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ORIGINAL CONTRIBUTIONS

Acute Changes of Bile Acids and FGF19 After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass

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Abstract

Context Gastric bypass (GBP) and sleeve gastrectomy (SG) are both effective bariatric treatments that cause sustained weight loss as well as improvement of type 2 diabetes mellitus (T2DM). The underlying mechanisms are under investigation, including the contribution of alterations in bile acids (BAs) in achieving or maintaining the beneficial metabolic effects after bariatric surgery.

Aims The aim of this study is to investigate the acute and short-term effects of GBP and SG on BA compositions and fibroblast growth factor 19 (FGF19) in obese individuals with T2DM and to evaluate any correlations between changes in these measures with glucose metabolic improvements.

Methods The levels of both fasting and postprandial plasma BA compositions after oral glucose tolerance test (OGTT), fasting FGF19 and various metabolic indices were measured 1 day before and at 3 days and 3 months after GBP and SG in 19 obese patients (GBP = 8, SG = 11) with T2DM.

Results Body weight loss was observed after both GBP and SG 3 months post-operatively, with no significant difference between the two intervention groups (15.0 ± 3.1% vs. 13.9 ± 5.2%, $P = 0.761$).

At 3 days post-operation, FGF19 levels increased significantly in both surgery groups (GBP, 118.3 ± 57.3 vs. 363.6 ± 131.0 pg mL^{-1}, post-operation $P = 0.008$; SG, 173.2 ± 127.8 vs. 422.0 ± 243.6 pg mL^{-1}, post-operation $P = 0.001$). Fasting and postprandial increases from pre-operative values in secondary ($r = 0.57$, $P = 0.02$; r = 0.58, $P = 0.01$), conjugated ($r = 0.50$, $P = 0.01$; $r = 0.48$, $P = 0.04$), glycine-conjugated ($r = 0.52$, $P = 0.05$; $r = 0.46$, $P = 0.05$) and secondary-conjugated ($r = 0.53$, $P = 0.02$; $r = 0.60$, $P = 0.01$) BAs correlated with decreases in the postprandial states of glucose (defined by area under the curve (AUC) over 120 min ($AUC_{0\text{-}120min}$)). Increases in postprandial primary-conjugated BAs were found to be associated with decreases in HOMA-IR ($r = 0.45$, $P = 0.05$). However, increases in fasting and postprandial taurine-conjugated BA correlated with decreases in both basal insulin secretion rate ($r = 0.47$, $P = 0.04$; $r = 0.48$, $P = 0.04$) and C-peptide level ($r = 0.45$, $P = 0.05$; $r = 0.47$, $P = 0.04$).

After 3 months, fasting and postprandial increases in secondary ($r = 0.51$, $P = 0.03$; $r = 0.48$, $P = 0.04$), secondary-conjugated ($r = 0.52$, $P = 0.02$; $r = 0.51$, $P = 0.03$) and non-12α-OH ($r = 0.51$, $P = 0.02$; $r = 0.58$, $P = 0.01$) BAs were found to correlate with

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increases in Stumvoll Insulin Sensitivity Index. Increases in both fasting and postprandial 12α-OH BAs were correlated with the decreases in glucose AUC ($r = 0.46$, $P = 0.05$; $r = 0.41$, $P = 0.04$).

Conclusions Both GBP and SG achieve increases in many BA species as early as 3 days post-operation, which are sustained at 3 months post-operation. Rises in secondary BA and conjugated forms are correlated with early improvements in glucose metabolism at 3 days post-operation. These along with 12α-OH BA correlated with improved glucose metabolism at 3 months post-operation, suggesting they may contribute to the observed T2DM remission after bariatric surgery.

Keywords Diabetes · Sleeve gastrectomy · Gastric bypass · Bile acids · FGF19

Introduction

Bariatric surgery is currently the most effective treatment for obesity, and achieves improvement in metabolic comorbidities, such as type 2 diabetes mellitus (T2DM) [1]. While there are a number of distinct types of bariatric surgery that have been developed, the two most popular bariatric procedures are gastric bypass (GBP) and sleeve gastrectomy (SG) [2]. Both operations have been reported to have effectiveness in inducing long-term reduction in body weight, which is thought to associate with the remission of obesity-related T2DM [3, 4]. Interestingly, improvement in glycaemic control often occurs before significant weight loss after intervention [5], indicating that weight loss–independent mechanisms underpinning changes in glucose metabolism might be related to a direct effect of bariatric surgery. Alterations in bile acid (BA) composition and flow by bariatric treatment may, at least in part, explain the early remission of T2DM observed, prior to significant weight loss [6, 7].

BAs serve as signalling molecules that modulate numerous metabolic processes [8]. Secondary BAs are potent agonists of the membrane receptor, Takeda G protein–coupled receptor 5 (TGR5), whereas primary-unconjugated BAs are potent endogenous ligands of farnesoid X receptor (FXR) [9]. Activation of TGR5 by BAs can subsequently activate cAMP signalling in many cells, which plays a critical role in maintaining lipid, glucose and energy homeostasis [10, 11]. On the other hand, BAs released into the intestine after a meal bind to and activate FXR and stimulate the synthesis of fibroblast growth factor 19 (FGF19) [12]. FGF19 is shown to act as an endocrine hormone to repress cholesterol 7α-hydroxylase (CYP7A1) gene transcription and thereby down-regulate the synthesis and secretion of Bas and improve the metabolic rate by lowering serum glucose, hepatic triglyceride and cholesterol levels [12]. Gerhard et al. reported higher increases in serum BA and FGF19 concentrations from pre- to post-surgery in those T2DM patients who went into remission compared with those without diabetes and those who did not show remission after Roux-en-Y gastric bypass (RYGB), implicating the FGF19–CYP7A1–BA pathway in the remission of T2DM following bariatric surgery [6]. However, the timing of the changes in BAs and FGF19 corresponding with the resolution of T2DM has not been fully elucidated. Whether changes of FGF19 levels correlate with any metabolic improvements after the operations are also unclear.

Several studies have reported that fasting and postprandial circulating BA levels are increased after GBP or SG in cohorts without T2DM or with mixed T2DM status at the time points of 1 month [13], 1 year [14] and 2–4 years [15]. Only one study has reported on changes in BA and FGF19 as early as 4 days after GBP and after gastric banding in patients without T2DM, demonstrating that fasting total BAs only increase significantly at 42 days after GBP, but were not significantly increased after 4 days [16]. However, fasting FGF19 was significantly increased as early as 4 days after GBP and was sustained at 6 weeks post-operatively [16]. Additionally, there is some evidence that FGF19 levels increase at 1 year following RYGB [6, 17] as well as at 1 month and 6 months after SG [18]. In general, a number of studies show a general increase in BAs long-term after GBP or SG, but few studies have focused on the acute effects of both these operations on both fasting and postprandial rises in BAs among patients with pre-operative T2DM and investigate how these increments relate to early improvements in glucose metabolism, prior to significant weight loss.

The objective of this study was to investigate the acute effect of GBP and SG on circulating BA levels and the BA composition in the fasting and postprandial states, and to assess the fasting FGF19 levels measured at 3 days and 3 months (when routine clinical blood samples were drawn), relative to pre-operative values, in obese individuals with T2DM. We also investigated relationships between both BAs and FGF19 with body weight, and oral glucose tolerance–derived measures of glucose metabolism in this cohort.

Materials and Methods

Patients

Patients with T2DM scheduled for either GBP ($n = 8$) or SG ($n = 11$) in three different hospitals in the Auckland region (Auckland City Hospital, North Shore Hospital and

Middlemore Hospital) between August 2010 and March 2012 were recruited for the study. Patients with T2DM, between 25 and 55 years of age, were eligible for surgery if BMI was at least 35 kg/m^2. Patients receiving insulin therapy, incretin hormone–based therapy, or diet-controlled T2DM were excluded. All subjects consented to a 75-g oral glucose tolerance test (OGTT) 1 day before, and 3 days and 3 months after surgery. Plasma samples were collected from cannulated antecubital veins during fasting and at 30, 60, 90 and 120 min after the oral glucose load. Samples were immediately centrifuged at 4 °C, and subsequently stored as aliquots at − 80 °C until analysis. All procedures performed consistent with the ethical standards of the New Zealand Health and Disability Ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consents were obtained from all individuals who participated in the study.

Surgical Protocol

All subjects scheduled for either GBP or SG were prescribed a hypocaloric diet with three servings of Optifast® (152 cals) plus vegetables daily for 3 weeks before surgery. Surgery was conducted after an 8-h overnight fast. Eight patients underwent GBP with a 100-cm antecolic Roux limb with hand-sewn pouch jejunostomy, or a 60-cm biliopancreatic limb with a hand-sewn small bowel anastomosis. Eleven patients underwent SG, involving a longitudinal resection of the stomach against a 32-French bougie from just lateral to the angle of His to 2 cm proximal to the pylorus. After surgery, patients were administered PlasmaLyte® intravenous fluids 1 L every 24 h, until oral fluid intake began at approximately 48 h post-surgery. All patients were off glucose-lowering medications after the interventions.

Biochemical Analysis

Samples from fasting and all postprandial time points were used to measure BAs, glucose, insulin and C-peptide levels. Area under the curve (AUC) analyses of the indices over 120 min ($AUC_{0\text{-}120min}$) are the basis of the study's data collections. Plasma FGF19 levels were only measured in the fasting state.

All 13 individual BAs were measured by a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method described previously [19] with slight modifications to achieve optimal detection. The LC-MS/MS system consists of an HPLC Agilent 1200 series apparatus and the Agilent 6420 Triple Quadrupole MS/MS (Agilent Technologies, Santa Clara, CA, USA). BAs analysed include chenodeoxycholic acid (CDCA), cholic acid (CA), deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA) and each of their glycine (G-) and taurine (T-) conjugates.

FGF19 levels were measured by a commercially available human FGF19 sandwich ELISA kit (RayBiotech, Inc., Norcross, GA, USA).

Plasma glucose, insulin and C-peptide concentrations were determined by an autoanalyser (Roche Diagnostics, Basel, Switzerland) based on Roche's manufacturer protocols.

Calculation

BA compositions were classified based on their site of synthesis (primary vs. secondary), conjugation state (conjugated vs. unconjugated) or 12α-hydroxylation (12α-OH vs. non-12α-OH). The molar sum of BA concentrations in each category was used to determine the levels of each BA composition. Compositions included (1) total BAs = all 13 BAs; (2) primary BAs = CA, GCA, CDCA, GCDCA and TCDCA; (3) secondary BAs = DCA, GDCA, TDCA, UDCA, GUDCA, TUDCA, LCA and TLCA; (4) 12α-OH BAs = CA, GCA, DCA, GDCA and TDCA; (5) non-12α-OH BAs = CDCA, GCDCA, TCDCA, LCA, TLCA, UDCA, GUDCA, TUDCA; (6) conjugated BAs = all glycine and taurine-conjugated BAs; (7) unconjugated BAs = all unconjugated BAs; (8) glycine-conjugated; (9) taurine-conjugated; (10) primary-conjugated; (11) primary-unconjugated; (12) secondary-conjugated and (13) secondary-unconjugated.

Glucose metabolism evaluation indices for this study were the homeostatic model assessment of insulin resistance (HOMA-IR), as the product of the fasting concentrations of plasma insulin (units) and plasma glucose (units) divided by 22.5 [19], and the Stumvoll Insulin Sensitivity Index (ISI), calculated using OGTT values in the following formula [20]:

$$0.156-(0.0000459*\mathrm{INS}_{120min}[\mathrm{pmol/L}])$$
$$-(0.000321*\mathrm{INS}_{0min}\,[\mathrm{pmol/L}])$$
$$-(0.0054*\mathrm{Glucose}_{120min}\,[\mathrm{mmol/L}])$$

Established mathematical modelling which describes the relationship between insulin secretion and glucose concentration coupled with a model of C-peptide kinetics [21, 22] was used to obtain more sophisticated variables describing the β-cell insulin secretory process. Based on the model, our study evaluated the β-cell sensitivity to glucose (glucose sensitivity), β-cell sensitivity to the rate of change of glucose (rate sensitivity) and a potentiation factor (representing a relevant potentiation of insulin secretion throughout the OGTT), basal insulin secretion rate (BSR) and the total insulin secretion (TIS) during the OGTT before and at different time points post-surgery.

Statistical Analysis

RStudio Version 1.1.414 was used for statistical analysis. Normal distribution of model residuals was tested with the Shapiro–Wilk test. For normally distributed data, the results were presented as the mean ± standard deviation (s.d.). Non-normal distribution data were either log transformed or presented as the median (IQR). Comparisons within and between surgical groups were examined using paired and unpaired Student *t* tests for normally distributed data. For non-normally distributed data, Wilcoxon signed-rank test and the Mann–Whitney *U* test were conducted. Bivariate associations were examined by using Pearson correlation coefficients. AUCs were calculated according to the trapezoidal rule. Statistical significance was set at $P < 0.05$ (two-tailed).

Data Availability

Datasets generated and analysed during the current study are available from the corresponding authors upon reasonable request.

Results

Subject Clinical Characteristics Before and After Each Intervention

Subject characteristics and post-operative changes of those characteristics are outlined in Tables 1 and 2, respectively. At 3 months after surgery, mean body weight loss was 18.2 ± 4.7 kg (15.0 ± 3.1%) in the GBP group and 17.3 ± 6.7 kg (13.9 ± 5.2%) in the SG group. Corresponding BMI decreased 3 months after both GBP (43.0 ± 4.7 kg m^{-2} (pre-op) vs. 36.6 ± 4.3 kg m^{-2} (3 months post-op); $P < 0.001$) and SG (43.4 ± 6.1 kg m^{-2} (pre-op) vs. 37.4 ± 5.9 kg m^{-2} (3 months post-op); $P < 0.001$). No significant difference was observed between GBP and SG in reducing body weight at 3 months post-operatively.

Effect of Each Intervention on Diabetes Indices Post-operatively

As shown in Table 1, insulin sensitivity as measured by HOMA-IR was unchanged, but Stumvoll ISI significantly improved both 3 days and 3 months post-operatively in each group (GBP, 3 days post-op, $P = 0.002$; 3 months post-op, $P = 0.004$; SG, 3 days post-op, $P < 0.0001$; 3 months post-op, $P < 0.001$). Although the beta cell glucose sensitivity tended to be higher progressively with time, only the 3-month increases reached a significant level of difference (GBP, $P = 0.029$; SG, $P = 0.024$).

The fasting levels of glucose, insulin or C-peptide did not change significantly from pre-operative levels at either 3 days or at 3 months after both of the interventions ($P > 0.05$), although glucose-lowering therapy was withdrawn from the day of surgery. The insulin and C-peptide AUC values during OGTT tended to be higher in both interventions over time post-operatively, while only the 3-month change in the GBP group was significant (insulin AUC, $P = 0.016$; C-peptide AUC, $P = 0.003$). In the SG group, the AUC of glucose was significantly decreased after surgery (3 days post-op, $P = 0.036$; 3 months post-op, $P = 0.034$), and no significant differences were found between the 3-day and 3-month changes. Correspondingly, in the GBP group, significant reductions were observed in glucose AUC levels 3 days post-operation ($P = 0.013$), but the 3-month reductions were not significant.

Generally, the effects of both GBP and SG on all glucose metabolism indices under investigation were similar ($P > 0.05$). Exceptions to this are noted for the 3-month changes of C-peptide ($P = 0.007$) and basal insulin secretion rates ($P = 0.009$), in which SG induced a decrease, whereas an increase was observed in the GBP group (Table 2).

Effect of Each Type of Bariatric Surgery on Fasting Levels of BA Compositions and FGF19 Post-operatively

During the fasting state, total and almost all BA species increased substantially at 3 days, followed by a significant decrease 3 months post-operatively, although still higher than pre-operative levels (Fig. 1 a-f2; Table 3).

Several fasting BAs increased to a greater extent after GBP (at both 3 days and 3 months) for primary, secondary, primary-conjugated and 12α-OH species, and only by 3 months for unconjugated BAs and secondary unconjugated BAs.

In both surgery groups, FGF19 levels increased significantly 3 days post-operatively, but the levels did not differ from the baseline at 3 months (Table 3). The influences of GBP compared to SG on FGF19 levels showed no significant difference at either 3 days ($P = 0.962$) or 3 months ($P = 0.661$) between these two types of surgery.

Effect of Each Intervention on Postprandial Levels of BA Compositions

Postprandial ($AUC_{0\text{-}120min}$) BA fractions followed a similar pattern to fasting BAs in that these also increased substantially at 3 days, followed by a significant decrease 3 months post-operatively, although still higher than pre-operative levels.

Several postprandial ($AUC_{0\text{-}120min}$) BAs increased to a greater extent after GBP (at both 3 days and 3 months): total, unconjugated, primary-conjugated, secondary unconjugated and 12α-OH. There were also many more postprandial BAs that showed greater increases after GBP at 3 days but were

Table 1 Clinical characteristics and glucose metabolism indices before and after bariatric surgeries

	Gastric bypass ($n = 8$)			Sleeve gastrectomy ($n = 11$)		
Diabetes medication	Pre-GBP Metformin = 8	3 days post-GBP –	3 months post-GBP –	Pre-SG Metformin = 6, metformin + glipizide = 3, ibuprofen = 1, glipizide = 1	3 days post-SG –	3 months post-SG –
n	8	8	8	11	11	11
Clinical characteristics						
Gender (men/women)	1/7	1/7	1/7	2/9	2/9	2/9
Age (years)	42.9 ± 9.6			43.9 ± 6.7		
Weight (kg)	120.5 ± 14.9		102.3 ± 12.8*†	126.6 ± 17.0		109.2 ± 18.5*†
Weight loss (%)		0.0	15.0 ± 3.1		0.0	13.9 ± 5.2
BMI (kg m^{-2})	43.0 ± 4.7	43.0 ± 4.7	36.6 ± 4.3*†	43.4 ± 6.1	43.4 ± 6.1	37.4 ± 5.9*†
Fasting glucose metabolism indices						
Glucose (mmol L^{-1})	6.1 ± 2.1	6.7 ± 1.4	5.6 ± 1.1	6.4 ± 1.5	6.1 ± 1.5	5.6 ± 1.7
Insulin (pmol L^{-1})[a]	1.8 ± 0.5	1.8 ± 0.4	1.9 ± 0.4	2.1 ± 0.3	2.0 ± 0.2	1.2 ± 0.3
C-peptide (pg mL^{-1})[a]	3.2 ± 0.2	3.1 ± 0.2	3.2 ± 0.1†	3.4 ± 0.2	3.4 ± 0.2	3.3 ± 0.2*
HOMA-IR[a]	0.4 ± 0.6	0.5 ± 0.5	0.4 ± 0.4	0.7 ± 0.4	0.6 ± 0.3	0.5 ± 0.4
Postprandial glucose metabolism indices						
Glucose $AUC_{0\text{-}120min}$ (mol min L^{-1})	1.3 ± 0.5	1.07 ± 0.4*	1.18 ± 0.4	1.3 ± 0.4	1.2 ± 0.4*	1.2 ± 0.5*
Insulin $AUC_{0\text{-}120min}$ (nmol min L^{-1})	31.2 ± 16.2	32.2 ± 21.3	52.8 ± 18.5	45.9 ± 20.9	36.2 ± 16.6	62.93 ± 50.0
C-peptide $AUC_{0\text{-}120min}$ (ng min mL^{-1})	356.4 ± 58.2	363.3 ± 164.3	557.8 ± 122.8*†	638.4 ± 252.3	598.2 ± 261.3	756.2 ± 452.3
ISI composite (Stumvoll)	2.2 ± 1.3	3.5 ± 1.8*	5.1 ± 2.4*†	1.1 ± 1.3	3.0 ± 1.1*	4.6 ± 1.7*†
Total ISR (nmol m^{-2})	16.9 ± 2.7	16.6 ± 7.2	27.5 ± 8.2*†	28.7 ± 12.0	26.9 ± 13.5	35.5 ± 21.3
Basal ISR (pmol min^{-1} m^{-2})	59.3 ± 24.5	47.7 ± 19.8	65.5 ± 14.9†	110.0 ± 43.2	99.7 ± 44.5	83.8 ± 32.3*
Glucose sensitivity (pmol min^{-1} m^{-2} mM^{-1})	11.3(9.2–19.0)	19.1(7.7–33.7)	24.4(14.5–32.2)*	18.8(14.1–32.9)	29.1(16.6–47.6)	33.0(28.4–71.8)*
Rate sensitivity (pmol m^{-2} mM^{-1})	119.2(2.7–193.0)	111.0(11.0–732.1)	313.1(174.7–447.3)	179.2(0.0–659.9)	245.4(1.1–786.1)	571.1(145.0–1460.3)*†
Potentiation factor	1.2 ± 0.4	1.3 ± 0.6	1.3 ± 0.6	0.9 ± 0.3	0.9 ± 0.6	1.2 ± 0.8

Data are mean ± sd. or median (IQR)

GBP gastric bypass surgery, *SG* sleeve gastrectomy, *BMI* body mass index, *AUC* area under the curve, *HOMA-IR* homeostatic model of insulin resistance, *ISI* insulin sensitivity index, *total ISR* total insulin secretion rates, calculated from the integral of total insulin secretion, *basal ISR* basal insulin secretion rates

* $P < 0.05$ vs. pre-surgery values

† $P < 0.05$ vs. 3-day post-surgery values

[a] Transformed variables

Table 2 The changes in clinical characteristics and glucose metabolism indices after bariatric surgeries

Differences (Δ) vs. baseline	3 days post-surgery		3 months post-surgery		*P* value	
					GBP vs. SG	
	3 days post-GBP	3 days post-SG	3 months post-GBP	3 months post-SG	3 days	3 months
Clinical characteristics						
ΔWeight (kg)	0.0	0.0	− 18.2 ± 4.7	− 17.3 ± 6.7	NA	0.761
ΔBMI (kg m^{-2})	0.0	0.0	− 6.5 ± 1.6	− 6.0 ± 2.5	NA	0.647
Fasting glucose metabolism indices						
ΔFasting glucose (mmol L^{-1})	0.6 ± 2.3	− 0.3 ± 1.8	− 0.5 ± 1.5	− 0.8 ± 1.5	0.384	0.692
ΔFasting insulin (pmol L^{-1})	6.5 (− 7.2–28.9)	− 12.4 (− 103.4–15.4)	1.2 (− 6.3–23.9)	− 67.2 (− 97.2–1.8)	0.442	0.206
ΔC-peptide (pg mL^{-1})	− 305.9 ± 405.3	− 261.8 ± 1629.9	78.3 ± 383.7	− 775.5 ± 713.1	0.933	*0.007*
ΔHOMA-IR	1.1 (− 0.3–2.8)	− 2.1 (− 5.9–1.2)	0.1 (− 0.2–1.1)	− 3.9 (− 5.4–0.0)	0.272	0.206
Postprandial glucose metabolism indices						
Δ glucose $AUC_{0\text{-}120min}$ (mmol min L^{-1})	− 250.7 ± 215.3	− 149.6 ± 204.3	− 143.3 ± 286.6	− 188.9 ± 255.0	0.313	0.719
ΔInsulin $AUC_{0\text{-}120min}$ (nmol min L^{-1})	0.9 ± 17.7	− 9.7 ± 15.2	21.6 ± 19.2	17.0 ± 32.7	0.176	0.729
ΔC-peptide $AUC_{0\text{-}120min}$ (ng min mL^{-1})	6.9 ± 147.9	− 40.2 ± 223.1	201.5 ± 130.9	117.8 ± 266.8	0.611	0.427
ΔISI composite (Stumvoll)	1.3 ± 0.7	1.9 ± 0.8	2.8 ± 1.9	3.5 ± 1.6	0.100	0.415
ΔTotal ISR (nmol m^{-2})	− 0.3 ± 5.5	− 1.8 ± 9.0	10.6 ± 7.5	6.8 ± 12.2	0.689	0.455
ΔBasal ISR (pmol min^{-1} m^{-2})	− 11.7 ± 15.2	− 10.2 ± 63.3	6.1 ± 13.6	− 26.1 ± 28.5	0.943	*0.009*
ΔGlucose sensitivity (pmol min^{-1} m^{-2} mM^{-1})	13.3 ± 26.5	15.2 ± 40.3	11.3 ± 11.6	26.8 ± 33.4	0.913	0.177
ΔRate sensitivity (pmol m^{-2} mM^{-1})	65.1 (− 132.7–601.6)	0.0 (− 184.0–99.2)	170.6 (32.7–332.8)	571.1 (71.6–1243.0)	0.544	0.395
ΔPotentiation factor	0.1 ± 0.4	0.0 ± 0.6	0.1 ± 0.6	0.3 ± 0.9	0.772	0.487

Significant *p* values indicated in italics

Data are mean ± sd. or median (IQR)

GBP gastric bypass surgery, *SG* sleeve gastrectomy, *BMI* body mass index, *AUC* area under the curve, *HOMA-IR* homeostatic model of insulin resistance, *ISI* insulin sensitivity index, *total ISR* total insulin secretion rates, calculated from the integral of total insulin secretion, *basal ISR* basal insulin secretion rates, *N/A* data not applicable

similar to SG by 3 months, i.e. primary, secondary, conjugated, glycine-conjugated and non 12α-OH.

A significant increase in BA levels in response to glucose at 30 min for all composite variables was observed from the postprandial BA curves (Fig. 2 a–m, Fig. 3 a–m), regardless of longitudinal time relative to surgery or types of operation. For both interventions, the rise in peak BA levels 30 min after ingestion at the 3-day post-surgery time point was more exaggerated compared to the baseline and 3-month post-surgery levels. Indeed, the AUC of all BA compositions was significantly higher than the baseline regardless of operation types (Table 4).

Effect of Each Type of Bariatric Surgery on Ratios of BA Levels During Fasting and Postprandial

Computed ratios of the composite BA variables revealed a predominance of primary and conjugated BAs, compared with secondary and unconjugated BAs, respectively (Fig. 1 g1–g2; Table 3). During fasting states, there was a trend that primary/secondary BA ratios declined 3 days after surgery, then rose at 3 months. A difference between surgery groups was observed at 3 months post-operative for the primary/secondary BA ratio ($P = 0.022$), where the ratio was significantly lower than the baseline in the GBP group (1.83 (1.54–2.11) (pre-op) vs. 1.71 (1.52–1.73) (3 months post-op); $P = 0.033$). The ratio did not differ between baseline and 3-month values (1.71 (1.49–1.94) (pre-op) vs. 1.82 (1.49–1.95) (3 months post-op); $P = 0.766$). A trend that the primary/secondary BA ratio progressively declined over time in response to glucose was seen in both groups.

During fasting, the conjugated/unconjugated ratio declined at 3 days post-operative, but appeared relatively unchanged when compared with the baseline at 3 months in both surgery groups. Conjugated/unconjugated ratios tended to increase at 30 min after oral glucose was taken, and then ratios gradually reduced as the time points increased. A significant increase in 12α-OH/non-12α-OH ratios at the 3-day time point post-surgery compared with pre-surgery values was observed in the GBP group (0.68 (0.64–0.77) (pre-op) vs. 0.89 (0.78–1.00) (3 days post-op); $P = 0.011$), but not in the SG group (0.70 (0.63–0.82) (pre-op) vs. 0.86 (0.82–0.99) (3 days post-op); $P = 0.054$). The 12α-OH/non-12α-OH ratio showed a slight increase at 3 months relative to baseline values, but the changes were not significant in each group.

Associations Between Changes in Metabolic Characteristics and Changes in BA Compositions and FGF19 Post-operatively

Associations at the 3-day time point post-surgery are shown in Table 5. The change in glucose AUC was negatively correlated with most of the fasting as well as postprandial BA species, except fasting taurine-conjugated and fasting primary-conjugated BAs. The change in insulin AUC was positively associated with fasting 12α-OH BAs and the AUC of the taurine-conjugated BAs.

The change in Stumvoll Insulin Sensitivity Index (ISI) was negatively associated with fasting levels of primary-unconjugated BAs and AUC values of the total, primary, conjugated, glycine-conjugated, primary-conjugated, 12α-OH and non-12α-OH BA compositions.

The change in total insulin secretion was only positively correlated with postprandial taurine–conjugated BAs, while the change in basal insulin secretion positively correlated with both fasting and postprandial taurine–conjugated BAs. The change in pancreatic insulin rate sensitivity negatively correlated with fasting conjugate/unconjugated ratios.

The associations between 3-month changes in metabolic characteristics and changes in BA compositions and FGF19 are listed in Table 6. At 3 months, the change in glucose AUC was found to be negatively correlated with fasting and postprandial 12α-OH BAs significantly.

The change in Stumvoll ISI negatively correlated with fasting secondary, secondary-conjugated and non-12α-OH BAs, but positively correlated with fasting primary/secondary and 12α-OH/non-12α-OH ratio. The change in Stumvoll ISI also negatively correlated with the AUC of total, secondary, glycine-conjugated, secondary-conjugated and non-12α-OH BA compositions.

The change in total insulin secretion positively associated with fasting and postprandial secondary-conjugated BAs, postprandial secondary BAs and non-12α-OH BAs. The change in basal insulin secretion, as well as fasting C-peptide levels, had negative associations with the fasting primary/secondary ratio, and also negatively correlated with postprandial secondary-unconjugated BAs. There were no significant associations observed between changes in fasting FGF19 levels and changes in any clinical and metabolic characteristics at 3 months post-surgery.

Discussion

This study shows that most BAs (measured in the fasting and postprandial states) increased as early as 3 days after both GBP and SG types of bariatric surgeries and remained increased at 3 months, albeit at a lower level than observed at 3 days. GBP produced higher increases in several BAs measured in the fasting and postprandial states at both 3 days and 3 months, compared to SG. While fasting FGF19 levels increased at 3 days after both GBP and SG, this returned to baseline levels 3 months later. Our findings are in accordance with several studies showing that most BA compositions increase acutely within 1 week after different types of bariatric surgery [16, 23, 24].

Both surgeries produced improvements in insulin sensitivity assessed by Stumvoll ISI as early as 3 days and at 3 months after both types of surgery. In contrast, no improvements in insulin sensitivity assessed by HOMA-IR were seen at either the 3-day or 3-month time points after surgery. This is because fasting glucose and insulin values (used to derive HOMA-IR) appeared to be less impacted by bariatric surgery than the post-OGTT values (used to derive Stumvoll ISI). Fasting glucose and insulin values primarily reflect hepatic insulin sensitivity [25], while changes in insulin and glucose during the OGTT incorporate both peripheral and hepatic insulin sensitivity [26]. In addition, changes in gastric emptying, glucose absorption, insulin secretion and incretin hormones occurring after bariatric surgery also influence the OGTT results more than the fasting results. However, our finding is in contrast to many other studies reporting an improvement in HOMA-IR from as early as 1 week after RYGB [27–31]. This is likely due to the presence of a very low calorie diet immediately preceding the bariatric surgery in our study which is likely to have improved the baseline glucose metabolism considerably and minimized the discernible impact of the bariatric surgery on HOMA-IR in the early period. Such pre-operative dietary restriction was not described in previous bariatric studies reporting early improvements in HOMA-IR [27–31].

Our study is the first to report the relationship between increases in BAs and metabolic improvements which were seen as early as 3 days with Stumvoll ISI and glucose AUC improvements. There were more consistent and similar associations seen with changes in several postprandial BAs and changes in both Stumvoll ISI and glucose AUC (total, conjugated, glycine conjugated and 12α-OH BAs $AUC_{0\text{-}120min}$). There were several significant correlations with fasting BAs and glucose AUC (fasting secondary, conjugated, unconjugated, glycine-conjugated, taurine-conjugated), but these were not observed with Stumvoll ISI. In contrast, changes in fasting primary-unconjugated BA, postprandial primary BA, postprandial primary conjugated and postprandial non-12α-OH BA were correlated only with acute changes in Stumvoll ISI. While there were positive correlations between changes in fasting and postprandial taurine BAs with changes in basal insulin secretory rate, there were no significant correlations between BA changes and any other aspects of pancreatic β cell function improvements such as increases in total ISR, glucose sensitivity or potentiation factor.

The relationship between increases in BAs and metabolic improvements seen at 3 months were predominantly significant correlations with improvements in Stumvoll ISI. There were significant correlations between changes in both fasting and postprandial secondary BA, secondary-conjugated BAs and non-12α-OH BA and Stumvoll ISI changes. Our findings were inconsistent with secondary BAs being the predominant activators of the TGR5 pathway, which has been reported to affect glucose metabolism [32, 33]. In addition, there were also significant correlations between changes in postprandial levels of total BAs, conjugated BAs, glycine-conjugated BAs and Stumvoll ISI changes. Changes in several of these BAs were also correlated with changes in total insulin secretory rate (fasting and postprandial secondary-conjugated BAs, postprandial secondary BA and non-12α-OH BAs). Only changes in postprandial secondary-unconjugated BAs were correlated with changes in basal ISR. There were no other significant correlations between BA changes and any other aspects of pancreatic beta cell function improvements or with decreases in BMI.

We found that fasting 12α-OH/non-12α-OH BA ratios significantly increase 3 days after GBP. This finding was somewhat unexpected, considering that a higher 12α-OH /non-12α-OH BA ratio was thought to be associated with lower insulin sensitivity [34]. However, the Stumvoll ISI in the GBP group at 3 days were significantly increased. We did not find any correlation between the 3-day changes of 12α-OH/non-12α-OH BA ratios and insulin resistance.

In our study, the most striking change in FGF19 and BA fractions was that a sharp rise was observed for fasting FGF19 levels, where both fasting and postprandial BA compositions 3 days after surgeries were followed by a reduction for each of the measured fractions. The reason for such dramatic changes is unclear, but it might be partly explained by the acute alterations of gut microbiota caused by acute changes in perioperative nutrition accompanying bariatric surgery [35]. Gut microbiota are thought to have mutual interactions with BAs [36], including liberating the glycine/taurine conjugation [37], oxidation, sulphation and dehydroxylation of BAs [38]. The diversity of secondary BA species was directly affected [39]. Hypocaloric diet1)–related improvements in hepatic insulin sensitivity, the synthesis or excretion of BAs, enterohepatic cycling and gut permeability could be contributing to the acute changes in BA compositions after bariatric surgery [40].

The acute increase of FGF19 at 3 days post-surgery could reflect a systemic response to increased circulating BA levels, considering that BAs can bind to the nuclear receptor FXR, which is responsible for stimulating FGF19 synthesis [33, 41]. Afterwards, the targeted FGF receptor-4 might be activated with the increasing level of FGF19, which in turn negatively feeds back to inhibit hepatic BA synthesis [33]. BA-FXR activation might thereby become inhibited over time, leading to a reduction in FGF19 synthesis. As a result, fasting FGF19 levels, as well as both fasting and postprandial BA compositions, measured at 3 months were lower than the 3-day time points post-surgeries.

The lack of correlation we have found between changes in body weight and changes in most BA composition are in contrast to the negative correlation between body weight loss and BA modifications seen in other studies [6, 16, 40, 42]. Besides, the loss of correlation between the altered FGF19

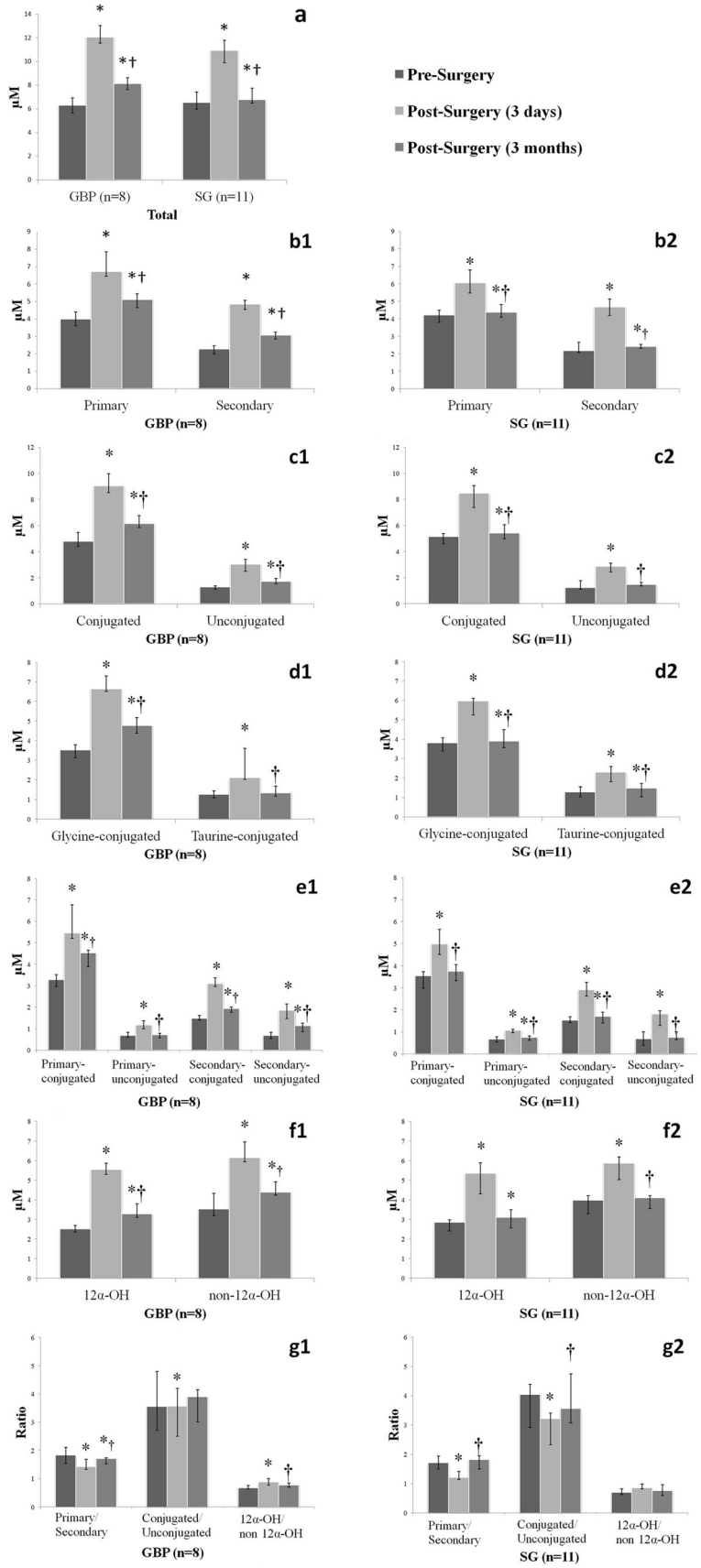

Fig. 1 During the fasting state, total and almost all BA species increased substantially at 3 days, followed by a significant decrease 3 months post-operatively, although still higher than pre-operative levels

Table 3 The concentrations of fasting BA fractions and fasting FGF 19 preoperatively and post-operatively in a given bariatric surgery

	Gastric bypass ($n = 8$)			Sleeve gastrectomy ($n = 11$)			Change from baseline *P* value GBP vs. SG	
Diabetes medications	Pre-GBP Metformin = 8	3 days post-GBP –	3 months post-GBP –	Pre-SG Metformin = 6, metformin + glipizide = 3, ibuprofen = 1, glipizide = 1	3 days post-SG –	3 months post-SG –	3 days	3 months
Fasting BA (μm L^{-1})								
Total	6.27 (5.63–6.91)	12.06 (11.56–13.04)*	8.10 (7.63–8.61)*†	6.43 (5.87–7.29)	10.93 (9.90–11.79)*	6.77 (6.48–7.75)*†	0.080	0.064
Primary	4.00 (3.60–4.40)	6.72 (6.46–7.84)*	5.11 (4.66–5.45)*†	4.21 (3.79–4.49)	6.05 (5.48–6.81)*	4.38 (4.09–4.82)*†	*0.003*	*0.004*
Secondary	2.27 (1.99–2.46)	4.86 (4.55–5.08)*	3.07 (2.84–3.25)*†	2.16 (2.07–2.65)	4.67 (4.19–5.14)*	2.42 (2.31–2.54)*†	*0.041*	*0.000*
Conjugated	4.80 (4.41–5.48)	9.06 (8.53–9.98)*	6.16 (5.84–6.75)*†	5.14 (4.61–5.39)	8.46 (7.37–9.04)*	5.40 (4.97–6.06)*†	0.086	0.098
Unconjugated	1.29 (1.13–1.38)	3.03 (2.50–3.41)*	1.70 (1.53–1.94)*†	1.23 (1.10–1.76)	2.86 (2.42–3.09)*	1.46 (1.37–1.63)†	0.245	*0.017*
Glycine-conjugated	3.52 (3.13–3.79)	6.64 (6.51–7.31)*	4.77 (4.38–5.17)*†	3.80 (3.38–4.07)	5.98 (5.25–6.11)*	3.90 (3.56–4.49)*†	0.091	0.095
Taurine-conjugated	1.27 (1.09–1.45)	2.10 (2.01–3.60)*	1.34 (1.18–1.68)†	1.27 (1.03–1.55)	2.29 (1.79–2.59)*	1.48 (1.04–1.70)*†	0.899	0.555
Primary-conjugated	3.28 (2.97–3.52)	5.46 (5.21–6.77)*	4.52 (3.90–4.65)*†	3.54 (2.99–3.74)	4.98 (4.50–5.65)*	3.76 (3.33–4.06)†	*0.006*	*0.004*
Primary-unconjugated	0.68 (0.61–0.84)	1.17 (0.99–1.37)*	0.71 (0.58–0.79)†	0.67 (0.54–0.78)	1.06 (0.95–1.11)*	0.74 (0.63–0.82)*†	0.202	0.255
Secondary-conjugated	1.48 (1.40–1.62)	3.10 (2.97–3.38)*	1.93 (1.76–2.01)*†	1.53 (1.42–1.69)	2.91 (2.63–3.25)*	1.70 (1.40–1.90)*†	0.271	0.230
Secondary-unconjugated	0.67 (0.54–0.83)	1.85 (1.47–2.16)*	1.13 (0.87–1.26)*†	0.69 (0.39–1.01)	1.82 (1.29–1.96)*	0.74 (0.66–1.01)†	0.367	*0.001*
12α-OH	2.51 (2.35–2.70)	5.55 (5.30–5.87)*	3.29 (3.10–3.80)*†	2.85 (2.40–2.98)	5.36 (4.31–5.90)*	3.10 (2.56–3.49)*	*0.002*	*0.006*
Non-12α-OH	3.53 (3.19–4.33)	6.16 (5.94–6.96)*	4.40 (4.24–4.93)*†	3.98 (3.28–4.21)	5.88 (5.04–6.20)*	4.11 (3.55–4.22)†	0.185	0.140
Primary/secondary	1.83 (1.54–2.11)	1.42 (1.32–1.69)*	1.71 (1.52–1.73)*†	1.71 (1.49–1.94)	1.21 (1.14–1.41)*	1.82 (1.49–1.95)†	0.589	*0.022*
Conjugated/unconjugated	3.56 (2.71–4.80)	3.57 (2.50–4.20)*	3.90 (3.01–4.15)	4.04 (2.91–4.39)	3.21 (2.32–3.41)*	3.56 (3.07–4.74)†	0.169	0.492
12α-OH/non-12α-OH	0.68 (0.64–0.77)	0.89 (0.78–1.00)*	0.78 (0.70–0.85)†	0.70 (0.63–0.82)	0.86 (0.82–0.99)	0.77 (0.60–0.97)	0.717	0.901
Fibroblast growth factor (pg mL^{-1})								
Fasting FGF19	118.3 ± 57.3	363.6 ± 131.0*	116.2 ± 110.2†	173.2 ± 127.8	422.0 ± 243.6*	151.6 ± 185.2†	0.277	0.423

Significant *p* values indicated in italics

All data are median (IQR) or mean ± sd

GBP gastric bypass surgery, *SG* sleeve gastrectomy, *FGF19* fibroblast growth factor 19

* $P < 0.05$ vs. pre-surgery values

† $P < 0.05$ vs. 3-day post-surgery values

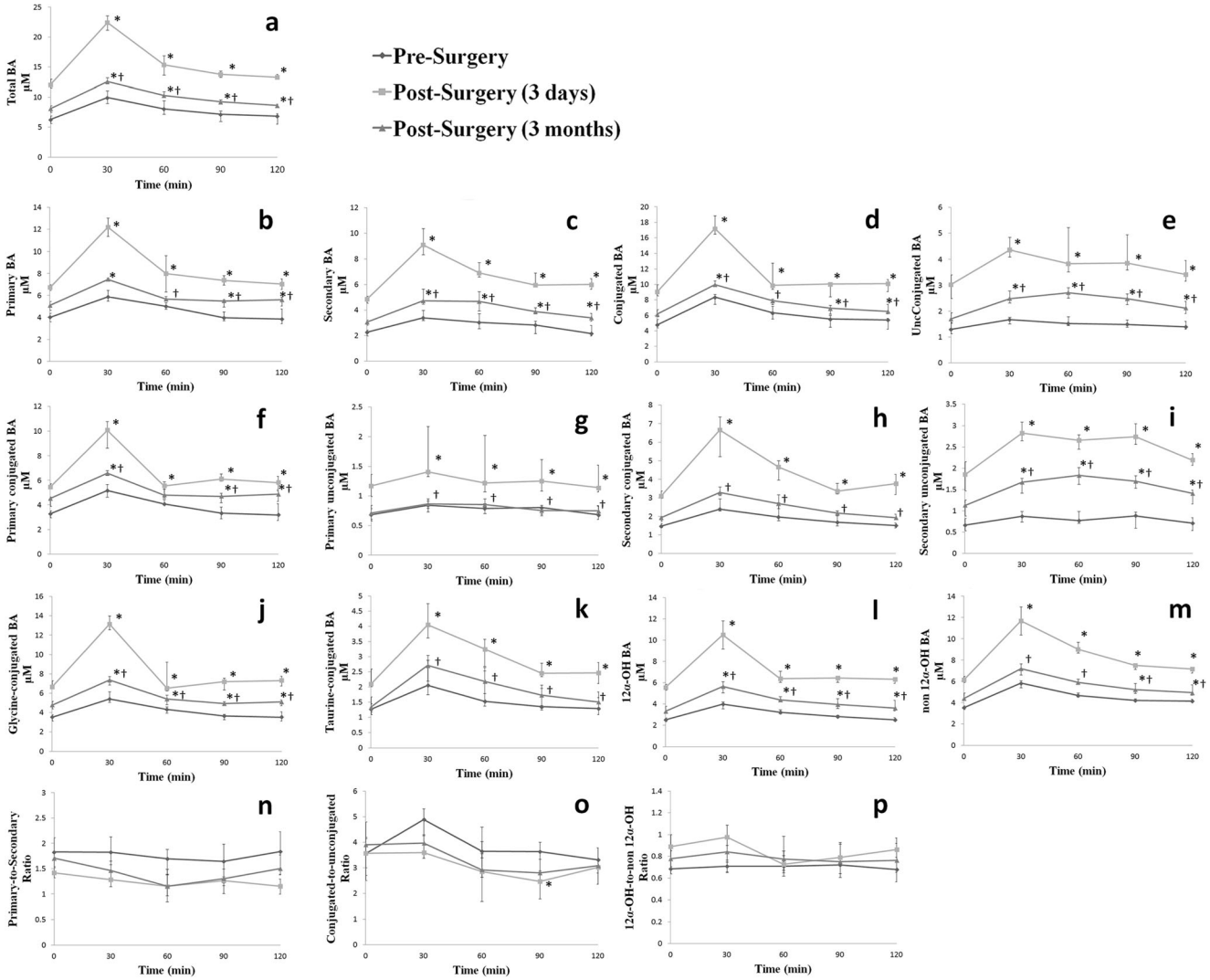

Fig. 2 A significant increase in BA levels in response to glucose at 30 min for all composite variables observed from the postprandial BA curves

levels and improvements of glucose metabolism indices seen here after interventions might suggest other factors that could be more important regulators of glucose metabolism after bariatric treatment.

We found that pancreatic glucose sensitivity improved significantly at 3 months after both interventions, and fasting C-peptide levels, insulin secretion rates, rate sensitivity and the potentiation factor improved after both GBP and SG. Our observations are in line with previous reports, suggesting that bariatric surgery is accompanied by improvement of glycaemic control as well as β-cell functions [13, 43]. Studies have shown that colesevelam hydrochloride, a precisely engineered BA sequestrant which can chelate with BAs in the gastrointestinal tract, prevent the BA ileal reabsorption, and thereby stimulate the BA synthesis at the expense of LDL-c, causing a remarkable improvement in glycaemic control among patients with T2DM receiving sulphonylurea [44] or insulin therapy [45]. Additionally, positive correlations were found between the above diabetes indices and specific BA compositions in our study. Thus, it is likely that therapies that modulate downstream pathways of BAs might be effective in improving glycaemic control.

Overall, differences between two types of surgery and their effects on BA levels, as either fasting or postprandial readings, were observed for various compositions, in which GBP induced higher increases. The differences were more exaggerated at 3 days compared with those at 3 months post-surgery. The reason attributed to such differences is unclear. These differences between the time point measurements might be related to malabsorption caused by GBP, or other mechanisms associated with a patient's nutritional status after either of the operations, or possibly alterations in liver metabolism between the two interventions [46].

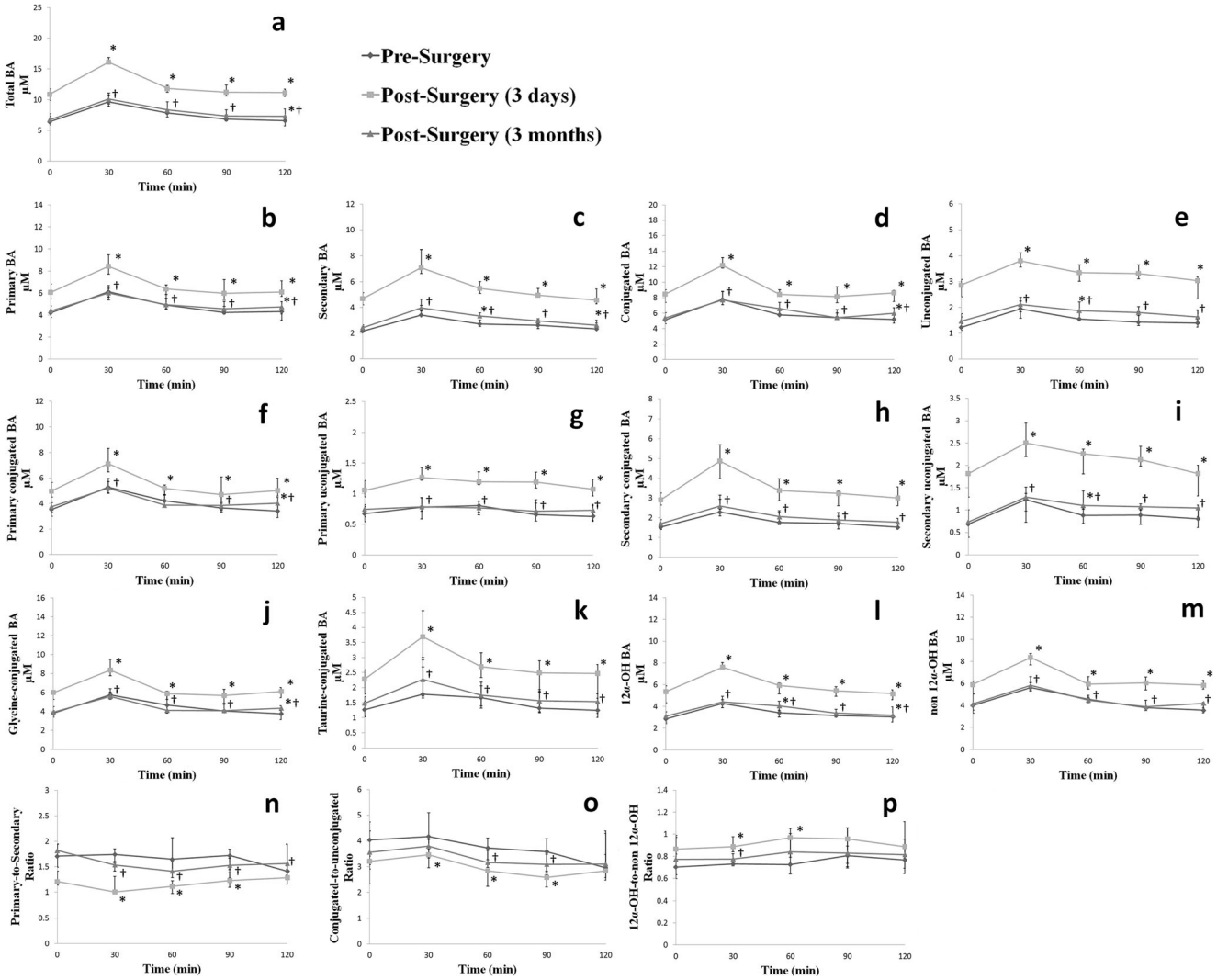

Fig. 3 A significant increase in BA levels in response to glucose at 30 min for all composite variables observed from the postprandial BA curves

Most previous reports have emphasized associations between the achieved levels of fasting BA compositions with the long-term clinical state after either GBP or SG among patients without T2DM [47–49]. Therefore, the present study makes a unique contribution to the existing literature as we focused on both acute (3-day) and relatively short-term (3-month) changes of the plasma BA compositions that occur with two different types of bariatric surgery among patients with T2DM and found that these correlated with improvements in several OGTT-derived glucose metabolic parameters but not with changes in weight. We also measured the BA values in both fasting and postprandial states and identified that there were additional correlations with postprandial BAs that were not seen with fasting BAs alone.

Our study has several limitations. Firstly, the sample size was relatively small, and the sex ratio and glucose tolerance status were different between intervention groups. We only measured the plasma BAs without evaluating portal blood BAs, which have been shown to correlate with peripheral BA levels in both fasting and postprandial states [50].

Overall, our study showed an acute increase in both fasting and postprandial BAs, as well as fasting FGF19 levels after GBP and SG, which was seen as early as 3 days and sustained till 3 months. The increases in fasting and postprandial total, secondary-conjugated and 12α-OH BAs were common to both types of surgery and at both early time points. Rises in secondary BA and conjugated forms were correlated with early improvements in glucose metabolism at 3 days, while these along with 12α-OH BA correlated with improved glucose metabolism at 3 months, suggesting that they may contribute to the improvements in glycaemic control after bariatric surgery.

Table 4 The $AUC_{0\text{-}120min}$ of BA fractions preoperatively and post-operatively in a given bariatric surgery

	Gastric bypass ($n = 8$)			Sleeve gastrectomy ($n = 11$)			Change from baseline *P* value GBP vs. SG	
Diabetes medications	Pre-GBP Metformin = 8	3 days post-GBP –	3 months post-GBP –	Pre-SG Metformin = 6, metformin + glipizide = 3, ibuprofen = 1, glipizide = 1	3 days post-SG –	3 months post-SG –	3 days	3 months
$AUC_{0\text{-}120min}$ of BAs (μm min L^{-1})								
Total	976.1 (824.5–1025.8)	1913.0 (1853.0–2015.0)*	1204.0 (1169.0–1327.0)*†	923.0 (852.5–1031.6)	1535.0 (1445.0–1547.0)*	967.5 (948.3–1106.0)*†	*0.000*	*0.037*
Primary	550.4 (538.8–644.5)	1024.7 (912.3–1139.2)*	710.1 (690.1–735.9)*†	583.2 (534.0–634.0)	817.5 (755.2–891.2)*	592.6 (561.7–666.8)†	*0.000*	0.558
Secondary	347.0 (294.9–399.9)	841.1 (770.0–881.4)*	486.1 (455.2–558.3)*†	339.5 (316.8–373.3)	655.7 (635.4–768.0)*	379.6 (365.5–418.8)*†	*0.028*	0.086
Conjugated	771.5 (655.2–812.9)	1366.0 (1312.0–1516.0)*	934.8 (884.6–993.1)*†	704.3 (673.2–808.3)	1136.0 (1033.0–1196.0)*	755.7 (709.2–848.7)*†	*0.002*	0.080
Unconjugated	181.1 (165.2–200.4)	446.2 (428.1–591.6)*	285.5 (269.9–310.7)*†	190.5 (165.4–224.9)	411.6 (355.7–423.0)*	219.6 (203.7–252.8)*†	*0.007*	*0.004*
Glycine-conjugated	505.5 (479.1–551.2)	987.2 (956.7–1103.5)*	675.7 (639.1–708.2)†	539.6 (499.9–569.6)	783.4 (714.7–830.3)*	524.2 (492.1–633.3)†	*0.002*	0.100
Taurine-conjugated	184.7 (165.2–280.4)	363.7 (339.9–396.5)*	242.2 (193.0–284.7)*†	176.3 (153.1–244.4)	340.6 (269.3–398.4)*	209.4 (161.8–263.0)*†	0.451	0.290
Primary-conjugated	466.4 (442.6–556.4)	782.5 (767.8–962.1)*	610.1 (589.6–657.3)*†	476.6 (467.4–540.5)	660.2 (618.5–749.5)*	496.1 (462.4–579.8)†	*0.004*	*0.005*
Primary-unconjugated	94.3 (82.1–104.8)	148.4 (138.0–234.8)*	94.6 (88.15–104.9)†	85.0 (70.8–102.6)	142.1 (135.4–151.0)*	89.4 (81.2–106.5)†	0.117	0.886
Secondary-conjugated	225.3 (211.6–279.3)	556.3 (475.9–573.0)*	302.6 (285.8–330.7)†	212.3 (199.0–276.1)	436.2 (367.5–488.1)*	237.3 (222.8–282.2)*†	0.066	0.207
Secondary-unconjugated	97.9 (79.17–107.3)	294.4 (290.5–313.4)*	194.8 (168.5–199.7)*†	110.9 (80.2–139.7)	243.0 (225.4–285.7)*	132.5 (112.6–156.5)*†	*0.021*	*0.002*
12α-OH	367.5 (356.5–389.1)	849.0 (840.9–917.8)*	515.5 (490.5–587.1)*†	410.3 (376.5–440.0)	708.5 (685.7–762.1)*	458.9 (407.9–504.6)*†	*0.000*	*0.002*
Non-12α-OH	578.9 (462.5–632.0)	1059.4 (936.0–1111.3)*	696.8 (617.1–731.9)†	512.7 (503.7–582.3)	778.6 (733.4–831.0)*	546.2 (511.5–613.7)†	*0.004*	0.105

Significant *p* values indicated in italics

All data are median (IQR)

GBP gastric bypass surgery, *SG* sleeve gastrectomy, *AUC* area under the curve

* $P < 0.05$ vs. pre-surgery values

† $P < 0.05$ vs. 3-day post-surgery values

Table 5 Correlations of 3-day changes in fasting and $AUC_{0\text{-}120min}$ of BA fractions and fasting FGF19 with changes in metabolic characteristics

	r with ΔAUC glucose	*r* with ΔAUC INS	*r* with ΔISI	*r* with ΔTISR	*r* with ΔBISR	*r* with ΔGS	*r* with ΔRS	*r* with ΔPF
ΔTotal	−0.54	0.21	−0.33	0.10	0.06	0.04	−0.08	−0.19
ΔAUC total	*−0.47**	0.26	*−0.49**	0.88	0.01	−0.01	0.15	0.06
ΔPrimary	−0.01	0.32	−0.38	0.26	0.32	0.15	−0.18	−0.17
ΔAUC primary	−0.12	0.03	*−0.46**	−0.10	−0.11	−0.06	0.09	0.03
ΔSecondary	*−0.57**	0.13	−0.24	0.03	−0.03	0.00	−0.03	−0.15
ΔAUC secondary	*−0.58**	0.34	−0.35	0.18	0.09	0.03	0.14	0.05
ΔConjugated	*−0.50**	0.19	−0.34	0.08	0.09	0.03	−0.11	−0.22
ΔAUC conjugated	*−0.48**	0.16	*−0.46**	−0.04	−0.03	−0.02	0.07	−0.01
ΔUnconjugated	*−0.46**	0.23	−0.11	0.16	−0.19	0.12	0.20	0.08
ΔAUC unconjugated	−0.19	0.40	−0.30	0.35	0.09	0.02	0.27	0.22
ΔGlycine-conjugated	*−0.52**	0.17	−0.32	0.05	0.05	0.03	−0.09	−0.22
ΔAUC glycine-conjugated	*−0.46**	0.08	*−0.46**	−0.11	−0.12	−0.05	0.04	−0.08
ΔTaurine-conjugated	*0.31**	0.22	−0.18	0.33	*0.47**	−0.07	−0.28	0.01
ΔAUC taurine-conjugated	−0.23	*0.45**	−0.10	0.41	*0.48**	0.14	0.16	0.36
ΔPrimary-conjugated	0.00	0.30	−0.32	0.25	0.31	0.11	−0.16	−0.13
ΔAUC primary-conjugated	−0.12	−0.05	*−0.44**	−0.17	−0.15	−0.09	0.07	0.03
ΔPrimary-unconjugated	−0.10	0.16	*−0.44**	0.08	0.08	0.32	−0.17	−0.28
ΔAUC primary-unconjugated	−0.01	0.25	−0.17	0.20	0.10	0.08	0.08	0.02
ΔSecondary-conjugated	*−0.53**	0.11	−0.26	0.00	0.00	0.00	−0.07	−0.19
ΔAUC secondary-conjugated	*−0.60**	0.27	−0.31	0.09	0.09	0.04	0.04	−0.05
ΔSecondary-unconjugated	*−0.48**	0.21	0.02	0.16	−0.24	0.03	0.28	0.18
ΔAUC secondary-unconjugated	−0.27	0.39	−0.31	0.36	0.05	−0.04	0.35	0.32
Δ12α-OH	−0.37	*0.42**	−0.30	0.27	0.14	0.24	0.05	0.00
ΔAUC 12α-OH	*−0.42**	0.27	*−0.44**	0.03	−0.05	0.10	0.14	0.12
ΔNon-12α-OH	*−0.50**	0.14	−0.30	0.04	0.03	−0.01	−0.10	−0.21
ΔAUC non-12α-OH	−0.43	0.21	*−0.45**	0.09	0.04	−0.08	0.13	0.01
ΔPrimary/secondary	0.25	−0.42	0.02	−0.20	0.05	−0.18	−0.78	−0.40
ΔConjugate/unconjugated	−0.21	0.04	−0.08	0.05	0.17	0.00	*−0.30**	−0.32
Δ12α-OH/non-12α-OH	−0.11	0.06	0.29	0.07	−0.15	0.10	0.21	0.22
ΔFGF19	−0.10	−0.22	0.14	−0.44	−0.15	0.04	−0.32	−0.28

Significantly strong correlations indicated in italics

FGF19 fibroblast growth factor 19, *AUC* area under the curve, *INS* insulin, *ISI* Stumvoll Insulin Sensitivity Index, *TISR* total insulin secretion rates, calculated from the integral of total insulin secretion, *BISR* basal insulin secretion rates, *GS* glucose sensitivity, *RS* rate sensitivity, *PF* potentiation factor

* $P < 0.05$

Table 6 Correlations of 3-month changes in fasting and $AUC_{0\text{-}120min}$ of BA fractions and fasting FGF19 with changes in clinical and metabolic characteristics

	r with ΔBMI	*r* with ΔAUC glucose	*r* with ΔAUC INS	*r* with ΔISI	*r* with ΔTISR	*r* with ΔBISR	*r* with ΔGS	*r* with ΔRS	*r* with ΔPF	*r* with ΔCP
ΔTotal	−0.09	−0.12	0.09	−0.41	0.35	0.34	−0.05	−0.12	−0.13	0.35
ΔAUC total	0.15	−0.07	0.14	*−0.47**	0.41	0.41	−0.15	0.01	−0.10	0.42
ΔPrimary	−0.12	−0.41	−0.07	0.13	−0.04	0.30	−0.15	−0.10	−0.11	0.29
ΔAUC primary	0.03	−0.07	0.00	−0.27	0.14	0.36	−0.37	0.06	−0.06	0.35
ΔSecondary	0.14	−0.03	0.12	*−0.51**	0.41	0.31	−0.01	−0.12	−0.12	0.32
ΔAUC secondary	0.17	−0.06	0.16	*−0.48**	*0.44**	0.37	−0.06	−0.01	−0.10	0.38
ΔConjugated	0.10	−0.14	0.10	−0.41	0.36	0.32	−0.02	−0.07	−0.10	0.32
ΔAUC conjugated	0.15	−0.03	0.14	*−0.52**	0.42	0.36	−0.10	−0.01	−0.13	0.37
ΔUnconjugated	−0.07	0.06	−0.04	−0.18	0.09	0.32	−0.19	−0.39	−0.12	0.31
ΔAUC unconjugated	0.05	−0.25	0.04	−0.01	0.18	0.43	−0.33	0.09	0.10	0.44
ΔGlycine-conjugated	0.08	−0.13	0.12	−0.40	0.37	0.31	−0.01	−0.07	−0.12	0.31
ΔAUC Glycine-conjugated	0.16	−0.05	0.13	*−0.51**	0.41	0.33	−0.08	−0.02	−0.12	0.33
ΔTaurine-conjugated	0.25	−0.18	−0.22	0.01	−0.28	0.08	−0.18	−0.01	−0.03	0.07
ΔAUC taurine-conjugated	−0.02	0.21	0.17	−0.12	0.10	0.36	−0.15	0.05	−0.04	0.39
ΔPrimary-conjugated	−0.19	−0.40	−0.10	0.13	−0.06	0.30	−0.16	−0.10	−0.13	0.29
ΔAUC primary-conjugated	0.00	−0.04	−0.02	−0.29	0.12	0.37	−0.39	0.04	−0.10	0.36
ΔPrimary-unconjugated	−0.40	0.10	0.22	−0.02	0.10	−0.11	0.09	0.07	0.14	−0.10
ΔAUC primary-unconjugated	0.20	−0.21	0.14	0.19	0.10	−0.08	0.13	0.12	0.26	−0.08
ΔSecondary-conjugated	0.19	−0.03	0.16	*−0.52**	*0.44**	0.27	0.03	−0.05	−0.10	0.28
ΔAUC secondary-conjugated	0.18	−0.02	0.18	*−0.51**	*0.45**	0.29	0.03	−0.03	−0.12	0.31
ΔSecondary-unconjugated	−0.22	0.03	−0.12	−0.18	0.06	0.38	−0.24	−0.44	−0.16	0.37
ΔAUC secondary-unconjugated	0.00	−0.22	0.01	−0.06	0.17	*0.49**	−0.39	0.07	0.05	*0.49**
Δ12α-OH	−0.33	*−0.46**	0.04	0.25	0.01	0.22	0.14	−0.22	−0.12	0.19
ΔAUC 12α-OH	−0.23	*−0.41**	−0.07	0.16	0.02	0.28	−0.14	−0.07	−0.04	0.26
ΔNon-12α-OH	0.18	−0.02	0.09	*−0.52**	0.38	0.33	−0.09	−0.08	−0.11	0.34
ΔAUC non-12α-OH	0.24	0.04	0.17	*−0.58**	*0.46**	0.38	−0.13	0.03	−0.10	0.39
ΔPrimary/secondary	0.05	−0.33	−0.05	*0.53**	−0.29	*−0.46**	0.19	0.27	0.00	*−0.47**
ΔConjugate/unconjugated	0.17	−0.19	0.23	−0.25	0.37	0.08	0.15	0.25	−0.06	0.08
Δ12α-OH/non-12α-OH	−0.17	−0.30	0.13	*0.45**	−0.13	−0.31	0.41	−0.05	−0.26	−0.34
ΔFGF-19	−0.03	−0.56	−0.15	0.18	−0.09	0.12	−0.10	−0.04	0.05	0.09

Significantly strong correlations indicated in italics

FGF19 fibroblast growth factor 19, *BMI* body mass index, *AUC* area under the curve, *INS* insulin, *ISI* Stumvoll Insulin Sensitivity index, *TISR* total insulin secretion rates, calculated from the integral of total insulin secretion, *BISR* basal insulin secretion rates, *GS* glucose sensitivity, *RS* rate sensitivity, *PF* potentiation factor, *CP* C-peptide

* $P < 0.05$

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Statement All procedures performed consistent with the ethical standards of the New Zealand Health and Disability Ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent Statement Informed consent was obtained from all individual participants included in the study.

References

1. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med. 2014;370:2002–13.
2. Chang S-H, Stoll CR, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA surgery. 2014;149:275–87.
3. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017;376:641–51.
4. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric–metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-Centre, randomised controlled trial. Lancet. 2015;386:964–73.
5. Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol. 2014;2:152–64.
6. Gerhard GS, Styer AM, Wood GC, et al. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. Diabetes Care. 2013;36:1859–64.
7. Penney N, Kinross J, Newton R, et al. The role of bile acids in reducing the metabolic complications of obesity after bariatric surgery: a systematic review. Int J Obes. 2015;39:1565–74.
8. Fiorucci S, Mencarelli A, Palladino G, et al. Bile-acid-activated receptors: targeting TGR5 and farnesoid-X-receptor in lipid and glucose disorders. Trends Pharmacol Sci. 2009;30:570–80.
9. Li T, Chiang JY. Bile acid signaling in metabolic disease and drug therapy. Pharmacol Rev. 2014;66:948–83.
10. Donepudi AC, Boehme S, Li F, et al. G-protein-coupled bile acid receptor plays a key role in bile acid metabolism and fasting-induced hepatic steatosis in mice. Hepatology. 2017;65:813–27.
11. Thomas C, Gioiello A, Noriega L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009;10:167–77.
12. Kir S, Kliewer S, Mangelsdorf D. Roles of FGF19 in liver metabolism. In: Cold Spring Harbor symposia on quantitative biology, vol. 2011: Cold Spring Harbor Laboratory Press. p. 139–44.
13. Nakatani H, Kasama K, Oshiro T, et al. Serum bile acid along with plasma incretins and serum high–molecular weight adiponectin levels are increased after bariatric surgery. Metab Clin Exp. 2009;58:1400–7.
14. Nemati R, Lu J, Dokpuang D, et al. Increased bile acids and FGF19 after sleeve gastrectomy and Roux-en-Y gastric bypass correlate with improvement in type 2 diabetes in a randomized trial. Obes Surg. 2018:1–15.
15. Patti ME, Houten SM, Bianco AC, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity. 2009;17:1671–7.
16. Pournaras DJ, Glicksman C, Vincent RP, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. Endocrinology. 2012;153:3613–9.
17. Sachdev S, Wang Q, Billington C, et al. FGF 19 and bile acids increase following Roux-en-Y gastric bypass but not after medical management in patients with type 2 diabetes. Obes Surg. 2016;26:957–65.
18. Shimizu H, Hatao F, Imamura K, et al. Early effects of sleeve gastrectomy on obesity-related cytokines and bile acid metabolism in morbidly obese Japanese patients. Obes Surg. 2017;27:3223–9.
19. Tagliacozzi D, Mozzi AF, Casetta B, et al. Quantitative analysis of bile acids in human plasma by liquid chromatography-electrospray tandem mass spectrometry: a simple and rapid one-step method. Clin Chem Lab Med. 2003;41:1633–41.
20. Stumvoll M, Van Haeften T, Fritsche A, et al. Oral glucose tolerance test indexes for insulin sensitivity and secretion based on various availabilities of sampling times. Diabetes Care. 2001;24:796–7.
21. Mari A, Schmitz O, Gastaldelli A, et al. Meal and oral glucose tests for assessment of β-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab. 2002;283:E1159–66.
22. Mari A, Tura A, Gastaldelli A, et al. Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. Diabetes. 2002;51:S221–6.
23. Jahansouz C, Xu H, Hertzel AV, et al. Bile acids increase independently from hypocaloric restriction after bariatric surgery. Ann Surg. 2016;264:1022–8.
24. Ahmad N, Pfalzer A, Kaplan L. Roux-en-Y gastric bypass normalizes the blunted postprandial bile acid excursion associated with obesity. Int J Obes. 2013;37:1553–9.
25. DeFronzo RA, Ferrannini E, Simonson DC. Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. Metabolism. 1989;38:387–95.
26. Abdul-Ghani MA, Matsuda M, Balas B, et al. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. Diabetes Care. 2007;30:89–94.
27. Bose M, Teixeira J, Olivan B, et al. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. J Diabetes. 2010;2:47–55.
28. Yan H, Tang L, Chen T, et al. Defining and predicting complete remission of type 2 diabetes: a short-term efficacy study of open gastric bypass. Obes Facts. 2013;6:176–84.
29. Jørgensen NB, Jacobsen SH, Dirksen C, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab. 2012;303:E122–31.
30. Kashyap SR, Daud S, Kelly KR, et al. Acute effects of gastric bypass versus gastric restrictive surgery on β-cell function and

insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes. 2010;34:462–71.
31. Salinari S, Bertuzzi A, Guidone C, et al. Insulin sensitivity and secretion changes after gastric bypass in normotolerant and diabetic obese subjects. Ann Surg. 2013;257:462–8.
32. Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. Trends Mol Med. 2015;21:702–14.
33. Chiang JY. Bile acids: regulation of synthesis. J Lipid Res. 2009;50:1955–66.
34. Haeusler RA, Astiarraga B, Camastra S, et al. Human insulin resistance is associated with increased plasma levels of 12α−hydroxylated bile acids. Diabetes. 2013:DB_130639.
35. Sweeney TE, Morton JM. The human gut microbiome: a review of the effect of obesity and surgically induced weight loss. JAMA Surg. 2013;148:563–9.
36. Wahlström A, Kovatcheva-Datchary P, Ståhlman M, et al. Crosstalk between bile acids and gut microbiota and its impact on Farnesoid X receptor signalling. Dig Dis. 2017;35:246–50.
37. Ridlon JM, Kang D-J, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. J Lipid Res. 2006;47:241–59.
38. Staels B, Fonseca VA. Bile acids and metabolic regulation: mechanisms and clinical responses to bile acid sequestration. Diabetes Care. 2009;32:S237–45.
39. Kübeck R, Bonet-Ripoll C, Hoffmann C, et al. Dietary fat and gut microbiota interactions determine diet-induced obesity in mice. Mol Metab. 2016;5:1162–74.
40. Dutia R, Embrey M, O'brien S, et al. Temporal changes in bile acid levels and 12α-hydroxylation after Roux-en-Y gastric bypass surgery in type 2 diabetes. Int J Obes. 2015;39:806–13.
41. Wahlström A, Sayin SI, Marschall H-U, et al. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab. 2016;24:41–50.
42. Risstad H, Kristinsson JA, Fagerland MW, et al. Bile acid profiles over 5 years after gastric bypass and duodenal switch: results from a randomized clinical trial. Surg Obes Relat Dis. 2017;13:1544–53.
43. Guidone C, Manco M, Valera-Mora E, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes. 2006;55:2025–31.
44. Brunetti L, DeSantis EH. Patient tolerance and acceptance of colesevelam hydrochloride: focus on type-2 diabetes mellitus. Pharm Ther. 2015;40:62.
45. Sandhu S, Moosavi M, Golmohammadi K, et al. Colesevelam as an add-on treatment for control of dyslipidemia and hyperglycemia in type 2 diabetes. Can J Diabetes. 2016;40:112–4.
46. Coupaye M, Rivière P, Breuil MC, et al. Comparison of nutritional status during the first year after sleeve gastrectomy and Roux-en-Y gastric bypass. Obes Surg. 2014;24:276–83.
47. Steinert RE, Peterli R, Keller S, et al. Bile acids and gut peptide secretion after bariatric surgery: a 1-year prospective randomized pilot trial. Obesity. 2013;21:E660–8.
48. Khan FH, Shaw L, Zhang W, et al. Fibroblast growth factor 21 correlates with weight loss after vertical sleeve gastrectomy in adolescents. Obesity. 2016;24:2377–83.
49. Simonen M, Dali-Youcef N, Kaminska D, et al. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. Obes Surg. 2012;22:1473–80.
50. Angelin B, Björkhem I, Einarsson K, et al. Hepatic uptake of bile acids in man: fasting and postprandial concentrations of individual bile acids in portal venous and systemic blood serum. J Clin Invest. 1982;70:724–31.