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Duodenal-jejunal lining increases postprandial unconjugated bile acid responses and disrupts the bile acid-FXR-FGF19 axis in humans ☆

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ABSTRACT

Background and Aims: Placement of the duodenal-jejunal bypass liner (DJBL) leads to rapid weight loss and restoration of insulin sensitivity in a similar fashion to bariatric surgery. Increased systemic bile acid levels are candidate effectors for these effects through postprandial activation of their receptors TGR5 and FXR. We aimed to quantify postprandial bile acid, GLP-1 and FGF19 responses and assess their temporal relation to the weight loss and metabolic and hormonal changes seen after DJBL placement.
Methods: We performed mixed meal testing in 17 obese patients with type 2 diabetes mellitus (DM2) directly before, one week after and 6 months after DJBL placement.
Results: Both fasting and postprandial bile acid levels were unchanged at 1 week after implantation, and greatly increased 6 months after implantation. The increase consisted of unconjugated bile acid species. 3 hour-postprandial GLP-1 levels increased after 1 week and were sustained, whereas FGF19 levels and postprandial plasma courses were unaffected.
Conclusions: DJBL placement leads to profound increases in unconjugated bile acid levels after 6 months, similar to the effects of bariatric surgery. The temporal dissociation between the changes in bile acids, GLP-1 and FGF19 and other gut hormone responses warrant caution about the beneficial role of bile acids after DJBL placement. This observational uncontrolled study emphasizes the need for future controlled studies.

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1. Introduction

Bile acids have gained attention as hormone-like factors in metabolism exerting effects via the transmembrane receptor Takeda G-coupled protein receptor 5 (TGR5) [1–4]. The feedback repression of hepatic bile acid synthesis is managed through the nuclear farnesoid X receptor (FXR) and involves ileal Fibroblast Growth Factor 19 (FGF19) [4,5]. Intestinal L-cell secretion of glucagon-like peptide 1 (GLP-1) is one of the best-described ways of in-vivo stimulation of TGR5 by bile acids [6].

Bile acids have been implicated in the deranged glucose metabolism of patients with obesity and type 2 diabetes mellitus (DM2) [7,8]. Obesity is characterized by decreased postprandial bile acid concentrations [9] and increased bile acid synthesis [10]. DM2 patients have increased postprandial plasma concentrations of the bile acids cholate (CA), deoxycholate (DCA) and chenodeoxycholic acid (CDCA) [11].

Bariatric surgery, and the Roux-en-Y gastric bypass procedure (RYGB) in particular, increases fasting and postprandial bile acid levels and results in 45% of patients not needing medication after 5 years [12,13]. The Duodenal-Jejunal Bypass Liner (DJBL, GI Dynamics, Lexington, MA) is a 60 cm long impermeable liner, which is delivered and retrieved endoscopically. Its placement results in weight loss and improvement of DM2 with lowering of the use of antidiabetic medication such as sulfonylurea derivatives, metformin and insulin [14–16].

Given the proposed role of bile acids in DM2 and RYGB, we examined the effects of DJBL placement on the postprandial bile acid response at different time points after the procedure.

2. Material and Methods

2.1. Subjects

Seventeen subjects with obesity and DM2 were included in the Maastricht University Medical Center, Maastricht, and the Atrium Medical Center Parkstad, Heerlen, the Netherlands between February and July 2010 as reported previously [17]. Inclusion criteria were: age between 18 and 65 years; body mass index (BMI) between 30 and 50 kg/m^2; duration of DM2 <10 years; and HbA1c between 7.5 and 10.0%. Main exclusion criteria have been depicted earlier [17].
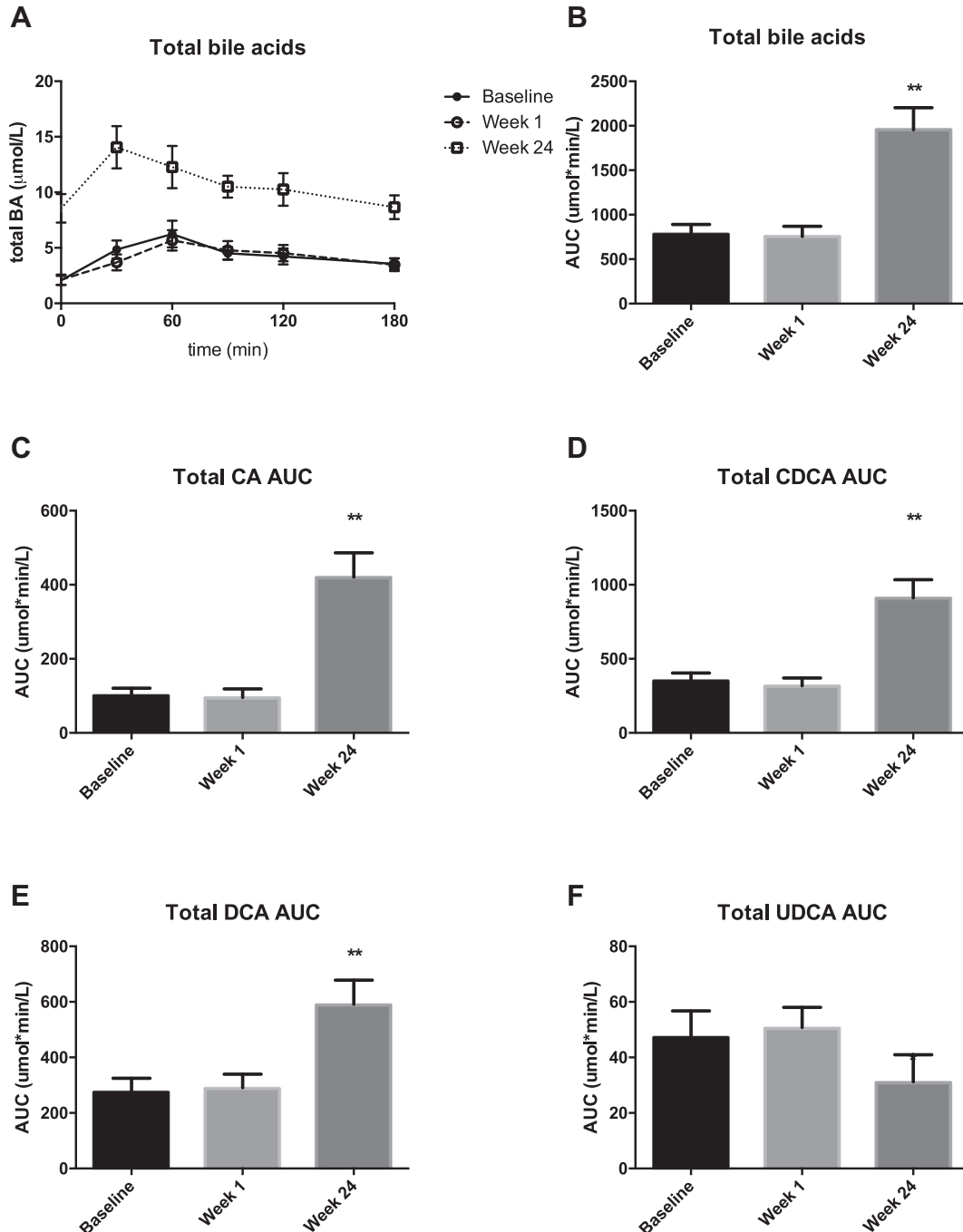

Fig. 1. Postprandial course of bile acids and AUC before DJBL placement and after 1 and 24 weeks of DJBL placement. ** = $p < 0.05$.

2.2. Study Design

The DJBL was delivered and retrieved endoscopically where after subjects were studied and followed up upon as described previously [17]. Here, we report on three visits: 1) within one month prior to implantation (baseline), 2) one week after implantation (week 1), and 3) 24 weeks after implantation, just *prior* to removal (week 24). Standardized meal tolerance tests were performed. An intravenous cannula was placed for blood sampling. The first sample was drawn after an overnight fast; subsequently a standard liquid meal was consumed (Ensure Plus, Abbott Laboratories, IL; 333 mL, 500 kcal, 20.8 g protein, 67.3 g carbohydrates, and 16.4 g fat), followed by collection of blood samples after 30, 60, 90, 120 and 180 min (BD Vacutainer EDTA tube/EDTA aprotinin tube, BD diagnostics, Erembodegem-Aalst, Belgium). Samples were immediately cooled, centrifuged, and stored at −80 °C until analysis.

2.3. Laboratory Analysis

Bile acid concentrations were determined using a UPLC-tandem MS method to quantify CA, CDCA, DCA and ursodeoxycholic acid (UDCA) in their conjugated and unconjugated forms [18]. FGF19 was measured using an in-house developed ELISA as published previously [19]. Total bile acids were calculated by adding up all the individual bile acids measurements.

2.4. Ethics

The study was approved by the Medical Ethics Committee of both centers and conducted according to the revised version of the Declaration of Helsinki. Written informed consent was obtained from every subject prior to study participation. Clinical Trial Registration Number: NCT00985114.

2.5. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). Data were visually and statistically assessed for normality and logarithmically transformed where appropriate. Area-under-the-curve (AUC) of postprandial plasma levels was calculated using the trapezoidal method; subsequent correction for baseline values yielded the incremental-area-under-the-curve (iAUC). Peak time was defined as the first time point at which maximal concentration was reached. Comparisons between 3 test conditions were made using Friedman's test to determine significant differences. Individual comparisons between 2 test conditions were made with Wilcoxon matched-pairs signed rank testing. Correlations were assessed using Pearson's correlation for normally distributed populations or Spearman's Rho for other data. A *p*-value of <0.05 was considered statistically significant after Bonferroni corrections. Data presented are mean and standard deviation ($\mu \pm \sigma$) for normally distributed variables or median and interquartile range (m [IQR]) for other variables. Graphs were made using GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Lining of the Proximal Small Intestine by DJBL Reduces Body Weight

The weight loss effects of the DJBL have been published previously [17]. At baseline, subjects (14 males, 3 females) were 51 ± 2 years old and weighed 116.0 ± 5.8 kg with a BMI of 37.0 ± 1.3 kg/m^2. One week after placement of the DJBL, body weight had decreased by 4.3 ± 0.6 kg, corresponding to an excess weight loss of $10.2 \pm 1.7\%$ and a BMI reduction of 1.4 ± 0.2 kg/m^2 ($p < 0.01$). After 24 weeks, at the time of device removal, mean body weight had further decreased resulting in a total weight loss of 12.7 ± 1.3 kg, and a BMI reduction of 4.1 ± 0.4 kg/m^2 ($p < 0.01$). All

Table 1
Bilogram & FGF19.

Bile acid fraction		Baseline	Week 1	Week 24	p
Total bile acids	Baseline	1.1 (1.5)	1.6 (1.4)	7.8 (3.9)*†	**<0.01**
(μmol/L)	Peak	4.8 (9.0)	5.9 (8.4)	13.1 (6.5)*†	**<0.01**
	AUC	679 (642)	602 (722)	1661 (966)*†	**<0.01**
Total CA	Baseline	0.1 (0.1)	0.2 (0.3)	1.6 (1.3)*†	**<0.01**
(μmol/L)	Peak	0.8 (1.3)	0.6 (0.6)	3.0 (2.9)*†	**<0.01**
	AUC	80 (123)	69 (261)	315 (306)*†	**<0.01**
Total CDCA	Baseline	0.4 (0.9)	0.5 (0.6)	3.3 (2.8)*†	**<0.01**
(μmol/L)	Peak	2.5 (3.7)	2.4 (2.7)	6.0 (4.3)*†	**<0.01**
	AUC	318 (348)	246 (222)	722 (657)*†	**<0.01**
Total DCA	Baseline	0.5 (0.4)	0.6 (0.6)	2.8 (2.3)*†	**<0.01**
(μmol/L)	Peak	1.6 (3.0)	2.4 (2.9)	4.0 (2.6)*†	**<0.01**
	AUC	222 (278)	246 (327)	519 (326)*†	**<0.01**
Total UDCA	Baseline	0.0 (0.1)	0.2 (0.2)	0.0 (0.2)	0.13
(μmol/L)	Peak	0.5 (0.6)	0.4 (0.2)	0.2 (0.3)*	**0.03**
	AUC	45 (39)	53 (33)	14 (41)	0.08
Total taurine-conjugated BA	Baseline	0.1 (0.8)	0.1 (0.2)	0.0 (0.1)*†	**0.01**
(μmol/L)	Peak	0.7 (1.2)	0.5 (0.8)	0.1 (0.1)*†	**<0.01**
	AUC	50 (126)	54 (56)	6 (24)*†	**<0.01**
Total glycine-conjugated BA	Baseline	0.5 (0.8)	0.6 (1.0)	1.3 (0.9)	0.39
(μmol/L)	Peak	3.4 (5.4)	3.9 (5.0)	4.2 (3.3)	0.79
	AUC	468 (543)	366 (438)	422 (306)	0.19
Total unconjugated BA	Baseline	0.5 (0.6)	0.8 (0.4)	6.2 (3.7)*†	**<0.01**
(μmol/L)	Peak	1.3 (1.6)	1.5 (0.6)	8.1 (6.2)*†	**<0.01**
	AUC	156 (125)	182 (53)	1118 (789)*†	**<0.01**
Total 12α-OH BA	Baseline	0.6 (0.7)	0.8 (0.7)	4.6 (2.8)*†	**<0.01**
(μmol/L)	Peak	2.5 (5.0)	3.2 (3.5)	6.4 (4.0)*†	**<0.01**
	AUC	335 (401)	324 (404)	834 (467)*†	**<0.01**
FGF19	Baseline	51.9 (37.5)	61.9 (20.4)	43.7 (24.2)	0.09
(pg/mL)	Peak	70.7 (199.7)	111.9 (74)	91.8 (127.0)	0.84
	AUC	6303 (7661)	7986 (2712)	6694 (3272)	0.10

Bilogram Baseline, peak concentration and AUC of bile acid subtypes and FGF19. Values are presented as median (IQR). The unit of bile acid peak and baseline values is μmol/L, the unit of AUC is μmol/L×min. Overall difference between the three study days was assessed using the Friedman test. If significant, *p*-values were calculated using the related-samples Wilcoxon signed-rank test.

* Denotes significant difference compared to baseline.
† Denotes significant difference compared to week 1.

subjects reported lowered caloric intake during the study and 88% of the subjects (15/17) reported increased feelings of satiety.

3.2. Lining of the Proximal Small Intestine by DJBL Increases Fasting and Postprandial Unconjugated Bile Acid Levels

All subjects completed the study. AUC, fasting and peak levels of total bile acids and all bile acid subsets except UDCA were markedly increased 24 weeks after placement but not after 1 week (see Fig. 1 and Table 1). In fact, the increase of AUCs relied primarily on the increase

in fasting plasma bile acids since incremental AUCs were unaffected by DJBL placement (*data not shown*). Peak times (time from start of the meal to the peak of the plasma bile acids) were unchanged for all bile acids and bile acid subfractions (*data not shown*).

3.3. The Increase in Plasma Bile Acids by DJBL is Completely Caused by Unconjugated Bile Acids

To gain further insight in the composition of the bile acid pool after overnight fasting, we analysed the different bile acids species as well
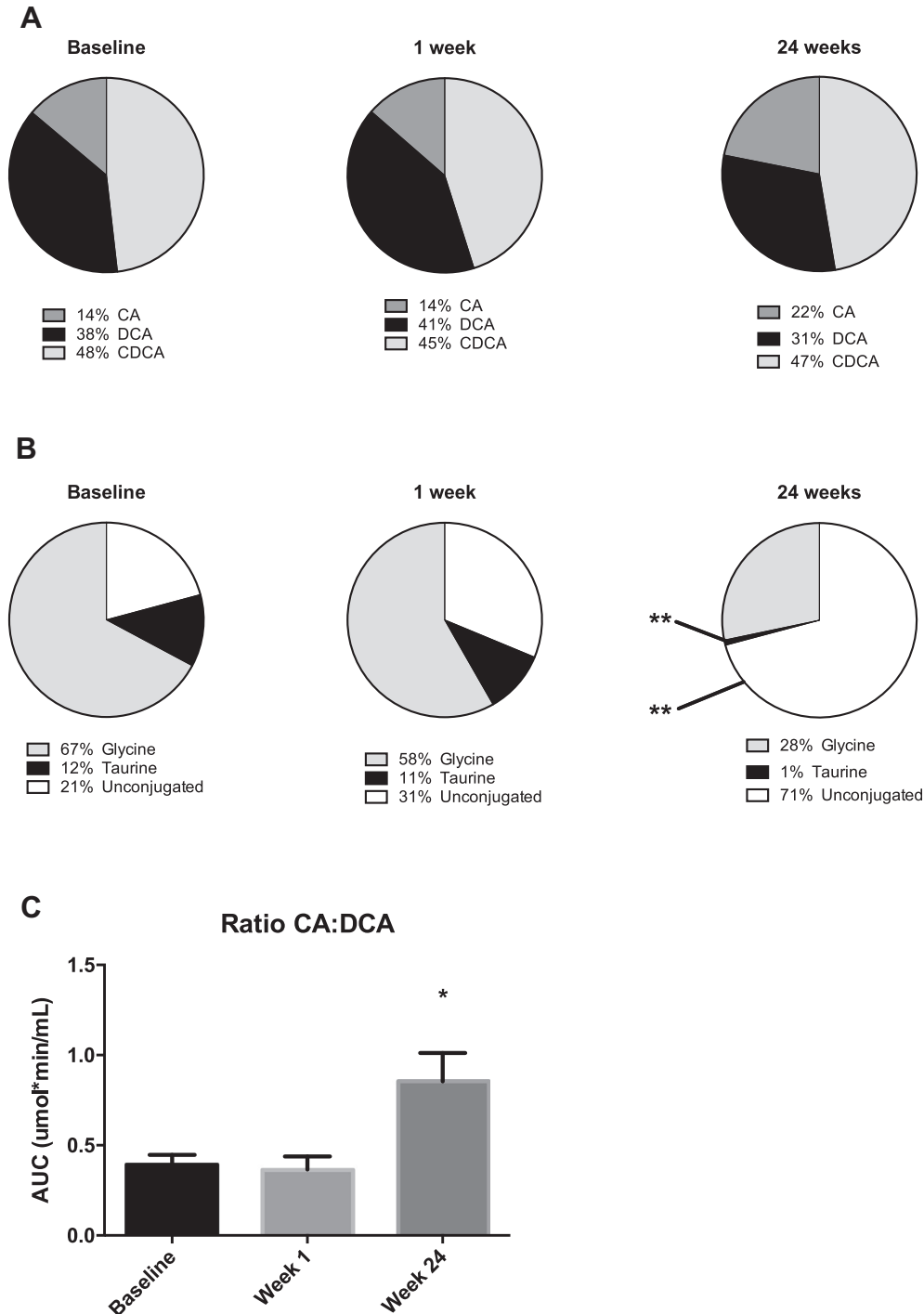
Fig. 2. Composition of the postprandial bile acid pool composition (AUC) for the bile acids CA, CDCA, DCA and UDCA before DJBL placement and after 1 and 24 weeks of DJBL placement (panel A). Composition of the postprandial bile acid pool composition (AUC) for the taurine-, and glycine-conjugated and unconjugated bile acids before DJBL placement and after 1 and 24 weeks of DJBL placement (panel B). ** = $p < 0.05$. Ratio postprandial CA:DCA AUCs before DJBL placement and after 1 and 24 weeks of DJBL placement (panel C). * = $p < 0.05$.

Fig. 3. Postprandial courses of individual glycine-conjugated bile acid species, before and 1 and 24 weeks after DJBL placement (panel A). Postprandial courses of individual unconjugated bile acid species, before and 1 and 24 weeks after DJBL placement (panel A). ** = *p* < 0.05.

Fig. 4. Postprandial curves of glucose (panel A), insulin (panel B), GLP-1 (panel C), CCK (panel D) and FGF19 (panel E) before DJBL placement and after 1 and 24 weeks of DJBL, ** = $p < 0.05$. $T = 180$ values are missing for FGF19 at baseline.
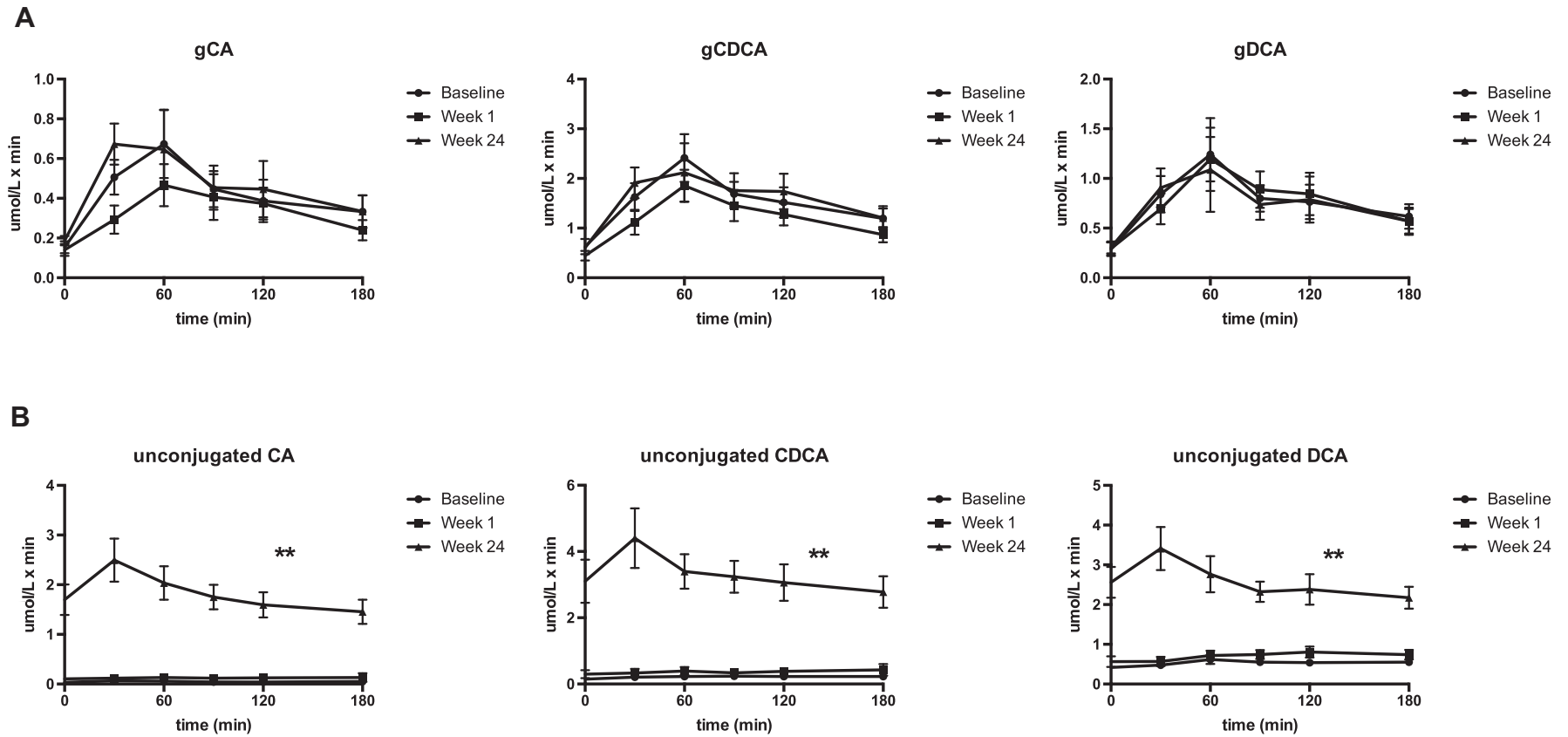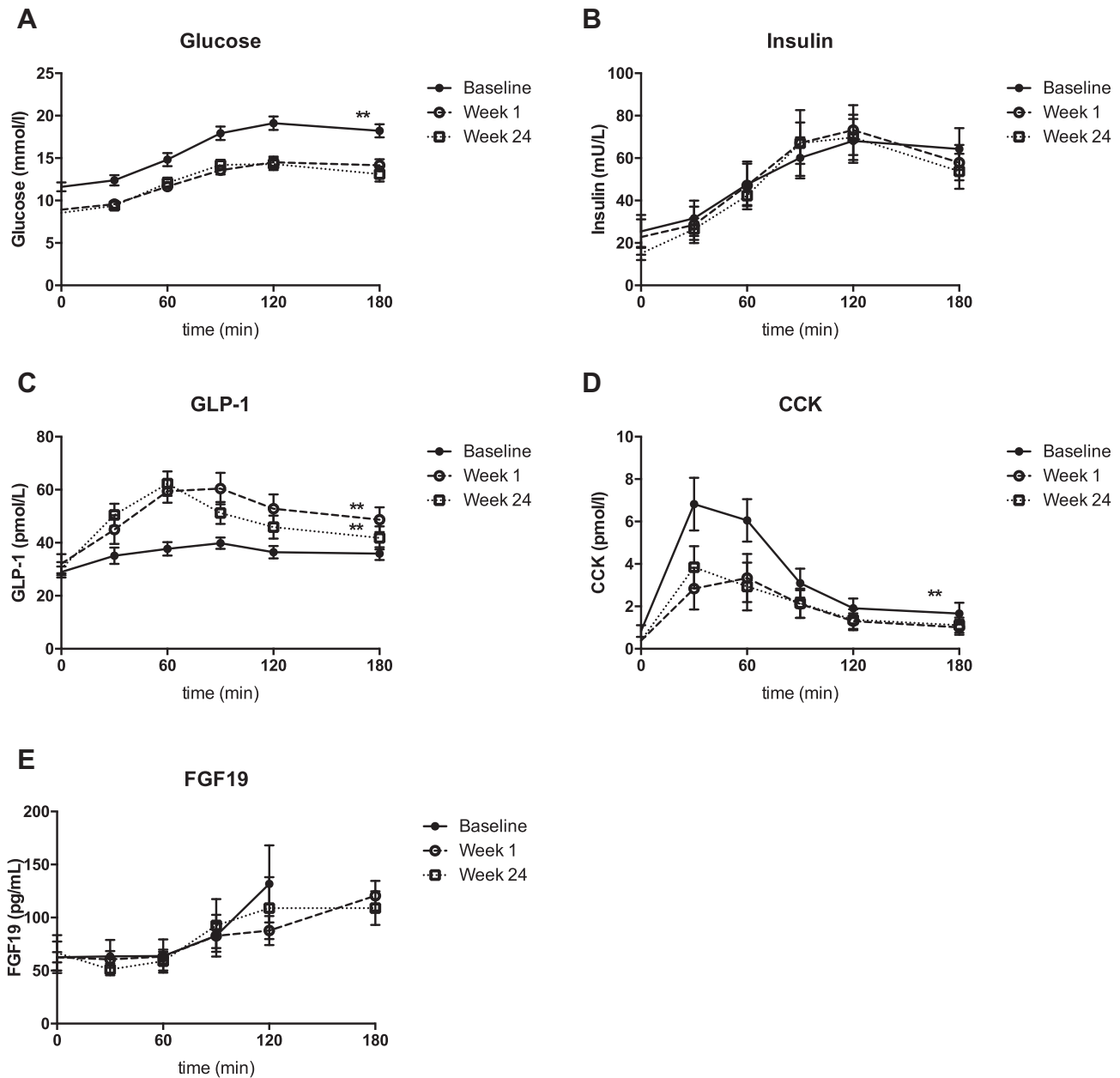
as the conjugation status (Fig. 2, panel A). In general, CDCA was the largest contributor to the pool during the entire study, followed by DCA and CA respectively. Remarkably, the increase in plasma bile acids was completely caused by unconjugated bile acids (Fig. 2, panel B), which reached significance after 24 weeks. Expressed as the fraction of total bile acids, unconjugated bile acid AUC rose from a median of 22% (IQR 13%) at baseline to 26% (IQR 20%, $p < 0.01^{**}$) at week 1 and 76% (IQR 19%, $p < 0.01^{**}$) at week 24 after placement. Total glycine conjugates were unaltered after 24 weeks in contrast to the taurine conjugates that showed a ~90% reduction (Table 1). This pattern was also observed for the individual conjugated forms of CA, CDCA and DCA as shown in Fig. 3, emphasizing the fact that the increase in unconjugated plasma bile acids after DJBL was not due to one bile acid species. We found no changes in the ratio of 12α-hydroxylated/non12α-hydroxylated bile acids (data not shown).

3.4. Postprandial Levels of Glucose, Insulin, GLP-1 Cholecystokinin (CCK) and FGF19

The effects of DJBL on glucose, insulin, GLP-1 and CCK in the studied subjects have been published previously [16,17]. In summary, duodenal lining lowered glucose and CCK within one week and led to increased postprandial AUC of GLP-1 at week 1 and week 24 after DJBL placement (Fig. 4). Insulin levels were not affected. The only bile acid species that consistently correlated with the AUC of GLP-1 on all study days, was fasting DCA: baseline: $r = 0.50$, $p < 0.05^*$; week 1 after placement: $r = 0.56$, $p < 0.05^*$; week 24 after placement: $r = 0.63$, $p < 0.01^{**}$. No other correlations were detected for bile acid species to AUC, fasting or peak levels of either glucose, CCK or GLP-1 (data not shown).

There were no significant differences in either fasting levels, postprandial plasma course, or postprandial levels of FGF19 at baseline,

week 1 or week 24 after DJBL placement (see Table 1). However, at baseline, there were strong correlations between peak FGF19 and virtually all bile acids (peak total bile acids $r = 0.79$, $p < 0.001$***; peak total CA, $r = 0.78$, $p < 0.001$***; peak total CDCA, $r = 0.79$, $p < 0.001$*** and peak total DCA, $r = 0.63$, $p < 0.007$*** that were lost after DJBL placement. Likewise, postprandial AUC of FGF19 and AUC of total bile acids correlated ($r = 0.84$, $p < 0.001$***) at baseline but not after treatment. Individual AUCs of CA, CDCA or DCA did not correlate significantly with FGF19 AUC after Bonferroni correction. FGF19 samples at week 0 for timepoint 180 min were missing due to insufficient sample volume.

4. Discussion

Duodenal lining markedly increases fasting and postprandial levels of unconjugated bile acids 24 weeks after placement of the DJBL. The TGR5 target GLP-1 was higher after 1 and 24 weeks. Initial strong correlations of bile acids and FGF19 were lost at 1 week after placement. Bile acid levels were unchanged 1 week after placement, which supports the notion that the bile acid pool size may have increased gradually over time although metabolic improvements occurred immediately after placement [17]. This is in line with several studies performed in patients after RYGB surgery [12,20–23].

The DJBL-induced increase of bile acids was dependent on unconjugated bile acids, and more exaggerated compared to changes seen after RYGB surgery [12,21,23–25]. Dietary weight loss only marginally increases specific bile acids [26]. Hepatic conjugation of *newly* synthesized bile acids to occurs in the peroxisome, whereas re-conjugation of deconjugated bile acids occurs in the cytosol [27]. The reconjugation machinery is able to conjugate a potentially enlarged bile acid pool, as >99% of serum bile acids in patients treated with large doses of unconjugated ursodeoxycholate is conjugated [28]. Changes in the gut microbiome are possibly responsible for our results. Bacterial deconjugation is complete in the cecum and gut biotransformation of bile acids (i.e. ratios of CA: DCA and CDCA:LCA) were altered after 24 weeks [29]. The DJBL may have led to a different interplay between bile acids, gut bacteria and the gut lumen with effects on entero-endocrine hormones that regulate motility, transit and bile salt reabsorption via the apical sodium-dependent bile acid transporter (ASBT). This could result in increased deconjugation and increased colonic uptake not buffered by liver clearance [30]. The initial increase in unconjugated bile acids after DJBL placement may go unnoticed until the amount of unconjugated bile acids reaches a tipping point, exceeding liver clearance.

It has been suggested that the increase in plasma bile acids after RYGB surgery may be due to increased bile acid recirculation and FXR dependent transcriptional upregulation [31,32]. The former could be achieved by adaptive growth and concomitant increases in ASBT. However, previous studies after RYGB were not unequivocal [12,21,23–25].

The increased GLP-1 seems attributable to increased TGR5 signalling in the gut, although insulin secretion remained unchanged. Moreover, GLP-1 levels increased at week 1 whereas bile acid levels increased later which may be explained by an early increase of bile acids in the gut that were not yet noticeable peripherally. Indeed, our findings are in partial agreement with a previous study that examined the effects of DJBL and also found increased GLP-1 levels [33]. However, this study did not investigate subfractions of bile acids. Interestingly, they were able to observe an increase in FGF19 that did not result in lower plasma bile acids. Most subjects with obesity or DM2 exhibit reduced serum FGF19 levels [34]. Here, FGF19 levels were unchanged throughout the entire study. The mismatch between plasma bile acid and FGF19 levels is difficult to explain FXR sensitivity to its ligand could be decreased, either as a cause of the increased circulating bile acid pool or as a consequence of it. A recent study in healthy subjects revealed that FXR agonist-induced repression of bile salt synthesis occurred without alterations in FGF19 level [35].

Our study has a few limitations. First, we were only able to perform a short mixed-meal test, which may have missed differences in postprandial signalling factors that occur later (such as FGF19 that peaks between 3 and 4 h). Also, we were not able to document the exact moment where changes in bile acid homeostasis became apparent due to the timing of experiments at week 1 and 24. Additionally, this was an observational uncontrolled study emphasizing the need for future controlled studies. Finally, we did not quantify satiety and appetite with visual analogue scores.

In this study, duodenal lining led to beneficial improvements in glucose metabolism and weight in patients with DM2. Surprisingly, unconjugated bile acids showed a marked increase after 24 weeks whereas the increase in GLP-1 was evident after one week. In contrast, correlations of bile acids and FGF19 were abolished immediately. Our data suggest that future studies should be comparing effects of duodenal lining and other means of weight loss on bile acids, GLP-1 and FGF19 taking into account the time course of these changes.

Disclosures

No potential conflicts of interest or financial disclosures relevant to this article were reported.

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