Stimulated expression of ileal Fibroblast Growth Factor 19 by bile acids is impaired in patients with primary and secondary bile acid diarrhoea

Jonathan D Nolan, Gaganjit K Madhan, Richard N Appleby, Ian M Johnston, Justine H Zhang, Sarah L Kennie, Julian RF Walters.

**Background & Aims:** Bile acid diarrhoea (BAD) results from excess luminal bile acids (BA) in the colon. Most BAs are reabsorbed at the terminal ileum. Increased colonic BA occur secondary to ileal disease or resection (common in Crohn’s disease [CD]) leading to BA malabsorption and secondary BAD (SBAD). Primary BAD (PBAD) occurs in the absence of overt ileal disease or malabsorption. The peptide FGF19 is produced from enterocytes in response to BA absorption and maintains homeostasis of the BA pool size by inhibiting hepatic BA synthesis. Impaired ileal FGF19 production may underlie the excess faecal BA observed in PBAD and may be contributory in CD as a result of increased hepatic BA synthesis. We aimed to investigate whether BA-induced expression of FGF19 in the ileum is reduced in patients with PBAD or CD.

**Methods**: Patients attending for colonoscopy (n=58) were prospectively recruited and gave informed consent to give additional ileal biopsies. 14 patients had CD (4 with previous right hemi colectomy and 10 without), 16 patients had unexplained diarrhea and had SeHCAT tests, and 28 controls. Groups of 2-3 biopsies (explants) were incubated separately for 6h with either BA-free culture media (unstimulated controls), chenodeoxycholate (CDCA) or glyco-CDCA (GCDCA), both at 50uM. After RNA extraction and cDNA synthesis, FGF19 expression was quantified relative to GAPDH by RT-PCR.

**Results**: In patients with unexplained diarrhoea SeHCAT 7d retention values were <15% in 7 patients, indicating primary BAD, and >15% in 9 who were normal diarrhea controls. A positive correlation was found between SeHCAT retention and the magnitude of the fold change in FGF19 expression stimulated by either CDCA (r=0.50, n=16, p=0.02) or by GCDCA (r=0.76, n=7, p=0.02). The median CDCA stimulated fold change in FGF19 expression was significantly lower in CD compared to controls (87, n=12 vs 251, n=28, p=0.03) and a similar non-significant trend was observed for median GCDCA stimulated expression (97, n=10 vs 156, n=13, p=0.18).

**Conclusion**: Ileal explants from patients with lower SeHCAT 7d retention had a lower response to both CDCA and GCDCA. Patients with CD had lower responses to CDCA. As uptake of GCDCA is dependent on carrier-mediated apical BA uptake but CDCA is not, this implies abnormalities in the intracellular ileal FGF19 response to BA. A reduced capacity to induce ileal FGF19 expression in response to absorbed BA is proposed to increase faecal BA due to increased hepatic BA synthesis in primary BAD. In secondary BAD an impaired ileal BA FGF19 response may lead to an increase in BA synthesis and faecal BA that is disproportionate to the degree of ileal BA malabsorption.