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Remission of bile acid malabsorption symptoms following treatment with the glucagon-like peptide 1 receptor agonist liraglutide

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M.L.K. drafted and revised the manuscript; A.B. reviewed and edited the manuscript; M.E.R. provided patient data, reviewed and edited the manuscript S.L. provided patient care and reviewed and edited the manuscript; D.P.S. reviewed and edited the manuscript; F.K.K. conceptualized, reviewed and edited the manuscript.
Introduction

As much as 50% of patients with chronic diarrhea may suffer from bile acid malabsorption (BAM) [7]. BAM is associated with spillover of bile acids from the small intestine to the colon triggering osmotic-induced fluid secretion with subsequent watery diarrhea and high stool frequency alongside gastrointestinal symptoms such as abdominal pain and bloating [7]. The gold standard for the diagnosis of BAM is the $^{75}$selenium-homotaurocholic acid test (SeHCAT), which evaluates the 7-day retention of orally administered $^{75}$selenium-labeled bile acids. Retention of $\geq 15\%$ is consistent with normal bile acid reabsorption, 10-15% is considered mild BAM, 5–10% moderate and <5% retention severe BAM [5]. Bile acid sequestrants are the only approved pharmacological treatment for BAM. These drugs act through luminal binding of bile acids, which eliminates the osmotic effects of bile and thereby causes a reduction of colonic fluid secretion. However, many patients respond poorly to bile acid sequestrant treatment [7] and new treatment options for BAM are highly needed.

Cases

Here we present two cases of BAM in which the glucagon-like peptide 1 (GLP-1) receptor agonist liraglutide (Victoza®) was initiated as a treatment of overweight and type 2 diabetes, respectively, and caused complete remission of BAM symptoms.

Case 1

A 65-year-old woman experienced diarrhea with up to seven watery stools per day, abdominal pain and bloating following a cholecystectomy in 2011. The woman was diagnosed with severe BAM by SeHCAT (5% retention) in 2013. Treatment with the bile acid sequestrant cholestyramine was initiated with only modest effect and the woman continued to experience high stool frequency and reduced quality of life. In 2015, the woman initiated subcutaneous liraglutide treatment for her overweight (initiated at 0.6 mg once-daily and up-titrated to 1.2 mg once-daily). A few days after treatment initiation, the woman experienced total remission of BAM symptoms including normalization of stool frequency and consistency. Relapses of BAM symptoms were reported on days when the liraglutide dose was missed and during an attempt to down-titrate liraglutide from 1.2 mg to 0.6 mg daily. SeHCAT performed following initiation of liraglutide treatment demonstrated a normal $^{75}$selenium-labeled bile acid retention above 20%. At control visits in 2016, 2017 and 2018, the woman reported no BAM-related symptoms and at her last visit, she reported one daily bowel movement with normal consistency and a high quality of life on liraglutide treatment.

Case 2

A 49-year-old man experienced watery diarrhea with high stool frequency and was diagnosed with severe BAM by SeHCAT (5% retention) in 2013. Treatment with cholestyramine caused no relief of BAM symptoms. In September 2017, the man was diagnosed with type 2 diabetes
and initiated liraglutide treatment, which resulted in an immediate and total remission of gastrointestinal symptoms. At a control visit in February 2018, the man reported one bowel movement per day with normal consistency. SeHCAT performed in June 2018 showed an unchanged $^{75}$selenium-labeled bile acid retention of 5%, but the man continued to be without BAM-related symptoms and experienced increased quality of life on liraglutide treatment.

**Discussion and conclusion**

The incretin hormone GLP-1 is well known for its glucose-lowering and satiety-promoting actions. In addition, GLP-1 delays upper gastrointestinal motility and treatment with the GLP-1 receptor agonist liraglutide increases small intestinal transit time [1, 4]. Likely, this enhances passive reabsorption of bile acids from the gut to the bloodstream with a subsequent reduction in spill-over of bile acids to the colon (Fig. 1). During the process of passive reabsorption, bile acids stimulate the nuclear farnesoid X receptor (FXR) in enterocytes [7]. The activation of FXR stimulates the synthesis and secretion of fibroblast growth factor 19 (FGF19), which in turn reduces the de novo synthesis of bile acids via suppression of CYP7a1 activity in the liver [2, 3]. Interestingly, individuals with BAM have reduced plasma concentrations of FGF19 compared to healthy subjects [6], which points to a compromised negative feedback on bile acid synthesis that could potentially add fuel to the fire by which BAM symptoms burn. Thus, liraglutide-induced deceleration of small intestinal transit time and ensuing greater passive reabsorption of bile acids in these patients may not only reduce spill-over of bile acids to the colon, it may also increase FXR activation and restore FGF19-mediated negative feedback on bile acid synthesis (Fig. 1), grabbing BAM pathophysiology by the root.

In conclusion, treatment with liraglutide in two individuals with BAM led to remission of BAM-related gastrointestinal symptoms accompanied by normalization of SeHCAT in one of the cases. Randomized controlled studies are warranted to delineate the treatment potential of liraglutide in patients suffering from BAM.
References

**Figure and legend**

*Figure 1. Hypothesized effects of liraglutide on bile acid malabsorption*

Left panel: Bile acid malabsorption (BAM) is characterized by hepatic overproduction of bile acids, incomplete small intestinal absorption of bile acids (resulting in reduced negative feedback on hepatic bile acid production by fibroblast growth factor 19 (FGF19) and bile-mediated hepatic FXR activation) and spillover of bile acids from the small intestine to the colon triggering osmotic-induced watery diarrhea. Right panel: We hypothesize liraglutide-induced deceleration of small intestinal transit time to increase the passive absorption of bile acids throughout the small intestine allowing active bile acid absorption in the distal part of the small intestine to clear any remaining intraluminal content of bile acids. Also, we speculate the liraglutide-induced increase in small intestinal absorption of bile acids to elicit an increase in circulating FGF19 levels as well as hepatic FXR activation, which will elicit a decrease in the hepatic synthesis of bile acids.
Bile acid malabsorption

Bile acid synthesis

FGF19

Bile acids

Portal circulation

Normal small intestinal transit time

Bile acid malabsorption + GLP-1 receptor agonist treatment

Bile acid synthesis

FGF19

Bile acids

GLP-1 receptor

Liraglutide

Decelerated small intestinal transit time