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ORIGINAL CONTRIBUTIONS

Changes in Bile Acid Profile After Laparoscopic Sleeve Gastrectomy are Associated with Improvements in Metabolic Profile and Fatty Liver Disease

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Abstract
Background Bile acids (BA) modulate lipid and glucose metabolism in a feedback loop through production of fibroblast growth factor (FGF) 19 in the terminal ileum. Changes in BA after bariatric surgery may lead to improvements in the metabolic syndrome, including fatty liver disease. This study investigated the relationship between BA and metabolic and inflammatory profiles after laparoscopic sleeve gastrectomy (LSG).
Methods Patients undergoing LSG had fasting blood samples taken pre-operatively and 6 months post-surgery. Liver injury was measured using cytokeratin (CK) 18 fragments. BA were measured using liquid chromatography tandem-mass spectrometry. FGF-19 was measured using enzyme-linked immunosorbent assay.
Results The study included 18 patients (12 females), with mean age 46.3 years (SEM±2.9) and BMI 60.1 kg/m^2 (±2.6). After 6 months, patients lost 39.8 kg (±3.1; $p<0.001$). Fourteen patients (78 %) had steatosis. FGF-19 increased from median 128.1 (IQR 89.4–210.1) to 177.1 (121.8–288.9, $p=0.045$) at 6 months. Although total BA did not change, primary glycine- and taurine-conjugated BA, cholic acid decreased, and secondary BA, glycine-conjugated urodeoxycholic acid increased over the study period. These changes are associated with reduction in insulin resistance, pro-inflammatory cytokines and CK-18 levels.
Conclusions The profile of individual BA is altered after LSG. These changes occur in the presence of reductions in inflammatory cytokines and markers of liver injury. This study supports evidence from recent animal models that LSG may have an effect on fatty liver through changes in BA metabolism.

Keywords Bariatric surgery · Sleeve gastrectomy · Bile acids

Introduction

Elevations in pro-inflammatory cytokines, including C-reactive protein (CRP), interleukin (IL)-6 and tumour necrosis

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factor (TNF) α, and oxidative stress are a causative link between obesity, increased adipose tissue, hyperlipidaemia and atherosclerotic cardiovascular disease [1].

Non-alcoholic fatty liver disease (NAFLD), with or without steatohepatitis (NASH), is found in up to 86 % of patients undergoing bariatric surgery and is the fastest growing cause of liver disease in the Western Hemisphere [2]. Accumulation of intracellular lipid and the pro-inflammatory cytokine milieu leads to reduced capacity in fat-laden hepatocytes to tolerate any insult, leading to increased hepatocellular injury and death [3]. Cytokeratin (CK)-18 is a marker of hepatocyte apoptosis. CK-18 M30 fragment levels are increased in NASH compared with obese NAFLD controls and correlate with fibrosis scores [4, 5]. NASH/NAFLD improves after bariatric surgery [6].

Bile acids (BA) are end products of cholesterol metabolism and are also signalling molecules, stimulating production of fibroblast growth factor (FGF) 19 in the terminal ileum. FGF-19 acts in the liver in a negative feedback loop by regulating cholesterol 7α-hydroxylase (*CYP7A1*) activity via the nuclear RXR farnesoid X receptor-α (FXR) [7]. BA also act via transmembrane G-protein coupled receptor (TGR5) [8]. Both FXR and TGR5 are involved in regulating lipid metabolism and modulating inflammatory cytokines production by liver macrophages, monocytes and Kuppfer cells [9]. Insulin regulates BA composition, in part by regulating the BA 12α-hydroxylase (*CYP8B1*), and it has been shown that the ratio of 12α-hydroxylated/non-12α-hydroxylated BAs is associated with key features of insulin resistance [10].

Roux-en-Y gastric bypass (RYGB) increases FGF-19 and BA (fasting and postprandial) [11–14]. The effect of laparoscopic sleeve gastrectomy (LSG) on enterohepatic circulation in humans is less certain. Steinert et al. report no difference in the total BA over the first year after LSG, compared with the increases seen in the RYGB group [15]. Haluzikova et al. noted an increase in FGF-19 after 6 months of LSG without a change in the total BA [16].

Bechmann et al. investigated BA profiles in obese patients with NAFLD/NASH and found that serum BA was higher in NASH than that in the simple steatosis, as was CK-18 M30 [17]. Recently, Myronovych et al. have shown that sleeve gastrectomy (SG) in a high-fat diet mouse model leads to reduction in hepatic steatosis, independent of weight loss, associated with changes in cholic acid (CA) and glycine-conjugated ursodeoxycholic acid (GUDCA) [18]. The same group have demonstrated that the beneficial metabolic effects of increased BA after SG are not seen in FXR knockout mice which have elevated plasma TG levels, hepatic steatosis and elevated levels of TNFα and other pro-inflammatory cytokines [19]. These studies suggest that SG has a weight-independent metabolic effect on hepatic lipid metabolism and glycaemic control, mediated by BA through FXR.

Clinical studies have demonstrated that the FXR-FGF-BA axis is important in humans [20, 21]. Ursodeoxycholic acid (UDCA) is a secondary BA that exerts an anti-apoptotic effect on hepatocytes, reducing circulating TNFα levels and improving hepatic insulin sensitivity [22]. A systematic review of 12 studies of UDCA in 1160 patients has shown that treatment with oral UDCA leads to reduction in alanine aminotransferase (ALT) and reduced fibrosis and steatosis [23].

The aim of this study was to investigate whether changes in BA profile after LSG were associated with reduction in inflammation, insulin resistance, circulating lipids and markers of liver injury.

Methods

Participants

Patients undergoing LSG were recruited prospectively. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Inclusion criteria were age 18 to 75 years, meeting the National Institute of Health and Care Excellence (NICE) 2006 guidelines for bariatric surgery, that is BMI >40 kg/m^2 or >35 kg/m^2 with obesity-related complications [24]. Exclusions were known alcohol intake of over 20 g per day, any known chronic pre-existing liver disease (including alcoholic liver disease, autoimmune liver disease, metabolic storage diseases such as haemochromatosis), elevated transaminases, abnormal hepatitis serology or autoantibody screen, previous liver surgery, active psychiatric illness, bleeding tendency or prescribed anticoagulant medications. Informed consent was obtained from all individual participants included in the study.

Fasting venous blood samples were taken before surgery and 6 months after surgery. Samples underwent routine biochemistry and haematology analysis using an automated multi-analyser, The remaining samples were stored in aliquots at −80 °C for batch analysis of other markers. Liver tissue samples were taken using a 16 gauge Tru-Cut® spring-loaded biopsy needle (UK Medical Limited, Sheffield, UK) at the beginning of surgery for histopathological analysis.

All LSG were performed by a single surgeon (AGP), according to a previously described technique using a 38 French bougie [25].

Assays

Routine assays

The following were measured on the Advia 2400 (Siemens Healthcare, Frimley, UK): ALT, aspartate transaminase

(AST), CRP, full lipid profile [(total cholesterol, TG, low-density lipoprotein (LDL), HDL], glucose and non-esterified fatty acids (NEFA). Insulin was measured using Advia Centaur (Siemens Healthcare, Frimley, UK) and glycated haemoglobin (HbA1c) by Menarini 9210 (A.Menarini Diagnostics Ltd., Berkshire, UK).

Insulin resistance was measured by calculating HOMA-IR as Fasting glucose (mmol/l) $\times$fasting insulin $\frac{(\mathrm{mU/l})}{22.5}$ [26].

Biomarkers

The following assays were performed according to the manufacturer's instructions: cytokines IL-6 and IL-10, TNFα and markers of liver injury, cytokeratin M30 and M65. TNFα, IL-6, IL-10 and leptin were measured using a bead-based multiplex array (Fluorokine® MultiAnalyte Profiling Kit, R&D Systems Europe Ltd, Abingdon, UK), and the results were read on a Luminex® Analyzer (Luminex B.V., Oosterhout, The Netherlands). Enzyme-linked immunosorbent assay (ELISA) were used for CK-18 M65 and M30 (M65® Classic and M30 Apoptosense®, PEVIVA AB, Bromma, Sweden, supplied through BIOAXXESS® UK, Malvern, UK), TRAIL and FasL (Quantikine ELISA, R&D Systems Europe Ltd., Abingdon, UK).

FGF-19 was measured using Quantikine Human FGF-19 Immunoassay (R&D Systems Europe Ltd., Abingdon, UK).

Bile Acids

Plasma unconjugated and glycine- or taurine-conjugated primary and secondary BA (15 fractions) were analysed using a high-performance liquid chromatography (JascoTM, USA) coupled to tandem mass spectrometry (Applied Biosystems, Cheshire, UK), with a modified and extended methodology initially described by Tagliacozzi et al. [27]. The 12α-hydroxylated BA [CA, deoxycholic acid (DCA) and their conjugated forms] and non-12α-hydroxylated BA (chenodeoxycholic acid (CDCA), lithocholic acid (LCA), UDCA and their-conjugated forms) were calculated.

Statistical Analysis

Statistical analyses were performed using SPSS 20 (SPSS, USA). Before comparative statistical tests were performed, outliers were sought visually using boxplots. The assumption of normality was tested for each parameter, using values of the difference between paired samples before and 6 months after surgery using Shapiro-Wilk's test ($p>0.05$). Only BMI, ALT and AST met the criteria of having minimal numbers of outliers and normally distributed paired differences. These data are therefore presented as mean with 95 % confidence intervals, and paired t tests were performed to compare the two time points. All other parameters are presented median±interquartile range (IQR) unless otherwise stated and Mann-Whitney U tests were performed to compare time points.

For parameters whose values changed significantly between time points, a fold change ratio was calculated as [6-month value]/[Baseline value]. These values were log2 transformed. The assumption of normality was tested using Shapiro-Wilk's test ($p>0.05$). Linearity was checked visually using scatter plots. Pearson's correlation was performed between these parameters to look for any significant associations. Clinical significance was determined if $p<0.05$.

Results

Clinical Parameters and Biomarkers

The study included 18 patients (12 females), with mean age 46.3 years (SEM±2.9) and mean BMI 60.1 kg/m^2 (±2.6). Liver biopsies showed that 14 patients (78 %) had steatosis, with a median NAFLD activity score of 5 (IQR 2.5–5), where a score of 5 or more is indicative of NASH [28]. After 6 months, patients lost mean 39.8 kg (±3.1) which represents mean total body weight loss of 23.6 % (±1.5). Liver transaminase levels were all within the normal range at outset and both ALT and AST decreased. Markers of glycaemic control and insulin resistance improved (Table 1). Seven patients had impaired fasting glycaemia pre-operatively, but at 6 months, six had normalised.

Pre-operative lipid profiles were all in the normal range, presumably as all patients with dyslipidemia were being treated with lipid-lowering medications ($n=11$). All patients had discontinued statin therapy before the 6-month follow-up. Fasting NEFA levels decreased after 6 months (see Table 1). Pro-inflammatory markers, IL-6, leptin and CRP decreased. Furthermore, CK-18 fragments decreased.

FGF-19 and Bile Acids

FGF-19 levels rose significantly over the study period, from a baseline median 128.1 (89.4–210.1) to 177.1(121.8–288.9, $p=0.045$). This was not accompanied by a change in total BA concentration. More detailed analysis of specific constituent BA showed rises in secondary conjugated BA,

Table 1 Changes in clinical and biomarker values before and 6 months after laparoscopic sleeve gastrectomy

	Before LSG	After 6 months	*p* value
Weight (kg)	167 (155–182)	128 (104–139)	<0.001
BMI (kg/m^2)	60.6 (55.3–65.8)	45.8 (41.5–50.1)	<0.001
ALT (IU/L)	31 (26–37)	18 (15–22)	<0.001
AST (IU/L)	27 (23–30)	20 (17–23)	<0.001
Fasting glucose (mmol/L)	7.2 (6–8.8)	4.8 (4.4–5.7)	0.004
Fasting insulin (mIU/L)	25 (14.2–33.8)	8.6 (5.5–13.4)	0.001
HOMA-IR	7.7 (5.3–11.8)	1.7 (1.2–3.1)	0.001
HBA1$_c$ (%)	6.5 (5.9–7.7)	5.5 (5.1–6.1)	0.008
Cholesterol (mmol/L)	4 (3.7–4.6)	4 (3.6–4.7)	ns
Triglycerides (mmol/L)	1.6 (1.1–2.2)	1.3 (0.9–1.7)	ns
LDL (mmol/L)	2.2 (1.7–2.7)	2.4 (1.8–3.3)	ns
HDL (mmol/L)	1.1 (1–1.2)	1.1 (0.9–1.2)	ns
NEFA (mmol/L)	0.7 (0.48–0.93)	0.45 (0.37–0.56)	0.008
CRP (mg/L)	10.3 (6.8–20.7)	6 (5–17.4)	0.05
IL-6 (pg/ml)	6 (3.5–8.3)	4.3 (3.2–5.5)	0.04
IL-10 (pg/ml)	0.7 (0.3–1.1)	0.7 (0.7–0.7)	ns
TNFα (pg/ml)	7 (4.1–7.6)	7.3 (6.2–9.4)	ns
Leptin (ng/ml)	142 (101–206)	48 (20–84)	0.001
M65 (IU/L)	249 (202–535)	240 (163–264)	0.015
M30 (IU/L)	174 (123–251)	132 (105–140)	0.001
AST/ALT ratio	0.9 (0.8–1)	1 (0.9–1.4)	0.005

P values were calculated using either Mann-Whitney *U* tests or Student's paired *t* test. A p value<0.05 was considered significant

BMI body mass index, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *HOMA-IR* homeostatic model assessment insulin resistance index, *HBA1$_c$* glycated haemoglobin percentage, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *NEFA* non-esterified fatty acids, *CRP* C-reactive protein, *IL* interleukin, *TNF* tumour necrosis factor, *M65*, *M30* cytokeratin-18 epitope M65 or M30, *NS* non significant

glycoursodeoxycholic acid (GUDCA) and reductions in primary conjugated BA, glycocholic acid (GCA), and taurocholic acid (TCA) as well as secondary BA and DCA (Table 2).

Correlations

These results are summarised in Table 3. Pre-operatively, BMI correlated with CRP (Spearman's rho=0.596, p=0.007) and post-operative BMI correlated with IL-6 (rho=0.554, p=0.04).

The reduction in GCA correlated with M30 (p=0.003). The decrease in TCA correlated with the decrease in leptin (p=0.04), and the reduction in DCA was associated with a decrease in fasting insulin (p=0.019). There was no correlation between the increase in FGF-19 and BA concentrations, nor with HOMA-IR or inflammatory markers. The reduction in GCA and decrease in M30 levels also correlated (after log2 transformation, Pearson's r=0.700, p=0.003).

Discussion

This is the first study to report significant changes in levels of individual primary and secondary BA and corroborates the findings of Haluzikova et al., who also showed an increase in FGF-19 after 6 months of LSG, with no change in total BA [16]. Of particular interest is the rise in UDCA following LSG and the associations between GCA, DCA and TCA with the expected post-LSG metabolic improvements, including lower insulin resistance and circulating CK-18 fragments.

Although lipid profiles did not change over the 6 months, this study shows for the first time that LSG leads to a decrease in circulating NEFA, associated with improved glycaemic control. NEFA levels are higher in obese and diabetic subjects [29]. The fall in NEFA may reflect a change in lipid processing and supports the hypothesis that LSG could lead to improvements in NAFLD through mechanisms other than weight loss or improved glycaemic control alone. RYGB has been shown to impact lipid profiles, and this effect may be independent of weight loss [30]. Further studies are required to confirm this effect in patients undergoing LSG.

Table 2 Bile acid profiles before and 6 months after LSG surgery

Bile acid profiles	Before LSG	6 months after LSG	*p* value
Fasting BAs (μmol/L)			
Total BA	2.35 (1.41–3.66)	2.41 (1.84–3.04)	ns
Total GCBA	1.14 (0.67–1.96)	1.49 (0.73–2.14)	ns
Total TCBA	0.24 (0.16–0.36)	0.17 (0.14–0.32)	ns
Total unconjugated BA	0.58 (0.41–0.95)	0.46 (0.25–0.81)	ns
Primary BAs			
CA	0.06 (0.02–0.2)	0.03 (0.03–0.08)	ns
CDCA	0.14 (0.08–0.31)	0.09 (0.05–0.23)	ns
Primary conjugated BAs			
GCA	0.2 (0.08–0.3)	0.09 (0.04–0.17)	0.048*
TCA	0.01 (0–0.07)	0 (0–0.02)	0.039*
GCDC	0.51 (0.22–1.21)	0.56 (0.25–1.12)	ns
TCDC	0.09 (0.04–0.15)	0.03 (0.02–0.14)	ns
Secondary BAs			
DCA	0.24 (0.16–0.42)	0.13 (0.09–0.23)	0.048*
UDCA	0.06 (0.04–0.07)	0.07 (0.03–0.32)	ns
LCA	0.01 (0.01–0.02)	0.01 (0.01–0.02)	ns
Secondary conjugated BAs			
GDCA	0.19 (0.12–0.36)	0.15 (0.10–0.37)	ns
TDCA	0.08 (0.05–0.11)	0.07 (0.05–0.08)	ns
GUDCA	0.1 (0.05–0.15)	0.26 (0.06–0.63)	0.004*
TUDCA	<LOD	<LOD	
GLCA	0.07 (0.06–0.08)	0.07 (0.06–0.08)	ns
TLCA	0.06 (0.06–0.06)	0.06 (0.06–0.07)	Ns
12a-hydroxylated/non–12a-hydroxylated ratio	0.77 (0.66 to 0.89)	0.48 (0.34 to 0.62)	<0.001*

Values are expressed as median with inter-quartile ranges (IQR). *P* value was obtained by Mann-Whitney *U* test

RYGB Roux-en-Y gastric bypass, *BAs* Bile acids, *CA, CDCA, DCA, LCA, UDCA* cholic, chenodeoxycholic, deoxycholic, lithocholic and ursodeoxycholic acids, respectively, *G, T* indicates glycine or taurine conjugation, *LOD* limit of detection, *ns* non-significant

*$p<0.05$

Cytokines

LSG had a measurable impact on inflammatory markers, reducing CRP and IL-6 [31]. Leptin levels reduced by >50 % over the 6 months [32]. Consistent with multiple other studies, TNFα levels did not change significantly in this study [31]. IL-10 levels were also unchanged. Although it has anti-inflammatory effects in animal models and in vitro, the relationship between IL-10, obesity and NAFLD/NASH is not clearly elucidated [33]. Levels of pro-inflammatory cytokines

Table 3 Correlations between changing BA and biomarkers (Pearson's *r*)

	FGF19	BMI	Insulin	HOMA-IR	NEFA	IL-6	CRP	Leptin	M30	M65
GCA	0.21	0.21	0.45	0.47	0.26	0.14	−0.05	0.48	0.70**	0.32
TCA	0.56	0.31	0.56	0.59	0.46	−0.34	−0.52	0.68*	0.63	0.14
DCA	0.27	0.02	0.60*	0.42	−0.31	0.48	−0.08	0.24	0.41	0.50*
GUDCA	0.11	−0.28	0.11	0.09	−0.40	−0.06	0.20	−0.07	0.30	0.35

All parameters transformed log [base 2]

GCA glycocholic acid, *TCA* taurocholic acid, *DCA* deoxycholic acid, *GUDCA* glycoursodeoxycholic acid, *FGF* fibroblast growth factor, *BMI* body mass index, *HOMA-IR* homeostatic model assessment insulin resistance index, *NEFA* non-esterified fatty acids, *IL* interleukin, *CRP* C-reactive protein, *M65*, *M30* cytokeratin-18 epitope M65 or M30

*$p<0.05$; **$p<0.01$

correlate with BMI and confirm the relationship between increasing obesity and inflammation [34].

Liver Injury and Apoptosis

Improvement in NAFLD/NASH after bariatric surgery has been demonstrated using serial liver biopsies [6]. CK-18 levels fell after 6 months, and this study adds to the growing weight of evidence for its usefulness as a marker of fatty liver disease [4, 5]. Only two other studies have serially measured CK-18 levels after bariatric surgery. Diab et al. reported a median M30 level of 226U/L (IQR 177–298), which reduced by 44 % after 6 months [35], and Kahraman et al. report a reduction in both M30 and M65 after various types of bariatric surgery [36]. M30 also correlates with NAS, confirming its utility as a marker of NAFLD severity [35].

Bile Acids and Their Potential Effects on Fatty Liver and Metabolism

Total BA concentration did not change after LSG whilst FGF-19 levels increased by 51 % after 6 months, as shown previously [16].

One proposed mechanism for the increase in FGF-19 is through increased delivery of unmixed BA to the terminal ileum due to faster gastric emptying and intestinal transit post-LSG [37]. The increase in FGF-19 is accompanied by an increase in incretin release. This has also been postulated as a mechanism for improvement in T2DM post-RYGB [38] and confirmed in small animal models [39].

In this study, two primary conjugated BA, TCA and GCA levels decrease along with secondary BA DCA. The secondary BA GUDCA increased. Taken together, these changes may be due to altered BA conjugation/deconjugation metabolism by gut microbiota. The variety of species of gut microbiota changes after RYGB and is associated with altered expression of inflammation-associated genes in adipose tissue and alterations in BA profile [40]. These microbiota-induced changes may be due to alterations in circulating bacterial endotoxins, lipopolysaccharides (LPS), which produce an immune response [41]. Monte et al. have found that circulating LPS reduced after RYGB, with associated decrease in insulin resistance [42]. Although LSG has been shown to alter gut microbiota in a pilot study, no data regarding the effect on LPS are available at present [43]. Furthermore, the decrease in 12α-hydroxylated BA to non-12α-hydroxylated BA ratio 6 months post-LSG also reflects improvements in insulin sensitivity [10].

Given the interest and substantial experimental evidence that UDCA may be a potential treatment for NASH, it is pertinent to consider the importance of this finding, as GUDCA is the active metabolite of UDCA after glycine conjugation. In a mouse hepatocyte model, UDCA administration was associated with a hepato-protective effect, inhibiting apoptosis [22]. In both high-fat diet steatotic mice and a NASH mouse model, Pathil et al. showed that intraperitoneal injections of UDCA ameliorated signs of liver injury and altered lipid metabolism [44]. Similarly, Buko et al. found that UDCA reduced liver steatosis and inflammatory markers in a rat model of NASH [45]. In a rat model of SG, Myronovich et al. found that taurine-UDCA (the rat homolog of GUDCA) was increased. They also demonstrated that these changes were associated with altered hepatic gene expression and reduction in hepatic steatosis [18].

The fall in GCA correlates with a reduction in post-operative CK-18 M30 levels. Although there is little other supporting evidence for a direct role of GCA in inducing NASH from either in vitro or animal studies, there are studies suggesting that GCA is involved in liver injury. Luo et al. looked at patterns of BA fractions in various mouse models of drug-induced liver injury and found differentially altered CA, GCA and TCA levels associated with particular patterns of injury [46]. In NASH, CA, DCA and CDCA were found in elevated concentrations compared with controls and CA levels correlated with histological grading of inflammation [47].

This is the first study in humans to show that individual BA may have a role in reducing obesity-related inflammation, with reductions in both leptin and other pro-inflammatory cytokines also occurring over the study period. Changes in BA are associated with alterations in gut microbiota, LPS and, consequently, inflammation [19]. In another recent study in a rat model of VSG, Myronovich et al. have shown that small heterodimer partner (SHP), another orphan nuclear receptor downstream of FXR, is involved in the inflammatory response and in hepatic steatosis [48]. This supports the hypothesis that the BA-FXR pathway is key to understanding how LSG is associated with reduction in pro-inflammatory cytokines and improvements in NAFLD/NASH.

Limitations

This study was limited by only having 6-month post-operative follow-up with more profound changes possibly happening later. Others have reported that the total BA concentration peaked at 1 year after both LSG and RYGB [15], with IL-6 lowest at 12 months after bariatric surgery, with significant changes between 6 and 12 months [49]. Although this is the largest study of BA in patients undergoing LSG to date, the study sample size was relatively small [15, 16]. Future large-scale studies can be designed, with stratification based on severity of NAFLD, and to control the effect of pre-existing T2DM and concomitant medication usage, especially statins.

Further exploration is required of the relationships between individual BA, changes in gut microbiota and improved markers of NAFLD/NASH. These studies will benefit from measurement of circulating LPS, as a marker of gut bacterial

load, and 7alpha-hydroxy-4-cholesten-3-one (C4), which is an indirect measure of BA synthesis via the action of the rate-limiting enzyme *CYP7A1* [50]. Measurement of faecal BA levels would aid the understanding of changes in BA absorption after LSG [43, 51]. Finally, dynamic measurement of BA in the pre- and postprandial period may be a more accurate reflection of BA production and physiology [52].

Conclusions

The profile of individual BA and enterohepatic circulation is altered after LSG. These changes occur in the presence of reductions in inflammatory cytokines and markers of liver injury. This study supports evidence from recent reports from animal models that sleeve gastrectomy may have an effect on NAFLD/NASH through changes in BA metabolism, probably through the FXR pathway.

Compliance with Ethical Standards Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare that they have no competing interests.

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