Effects of Elobixibat, an Inhibitor of Ileal Bile Acid Transporter, on Glucose and Lipid Metabolism: A Single-arm Pilot Study in Patients with T2DM

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ABSTRACT

Purpose: The ileal bile acid transporter inhibitor elobixibat was recently approved in Japan for use in the treatment of patients with chronic constipation. Elobixibat has been associated with increased plasma glucagon-like peptide 1 level through Takeda G protein receptor 5, which is a membrane receptor of bile acids. The present study assessed the metabolic effects of elobixibat in patients with type 2 diabetes mellitus (T2DM)-related constipation.

Methods: In this single-arm pilot study, 21 patients with T2DM and constipation were administered elobixibat 10 mg/d for 12 weeks (period 1). The primary end point was the change in hemoglobin (Hb) A_{1c} at week 12. Secondary end points included physical parameters; constipation symptoms; and blood parameters, such as low-density lipoprotein cholesterol (LDL-C), arachidonic acid (AA), and fatty acid fractions. Thereafter, the study participants chose whether to continue therapy for an additional 12 weeks (period 2), at which point HbA_{1c} and lipid levels were reevaluated. Safety information, including adverse events, discontinuation and interruption of the drug, was collected at each visit during the trial.

Findings: Period 1: the levels of HbA_{1c}, LDL-C, and AA were significantly reduced after administration of elobixibat for 12 weeks (–0.2%, –21.4 mg/dL, and –16.1 μg/dL, respectively; $P = 0.016$, $P < 0.001$, and $P = 0.010$). Period 2: at week 24, the change from baseline in HbA_{1c} was significantly greater among those who continued elobixibat treatment than in those who discontinued after 12 weeks (–0.23% vs +0.21%; $P = 0.038$). No serious or severe adverse events were observed.

Implications: Elobixibat may benefit patients with T2DM by improving glucose metabolism and lowering serum LDL-C and AA levels, in addition to ameliorating constipation. This single-arm pilot study was of a small sample size. The findings provide a basis for designing a larger-scale study to confirm the effects of elobixibat on glucose and lipid metabolism. (UMIN Clinical Trials Registry identifier: UMIN000045508; https://www.umin.ac.jp/ctr/index.htm) (*Clin Ther.* 2022;44:1418–1426.) © 2022 Elsevier Inc.

Keywords: Bile acid, Elobixibat, HbA_{1c}, Ileal bile acid transporter inhibitor, LDL-C, Type 2 diabetes.

INTRODUCTION

Bile acids (BAs) are amphipathic molecules synthesized in the liver. They are a major component of bile, which is released through the biliary tract into the gastrointestinal tract, where they emulsify dietary lipids and lipid-soluble vitamins to facilitate digestion and absorption. In the terminal ileum, approximately 95% of BAs are reabsorbed via the ileal BA transporter (IBAT), and they reach the liver through the portal

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venous system, where they accumulate in hepatocytes to be recycled.[1] This process, called *enterohepatic circulation,* is expected to occur 4 to 12 times per day. BAs that escape intestinal uptake are excreted via feces (~0.5 g/d) and replenished via synthesis in the liver to maintain the BA pool size (~3 g).

Farnesoid X receptor (FXR), a nuclear receptor highly expressed in the liver and small intestine,[2] is activated by BAs, and it contributes to maintaining the BA pool size. In hepatocytes, FXR activation represses BA synthesis by regulating short heterodimer partner protein, liver receptor homolog 1, and cytochrome P-450 isozyme 7A1. In intestinal epithelial cells, FXR induces fibroblast growth factor (FGF)-19, which also participates in the feedback repression of BA synthesis, via FGF receptor 4 in hepatocytes.[3]

BAs have attracted substantial attention for their range of metabolic functions through interaction with both nuclear receptors (ie, FXR) and membrane receptors (ie, Takeda G protein receptor [TGR]-5). FXR activation lowers the levels of plasma and liver triglycerides (TGs) by inhibiting sterol regulatory element binding protein and other lipogenic genes in hepatocytes to suppress the production of fatty acids and TGs.[4] Additionally, one study reported that FXR activation was associated with improved insulin sensitivity in mice.[5] TGR-5 is widely expressed in various tissues, including the intestine, liver, skeletal muscles, and brown and white adipose tissue.[6–8] In intestinal L cells, TGR-5 activation promotes the secretion of glucagon-like peptide (GLP)-1 and peptide YY.[7,9,10]

Elobixibat is a selective inhibitor of IBAT that was recently approved in Japan for use in the treatment of patients with chronic constipation (excluding structural disease–induced constipation). Elobixibat tablet (Goofice; EA pharma, Tokyo, Japan) is administered orally once daily. In a placebo-controlled, double-blind, Phase III clinical study conducted in Japan, the mean frequency of spontaneous bowel movements per week was significantly improved in an elobixibat-treated group compared with a placebo group, with no serious adverse events reported.[11] Because elobixibat has been reported to stimulate both motor and secretory functions in the colon, it is recommended as a second-line treatment in patients with chronic constipation, including those with constipation-predominant irritable bowel syndrome.[12] Elobixibat has been associated with a reduced absorption of BAs and increased BA delivery to the colon, which induces colonic contractility, colonic water accumulation, and electrolyte secretion.[12] In a Phase Ib trial, elobixibat was minimally absorbed and was present in picomolar concentrations in plasma, supporting the mechanism of action of elobixibat as a local IBAT inhibitor.[13] Elobixibat has also been reported to modulate the enterohepatic circulation of BAs, with an increase in BA synthesis of up to threefold, and a reduction in plasma FGF-19 level.[13] Furthermore, elobixibat has been associated with significant reductions in levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) in a dose-dependent manner, presumably by directing sterols toward BA synthesis and away from cholesterol synthesis in the liver.[14] In another study, elobixibat reportedly also was associated with an increased plasma GLP-1 level,[15] possibly because of TGR-5 stimulation in response to elevated BA levels in the colon.

Chronic constipation is a common symptom among patients with type 2 diabetes mellitus (T2DM). Concepción-Zavaleta et al.[16] reported diabetic gastroenteropathy as an underdiagnosed complication, with approximately 60% of patients with diabetes presenting with constipation. Patients with diabetes show dysregulated BA metabolism, including an alteration in BA composition.[17] The effects of TGR-5 activation on plasma GLP-1 level, and of FXR activation on glucose tolerance, suggest that, in addition to the amelioration of constipation, elobixibat can have beneficial effects on glucose metabolism in patients with T2DM. With the exception of its influence on plasma LDL-C level, the effects of elobixibat on glucose and lipid metabolism have not been investigated. Therefore, this study assessed the metabolic effects of elobixibat in patients with T2DM-related constipation.

PATIENTS AND METHODS

Study Design and Population

This single-arm prospective study was conducted from October 2018 to March 2020 at the Kurume University Hospital (Kurume, Japan), and included patients with T2DM and symptoms of constipation. The inclusion criteria were a diagnosis of T2DM, age of ≥20 years, a diagnosis of chronic constipation as per the Rome IV criteria,[18] and treatment with a stable antidiabetic regimen for at least 12 weeks prior to the study. Pregnant or breast-feeding women and patients

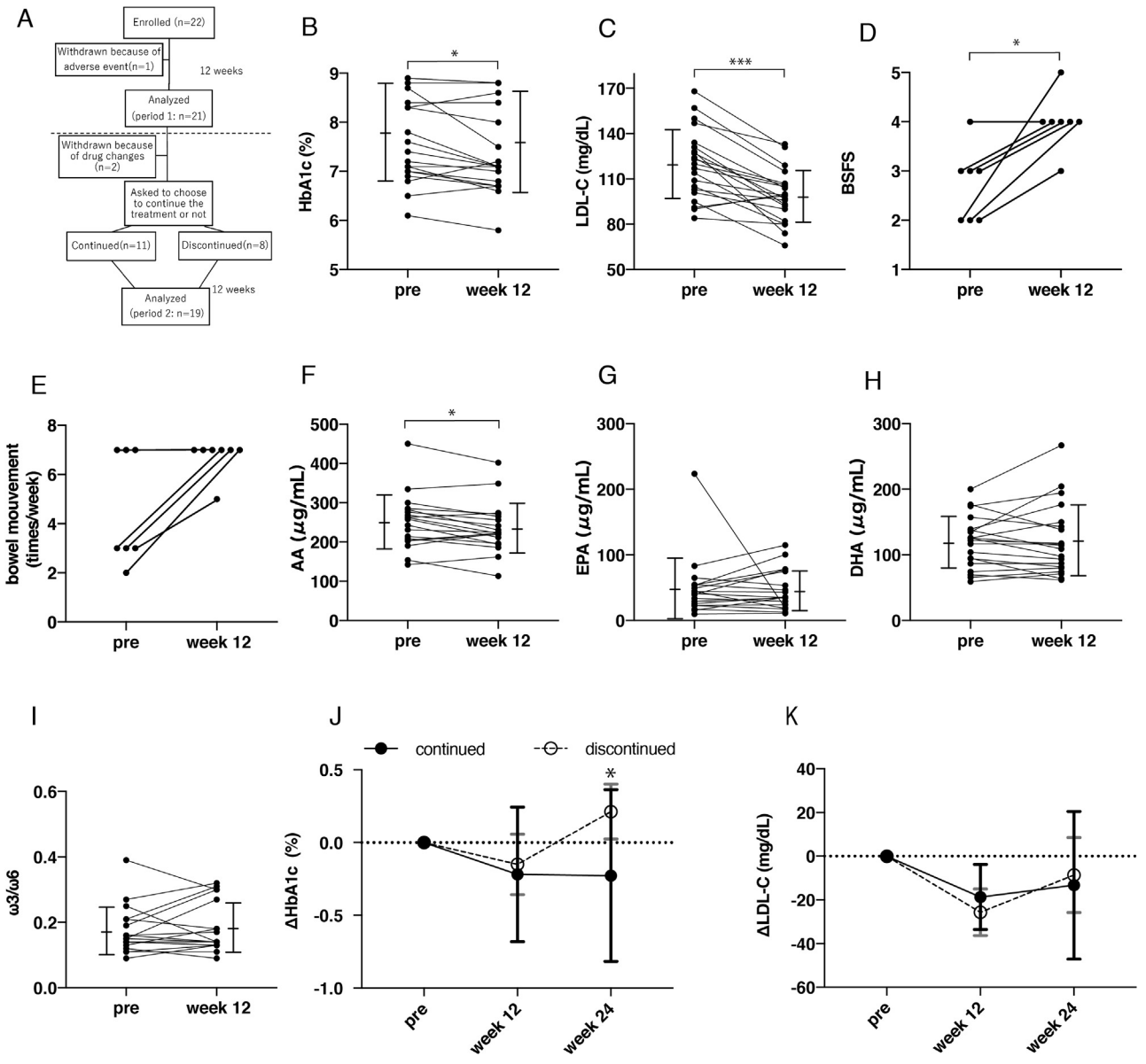

Figure 1. Flow chart of subject enrollment and the levels of clinical parameters. A: Flow chart of subject enrollment. B–I: Levels of clinical parameters before and after elobixibat treatment for 12 weeks (n = 21): hemoglobin (Hb) A_{1c} (National Glycohemoglobin Standardization Program; B); low-density lipoprotein cholesterol (LDL-C; C); Bristol Stool Form scale (BSFS; D); bowel movements (E); arachidonic acid (AA; F); eicosapentaenoic acid (EPA; G); docosahexaenoic acid (DHA; H); and ω-3/ω-6 fatty acid ratio (I). J and K: Mean (SD) changes from baseline in HbA_{1c} (J) and LDL-C (K) in patients who continued (n = 11) or discontinued (n = 8) treatment. $^{*}P < 0.05$.

with intestinal obstruction caused by a tumor or hernia were excluded. The flow chart of patient enrollment is presented in Figure 1**A**.

After the examinations at baseline, all patients underwent treatment with elobixibat (10 mg/d), along with a conventional antidiabetic regimen. They were asked to maintain their lifestyles during the study and to visit the hospital every 6 weeks for follow-up. Clinical and questionnaire data were obtained at

baseline and week 12 (end of period 1). At 12 (±2) weeks from the start of treatment, patients were asked whether they wished to continue elobixibat therapy. At 24 (±2) weeks (end of period 2), clinical and questionnaire data were collected. The results of those who continued elobixibat treatment and those who did not were compared (period 2). Safety information, including adverse events and discontinuation and interruption of the drug, was collected at each visit during the trial.

This study protocol was approved by the ethics committee of Kurume University and complied with the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Study End Points

The primary end point was the change in the level of hemoglobin (Hb) A_{1c} at week 12 after elobixibat treatment. Secondary end points included changes in body mass index, number of bowel movements, stool appearance according to the Bristol Stool Form Scale, and blood parameters including the levels of LDL-C, high-density lipoprotein cholesterol, TGs, fatty acid fractions, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total BAs, thyroid-stimulating hormone, free triiodothyronine, free thyroxine, C-reactive protein, uric acid, ferritin, arachidonic acid (AA), eicosapentaenoic acid, and docosahexaenoic acid. All laboratory analyses were performed by SRL Inc (Tokyo, Japan). LDL-C level was evaluated via direct assays. After the patients conveyed their decision to continue or discontinue of their own free will, a follow-up analysis of glucose, lipid, and hepatic profiles was conducted at week 24.

Statistical Analyses

The Shapiro–Wilk test was performed to assess the normality of the data. To test the homogeneity of variance, the Levene test was conducted. Data are reported as means (SD) or medians (interquartile range) depending on the distribution. For normally distributed data, the statistical significance of differences was analyzed using the paired (period 1) or unpaired (period 2) *t* test. For non-normally distributed data, the differences were tested using the Wilcoxon signed-rank test. All comparisons were two-tailed, with a *P* value of <0.05 indicating significance. All statistical analysis was performed using Prism software version 7.0 (GraphPad, San Diego, California) or SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Table I. Baseline characteristics of all patients who underwent 12 weeks of elobixibat treatment (N = 21).

Characteristics	Value
Age, mean (SD), y	63.0 (12.1)
Male, no. (%)	9 (42.9)
Body weight, mean (SD), kg	67.8 (11.0)
Body mass index, mean (SD), kg/m^2	26.2 (4.1)
Duration of diabetes, mean (SD), y	16.6 (8.6)
Complications of DM, no. (%)	
Retinopathy	10 (47.6)
Neuropathy	9 (42.9)
Nephropathy	6 (28.6)
Medication, no. (%)	
Metformin	15 (71.4)
GLP-1 RA	14 (66.7)
SGLT-2 inhibitor	14 (66.7)
Statin	12 (57.1)
Insulin	6 (28.6)
Sulfonylurea	6 (28.6)
DPP-4 inhibitor	4 (19.0)
α-Glucosidase inhibitor	3 (14.3)
Glinides	2 (9.5)
Pioglitazone	0

DM = diabetes mellitus; DPP = dipeptidyl peptidase; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT = sodium glucose cotransporter.

RESULTS

Baseline Characteristics

A total of 22 patients were enrolled in the study. One patient withdrew at week 1 because of an adverse event (diarrhea), whereas the remaining 21 completed 12 weeks of elobixibat treatment (period 1) (Figure 1**A**). The mean age of the 21 patients was 63.0 years, and 57.1% were female. The mean duration of diabetes was 16.6 years, and the mean body mass index was 26.2 kg/m^2. The clinical characteristics of the 21 patients are summarized in Table I.

HbA_{1c} and LDL-C After 12-Week Elobixibat Treatment

Changes in HbA_{1c} and LDL-C levels, Bristol Stool Form Scale score, and the number of bowel movements in all patients are presented in Figure 1, B–E. After 12 weeks of elobixibat treatment, the mean HbA_{1c} level was significantly reduced versus baseline (from 7.80% [0.97%] to 7.60% [1.00%] [International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), from 62 to 59 mmol/mol]; $P = 0.016$), with no significant changes in body weight or body mass index. The change from baseline in HbA_{1c} level after the elobixibat treatment was −0.2% (0.34%) (IFCC, −2 mmol/mol). The number of bowel movements was not significantly different after treatment (change, from 3 to 7, $P = 0.13$), but the Bristol Stool Form Scale score was significantly improved (from 3 to 4; $P = 0.031$). In terms of lipid metabolism, the LDL-C level was significantly decreased after treatment, by 21.4 mg/dL ($P < 0.001$), but there were no significant changes in total cholesterol, high-density lipoprotein cholesterol, or TG levels (Figure 1C and Table II). This effect was independent of the effect of statins (change in patients treated with statins, from 115.1 [23.8] to 94.4 [17.3] mg/dL [$P = 0.0017$]; patients not treated with statins, from 126.3 [18.3] to 103.9 [14.3] mg/dL [$P = 0.0027$]). The thyroid-stimulating hormone level was numerically decreased after elobixibat treatment; this finding may have been due to the binding of BAs with TGR-5 in brown adipose tissue, which reportedly increases the activity of type 2 iodothyronine deiodinase.[19] However, the difference in neither thyroid-stimulating hormone nor serum total BA reached statistical significance. Free triiodothyronine and free thyroxine levels remained stable throughout the study. There were no significant changes in the levels of ferritin, C-reactive protein, or uric acid after treatment (Table II).

Fatty Acid Metabolism After 12-Week Elobixibat Treatment

AA concentrations were decreased significantly after elobixibat treatment (from 251.4 [67.1] to 235.3 [61.6] μg/mL; $P = 0.010$). Conversely, the eicosapentaenoic acid level (from 47.5 [44.3] to 43.7 [29.7] μg/mL; $P = 0.74$), docosahexaenoic acid level (from 119.3 [38.0] to 122.1 [52.7] μg/mL; $P = 0.67$), and ω-3/ω-6 ratio (from 0.17 [0.07] to 0.18 [0.07]; $P = 0.63$) were unchanged after 12 weeks of observation (Figure 1, F–I). Changes in the levels of other fatty acids are summarized in **Supplemental Table S1** (see the online version at doi:10.1016/j.clinthera.2022.08.009).

Association Between Discontinuation of Elobixibat Treatment and HbA_{1c}

After 12 weeks of elobixibat administration, when the patients were asked whether they wished to continue treatment, 11 patients continued treatment, 8 elected to discontinue treatment after considering the improvement in constipation versus the costs and benefits of elobixibat, and 2 patients withdrew from the study as their prescribed antidiabetic drugs had been changed (Figure 1A). The patients were not randomized in this study; therefore, the baseline characteristics were not balanced between the groups that continued and discontinued treatment. The duration of T2DM and the percentage of patients with diabetic neuropathy and nephropathy were significantly greater in the group that continued treatment. The differences in mean HbA_{1c} and LDL-C levels between the two groups at the beginning of period 2 were not significant (see **Supplemental Table S2** in the online version at doi:10.1016/j.clinthera.2022.08.009). In the continuation group, the mean HbA_{1c} levels at baseline, week 12, and week 24 were 7.92% (0.78%), 7.70% (0.77%), and 7.69% (0.64%), respectively (IFCC, 63, 61, and 61 mmol/mol), and those in the discontinuation group were 7.48% (1.03%), 7.33% (1.1%), and 7.69% (1.2%) (IFCC, 58, 57, and 61 mmol/mol). HbA_{1c} levels did not differ significantly between the groups at any time point. However, the change from baseline in HbA_{1c} was significantly greater at week 24 in the group that continued versus the group that discontinued elobixibat treatment (−0.23% [0.56%] vs +0.21% [0.18%] [IFCC, −2 vs +2 mmol/mol]; $P = 0.038$) (Figure 1J). In terms of lipid metabolism, the levels of and changes in LDL-C were not significantly different between the two groups (Figure 1K). The clinical parameters at baseline, week 12, and week 24 in the groups that continued and discontinued treatment are summarized in **Supplemental Table S3** (see the online version at doi:10.1016/j.clinthera.2022.08.009).

DISCUSSION

In the present study, HbA_{1c} level was significantly lowered versus baseline with elobixibat administration for 12 weeks in these patients with T2DM. Discontinu-

Table II. Values of clinical parameters at baseline and after 12 weeks of elobixibat treatment (N = 21). Data are given as mean (SD).

Parameter	Baseline	Week 12	*P*
Body weight, kg	67.8 (11.0)	67.2 (10.7)	0.21
BMI, kg/m^2	26.2 (4.09)	25.6 (3.61)	0.14
Bowel movements per week, median (IQR)	3 (3–7)	7 (7–7)	0.13
BSFS, median (IQR)	3 (2–3)	4 (4–4)	0.031*
HbA_{1c}, %	7.80 (0.97)	7.60 (1.00)	0.016*
LDL-C, mg/dL	119.9 (22.3)	98.5 (16.8)	<0.001***
HDL-C, mg/dL	56.3 (14.4)	55.8 (14.6)	0.61
TG, mg/dL	140.5 (69.1)	156.0 (73.6)	0.13
TC, mg/dL	202.2 (26.4)	193 (43.7)	0.25
AST, U/L	22.6 (11.5)	23.6 (15.7)	0.48
ALT, U/L	22.5 (12.1)	25.7 (15.3)	0.22
γ-GTP, U/L	35.1 (41.2)	39.4 (55.0)	0.25
TBA, μmol/L	3.09 (1.35)	2.85 (0.95)	0.50
TSH, μIU/mL	2.90 (1.75)	2.18 (1.33)	0.059
FT3, pg/mL	2.74 (0.39)	2.74 (0.40)	0.64
FT4, ng/dL	1.29 (2.0)	1.31 (0.20)	0.71
Ferritin, ng/mL	112.3 (160.1)	72.4 (35.2)	0.47
CRP, mg/dL	0.14 (0.10)	0.12 (0.89)	0.65
UA, mg/dL	5.24 (1.30)	5.02 (0.81)	0.70
AA, μg/mL	251.4 (67.1)	235.3 (61.6)	0.010*
EPA, μg/mL	47.5 (44.3)	43.7 (29.7)	0.74
DHA, μg/mL	119.3 (38.0)	122.1 (52.7)	0.67
ω-3/ω-6	0.17 (0.07)	0.18 (0.07)	0.63

*$P < 0.05$.

***$P < 0.001$.Mean TBA levels <2.0 are indicated as 2.0.AA = arachidonic acid; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BSFS = Bristol Stool Form scale; CRP = C-reactive protein; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FT3 = free triiodothyronine; FT4 = free thyroxine; GTP = glutamyl transpeptidase; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TBA = total bile acid; T-chol = total cholesterol; TG = triglyceride; TSH = thyroid-stimulating hormone; UA = uric acid.

ation of elobixibat treatment at week 12 was associated with a significantly increased change from baseline to week 24 in HbA_{1c} level compared with that in the patients who continued on elobixibat therapy. To the best of our knowledge, this is the first study to demonstrate that elobixibat treatment was associated with a lower HbA_{1c} level in patients with T2DM.

It is well established that BA-induced TGR-5 activation is associated with enhanced GLP-1 secretion from intestinal L cells.[9,10] BA binding resin (BABR), such as cholestyramine, has been associated with a lower LDL-C level, likely by the absorption of BAs in the intestine, and with an improved glucose tolerance in an animal model and in humans.[9,20] Metformin has also been associated with enhanced GLP-1 secretion, likely by suppressing active BA absorption in the ileum.[15] It is plausible that the effects of elobixibat on glucose metabolism are attributable to TGR-5 activation in the intestinal L cells. Given that TGR-5 activation in macrophages exerts an anti-inflammatory effect by repressing nuclear factor-κB signaling pathways,[21,22] elobixibat might improve

insulin sensitivity through this mechanism in the local hepatic environment.

Because elobixibat increases BA production in the hepatocytes by reducing BA absorption in the gut, FXR activation in the liver may be involved in the effect of elobixibat on glucose metabolism. Several studies have indicated that $FXR^{-/-}$ mice exhibit high levels of fasting glucose and poor insulin sensitivity and that FXR agonists restore both hepatic and peripheral insulin sensitivity in mice.[23,24] However, the role of FXR in glucose metabolism remains controversial. It has been reported that FXR deficiency improves glucose homeostasis and insulin sensitivity in *ob/ob* and mice fed a high-fat diet.[25] Furthermore, increased fasting levels of serum total BAs have been associated with blunted fasting and systemic insulin sensitivity in patients with T2DM.[26] In the present study, serum BA levels were not significantly altered after elobixibat administration. Thus, further research is necessary to elucidate the influence of elobixibat administration on FXR activity.

In the present study, elobixibat treatment was associated with a lower LDL-C level (by >20 mg/dL), even among patients treated with statins, suggesting its potential as a treatment in patients with dyslipidemia. The apparent inhibition of BA absorption in the ileum by elobixibat may shunt cholesterol synthesized in hepatocytes toward BA synthesis.

Antibiotic drugs affect glucose and TG metabolism by changing the intestinal flora, particularly that of secondary BA-producing bacteria.[27] Interestingly, the BABR colestimide induces changes in the composition of the BA pool and serum BA levels in a manner similar to the administration of cholic acid, a BA.[28] BABRs have a high adsorptive capacity for mono- and dihydroxy BAs, such as chenodeoxycholic acid and lithocholic acid but a relatively low capacity for trihydroxy BAs, such as cholic acid. Conversely, elobixibat has been reported to inhibit the reabsorption of all types of BAs from IBAT. Thus, additional investigations are required to clarify the effect of elobixibat on the composition of the BA pool and intestinal flora.

The present study is the first to elucidate the effects of elobixibat on fatty acid metabolism. Elobixibat was associated with a significant decrease in AA (ω-6 fatty acid) level, without significant changes in the levels of ω-3 fatty acids such as eicosapentaenoic acid and DHA. AA is an integral constituent of biological cell membranes and confers them with the fluidity and flexibility necessary for the function of all types of cells, particularly in the nervous, skeletal muscle, and immune systems; moreover, it is a precursor to a number of potent proinflammatory mediators, including well-described prostaglandins and leukotrienes.[29] AA-derived leukotrienes have been linked to the development of atherosclerosis.[30] AA is obtained from food or by the desaturation and chain elongation of linoleic acid, and increased AA intake enhances leukotriene production.[31] It is conceivable that the changes in intestinal bacteria affected AA absorption; however, further studies are required to identify the mechanism underlying elobixibat-associated reduction in serum AA levels.

This study had some limitations. First, the trial included only 21 patients. As no report on the HbA_{1c}-improving effect of elobixibat was available at the time that the study was conducted, the number of cases could not be determined by assuming the expected change in HbA_{1c} levels after elobixibat treatment according to previous studies. Therefore, the following null hypothesis was tested: elobixibat administration does not affect HbA_{1c} levels. In terms of feasibility, a single-arm study in 21 patients was designed to compare HbA_{1c} levels before and after treatment. A statistically significant improvement in HbA_{1c} level was observed, with an α error of 0.05. This result led to the rejection of the null hypothesis. For reference, on post hoc analysis, the statistical power of the observed changes in HbA_{1c} level was 0.728. Given that this was an exploratory-phase study, a power of >0.70 obtained herein was considered acceptable for providing a basis for the design of a larger-scale study in the future. Second, serum insulin levels were not measured. In the analysis of the effect of elobixibat on glucose metabolism, it would have been better to measure insulin levels for the evaluation of insulin sensitivity and secretion. However, because six of the study participants were receiving insulin therapy, insulin levels were not measured, given that they could not be used as a surrogate measure for insulin sensitivity or secretion. Finally, the serum concentrations of lipoproteins, including apolipoprotein B, were not evaluated. Apolipoprotein B and lipoprotein(a) are well-recognized markers of atherosclerosis. Hence, future trials are necessary for elucidating the effects of elobixibat on insulin and lipoprotein metabolism.

CONCLUSIONS

In the present study, in addition to constipation amelioration, improved glucose and lipid metabolism and lowered AA levels were found with elobixibat use in patients with T2DM. These results suggest that elobixibat has potential as a therapeutic approach to multiple aspects of metabolic syndrome.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

All authors were involved in the authorship of the manuscript, figures and tables. Study design and oversight (SY, NH, AN, YM, KA, MN), data collection (SY, AN, SI, JY, RT, MK, MG, KH), data interpretation (SY, NH, YM, KA, MN), writing (SY, NH, YM, KA, MN), literature search (SY, NH) and figure generation (SY, NH).

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DECLARATIONS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.08.009.

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