Safety and efficacy of liraglutide versus colesevelam for the treatment of bile acid diarrhoea: a randomised, double-blind, active-comparator, non-inferiority clinical trial

Martin L Kårhus, Andreas Brønden, Julie L Forman, Anne Haaber, Elisabeth Knudsen, Ebbe Langholz, Lars O Dragsted, Svend H Hansen, Martin Krakauer, Tina Vilsbøll, David P Sonne, Filip K Knop

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Center for Clinical Metabolic Research (M L Kårhus MD PhD, A Brønden MD PhD, Prof T Vilsbøll MD DMSC, D P Sonne MD PhD, Prof F K Knop MD PhD), **Department of Gastroenterology** (E Langholz MD DMSC), **and Department of Nuclear Medicine** (M Krakauer MD PhD), **Copenhagen University Hospital Herlev and Gentofte, Hellerup, Denmark; Department of Clinical Medicine** (M L Kårhus, E Langholz, Prof T Vilsbøll, Prof F K Knop), **Section of Biostatistics, Department of Public Health,** (J L Forman PhD), **and Novo Nordisk Foundation Center for Basic Metabolic Research** (Prof F K Knop), **Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; Department of Clinical Pharmacology** (A Brønden, D P Sonne), **Department of Clinical Physiology and Nuclear Medicine** (M Krakauer), **Copenhagen University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark; Mavespecialisten, Charlottenlund, Denmark** (A Haaber MD); **Søndervangen 47, Birkerød, Denmark** (E Knudsen MD); **Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark** (Prof L O Dragsted PhD); **Department of Biochemistry, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark** (S H Hansen MSc); **Steno Diabetes Center Copenhagen,**

Summary

Background Bile acid diarrhoea is an underdiagnosed disease estimated to affect 1–2% of the general population. Case reports indicate that the glucagon-like peptide 1 receptor agonist liraglutide might be an effective treatment for bile acid diarrhoea. We aimed to investigate the safety and efficacy of liraglutide for the treatment of bile acid diarrhoea.

Methods We conducted a randomised, double-blind, active-comparator, double-dummy, non-inferiority clinical trial at the Center for Clinical Metabolic Research at Copenhagen University Hospital–Herlev and Gentofte, Hellerup, Denmark. Patients aged 18–75 years with ^{75}selenium-homotaurocholic acid test (SeHCAT)-verified moderate-to-severe primary bile acid diarrhoea were randomly assigned (1:1) to receive liraglutide (one daily subcutaneous injection uptitrated from 0·6–1·8 mg per day over 3 weeks) or colesevelam (three capsules of 625 mg twice daily), the standard of care, for 6 weeks following one run-in week with no treatment. The primary endpoint was the proportion of participants experiencing a reduction in daily stool frequency of 25% or greater after 6 weeks. Data from all participants were included in the analysis of the primary outcome. The non-inferiority limit was set to 15% in favour of colesevelam. This trial is registered with EudraCT (2018-003575-34) and is completed.

Findings Between April 1, 2019, and Jan 31, 2021, 52 patients were enrolled; 26 were assigned to liraglutide and 26 to colesevelam. 20 (77%) of 26 participants on liraglutide and 13 (50%) of 26 on colesevelam experienced a 25% or greater reduction in stool frequency, corresponding to a significant risk difference of –27% in favour of liraglutide (one-sided 95% CI –100 to –6). Liraglutide was therefore superior to colesevelam in reducing daily stool frequency. Mild nausea with a duration of 10–21 days was reported by six participants in the liraglutide group and by one participant in the colesevelam group. No other adverse events were reported.

Interpretation The superiority of liraglutide compared with colesevelam in reducing stool frequency suggests consideration of liraglutide as a potential new treatment modality for bile acid diarrhoea, although larger confirmatory trials powered for superiority are warranted.

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Introduction

Bile acid diarrhoea is an underdiagnosed disease estimated to affect up to 1–2% of the general population.[1] The main symptoms of bile acid diarrhoea are high stool frequency, defecation urgency, and faecal incontinence, making it a socially debilitating disease.[2] Bile acid diarrhoea can be divided into three groups: types 1 and 3 are secondary to other conditions, such as Crohn's disease, coeliac disease, intestinal resection, and post-cholecystetomy diarrhoea, among others, whereas type 2, also known as primary bile acid diarrhoea, does not have a known underlying pathophysiology.[1]

In normal physiology, bile acids are synthesised in the liver, stored in the gallbladder, secreted to the duodenum upon food ingestion, and reabsorbed from the small intestine.[3] Bile synthesis is regulated in a negative feedback loop where bile acids in the small intestine induce the release of fibroblast growth factor 19 (FGF19), thereby inhibiting the synthesis of bile in the liver. Symptoms of bile acid diarrhoea are caused by excessive spillover of unabsorbed bile acids from the small intestine to the colon, causing the abovementioned symptoms.[3,4] It has been speculated whether overproduction of bile acids due to defective negative inhibition is part of the pathophysiology of type 2 bile acid diarrhoea.[5] The reference standard for diagnosing bile acid diarrhoea is the ^{75}selenium-homotaurocholic acid test (SeHCAT), where the 7-day retention of orally administered ^{75}selenium-labelled homotaurocholic acid is measured with a gamma camera.[6] Retention greater than 15% is considered normal, 10–15% is defined as mild bile acid diarrhoea, 5–10% is defined as moderate bile acid diarrhoea, and less than 5% is defined as severe bile acid diarrhoea.[6] Interestingly, emerging evidence suggests that patients with bile acid

Research in context

Evidence before this study

Bile acid diarrhoea is estimated to affect 1–2% of the general population. The main symptoms of bile acid diarrhoea are high stool frequency, defecation urgency, and faecal incontinence, making it a socially debilitating disease. Evidence shows that individuals with bile acid diarrhoea are also characterised by a dysmetabolic, prediabetes-like state. Bile acid diarrhoea is usually treated with bile acid sequestrants, but many individuals with bile acid diarrhoea experience an inadequate effect or intolerable side-effects from these drugs. Therefore, new treatment modalities are highly needed. Liraglutide is a glucagon-like peptide 1 receptor agonist that is approved for the treatment of type 2 diabetes and obesity, and has been shown to interfere with the enterohepatic circulation of bile acids and gastrointestinal motility. Case reports indicate that liraglutide might be an effective treatment for bile acid diarrhoea, but the effectiveness of liraglutide has never formally been investigated as a treatment modality for bile acid diarrhoea. We searched PubMed and ClinicalTrials.gov using the terms "bile acid malabsorption" and "liraglutide" for English language publications; the first search was done on Sept 1, 2017, and searches were repeated on a monthly basis. We found two case reports and the published protocol for the present study along with its records on ClinicalTrials.gov.

Added value of this study

In this randomised controlled trial we compared head to head the effectiveness of liraglutide and the current standard of care (ie, the bile acid sequestrant colesevelam) on stool frequency in patients with moderate-to-severe bile acid diarrhoea. Liraglutide was superior to colesevelam in reducing stool frequency in patients with bile acid diarrhoea. Liraglutide treatment was also associated with added glucometabolic benefits. One participant from each group dropped out because of nausea, which is a common side-effect of both liraglutide and colesevelam; otherwise, no safety issues were observed. Taken together, the results of the present study point to liraglutide as a potential new treatment modality for bile acid diarrhoea. The study also provides valuable data on the enterohepatic and glucometabolic effects of the two drugs, providing novel insights into their mode of action.

Implications of all the available evidence

Liraglutide is a well-known, safe, and commonly used drug for the treatment of type 2 diabetes and obesity. It is administered once daily as a subcutaneous injection and is well tolerated (the most common side-effect is temporary, mild-to-moderate nausea). The observed superiority of liraglutide compared to colesevelam in reducing stood frequency in patients with bile acid diarrhoea suggests consideration of liraglutide as a new treatment for bile acid diarrhoea, although larger confirmatory trials powered for superiority are warranted. Future research should focus on understanding the long-term effects of liraglutide on bile acid diarrhoea and the potential beneficial glucometabolic effects of liraglutide in these patients.

Herlev, Denmark (Prof T Vilsbøll, Prof F K Knop)

Correspondence to:
Professor Filip K Knop, Center for Clinical Metabolic Research, Copenhagen University Hospital, Herlev and Gentofte, DK-2900 Hellerup, Denmark
filip.krag.knop.01@regionh.dk

diarrhoea, in addition to their enterohepatic pathophysiology, are also characterised by a glucometabolic profile indicative of a dysmetabolic prediabetic-like state.[7]

Currently, patients with bile acid diarrhoea are treated with bile acid sequestrants that bind to bile acids in the gut, thus alleviating symptoms. However, the efficacy of bile acid sequestrants is highly variable,[5] and in some studies bile acid sequestrant therapy had no effect on high stool frequency, one of the core symptoms of bile acid diarrhoea. High stool frequency has been shown to be directly related to impaired quality of life.[8] Furthermore, common adverse effects of bile acid sequestrants include constipation and overflow diarrhoea, stomach pain, bloating, flatulence, nausea, and vomiting. Hence, better modalities for the treatment of bile acid diarrhoea are needed.

The present study was inspired by case reports of two patients who experienced total remission of their bile acid diarrhoea symptoms after treatment with the glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1RA) liraglutide,[9] which they initiated because of concomitant overweight and type 2 diabetes. Liraglutide is a commonly used drug for treating type 2 diabetes and obesity. Apart from improving glycaemic control and reducing bodyweight, liraglutide slows gastric emptying and small intestinal motility.[10] GLP-1RA therapy has also been reported to reduce gallbladder emptying[11] and delay gallbladder refilling,[12] an effect that might contribute to the beneficial effects of liraglutide in primary bile acid diarrhoea. Reduced gallbladder emptying combined with increased small intestinal transit time, and thus increased time for passive reabsorption of bile acids in the small intestine, might reduce spillover of bile acids to the colon. Based on this notion and the abovementioned cases, we hypothesised that treatment of bile acid diarrhoea with liraglutide would reduce the exposure of the colonic mucosa to bile acids and thus ameliorate symptoms of bile acid diarrhoea to the same extent as bile acid sequestrants (ie, liraglutide would be non-inferior to the best-in-class bile acid sequestrant). We aimed to investigate the safety and efficacy of liraglutide compared to the current standard of care (ie, treatment with the bile acid sequestrant colesevelam) in patients with bile acid diarrhoea.

Methods

Study design and participants

We conducted an investigator-initiated randomised, double-blind, active-comparator, double-dummy, parallel-group, non-inferiority clinical trial that was designed to evaluate the safety and efficacy of liraglutide compared to colesevelam for the treatment of moderate-to-severe bile acid diarrhoea. The trial was done at the Center for

Clinical Metabolic Research at Copenhagen University Hospital–Herlev and Gentofte, Hellerup, Denmark. The trial protocol has previously been published[13] and was approved by the Danish Medicines Agency, the Regional Committee on Health Research Ethics of the Capital Region of Denmark, and the Danish Data Protection Agency. The study was done in accordance with good clinical practice according to the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines and monitored by the Capital Region of Denmark's Good Clinical Practice Unit.

White individuals aged 18–75 years with SeHCAT-verified moderate-to-severe primary bile acid diarrhoea (≤10% 7-day bile acid retention), with no diabetes, other gastrointestinal diseases including Crohn's disease, ileal resection, previous history of radiation to the abdomen or the pelvis, or recent or active malignancy, were eligible for inclusion. Patients with a history of hepatobiliary disorders (except for simple non-alcoholic steatosis) or elevations in serum alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal were excluded. Cholecystectomy was not an exclusion criterion. All participants underwent a SeHCAT due to unexplained diarrhoea fulfilling the Rome criteria IV for irritable bowel syndrome with diarrhoea (IBS-D). The full list of inclusion and exclusion criteria has been published.[13] All participants gave written informed consent to participate in this trial.

See Online for appendix

Randomisation and masking

The randomisation to colesevelam or liraglutide was done by the central pharmacy of the Capital Region of Denmark using the website randomiser.com. Simple randomisation was used. A person not otherwise involved in the study matched active-colesevelam with placebo-liraglutide and vice versa.[13] The placebo versions of the two drugs were indistinguishable from the active drugs.[13] For safety reasons, a sealed envelope per participant with the unblinded data was available if needed. None of the envelopes was opened during the trial.

Procedures

After a 1-week run-in period with no treatment for their bile acid diarrhoea symptoms, participants were randomly assigned to receive either active liraglutide (one daily subcutaneous injection up-titrated from 0·6 mg to 1·8 mg over 3 weeks) or colesevelam (three capsules of 625 mg twice daily) and the opposite dummy for 6 weeks. A stool diary was filled out daily. At the end of the run-in baseline week (ie, just before treatment initiation), after 3 weeks of treatment, and after 6 weeks of treatment, blood and stool samples were collected, and the last day of the SeHCAT was done at the end of the baseline week and at the end of weeks 3 and 6 of treatment. Total bile acids were measured in stool, while fasting serum and plasma concentrations of total bile acids, low-density lipoprotein, high-density lipoprotein, very-low-density lipoprotein, and total cholesterol, triglycerides, C4, FGF19, glucose, HbA_{1c}, insulin, C-peptide, and glucagon were measured in the blood. Questionnaires about symptoms were filled out every week and questionnaires about quality of life were filled out every third week. As no validated questionnaires for bile acid diarrhoea exist in Danish, we developed in-house questionnaires in Danish based on the Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome (IBS)[14] and IBS–Quality of Life questionnaires.[15] In Denmark, people diagnosed with bile acid diarrhoea are recommended to adhere to a low-fat diet. No further diet instructions were given to the participants in this trial. The participants handed in their used injection pens and empty pillboxes, and were asked to self-report any missed doses to control for compliance. A detailed description of experimental procedures, including SeHCAT and measurement of plasma and faecal analytes is provided in the appendix (pp 3–6).

Outcomes

The primary endpoint was the proportion of participants with a reduction in daily stool frequency of 25% or greater after 6 weeks of treatment. This primary endpoint was chosen as a measure of a clinically relevant effect on the basis of feedback from clinicians and experts as well as feedback from patients. Secondary endpoints were the proportion of participants who experienced remission of bile acid diarrhoea symptoms (two or less bowel movements per day, with the Bristol Stool Form Scale types 3–5,[16] as a post-hoc analysis), tolerability to the treatment, relief of symptoms (as assessed by the in-house questionnaires described above), and change in quality of life (as assessed by the in-house questionnaires described above).[13] The symptom score and quality of life values were assessed as the mean from all questions from each timepoint. Additional secondary endpoints were changes from baseline to week 6 in circulating concentrations (in serum or plasma from blood sampled in the fasting state) of 7 alpha-hydroxy-4-cholesten-3-one (C4), FGF19, lipids, glucose, HbA_{1c}, insulin, and C-peptide were evaluated. Change in SeHCAT-assessed bile acid retention from baseline to 6 weeks was an exploratory secondary endpoint. The faecal output of total bile acids was also evaluated as an exploratory endpoint. Participants reported adverse events at visits to the clinic site every third week or via telephone at any time during the study.

Statistical analysis

Statistical analyses were done in accordance with the published protocol.[13] The power calculation for this investigator-initiated clinical trial was pragmatic in the sense that we had to consider budget constraints. Anticipating that 90% or more participants on liraglutide would experience a 25% or greater reduction in stool frequency compared to 80% of participants on standard

of care (colesevelam),[1,3] we estimated that a minimum of 25 participants in each treatment group would be required to show non-inferiority at a 15% limit with 80% power. We did hierarchical tests of non-inferiority and superiority based on the one-sided 95% CI for the risk difference.[17] However, as the power for showing superiority was only 25%, these statistical results should be interpreted with caution. Missing data were included as negative outcomes in the primary analysis since we assumed that discontinuation will revoke the potential improvements obtained from the treatments. Supplementary best-case worst-case analyses were done to assess whether the results were sensitive to this assumption. Quantitative secondary endpoints (symptom scores, quality of life, SeHCAT, and biomarkers) were analysed by use of a constrained linear mixed model.[18,19] An unstructured covariance pattern was assumed to account for repeated measurements on each study participant. Model assumptions were assessed with residual diagnostics. Missing data were handled implicitly by maximum likelihood estimation. Substantially skewed outcomes were log-transformed before analysis and were back-transformed and reported as geometric mean ratios and 95% CIs. Results are reported as the expected change (expected relative change) for an average (median) patient with each treatment and estimated treatment difference (ETD) with 95% CIs. Proportions of participants tolerating the treatment and participants experiencing remission of bile acid diarrhoea were compared with risk differences (RDs) and Fisher's exact tests, including missing data as negative outcomes. Analyses were done in the intention-to-treat population, including data from all randomised participants, regardless of treatment adherence. The p values from the secondary endpoints were adjusted by the method of Benjamini and Hochberg, which controls the false discovery rate. An adjusted p value less than 0·05 was considered statistically significant. Dropouts were replaced.

This trial is registered with the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT; 2018-003575-34) and is completed.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 1, 2019, and Jan 31, 2021, 52 individuals with moderate-to-severe bile acid diarrhoea were enrolled; 26 were assigned to liraglutide and 26 to colesevelam (table 1, figure 1). The mean age was 50·2 years, mean BMI was 29·9 kg/m², and mean SeHCAT was 4·0%. 32 participants were female and 18 were male; two participants dropped out (one female participant from the liraglutide group and one male participant from the colesevelam group).

	Liraglutide (n=25)	Colesevelam (n=25)
Sex		
Female	18 (69%)	14 (54%)
Male	7 (27%)	11 (42%)
Age, years	51·7 (13·3)	48·7 (12·8)
BMI, kg/m²	31·5 (5·6)	28·3 (4·1)
SeHCAT	3·6% (3·4)	4·4% (3·2)
Haemoglobin, mmol/L	8·7 (0·5)	8·9 (0·8)
Albumin, g/L	40·7 (3·2)	41·5 (3·1)
eGFR, mL/min per 1·73 m²	87·2 (8·1)	89·1 (2·6)
Potassium, mmol/L	3·8 (0·3)	4·0 (0·3)
Sodium, mmol/L	141·0 (2·0)	141·4 (1·8)
Creatinine, mmol/L	66·6 (10·4)	65·3 (9·6)
ALT, U/L	31·7 (14·7)	34·8 (17·7)
Alkaline phosphatase, U/L	81·2 (20·5)	75·3 (15·0)
Bilirubin, µmol/l	9·9 (3·4)	9·6 (3·0)
Glucose, mmol/L	6·0 (1·1)	5·8 (0·7)
HbA_{1c}, mmol/mol	34·6 (5·5)	33·2 (2·2)
HbA_{1c}	5·3% (0·5)	5·2% (0·2)
HDL cholesterol, mmol/L	1·3 (1·1–1·5)	1·3 (1·0–2·1)
LDL cholesterol, mmol/L	2·6 (0·6)	2·3 (0·7)
VLDL cholesterol, mmol/L	1·1 (0·7)	0·7 (0·4)
Total cholesterol, mmol/L	5·0 (0·9)	4·7 (1·0)
Triglycerides, mmol/L	2·1 (1·6–2·8)	1·6 (1·0–2·9)
TSH, IU/L	1·9 (0·7)	1·6 (0·7)

Data are n (%), mean (SD), or median (IQR). ALT=alanine aminotransferase. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. HDL=high-density lipoprotein. LDL=low-density lipoprotein. SeHCAT=^{75}selenium-homotaurocholic acid test. TSH=thyroid-stimulating hormone. VLDL=very-low-density lipoprotein.

Table 1: **Clinical characteristics of participants**

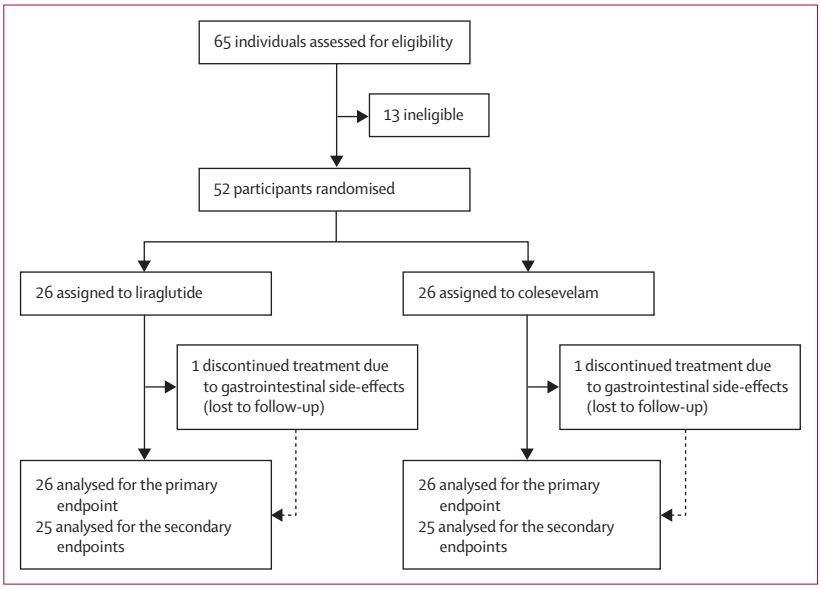

Figure 1: **Trial profile**

Liraglutide reduced daily stool frequency by 25% or greater in 20 (77%) of 26 participants, as did colesevelam in 13 (50%) of 26 participants. Thus, liraglutide was observed to be superior to colesevelam in reducing daily stool frequency by 25% or greater after 6 weeks of treatment (RD –27% [95% CI –100 to –6]; figure 2). After 6 weeks of treatment, liraglutide had decreased stool frequency by –1·83 stools per day (95% CI –2·32 to –1·35), corresponding to a percentage reduction of 54·0%, and colesevelam had decreased stool frequency by –1·08 stools per day (–1·56 to –0·59), corresponding to a percentage reduction of 24·6%. The ETD between the groups was 0·76 stools per day (95% CI 0·31 to 1·20; p=0·0042; table 2, figure 2). All 25 (100%) of 25 participants in the liraglutide group had a decrease in stool frequency, whereas four (16%) of 25 in the colesevelam group had an increase (data not shown). Both treatments resulted in firmer stools after 6 weeks of treatment (assessed by reductions in the Bristol Stool Form Scale; liraglutide: –0·66 [95% CI –1·02 to –0·29]; colesevelam: –0·94 [–1·31 to –0·58]), but the ETD between the groups was not significant (table 2, figure 2). After 6 weeks of treatment, 17 (65%) participants in the liraglutide group and 11 (42%) participants in the colesevelam group had a normalised stool frequency of two or fewer stools per day, and reached values of 3–5 on the Bristol Stool Form Scale[16] (RD –0·25 [95% CI –0·52 to 0·02; p=0·09]; post-hoc assessment).

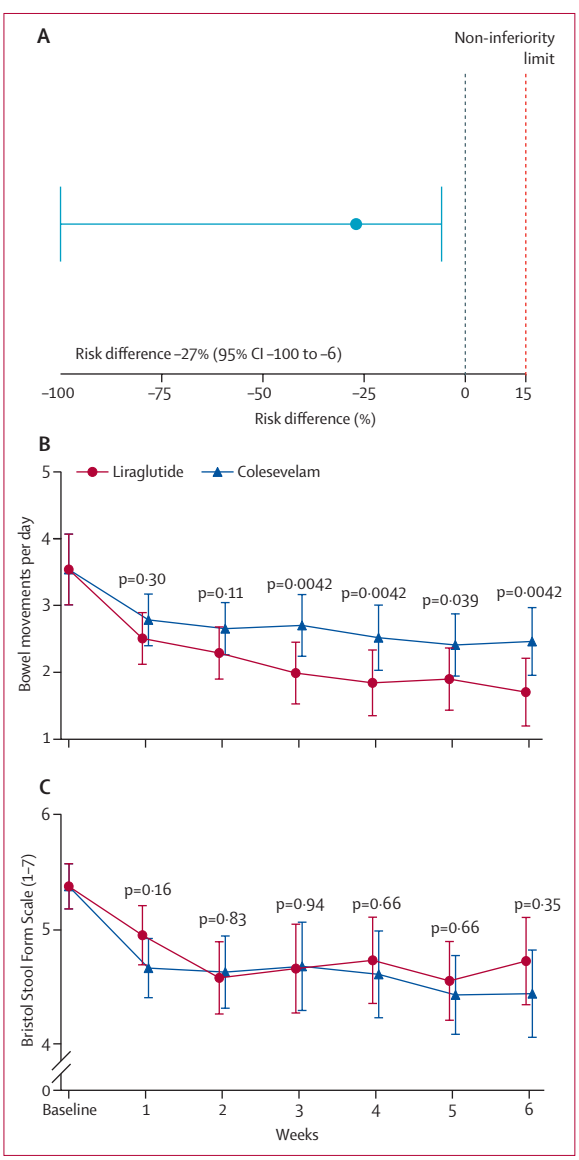

Figure 2: **Changes in stool frequency and type**
(A) A reduction of 25% or greater in stool frequency following 6 weeks of treatment with liraglutide or colesevelam. (B) Changes in bowel movements per day following 6 weeks of treatment with liraglutide or colesevelam. (C) Changes in stool type assessed by Bristol Stool Form Scale following 6 weeks of treatment with liraglutide or colesevelam. Data are presented as means with 95% CIs; p values are adjusted.

Liraglutide increased the retention of bile acids, assessed by SeHCAT, by 6·06% (95% CI 2·52 to 9·59) after 6 weeks of treatment, whereas colesevelam had no effect on bile acid retention (–0·89% [–4·42 to 2·63]). The ETD between the groups was 6·95% (95% CI 2·00 to 11·9; p=0·0019; table 2, figure 3). After 6 weeks of treatment, colesevelam caused a 65·0% (95% CI –74·2 to –52·6) decrease in circulating FGF19, while liraglutide had no effect (5·5% [–21·9 to 42·5]). The ETD between the groups was –66·9% (95% CI –77·3 to –51·7; p<0·0001; table 2, figure 3). C4 was decreased by –36·7% (95% CI –51·2 to –18·2) in the liraglutide group and increased by 160·1% (95% CI 100·3 to 237·9) in the colesevelam group after 6 weeks of treatment; the ETD between the groups was 311·3% (95% CI 203·7 to 457·0; p<0·0001; (table 2, figure 3). In contrast to colesevelam treatment, which increased the faecal output of bile acids by 194·6% (95% CI 111·4 to 310·5), 6 weeks of treatment with liraglutide did not significantly change the faecal output of bile acids (–11·3% [36·2 to 23·2]; table 2, figure 3).

Fasting concentrations of glucose after 6 weeks of treatment were decreased by –0·59 mmol/L (95% CI –0·97 to –0·20) with liraglutide and by –0·44 mmol/L (95% CI –0·82 to –0·06) with colesevelam, but no significant differences between the groups was seen (table 2, figure 4). After 6 weeks of treatment, only liraglutide significantly affected HbA_{1c} (–2·21 mmol/mol [95% CI –3·14 to –1·29]), insulin (42·6% [20·9 to 68·3]), and C-peptide (17·9% [6·4 to 30·6]), resulting in significant differences in insulin and C-peptide between the groups (table 2, figure 4). Liraglutide decreased fasting concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides after 6 weeks of treatment, whereas colesevelam only decreased LDL cholesterol (table 2, figure 4). The ETD of HDL cholesterol between the groups was 7·7% (95% CI 2·3 to 13·4; p=0·018; table 2, figure 4).

Decreased symptom scores and improved quality of life were observed following 6 weeks of treatment with both

	Baseline (mean)	3 weeks				6 weeks			
		Change with liraglutide	Change with colesevelam	Estimated treatment difference	p value	Change with liraglutide	Change with colesevelam	Estimated treatment difference	p value
Stool frequency (stools per day)	3·54 (3·02 to 4·06)	−1·55 (−1·99 to −1·11)	−0·84 (−1·27 to −0·40)	0·71 (0·29 to 1·14)	p=0·001 (p=0·004)	−1·83 (−2·32 to −1·35)	−1·08 (−1·56 to −0·59)	0·76 (0·31 to 1·20)	p=0·00089 (p=0·0042)
Stool type (Bristol Stool Form Scale)	5·38 (5·19 to 5·58)	−0·72 (−1·09 to −0·35)	−0·70 (−1·07 to −0·33)	0·02 (−0·48 to 0·52)	p=0·94 (p=0·94)	−0·66 (−1·02 to −0·29)	−0·94 (−1·31 to −0·58)	−0·29 (−0·79 to 0·22)	p=0·27 (p=0·35)
SeHCAT	3·75% (2·85 to 4·65)	9·53% (5·57 to 13·48)	−1·33% (−5·19 to 2·54)	10·85% (5·35 to 16·36)	p=0·00015 (p=0·00092)	6·06% (2·52 to 9·59)	−0·89% (−4·42 to 2·63)	6·95% (2·00 to 11·9)	p=0·0063 (p=0·0019)
FGF19, pmol/L	80·4 (63·5 to 101·8)*	44·3% (0·7 to 107)	−67·3% (−77·3 to −52·8)	−77·3% (−85·7 to −63·9)	p<0·0001 (p<0·0001)	5·5% (−21·9 to 42·5)	− 65·0% (−74·2 to −52·6)	−66·9% (−77·3 to −51·7)	p<0·0001 (p<0·0001)
C4, µg/L	54·7 (44·1 to 67·1)*	−42·1% (−56·6 to −22·9)	190·2% (117·7 to 286·9)	401·4% (244·6 to 629·6)	p<0·0001 (p<0·0001)	−36·7% (−51·2 to −18·1)	160·1% (100·3 to 237·9)	311·3% (203·7 to 457·0)	p<0·0001 (p<0·0001)
Faecal total bile acids, µmol/g	4·6 (3·6 to 5·8)*	−23·1% (−46·9 to 11·3)	210·5% (114·7 to 348·8)	304% (151·7 to 548·4)	p<0·0001 (p<0·0001)	−11·3% (−36·2 to 23·2)	194·6% (111·4 to 310·5)	232·3% (118·7 to 404·9)	p<0·0001 (p<0·0001)
Glucose, mmol/L	6·0 (5·5 to 6·5)	−0·68 (−1·02 to −0·35)	−0·34 (−0·67 to 0·001)	0·35 (0·09 to 0·60)	p=0·008 (p=0·02)	−0·59 (−0·97 to −0·20)	−0·44 (−0·82 to −0·06)	0·15 (−0·06 to 0·35)	p=0·16 (p=0·25)
HbA_{1c}, mmol/mol	34·3 (32·9 to 35·7)	−1·68 (−2·56 to −0·8)	0·04 (−0·84 to 0·92)	1·72 (0·51 to 2·93)	p=0·006 (p=0·02)	−2·21 (−3·14 to −1·29)	−0·83 (−1·77 to 0·1)	1·38 (0·19 to 2·57)	p=0·024 (p=0·051)
HbA_{1c}	5·3% (5·2 to 5·4)	−2·3% (−2·4 to −2·2)	2·15% (−2·20 to 2·20)	2·3% (2·3 to 2·4)	..	−2·4% (−2·4 to −2·3)	−2·2% (−2·3 to 2·2)	2·3% (2·2 to 2·4)	..
Insulin, pmol/L	68·4 (55·9 to 83·6)*	24·5% (5·9 to 46·6)	−3·1% (−17·3 to 13·5)	−22·2% (−36·7 to −4·5)	p=0·02 (p=0·04)	42·6% (20·9 to 68·3)	−13·5% (−26·6 to 2·0)	−39·3% (−49·7 to −26·8)	p<0·0001 (p<0·0001)
C-peptide, pmol/L	604 (528 to 692)*	−4,7% (−40·4 to 52·3)	−25% (−52·6 to 18·8)	−21·3% (−59·0 to 51·3)	p=0·47 (p=0·55)	17·9% (6·4 to 30·6)	−9·4% (−18·4 to 0·6)	−23·1% (−32·9 to −12·0)	p=0·00018 (p=0·00095)
Total cholesterol, mmol/L	5·3 (5·0 to 5·5)	−0·41 (−0·65 to −0·16)	−0·27 (−0·51 to −0·02)	0·14 (−0·18 to 0·46)	p=0·39 (p=0·50)	−0·32 (−0·18 to −0·04)	−0·19 (−0·47 to 0·09)	0·13 (−0·26 to 0·51)	p=0·52 (p=0·59)
HDL cholesterol, mmol/L	1·4 (1·3 to 1·6)*	−5·0% (−8·5 to −1·3)	2·5% (−1·3 to 6·5)	7·9% (2·5 to 13·5)	p=0·004 (p=0·01)	−5·4% (−9·0 to −1·7)	1·9 (−2·0 to 5·9)	7·7 (2·3 to 13·4)	p=0·0053 (p=0·018)
LDL cholesterol, mmol/L	2·8 (2·6 to 3·0)	−0·02 (−0·20 to 0·16)	−0·32 (−0·50 to −0·14)	−0·30 (−0·53 to −0·07)	p=0·01 (p=0·03)	0·06 (−0·17 to 0·29)	−0·23 (−0·46 to −0·002)	−0·29 (−0·60 to 0·02)	p=0·07 (p=0·12)
VLDL cholesterol, mmol/L	0·84 (0·72 to 0·96)	−0·14 (−0·23 to −0·04)	−0·02 (−0·12 to 0·07)	0·11 (−0·01 to 0·23)	p=0·07 (p=0·12)	− 0·09 (−0·22 to 0·04)	−0·05 (−0·18 to 0·08)	0·04 (−0·13 to 0·21)	p=0·64 (p=0·67)
Triglycerides, mol/L	1·8 (1·5 to 2·2)*	−21·3% (−31·9 to −9·0)	−0·9% (−14·3 to 14·6)	25·9% (4·2 to 52·1)	p=0·02 (p=0·04)	−18·2% (−31·3 to −2·6)	−4·1% (−19·6 to 14·3)	17·1% (−6·0 to 45·9)	p=0·16 (p=0·25)
Symptom score, 1–5	2·62 (2·43 to 2·82)	−0·44 (−0·66 to −0·22)	−0·52 (−0·75 to −0·30)	−0·08 (−0·34 to 0·18)	p=0·53 (p=0·59)	−0·66 (−0·90 to −0·43)	−0·77 (−1·00 to −0·53)	−0·11 (−0·39 to 0·18)	p=0·46 (p=0·55)
Quality of life, 1–5	2·57 (2·30 to 2·84)	−0·58 (−0·77 to −0·39)	−0·41 (−0·60 to −0·22)	0·17 (−0·09 to −0·43)	p=0·19 (p=0·27)	−0·74 (−0·98 to −0·50)	−0·62 (−0·86 to −0·38)	0·12 (−0·20 to 0·43)	p=0·46 (p=0·55)
BMI, kg/m^2	30·04 (28·58 to 31·49)	−0·79 (−1·17 to −0·41)	−0·38 (−0·76 to 0·02)	0·41 (−0·12 to 0·95)	p=0·13 (p=0·21)	−1·06 (−1·49 to −0·62)	−0·40 (−0·83 to 0·04)	0·66 (0·05 to 1·26)	p=0·03 (p=0·07)

Data are mean (95% CIs), unless otherwise stated. BMI=body mass index. C4=7 alpha-hydroxy-4-cholesten-3-one. FGF19=fibroblast growth factor 19. HbA_{1c}=glycated hemoglobin A_{1c}. HDL=high-density lipoprotein. LDL=low-density lipoprotein. SeHCAT=^{75}selenium-homotaurocholic acid test. VLDL=very-low-density lipoprotein. *Data are log-transformed geometric means (95% CIs). Adjusted p values are shown in parentheses.

Table 2: **Secondary endpoints following 3 and 6 weeks of treatment with liraglutide or colesevelam**

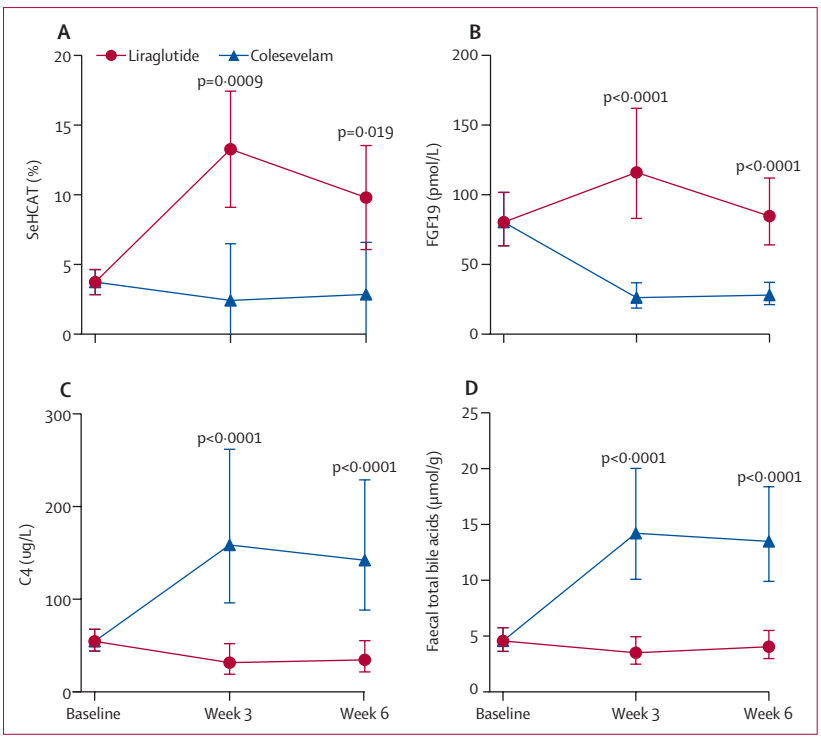

***Figure 3*: Effects on bile acid retention (SeHCAT), FGF19 signalling, bile acid biosynthesis (C4), and faecal bile content**

(A) Changes in ^{75}selenium-homotaurocholic acid test (SeHCAT) assessed at baseline and after 3 and 6 weeks of treatment with liraglutide or colesevelam. (B) Changes in plasma concentrations of fibroblast growth factor 19 (FGF19) assessed at baseline and after 3 and 6 weeks of treatment with liraglutide or colesevelam. (C) Changes in 7-alpha-hydroxy-4-cholesten-3-one (C4) concentrations (µg/L) assessed at baseline and after 3 and 6 weeks of treatment with liraglutide or colesevelam. (D) Changes in concentrations of total bile acids in faeces assessed at baseline and after 3 and 6 weeks of treatment with liraglutide or colesevelam. Data are presented as means with 95% CIs or for log-transformed data as geometric means with 95% CIs; p values are adjusted.

liraglutide and colesevelam. There were no significant differences between the groups (table 2).

Seven participants in the liraglutide group who had undergone a cholecystectomy had a 56·4% reduction from baseline in daily stool frequency by week 6, and eight participants in the colesevelam group who had undergone a cholecystectomy had a 22·7% reduction from baseline in daily stool frequency by week 6. These numbers correspond with the reductions in stool frequencies noted for the overall population.

Only liraglutide decreased BMI from baseline after 6 weeks of treatment (–1·06 kg/m² [95% CI –1·49 to –0·62]), with no significant differences between the groups (table 2).

Six participants in the liraglutide group and one participant in the colesevelam group reported mild nausea with a duration of 10–21 days. No other adverse events were reported. One participant from each group dropped out of the study due to nausea (appendix p 9). Sensitivity analyses did not change the primary outcome (appendix p 10). All participants reported that all medication was taken as per protocol during the entire study period. No dose adjustments, treatment discontinuations, or rescue therapies were necessary.

Discussion

In this investigator-initiated, randomised, double-blind, placebo-controlled, double-dummy, parallel-group, non-inferiority clinical trial, we confirmed our primary hypothesis that liraglutide would be non-inferior to colesevelam (the standard of care) in reducing daily stool frequency by 25% or greater during 6 weeks of treatment in patients with moderate-to-severe bile acid diarrhoea. In fact, liraglutide-treated participants had a 27% greater chance of achieving a reduction in daily stool frequency of 25% or greater than did those receiving colesevelam, corresponding to a number needed to treat of 3·7. Furthermore, liraglutide treatment reduced stool frequency more effectively than colesevelam (ETD 0·76 stools per day), increased reabsorption of bile acids (assessed by SeHCAT), and decreased bile acid synthesis (assessed by circulating C4), thus exerting beneficial effects on the core pathophysiological features of bile acid diarrhoea.

The mainstay pharmacological treatment of bile acid diarrhoea, bile acid sequestration (originally developed for the treatment of hypercholesterolaemia, as sequestering bile in the intestine causes loss of bile acids through faeces and compensatory conversion of cholesterol into bile acids in the liver), mainly rests on empirical data and a few studies investigating the bile acid sequestrants cholestyramine, colestipol, and colesevelam.[20–23] In a retrospective chart review and patient questionnaire, Wedlake and colleagues[24] found that the majority of colesevelam-treated individuals with cancer and SeHCAT-verified bile acid diarrhoea experienced symptom relief. Also, Beigel and colleagues[25] observed a colesevelam-induced reduction in stool frequency in patients with type 1 bile acid diarrhoea due to Crohn's disease. Three clinical trials found no effect of colesevelam versus placebo on stool frequency assessed as secondary or exploratory endpoints in patients with diarrhoea-predominant irritable bowel syndrome (not diagnosed with bile acid diarrhoea),[20,22,26] but a non-significant improvement in stool frequency was described in two of the trials.[22,26] Despite the limited evidence of bile acid sequestration being effective in bile acid diarrhoea and its off-label use, this treatment modality remains the mainstay pharmacological treatment.[27] Furthermore, SeHCAT is not widely available since it requires access to ^{75}selenium-labelled homotaurocholic acid and a gamma camera and involves radiation exposure (the test is not currently done in the USA), so diagnosis is often based on empirical treatment with bile acid sequestrants in patients with suspected bile acid diarrhoea. This approach is advocated by both British and Canadian gastroenterology organisations, in the absence of other diagnostic tests.[28,29] Last, based on interviews with patients with bile acid diarrhoea in our outpatient clinic, we found placebo monotherapy for 6 weeks to be unethical (based on the evidence from the literature and our own clinical experience that the mainstay treatment, bile acid

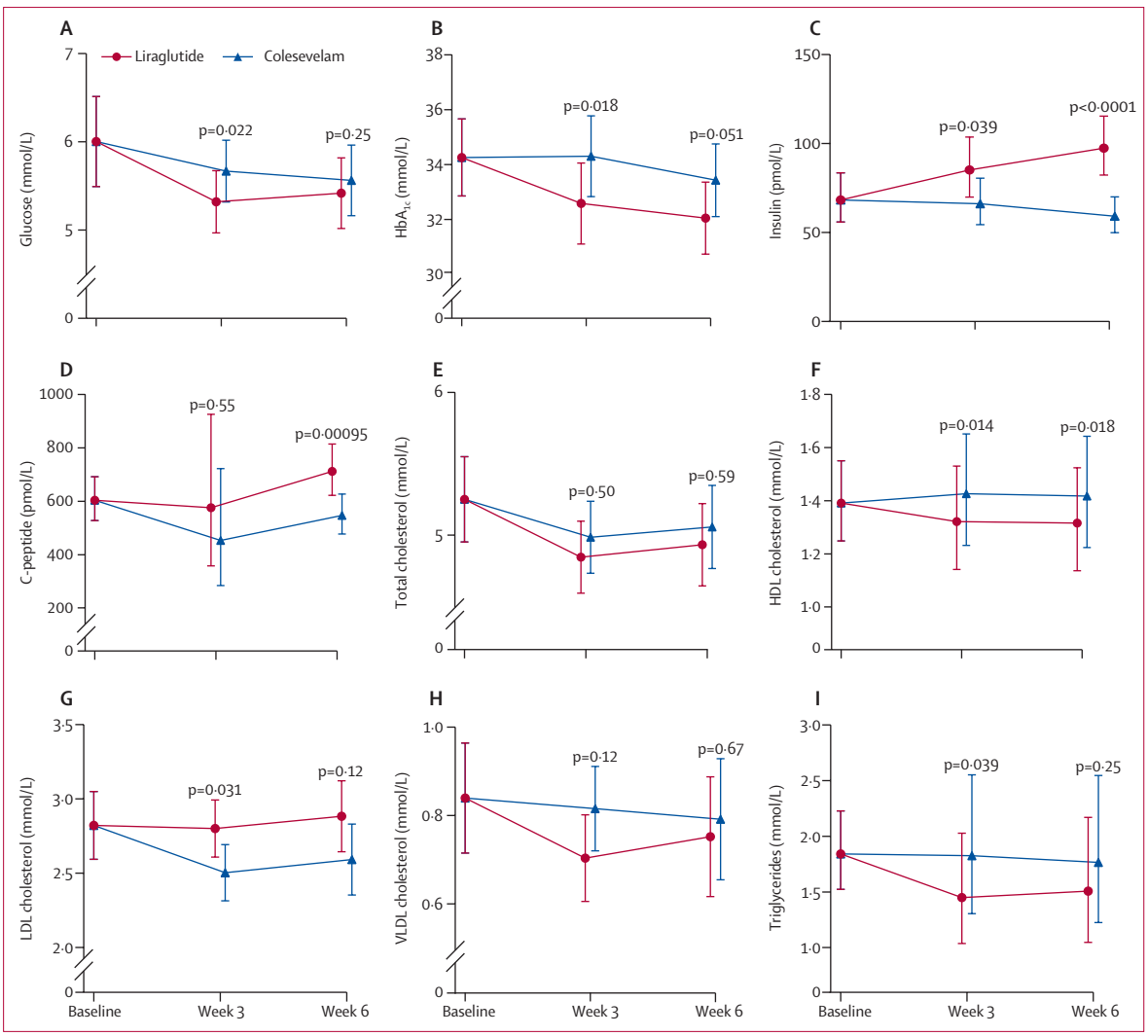

Figure 4: **Effects on glucometabolic markers and lipid profile**
(A) Changes in plasma concentrations of glucose. (B) Changes in plasma concentrations of HbA_{1c}. (C) Changes in plasma concentrations of insulin. (D) Changes in plasma concentrations of C-peptide. (E) Changes in plasma concentrations of total cholesterol. (F) Changes in plasma concentrations of high-density lipoprotein (HDL) cholesterol. (G) Changes in plasma concentrations of low-density lipoprotein (LDL) cholesterol. (H) Changes in plasma concentrations of very low-density lipoprotein (VLDL) cholesterol. (I) Changes in plasma concentrations of triglycerides. All changes in plasma concentrations assessed at baseline and after 3 and 6 weeks of treatment with liraglutide or colesevelam. Data are presented as means with 95% CIs or geometric means with 95% CIs for log-transformed data; p values are adjusted.

sequestrants, has an effect in patients) and unlikely to be accomplished without too many dropouts. For the abovementioned reasons, we chose to compare liraglutide with colesevelam in the present trial.

We observed that colesevelam treatment, while improving bile acid diarrhoea symptoms, decreased plasma FGF19, increased plasma C4, and increased faecal loss of bile acids (typical features of bile acid diarrhoea pathophysiology),[3,5] which is in line with the findings of Vijayvargiya and colleagues[22] who investigated placebo versus colesevelam in patients with irritable bowel syndrome with diarrhoea and previous evidence of increased bile acid synthesis or faecal excretion. Conversely, liraglutide increased the absorption of bile acids (as assessed by SeHCAT) and decreased bile acid synthesis (as assessed by circulating C4), thus improving important pathophysiological features of bile acid diarrhoea concomitantly with its greater efficacy in reducing daily stool frequency compared to colesevelam. GLP-1RA treatment has previously been shown to increase gastrointestinal transit time,[10] and we recently proposed that this effect—combined with GLP-1RA-mediated reduction of gallbladder emptying[11]—might increase time for passive reabsorption of bile acids in the small intestine, and thus reduce spillover of bile acids to the colon.[9] Future studies investigating the mode of action of liraglutide in bile acid diarrhoea will shed light on this issue.

Given our recent enterohepatic and glucometabolic characterisation of bile acid diarrhoea, revealing a dysmetabolic prediabetic-like state in patients with bile acid diarrhoea versus sex-matched, age-matched, and BMI-matched healthy controls,[7] the well described[30,31] beneficial glucometabolic effects of liraglutide might be considered an added benefit of this treatment in bile acid diarrhoea. Colesevelam worked as expected by reducing LDL cholesterol concentrations. In the liraglutide group, plasma concentrations of total and HDL cholesterol decreased over the 6 weeks of treatment.

Both liraglutide and colesevelam might cause mild to moderate and often transient gastrointestinal symptoms,[3,32] but only one participant dropped out from each group because of gastrointestinal side-effects.

Some limitations and strengths of our trial should be considered. The non-inferiority margin of 15% in favour of colesevelam might clinically be considered too high (ie, a favourable effect of colesevelam <15% might be missed with the present design). However, the observed outcome of superiority in favour of liraglutide obviates this limitation. Testing first for non-inferiority and then for superiority does not incur a statistical penalty,[17] but the observation of superiority in this non-inferiority-powered trial might nevertheless be considered a limitation as the risk of getting a statistically significant result when no true effect exists is higher than in a superiority-powered trial. As in all studies comparing treatments head to head without a placebo group, a so-called study effect affecting both treatment groups cannot be excluded. However, the randomised and double-blinded nature of the present study allows us to draw some important conclusions about differences between the investigated interventions. Missing data for continuous outcomes were implicitly handled by maximum likelihood estimation, which is statistically optimal under a missing at random assumption. In case dropout is related to a good or poor treatment outcome, results might be biased. Furthermore, the relatively small sample size and short treatment period might be considered limitations. Further investigations of the effect of liraglutide on colonic transit time in bile acid diarrhoea are warranted to better understand the mechanisms underlying the present findings. The in-house questionnaires used to evaluate symptom scores and increased quality of life represent another limitation as these were based on questionnaires not developed specifically for bile acid diarrhoea, and the results originating from these questionnaires should thus be interpreted with caution. SeHCAT-verified diagnosis of moderate-to-severe bile acid diarrhoea as an eligibility criterion, the randomised, double-blind, active-comparator, double-dummy, parallel-group design, the clinically relevant and well defined primary endpoint and supporting secondary endpoints as well as endpoints exploring the mechanisms of action for the two interventions contribute to the validity of the results. Taken together, these findings suggest consideration of liraglutide as a potential treatment of bile acid diarrhoea, and the conduct of larger trials powered for demonstrating superiority.

In conclusion, the GLP-1RA liraglutide, a well known and safe drug used for the treatment of type 2 diabetes and obesity, was observed in this study to be superior to colesevelam (considered the standard of care in bile acid diarrhoea) in reducing stool frequency by 25% or greater in patients with moderate-to-severe bile acid diarrhoea over 6 weeks, suggesting consideration of liraglutide as a potential treatment modality for patients with bile acid diarrhoea, although further studies are warranted in this setting.

Contributors

MLK, JLF, DPS, and FKK contributed to the study concept and design. MLK contributed to data collection. MLK, AB, JLF, AH, EK, EL, DSN, LOD, SHH, MK, TV, DPS, and FKK contributed to analysis and interpretation of data. MLK and FKK contributed to drafting of the manuscript. MLK, AB, JLF, AH, EK, EL, DSN, LOD, SHH, MK, TV, DPS, and FKK contributed to revision of the manuscript. MLK, DPS, and FKK obtained funding. MLK, AB, JLF, LOD, SHH, MK, DPS, and FKK accessed and verified the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

FKK received honorarium for consulting, lecturing, and teaching from the manufacturers of liraglutide (Novo Nordisk) and support for attending American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) meetings, including paid meeting registration, accommodation, and travel. All other authors declare no competing interests.

Data sharing

At present, data from this study are not publicly available.

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