HHS Public Access

Author manuscript

Obes Surg. Author manuscript; available in PMC 2015 May 11.

Published in final edited form as:

Obes Surg. 2012 September ; 22(9): 1473–1480. doi:10.1007/s11695-012-0673-5.

Conjugated Bile Acids Associate with Altered Rates of Glucose and Lipid Oxidation after Roux-en-Y Gastric Bypass

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Disclosure Statement All contributing authors (M Simonen, N Dali-Youcef, T Kuulasmaa, S Venesmaa, P Käkelä, M Pääkkönen, M Hallikainen, M Kolehmainen, M Uusitupa, L Moilanen, M Laakso, H Gylling, ME Patti, J Auwerx and J Pihlajamäki) declare that they have no conflicts of interests.

Conflict of Interest The authors have nothing to disclose.

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Abstract

Background—Laparoscopic Roux-en-Y gastric bypass (RYGB) induces a more favorable metabolic profile than expected by weight loss alone. In this study, we investigated the effect of RYGB on serum bile acid levels and their relation to clinical outcomes.

Methods—We included 30 obese patients who underwent RYGB (BMI=46.1±5.9 kg/m^2). Clinical measurements and laboratory determinations were performed before surgery and 1 year after surgery. Fasting serum bile acids were measured by an enzymatic method and individual bile acids were quantified by HLPC-tandem mass spectrometry. Indirect calorimetry was performed to measure the rates of energy expenditure and substrate oxidation.

Results—Fasting total serum bile acid levels increased twofold after RYGB (pre, 3.68±2.03 vs. post, 7.06± 9.65 μmol/l, +92 %, p=0.002). This increase in total bile acids was accompanied by a decrease in conjugated bile acids, which correlated with decreased glucose oxidation (r=0.571, p=0.002) and with increased lipid oxidation (r=−0.626, p=0.0004). The change in taurineconjugated bile acids correlated with altered *DIO2* mRNA expression in adipose tissue (r= −0.498, p=0.013) potentially linking bile acid conjugation to substrate oxidation through DIO2.

Conclusions—Fasting serum bile acid levels increase after RYGB. More specifically, changes in bile acid conjugation after RYGB associate with altered energy metabolism.

Keywords

Obesity surgery; Bile acids; Glucose and lipid oxidation; DIO2; CYP27A1

Introduction

Obesity surgery has rapidly gained more interest because of its capability to induce sustained weight loss and resolution of obesity-related co-morbidities including type 2 diabetes (T2DM) [1, 2]. It has been shown that laparoscopic Rouxen-Y gastric bypass (RYGB) induces more weight loss than purely restrictive laparoscopic adjustable gastric

banding (LAGB) [3, 4]. Furthermore, RYGB induces more favorable glucose and lipid metabolism than LAGB, which cannot be explained solely by additional weight loss [5].

The most common explanation for the more effective improvement in blood glucose levels after RYGB is altered secretion of gastrointestinal hormones, including GLP-1 and GIP, which stimulate insulin secretion [5–8]. It has been suggested that changes in bile acid metabolism could also contribute to improved metabolism [9–11]. Traditionally, bile acids are known to regulate lipid and glucose metabolism through the nuclear receptor FXR [12–15]. More recently, the G-protein family receptor TGR5 has been identified as a cell surface receptor for bile acids [16, 17]. Through this receptor, bile acids induce energy expenditure in mice by promoting FXR-independent intracellular thyroid hormone activation [18]. Furthermore, it has been shown that bile acids promote GLP-1 secretion through TGR5 activation in mouse models [19, 20]. Moreover, individual conjugated and unconjugated bile acids have different effects on their receptors between different tissues [11, 21].

Because serum bile acid levels are more than twofold higher in humans after RYGB compared to lean and obese individuals [22], RYGB forms an interesting human model to investigate interactions between serum bile acid levels and metabolic regulation. The purpose of this study was to investigate effects of RYGB on circulating levels of bile acids. We hypothesized that altered bile acid metabolism is a contributing factor to observed metabolic benefits after RYGB. We demonstrate in a longitudinal study that bile acid levels increase after RYGB surgery. Furthermore, we could link alterations in serum levels of conjugated bile acids after RYGB with the regulation of substrate oxidation.

Methods and Procedures

Subjects

All patients undergoing obesity surgery in Kuopio University Hospital are recruited into our ongoing study investigating metabolic consequences of obesity surgery (Kuopio Obesity Surgery Study) [23]. This study included 30 consecutive adult patients who were accepted for Roux-en-Y gastric bypass (RYGB) over the years 2005–2007 with the following criteria: (1) BMI>40 or 35 kg/m^2 with significant co-morbidity, (2) failure of dietary and drug treatments, and (3) no contraindication for operation. Every participant had a 1-day visit to the hospital for screening eligibility for obesity surgery. Fasting blood samples were drawn after 12 h of fasting followed by oral glucose tolerance test (OGTT), if T2DM had not been previously diagnosed. There were no dropouts with patients enrolled in study. This study was approved by the Ethics committee of the Kuopio University Hospital, and it was in accordance with the Helsinki Declaration.

Clinical Measurements

Body mass index (BMI) was calculated as weight (kilogram) divided by height (meter) squared. Bioelectrical impedance analysis (RJL Systems, Clinton Township, MI, USA) was used to determine lean body mass (LBM). Indirect calorimetry was performed with a computerized flow-through canopy gas-analyzer system (Deltatrac, Datex, Helsinki, Finland) at baseline and 1 year after surgery. This device has precision of 2.5 % for O_2 consumption and 1.0 % for CO_2 production. Data were used for calculation of respiratory

quotient (RQ) and resting energy expenditure (REE) [24]. RQ represents the ratio of CO_2 (VCO_2) exhaled to the amount of O_2 (VO_2) consumed by the subject. A Simplified Weir equation without urinary nitrogen was used to calculate 24-h resting energy expenditure (REE): REE(kcal/day)0[(3.941× VO_2)+(1.106×VCO_2)]1,440. The calorimetric values of VO_2 and VCO_2 were used to determine endogenous metabolism of lipids and carbohydrates in the fasting state [25]. The lean body mass (LBM)-corrected values of substrate oxidation were used in analysis. Macronutrient intake was estimated using the dietary records of 14 study subjects in the RYGB group at baseline and in follow-up.

Laboratory Determinations

Plasma glucose was measured by an enzymatic hexokinase photometric assay (Konelab Systems Reagents, Thermo Fischer Scientific, Vantaa, Finland). Insulin was determined by an immunoassay (ADVIA Centaur Insulin IRI, no 02230141, Siemens Medical Solutions Diagnostics, Tarrytown, NY). Serum free fatty acids (FFA) were analyzed by an enzymatic method (Wako Chemicals GmbH, Neuss, Germany). Insulin resistance and secretion indexes were calculated based on homeostasis model assessment (HOMA-IR and HOMA-IS).

Serum Bile Acid Measurements

Fasting levels of total serum bile acids were assayed by an enzymatic method (Fumouze Diagnostics, Levallois-Perret, France). Importantly, baseline and follow-up samples were paired for the analysis. Individual serum bile acids were measured by high-performance liquid chromatography (HPLC) tandem mass spectrometry (Waters™ S.A.S., St-Quentin En Yvelines, France) and quantified using deuterium-labeled internal standards [26]. The combined concentrations of primary, secondary, conjugated, and unconjugated bile acids were calculated from concentrations of individual bile acids.

Liver and Adipose Tissue Biopsies

Adipose tissues biopsies were taken during RYGB surgery and 1 year after surgery. Liver biopsies were obtained using Trucut needle (Radiplast AB, Uppsala, Sweden) during surgery. Eleven patients had clinical indication for a follow-up liver biopsy 1 year after surgery, and therefore, we could also obtain samples for gene expression analysis from these individuals. All samples for gene expression analysis were immediately frozen in liquid nitrogen.

RNA Extraction and Quantitative PCR Analysis

Total RNA from adipose tissue and liver was extracted using Tri-Reagent [Applied Biosystems (ABI) Foster City, CA, USA] and reverse transcribed using high capacity cDNA reverse transcription kit (ABI) according to manufacturer's protocol. Quantitative real-time PCR was carried out in the Applied Biosystems 7500 Real Time PCR System using KAPA SYBR FAST ABI Prism qPCR (Kapa Biosystems, Woburn, MA, USA). Reactions comprised of 1× qPCR Master Mix, 200 nM forward and reverse primers for *DIO2* (forward 5′-AGAGGGACTGCGCTGCGTCT-3′, reverse 5′-CTGGAGACATGCACCACACTGGAA-3′), *CYP7A1* (forward 5′-

CGTGGTCCTCTGGGCATCGC-3′, reverse 5′-AGGCACTGGAAAGCCTCAGCG-3′), *CYP27A1* (forward 5′-GGAGCTATGGAAGGAGCAC-3′, reverse 5′-AGCTGGTCCAGTCGAGTCAT-3′) and an endogenous control *RPLP0* (forward 5′-GGCGACCTGGAAG TCCAACT-3′, reverse 5′-CCATCAGCACCACAGCCTTC-3′) and 5 ng RNA (adipose tissue) or 3 ng (liver tissue) equivalent of sample cDNA.

Statistical Analysis

Data are presented as mean±SD. Nonparametric Wilcoxon signed-rank test was used for comparisons of differences between baseline and follow-up measurements. Relationships among parameters were analyzed by Spearman's correlation test. All analyses were conducted with the SPSS v.17.0 for Windows (SPSS, IL, USA). *P* value <0.05 was considered statistically significant.

Results

Baseline and follow-up characteristics are presented in Table 1. At baseline BMI was 46.1±5.9 kg/m^2 and 1 year after surgery BMI decreased to 34.3±5.9 kg/m^2 (−26 %). This result, as well as RYGB's favorable effect on serum lipid profile, has previously been published in our report investigating effects of RYGB and LAGB on cholesterol metabolism [23]. Resting energy expenditure (REE) decreased after RYGB (32.1±3.6 vs. 29.7±3.1 kcal/day/kg LBM, p=0.001). In addition, RQ decreased after RYGB (0.86±0.05 vs. 0.83±0.06, p=0.021), suggesting an increase in the ratio of lipid and glucose oxidation (Table 1).

Bile Acid Levels Increase after RYGB

Fasting total serum bile acid levels increased twofold after RYGB (3.68±2.03 vs. 7.06±9.65 μmol/L, p=0.002) (Fig. 1). This change in serum bile acid levels after surgery was not associated with weight loss (r=−0.109, p=0.453), and the levels after the surgery were not associated with the postsurgical BMI (r=−0.217, p=0.249).

The mean levels of primary, secondary and tertiary bile acids increased three- to fourfold after RYGB (Table 2). However, the difference between baseline and 1-year follow-up was statistically significant only for secondary bile acids (p=0.012). Levels of all individual bile acids are shown in Table 3 demonstrating a statistically significant 2.9-fold increase in deoxycholic acid (p=0.012). Taurineconjugated bile acids were the only bile acid levels that tended to decrease after RYGB (Tables 2, 3), decreasing from 9.4 % to 4.0 % (proportion of all bile acids) in response to RYGB (p=0.035). The ratio of taurine/glycine conjugation decreased significantly (p=0.009, Table 2).

We next asked if increased bile acid levels after RYGB could be related to alterations in expression of genes regulating classical (CYP7A1) or acidic (CYP27A1) bile acid synthesis pathway. The latter has been suggested to be affected after obesity surgery in rodents [27]. We found that the increased bile acid levels after RYGB could be related to increased hepatic production of bile acids. *CYP7A1* mRNA levels did not change in response to RYGB (0.10±0.08 at baseline and 0.11±0.09 at follow-up, p=0.657). However, *CYP27A1* mRNA levels tended to increase after RYGB (1.09±0.23 vs.1.51±0.67, p=0.091) and the

change in *CYP27A1* mRNA expression correlated positively with the change in total bile acids levels (r=0.670, p=0.029). We acknowledge that this analysis has to be considered preliminary because of a limited number of liver biopsies at follow-up (n=11).

Decrease in Serum-Conjugated Bile Acids is Linked with Decreased RQ after RYGB

We next asked if the increase in serum total bile acids or the changes in conjugated bile acids correlated with changes in energy metabolism after RYGB. The increase in serum total bile acid levels did not correlate with the observed decreases in REE and RQ after RYGB (Table 4). However, the decrease in serum-conjugated bile acid levels correlated positively with the change in RQ (r=0.664, p=0.0001, Table 4) and glucose oxidation (r=0.571, p=0.002), and negatively with the change in lipid oxidation (r=−0.626, p=0.0004), suggesting that altered conjugation of bile acids may link with energy metabolism. Next, we divided subjects to those who demonstrated an increase or a decrease in serum levels of conjugated bile acids. Figure 2a demonstrates that the characteristic increase in lipid oxidation and decrease in glucose oxidation after RYGB (see Table 1) was statistically significant only in those individuals who had a decrease in serum-conjugated bile acid levels (Fig. 2a), more specifically in those who demonstrated a decrease in levels of taurine-conjugated bile acids (Fig. 2b). We did not observe any significant associations of total bile acid or conjugated bile acids with weight loss, plasma glucose, HOMA-IR, HOMA-IS, or serum free fatty acid levels (data not shown).

Decrease in Serum Taurine-Conjugated Bile Acids Associates with an Increase in DIO2 Expression

To investigate potential mediators of the association between bile acid conjugation and energy metabolism, we tested the hypothesis that the link between serum taurineconjugated bile acids and energy metabolism is explained by the bile acid—TGR5—*DIO2* cascade [18]. To this aim, we assessed *DIO2* mRNA expression in adipose tissue. There was no correlation between changes in total serum bile acid levels and adipose tissue *DIO2* mRNA expression (r=−0.066, p=0.759, n=24). However, the decrease in serum levels of taurine-conjugated bile acids associated with an increase in *DIO2* mRNA expression in subcutaneous adipose tissue (r=−0.498, p=0.013, Fig. 2b). Accordingly, the change in *DIO2* correlated negatively with the change in glucose oxidation (r=−0.465, p=0.025) and positively with the change in lipid oxidation (r=0.474, p=0.022) after RYGB. We did not observe any statistically significant correlations between the change in *DIO2* mRNA levels and REE, weight loss, TSH, HOMA-IR, HOMA-IS, serum free fatty acids or plasma glucose levels (data not shown).

Discussion

In this 1-year prospective longitudinal study, we verified that serum bile acid levels increase approximately twofold after RYGB (Fig. 1). This increase could be related to a change in CYP27A1 mRNA expression, suggesting a link with acidic bile acid synthesis pathway. Interestingly, changes in the levels of conjugated bile acids linked with the characteristic decrease in RQ after RYGB [28, 29]. Overall, these results suggest that some of the

beneficial effects of RYGB on energy metabolism are mediated by altered bile acid metabolism.

Our study confirms the earlier observations that the levels of serum total bile acids increase after RYGB [22, 30]. In our prior cross-sectional study, we demonstrated that bile acid levels are twofold higher in subjects who have undergone RYGB 2–4 years earlier compared to pre- and postoperatively weight-matched cohorts [22]. Later, Nakatani et al. [30] reported that serum total bile acids were already increased at 1 and 3 months after obesity surgery. Interestingly, it was reported recently that ileal interposition increases bile acid recycling in rats [27] and also increases liver bile acid synthesis through acidic bile acid synthesis pathway regulated by *CYP27A1*, but not through classical *CYP7A1*. In our study, there was no association between bile acid levels and *CYP7A1* mRNA expression. However, increase in *CYP27A1* mRNA expression was associated with an increase in total bile acid levels in response to surgery, suggesting that increased hepatic production of bile acids could partly explain increased serum levels of total bile acids. We acknowledge that this analysis has to be considered preliminary because of difficulties to obtain human liver samples at follow-up (n=11).

The novel important finding in our current study is that, not the increases in serum total bile acids after RYGB, but the decrease in serum levels of conjugated bile acids links with observed decrease in RQ after RYGB (Table 4; Fig. 2a). This leads to the hypothesis that altered conjugation of bile acids after RYGB is an important mediator of metabolic consequences after RYGB, independent of changes in total serum bile acids. Although the mean levels of taurine-conjugated bile acids did not decrease significantly (Table 2), their relative abundance dropped from 9.4 % to 4.0 % (of all bile acids) in response to RYGB (p=0.035). At the same time, levels of unconjugated bile acids tended to increase (p=0.072, Table 2), suggesting that an alteration in conjugation occurs after RYGB.

A potential explanation for the link between serum-conjugated bile acids and substrate oxidation is that both are associated with decreased lipid absorption after RYGB. Because we have reported that cholesterol absorption is reduced after RYGB [23], we asked if changes in serum bile acid levels or conjugation associate with markers of cholesterol absorption (serum plant sterols, n=25, data not shown). However, there was no association between bile acid levels or conjugation and markers of cholesterol absorption. Similar to our observation in response to RYGB (Table 2), the ratio of taurine/glycine conjugation decreases in response to treatment with bile acid sequestrants or external biliary drainage [11]. Future experiments directly measuring lipid and bile acid absorption will be required to solve the exact mechanisms of altered conjugation after RYGB.

Although the reason for altered levels of conjugated bile acids remains unknown, the levels seem to associate with known biological targets of bile acid metabolism. We investigated if the link between altered bile acid levels and altered substrate oxidation after RYGB is explained by bile acid—TGR5—DIO2 cascade [18] by assessing *DIO2* gene expression in adipose tissue. Decreased levels of taurine-conjugated bile acids associated with increased expression of *DIO2* in white adi-pose tissue (Fig. 2b). Consistently, *DIO2* expression correlated negatively with glucose oxidation and positively with lipid oxidation supporting

the hypothesis that altered bile acid metabolism could lead to altered substrate oxidation by modifying *DIO2* activity. This explanation is supported by results showing that increased *DIO2* expression is associated with increased lipid oxidation in the brown adipose tissue of mice [18]. In conclusion, we propose that altered bile acid metabolism, possibly decreased conjugation, affects TGR5-DIO2 signaling after RYGB.

One of the limitations in the current and prior studies [22, 30] is that the serum bile acid levels were measured in a fasting state. Serum bile acids can increase 4.5–6-fold during the first 30 min after a single oral glucose tolerance test [31]. However, it has been reported that bile acid levels in peripheral venous samples correlate with portal venous samples in fasting and postprandial state and also that measurement of peripheral serum bile acids give information about the status of the enterohepatic circulation [32]. Secondly, we did not investigate links between serum gut peptides and bile acids; measurement of postprandial levels of both will be done in our ongoing studies. Thirdly, we had limited number of food records (14 study subjects) to exclude the effect of dietary changes after RYGB. Our food records showed that intake of energy (p=0.003), protein (p=0.003), fat (p=0.026), and carbohydrates (p=0.003) decreased after RYGB, as expected. However, food records did not show any significant change in the ratio of carbohydrate to fat intake (p=0.826) that could have explained the observed change in substrate oxidation. Finally, due to the relatively low number of individuals these results need to be verified in larger studies, including also other types of surgery.

In summary, serum bile acids increase twofold after RYGB. Increased hepatic synthesis through CYP27A1 pathway needs to be studied as an explanation for the elevated total bile acid levels after RYGB. However, the altered substrate oxidation after RYGB is more associated with changes in conjugation of bile acids than with the observed increase in serum total bile acid levels. We suggest that the mechanism behind this interaction is related to differentially activated bile acid regulated pathways, including *DIO2* [9]. Overall, these results support the concept that alterations in bile acid metabolism contribute to metabolic benefits after RYGB.

Acknowledgments

We thank Päivi Turunen and Tiina Sistonen for their careful work in patient recruitment and laboratory analyses. We also greatly thank greatly Carole Jamey for the technical assistance on bile acid measurements.

Funding This study was supported by the Finnish Diabetes Research Foundation (to JPI). JPI has an Academy of Finland Clinical Researcher fellowship (grant 120979 2008–2010 and 138006 2011– 2013). JA acknowledges grant support of the EU Ideas program (ERC-2008-AdG-23118), the Swiss National Science Foundation (FNS), and the Ecole Polytechnique Fédérale de Lausanne.

Abbreviations

BMI	Body mass index
DIO2	Type II iodothyronine deionidinase
FXR	Farnesoid X-receptor
GIP	Gastric inhibitory polypeptide

GLP1	Glucagon-like peptide-1
HOMA-IR	Homeostasis model of assessment-insulin resistance
HOMA-IS	Homeostasis model of assessment-insulin sensitivity
LAGB	Laparoscopic adjustable gastric banding
LBM	Lean body mass
OGTT	Oral glucose tolerance test
REE	Resting energy expenditure
RQ	Respiratory quotient
RYGB	Laparoscopic Roux-en-Y gastric bypass
TGR5	G protein-coupled bile acid receptor
TSH	Thyroid stimulating hormone

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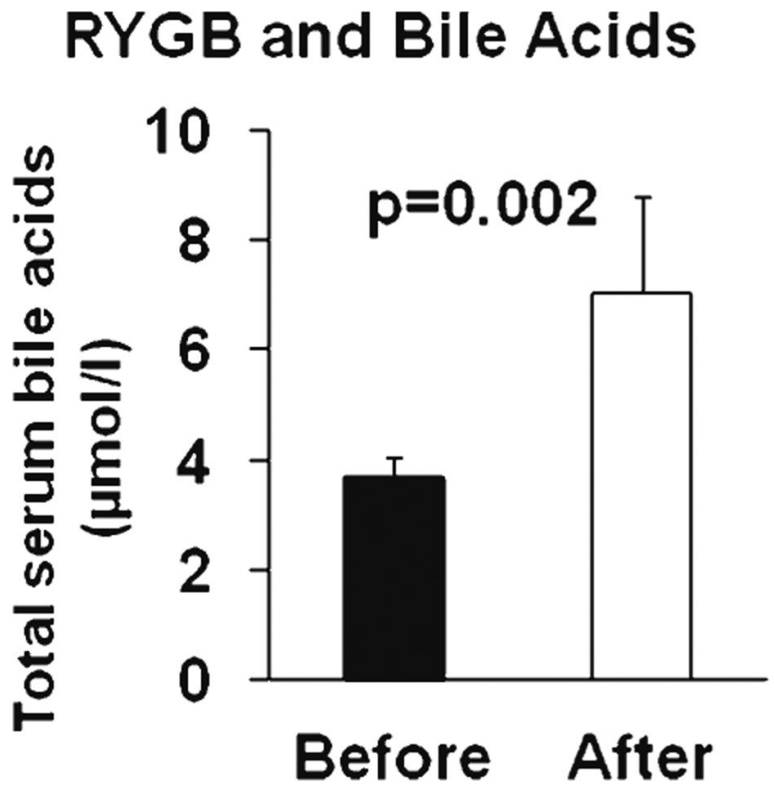

Fig. 1.

Fasting serum total bile acid levels before and 12 months after Roux-en-Y gastric bypass (RYGB). *P* indicates a difference between baseline and follow-up, mean±SEM shown

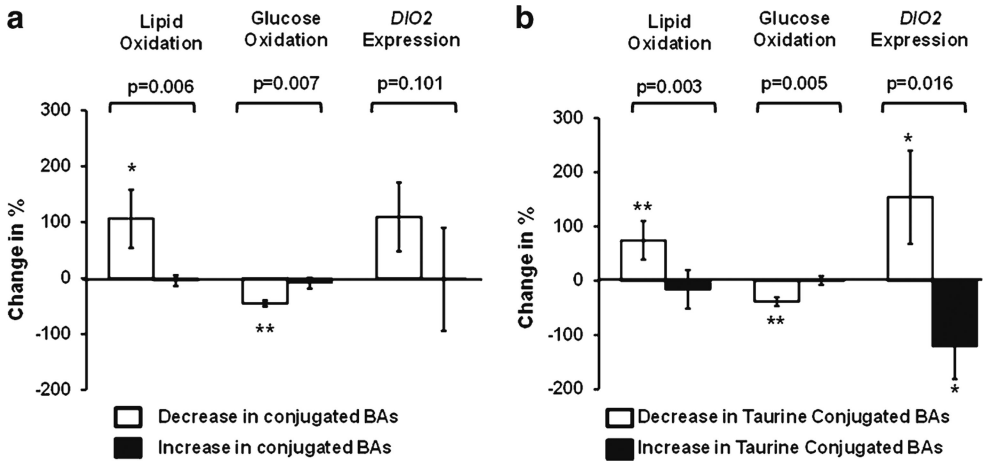

Fig. 2.

a Increased lipid oxidation and decreased glucose oxidation is observed in individuals demonstrating a decrease in levels of serum conjugated bile acids. **b** Increased lipid oxidation and DIO2 expression and decreased glucose oxidation is observed in individuals demonstrating a decrease in levels of serum taurine-conjugated bile acids. *P* shows the statistical significance between groups (decrease vs. increase bile acid levels). **p*<.05 and ***p*<.01 show statistically significant changes inside the groups compared to baseline. Mean ±SEM shown

Table 1

Characteristics of individuals who underwent RYGB before (baseline) and 12 months (follow-up) after obesity surgery

	Baseline	Follow-up	Change (%)	*p*
Gender (male/female)	3/27	–	–	–
Age (years)	45.2±7.9	–	–	–
Weight (kg)	129.9±19.9	96.7±18.9	–26 %	<0.001
Body mass index (kg/m^2)	46.1±5.9	34.3±5.9	–26 %	<0.001
Fasting glucose (mmol/L)	6.58±2.07	5.39±0.71	–18 %	<0.001
HOMA-IR (mmol/l×mU/L)	6.7±6.5	2.1±2.2	–69 %	<0.001
ALT (U/L)	38.2±26.1	20.7±8.9	–46 %	<0.001
TSH (mU/L)	1.75±0.88	1.64±0.74	–6 %	0.424
Energy expenditure(kcal/day/kg LBM)	32.1±3.6	29.7±3.1	–7 %	0.001
Respiratory quotient	0.86±0.05	0.83±0.06	–3 %	0.021
Glucose oxidation(g/day/kg LBM)	4.07±1.41	3.11±1.46	–24 %	0.002
Lipid oxidation (g/day/kg LBM)	1.70±0.63	1.88±0.71	+11 %	0.111

Mean±SD shown. Percentage change is the difference in percents between baseline and follow-up

Nonparametric Wilcoxon signed-rank test was used for paired difference between baseline and follow up (*p*=two-tailed significance)

HOMA-IR homeostasis model assessment of insulin resistance;

ALT serum alanine aminotransferase; *TSH* thyroid stimulating hormone; *LBM* lean body mass

Table 2

Changes in serum fasting bile acid levels (μmol/L, mean±SD shown) in response to Roux-en-Y gastric bypass

	Baseline	Follow-up	Change (%)	*p*
Primary bile acids	1.04±1.82	3.43±8.67	+230 %	0.185
Secondary bile acids	0.65±0.63	1.90±3.52	+191 %	0.012
Tertiary bile acids	0.10±0.12	0.43±1.83	+318 %	0.910
Unconjugated bile acids	1.79±2.27	5.75±13.88	+221 %	0.072
Conjugated bile acids	4.45±6.66	3.73±3.61	–16 %	0.877
Glycine-conjugated	3.06±2.88	3.49±3.39	+14 %	0.441
Taurine-conjugated	1.38±5.85	0.25±0.36	–82 %	0.153
Taurine/glycine (ratio)	0.44±1.80	0.07±0.49	–84 %	0.009
Unconjugated/conjugated (ratio)	0.81±1.06	1.85±3.28	+128 %	0.206

Percentage change is the difference in percents between baseline and follow-up. Non-parametric Wilcoxon signed-rank test was used for paired difference between baseline and follow up (*p* = two-tailed significance)

Table 3

Fasting levels of individual serum bile acids (micromole per liter) before and 12 months after Roux-en-Y gastric bypass

	Baseline	Follow-up	Change (%)	*p*
Primary bile acids				
Cholic acid	0.321 ±0.735	1.513±4.306	+371 %	0.141
Chenodeoxycholic acid	0.720±1.207	1.919±4.397	+167 %	0.185
Secondary bile acids				
Deoxycholic acid	0.643±0.623	1.881±3.506	+193 %	0.012
Lithocholic acid	0.008±0.013	0.014±0.025	+43 %	0.155
Tertiary bile acids				
Ursodeoxycholic acid	0.102±0.116	0.426±1.833	+318 %	0.910
Conjugated bile acids				
Glycocholic acid	0.357±0.403	0.301±0.366	–16 %	0.267
Glycochenooxycholid acid	1.961±2.196	2.057±2.141	+0.5 %	0.309
Glycodeoxycholic acid	0.575±0.671	0.942±0.929	+64 %	0.072
Glycolithocholic acid	0.019±0.022	0.041±0.047	+116 %	0.009
Glycoursodeoxycholic acid	0.152±0.173	0.145±0.174	–5 %	0.644
Taurocholic acid	0.109±0.159	0.062±0.148	–43 %	0.043
Taurochenodeoxycholic acid	0.097±0.155	0.077±0.143	–21 %	0.496
Taurodeoxycholic acid	1.170 ±5.825	0.098±0.149	–92 %	0.888
Taurolithocholic acid	0.003±0.005	0.003±0.008	+9 %	0.638
Tauroursodeoxycholic acid	0.005±0.005	0.007±0.010	+31 %	0.841

Mean±SD shown. Percentage change is the difference in percents between baseline and follow-up

Nonparametric Wilcoxon signed-rank test was used for paired difference between baseline and follow up (*p* = two-tailed significance)

Table 4

Spearman's correlations of changes (from baseline to follow-up) in serum bile acid levels with changes in resting energy expenditure (REE) and respiratory quotient (RQ) in subjects who underwent Roux-en-Y gastric bypass

	REE	RQ
Total bile acids	–0.230	0.333
Primary bile acids	0.184	0.285
CA	0.160	0.217
CDCA	0.210	0.325
Secondary bile acids	0.136	0.019
DCA	0.145	0.024
LCA	–0.014	–0.215
Tertiary bile acids	.	.
UDCA	0.084	0.402[a]
Unconjugated bile acids	0.260	0.135
Conjugated bile acids	–0.131	0.664[c]
Glycine-conjugated	0.065	0.545[b]
Taurine-conjugated	–0.267	0.559[b]
Unconjugated/conjugated	0.192	0.053

CA cholic acid; *CDCA* chenodeoxycholic acid; *DCA* deoxycholic acid; *LCA* lithocholic acid; *UDCA* ursodeoxycholic acid

[a] $p<0.05$ (significance; two-tailed)

[b] $p<0.01$(significance; two-tailed)

[c] $p<0.001$ (significance; two-tailed)