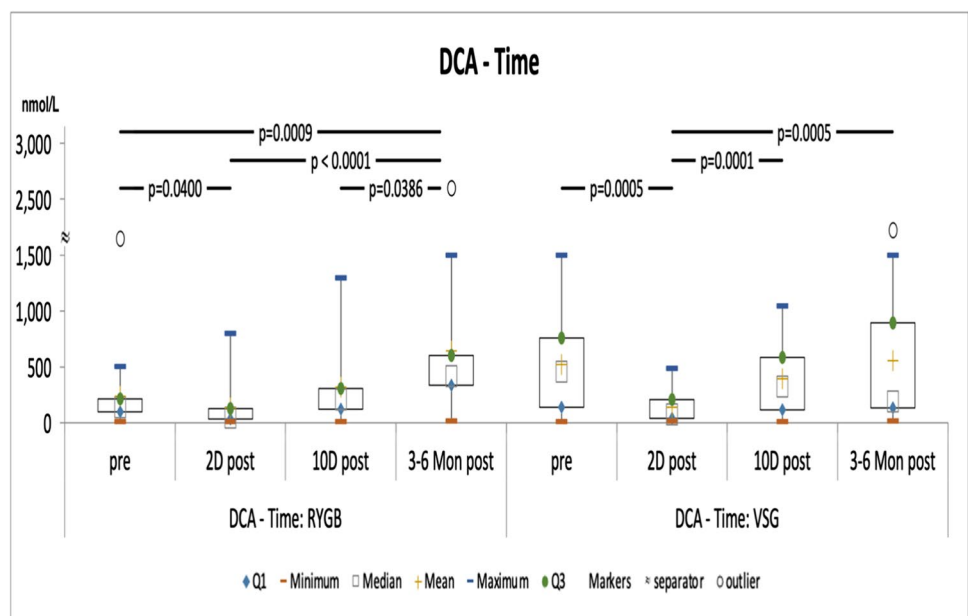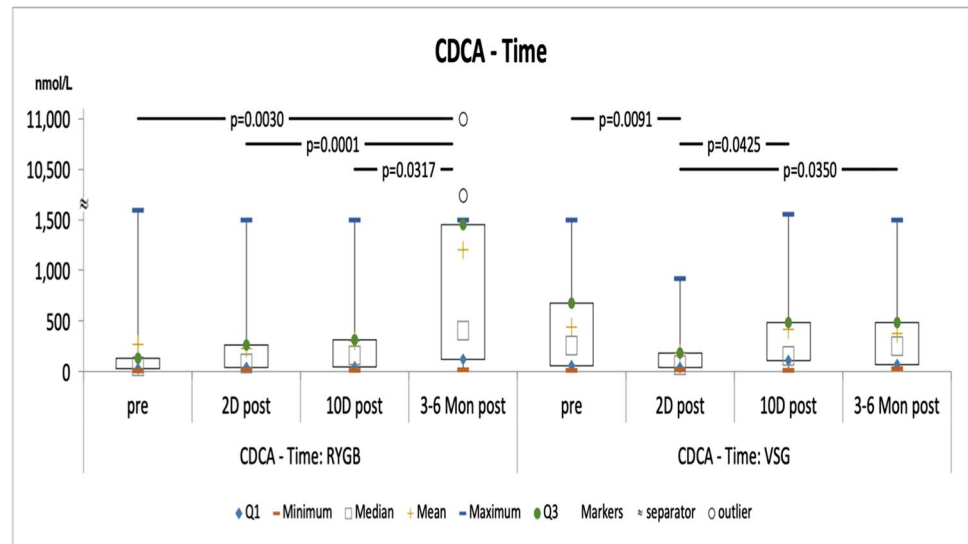
Fig. 4. Serum chenodeoxy-cholic acid (CDCA) in Roux-en-Y gastric bypass (RYGB) group and in vertical sleeve gastrectomy (VSG) group. Pre = preoperatively, 2D post = 2 days postoperatively, 10D post = 10 days postoperatively, 3–6 Mon post = 3–6 months postoperatively. Significant *p* values between time points are indicated

that DCA dropped immediately after surgery. Similarly, in rodents following VSG, increased primary BAs were seen in the jejunum and decreased secondary BAs in the ileum [23]. The different alterations in bile acid levels following RYGB and VSG were confirmed by a recent meta-analysis, in which the existence of a bile loop and different gut microbiota profiles were considered to be potential causes of the divergent effects of the bariatric procedures [43].

To date, very few publications have addressed the behavior of glucagon after bariatric surgical proce-dures. In our study, fasting glucagon levels continuously increased following RYGB at every point of measurement (2 days, 10 days, and 6 months) compared to preopera-tive concentrations. These findings have been reported rarely in the prior literature, for example, by Holst et al., as a paradoxical behavior of glucagon in hyperglycemia and an exaggerated GLP-1 response after RYGB [44]. It seems that glucagon concentrations after surgery do not follow the expected pattern of inhibition by GLP-1 and hyperglycemia. Alexiadou et al. described the dif-ferent effects on glucagon after RYGB in 19 patients, measuring fasting and postprandial concentrations after a mixed meal. In their study, fasting glucagon showed a significant decrease, but non-fasting glucagon was not altered [18]. Our study showed a similar pattern of fast-ing glucagon levels in VSG patients. These changes were also noted by Yang et al. [45] and might explain the sig-nificant improvement in glucose homeostasis in the early VSG postoperative stage.

Throughout the first months after surgery, hepatic bile acid production and enterohepatic circulation increased. These changes were commensurate with increased FGF-19 and GLP-1 production and improved hepatic insulin

sensitivity [38]. Based on the current known mechanisms controlling BA homeostasis, the observed increases in circu-lating BAs following bariatric procedures should negatively regulate synthetic mechanisms through direct (FXR tran-scriptional control) and/or indirect BA mediation (FGF-19) [15, 46, 47]. In our study, as in some previous studies, fast-ing levels of FGF-19 did not increase after RYGB. Neither was a significant decrease detected.

On the other hand, the VSG group showed a weak trend toward increasing levels of fasting FGF-19, although it did not reach statistical significance. This tendency is confirmed by the findings of Escalona et al. [31] and Haluzíková et al. [37], who also described increased FGF-19 after VSG, find-ing that reduction of BA synthesis may be partially second-ary to the inhibitory effect of FGF-19.

Limitations

Fasting blood samples were collected; however, the period of fasting time was not controlled. Owing to different indica-tions for both procedures, the BMI of the RYGB group was lower than the VSG group. Overall, there are more female than male participants in our study. To minimize the bias, patients indicated for bariatric surgery should be randomized into RYGB or VSG groups in further trials.

Conclusions

RYGB and VSG involve different surgical approaches and final anatomical configurations. Between postoperative day 2 and 6-month follow-up, RYGB and VSG resulted in diver-gent patterns of change in serum glucagon, bile acids, and FGF-19.

Declarations

Ethics Approval All procedures of the study are ethically compliant and were approved (EK 416092015) by the Institutional Review Board of University Medicine Mannheim, Germany. The study was performed in accord with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Consent to Participate Written informed consent was obtained from all study participants.

Conflict of Interest The authors declare that they have no conflicts of interest or financial ties to disclose. JN Buchwald received a small grant for manuscript development.

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