Association between duodenal bile salts and gastric emptying in patients with functional dyspepsia

We read with interest the study by Higuchi *et al*, which identified mechanisms of increased satiation in Cyp8b1−/− mice via slowed gastric empting.[1] Following data showing that deleting Cyp8b1, which is required to produce 12α-hydroxylated bile acids, impaired intestinal lipid absorption in mice, the authors convincingly demonstrated that lowering 12α-hydroxylated bile acids slowed gastric emptying in Cyp8b1−/− mice.[1] Duodenal lipid infusion affects gastric function, and duodenal hypersensitivity to lipids has been studied in GI disorders with gastric dysmotility, such as functional dyspepsia (FD).[2] FD is defined by upper GI symptoms originating from the gastroduodenal region with no structural disease on routine investigation.[3] Although studies showed that lipids are a major trigger of dyspeptic symptoms, the effect was only partially explained by duodenal release of cholecystokinin.[4] Interestingly, the release of bile salts has been linked to the generation of dyspeptic symptoms, possibly via duodenal luminal or mucosal changes including hyperpermeability.[5 6] However, duodenal alterations have not been studied in relation to gastric emptying in patients with FD.

We prospectively recruited patients with FD (Rome IV) without intake of antibiotics and proton pump inhibitors (<3 months), non-steroidal anti-inflammatory drugs, antiallergy drugs and bile acid sequestrants (<2 weeks) or history of cholecystectomy. Fasting bile salts were measured using liquid chromatography with tandem mass spectrometry[7] and paracellular dextran passage (4 kDa) was studied in Ussing chambers.[8] Gastric emptying for solids (gastric half-emptying time (T1/2) of 14C-octanoic acid breath test) was determined on a separate day.

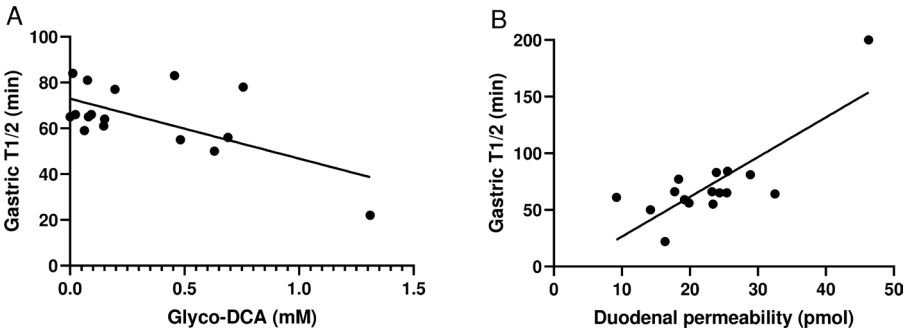

Figure 1 Correlations between gastric half-emptying time and duodenal bile salts (A) or mucosal permeability (B) in patients with functional dyspepsia. DCA, deoxycholic acid; T1/2, half-emptying time.

In total, 18 patients with FD (16 female) were included with a mean (±SE) age of 27.8±6.6 years and BMI of 22.2±3.6 kg/m^2. Concentrations of conjugated 12α-hydroxylated, that is, cholic acid (CA) and deoxycholic acid (DCA), and non-12α-hydroxylated bile salts, that is, chenodeoxycholic acid, are shown in table 1. The absence of unconjugated bile is explained by conjugation to glycine and taurine in humans before excretion in the duodenum.[7] This may also explain the absent association between duodenal bile salts and permeability, including conjugated DCA (table 1), which was claimed in previous studies using unconjugated DCA, which has a non-physiological direct epithelial effect.[9]

Mean gastric half-emptying time was 72.4±8.3 min (normal <75 min). Although no association was found between gastric emptying and conjugated CA (p>0.05), T1/2 was negatively correlated with glyco-DCA and tauro-DCA (both p<0.01). This indicated slower gastric emptying with lower concentrations of 12α-hydroxylated bile salts (figure 1A), translating the preclinical findings of Higuchi *et al* to humans. Interestingly, a positive correlation between duodenal permeability and gastric emptying time was found in patients with FD (r=0.78, p<0.001) (figure 1B), supporting the concept of altered duodenogastric feedback in dyspeptic symptom generation.[2 6]

While Higuchi *et al* linked gastric emptying to fat-dependent GPR119 activity in the distal intestine, investigating this mechanism in humans is less feasible. Also, the role of the gut microbiota remains underexplored as bacteria are responsible for bile salt transformation and changes in the duodenal microbiome have been reported in FD.[10] Interestingly, treatment with 12-hydroxylated bile acids normalised the slow gastric emptying in Cyp8b1−/− mice and caused faster emptying compared with non-12-hydroxylated bile acids in healthy mice.[1] Although confirmation is needed, it is possible that the effect differs in patients with FD with duodenal and/or gastric hypersensitivity.[2 4 6]

In conclusion, we showed that lower concentrations of 12α-hydroxylated bile salts were associated with slower gastric emptying in patients with FD, similar to Cyp8b1−/− mice. This also suggests a potential therapeutic benefit of bile salts in GI disorders with gastric dysmotility.

Table 1 Concentrations of and correlations between duodenal bile salts and mucosal permeability or gastric half-emptying time in patients with functional dyspepsia

		Correlation duodenal permeability		Correlation gastric T1/2	
Duodenal bile salts	**Concentration (mM)**	**r value**	**P value**	**r value**	**P value**
Glyco-CA	0.94±0.19	−0.23	0.28	−0.26	0.34
Tauro-CA	0.43±0.1	−0.13	0.55	−0.40	0.12
Glyco-DCA	0.31±0.07	−0.11	0.63	**−0.63**	**0.009**
Tauro-DCA	0.15±0.05	−0.11	0.61	**−0.65**	**0.007**
Glyco-CDC	0.69±0.15	−0.23	0.29	−0.12	0.66
Tauro-CDC	0.31±0.06	−0.13	0.61	−0.29	0.28

Bold values are statistically significant (P<0.05).
CA, cholic acid; CDC, chenodeoxycholic acid; DCA, deoxycholic acid; T1/2, gastric half-emptying time.

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REFERENCES

1 Higuchi S, Ahmad TR, Argueta DA, *et al*. Bile acid composition regulates GPR119-dependent intestinal lipid sensing and food intake regulation in mice. *Gut* 2020;69:1620–8.
2 Wauters L, Talley NJ, Walker MM, *et al*. Novel concepts in the pathophysiology and treatment of functional dyspepsia. *Gut* 2020;69:591–600.
3 Stanghellini V, Chan FKL, Hasler WL, *et al*. Gastroduodenal disorders. *Gastroenterology* 2016;150:1380–92.
4 Fried M, Feinle C. The role of fat and cholecystokinin in functional dyspepsia. *Gut* 2002;51 Suppl 1:i54–7.
5 Feinle-Bisset C, Azpiroz F. Dietary and lifestyle factors in functional dyspepsia. *Nat Rev Gastroenterol Hepatol* 2013;10:150–7.
6 Vanheel H, Farré R. Changes in gastrointestinal tract function and structure in functional dyspepsia. *Nat Rev Gastroenterol Hepatol* 2013;10:142–9.
7 Riethorst D, Mols R, Duchateau G, *et al*. Characterization of human duodenal fluids in fasted and fed state conditions. *J Pharm Sci* 2016;105:673–81.
8 Vanheel H, Vicario M, Vanuytsel T, *et al*. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. *Gut* 2014;63:262–71.
9 Forsgård RA, Korpela R, Stenman LK, *et al*. Deoxycholic acid induced changes in electrophysiological parameters and macromolecular permeability in murine small intestine with and without functional enteric nervous system plexuses. *Neurogastroenterol Motil* 2014;26:1179–87.
10 Zhong L, Shanahan ER, Raj A, *et al*. Dyspepsia and the microbiome: time to focus on the small intestine. *Gut* 2017;66:8–10.