**Bile acid sequestration with colesevelam enhances GLP-1 secretion and improves glycaemic control in type 2 diabetes**

**Aims**

Intestinal bile acids (BAs) are capable of stimulating the release of glucagon-like peptide-1 (GLP-1) to modulate glucose homeostasis. While augmenting luminal BAs increases GLP-1 secretion and lowers blood glucose, BA depletion using BA sequestrants (e.g. colesevelam) achieves similar benefits within 1-12 weeks in type 2 diabetes (T2D). The latter phenomenon may reflect changes in intestinal sensitivity to luminal BAs and/or nutrients. Accordingly, we evaluated the effects of two weeks treatment with colesevelam on GLP-1, insulin and plasma glucose responses to small intestinal BA and glucose infusion in T2D.

**Methods**

Eleven T2D participants (7 male, age 70.0±2.0years, BMI 29.6±0.8kg/m2, HbA1c 6.6±0.2%), managed by diet or metformin monotherapy (metformin withheld for ≥2 weeks prior), received colesevelam (3.75g/day) or placebo (cellulose), each for 14 days, in a double-blind, randomised, crossover design, with a 2-week ‘washout’ between treatments. Before and after each treatment period, a naso-jejunal catheter, incorporating a balloon 30cm beyond the pylorus to exclude endogenous bile, was positioned after an overnight fast. Taurocholic acid (TCA) 2g was infused into the jejunum (t=0-30min), followed by an additional 2g TCA mixed with 45g glucose (t=30-120min, i.e. 2kcal/min). Venous blood was sampled frequently for measurements of plasma glucose, insulin, C-peptide and GLP-1 concentrations. Insulin sensitivity was assessed using the Matsuda index.

**Results**

Compared with control, two weeks treatment of colesevelam, augmented plasma GLP-1 concentrations by 76% (p=0.024) and lowered the glycaemic excursion by 22% (p=0.037) in response to jejunal TCA and glucose. Although neither colesevelam nor placebo affected plasma insulin and C-peptide levels, colesevelam increased the Matsuda index by 18% (p=0.014).

**Conclusion**

These observations suggest that depleting intestinal BAs for two weeks may augment intestinal sensitivity to BA and nutrient stimulation, thereby improving postprandial glucose metabolism.