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Lubiprostone Reduces Fat Content on MRI-PDFF in Patients With MASLD: A 48-Week Randomised Controlled Trial

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ABSTRACT

Background and Aims: The laxative lubiprostone has been shown to decrease intestinal permeability. We aimed to assess the safety and efficacy of lubiprostone administered for 48 weeks in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Approach and Results: A randomised placebo-controlled trial was conducted in a specialised MASLD outpatient clinic at the National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt. The recruited patients had radiological evidence of MASLD along with other criteria for diagnosis. Eligible patients were randomly assigned to receive either placebo or lubiprostone 24 μg orally twice daily for 48 weeks. The liver fat content was quantified by magnetic resonance imaging estimated proton density fat fraction (MRI-PDFF). Between November 2020 and February 2023, 176 patients were screened, of whom 116 were eligible. Fifty-nine patients were randomised to receive placebo, while 57 patients were randomised to receive lubiprostone. Due mostly to patient dropout (i.e., loss to follow-up), complete data were available for 40 patients in each group. Compared with placebo group, 48-week lubiprostone treatment significantly reduced fat quantity ($p = 0.04$). Despite a significant reduction in body weight in the control group, no significant difference was found between both groups regarding fibrosis score by transient elastography or in serum ALT levels. One patient in the lubiprostone group developed severe diarrhoea requiring treatment stoppage. No other serious adverse events occurred.

Conclusion: Lubiprostone was well tolerated and reduced liver fat content as measured by MRI-PDFF in patients with MASLD over 48 weeks. Lubiprostone appears promising to treat MASLD and warrants more extensive studies to confirm such efficacy.

Trial Registration: ClinicalTrials.gov identifier: NCT05768334

Mohamed El-Kassas and Hala Mostafa are the co-first authors.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is an abnormal accumulation of fat in the liver strongly linked to obesity and metabolic syndrome [1]. MASLD is currently the most prevalent chronic liver disease [2], affecting 25% of the world population [3]. The most severe form of the disease is metabolic dysfunction-associated steatohepatitis (MASH), in which steatosis is combined with inflammation and sometimes fibrosis [4]. MASH can further advance to cirrhosis and hepatocellular carcinoma (HCC) [3].

Although one-fourth of the global population suffers from MASLD which impacts the quality of life and imposes a heavy burden on healthcare costs, no effective commercially available medications are available for treatment. However, resmetirom has recently been approved by the US FDA, but due to its high cost, its availability in most global regions remains problematic [5]. The mainstay of management has been diet and exercise to reduce weight. This is because, mechanistically, we have yet to find the pathways responsible for its development.

One hypothesis is that MASLD is related to intestinal permeability ("Leaky gut") [6]. Lubiprostone, a laxative, has been shown to improve the intestinal barrier in animal models [7, 8]. A recent short duration (12-weeks) randomised controlled trial in Japan testing lubiprostone in MASLD patients with constipation, elevated alanine aminotransferase (ALT) levels and absent fibrosis showed a 50% reduction in ALT levels [9]. However, it is well known that many patients with MASLD have normal ALT levels, thus it remains unclear whether lubiprostone is effective in all MASLD patients including those with normal ALT values. The present randomised controlled trial (RCT) aimed to assess the long-term effectiveness of lubiprostone on MASLD patients with normal and abnormal ALT values. We used magnetic resonance imaging estimated proton density fat fraction (MRI-PDFF), the most sensitive index, to assess liver fat content before and after 48-week treatment.

2 | Methods

This RCT was conducted in a specialised MASLD outpatient clinic at the National Hepatology and Tropical Medicine Research Institute (NHTMRI), Cairo, Egypt, and recruited 116 MASLD patients from November 2020 to February 2023.

2.1 | Study Population

Inclusion criteria included adult patients (18–65 years) of both sexes with MASLD detected by abdominal ultrasound or CT; the hepatic fat fraction was at least 5% when assessed by MRI-PDFF. Other liver diseases were excluded such as patients with positive HBsAg, anti-HCV antibodies and antinuclear antibody (ANA). The sample size was calculated based on the method of Thompson S.K. (Table S1). Patients with daily alcohol consumption exceeding 20/30 g/day for females and males, respectively, were also excluded [10]. Other exclusion criteria included cirrhotic patients with Child-Pugh score > 7, or transient elastography (FibroScan) scores > 14.6 Kpa [11], hepatic steatosis < 5% in the initial MRI-PDFF assessment, estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2, pregnancy, diagnosed or suspected HCC, and any other contraindication to MRI such as the presence of prosthetic heart valves, annuloplasty rings, metallic implants, pacemakers and contrast allergy.

All study participants were subjected to a full history including drug history and smoking, and also complete physical examinations. Baseline laboratory assessments included complete blood count (CBC), liver profile testing including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, and serum albumin, kidney function tests (urea and creatinine), lipid profile (total cholesterol, triglycerides, HDL and LDL) and glycosylated haemoglobin (HbA_1c). Body mass index (BMI) was calculated for all patients. FibroScan with controlled attenuation parameter (CAP) was performed to assess hepatic fibrosis and steatosis, in addition to fat quantification by MRI-PDFF.

2.2 | Randomisation and Grouping

After enrollment in the study and receiving a study-specific identification number, eligible patients were randomly assigned (by sealed envelopes), to receive either placebo (Group I) or lubiprostone 24 μg (Group II) orally, twice daily for 48 weeks. The random allocation sequence was generated by an independent statistician using a computerised random number generator.

Participants were enrolled by the clinical research team at the specialised MASLD outpatient clinic at NHTMRI. This was a double-blind study. Both participants and care providers were blinded to the assignments. The placebo and lubiprostone capsules were identical in appearance and packaging to ensure blinding. Outcome assessors, particularly those conducting the MRI-PDFF, were also blinded to the interventions to prevent bias in assessing efficacy outcomes.

2.3 | Follow-Up of Study Patients

Patients were followed up by phone after 4 weeks of treatment start and then interviewed in person after 12 weeks. These two follow-up sessions aimed to evaluate safety and compliance with treatment. During the phone call, we inquired about any possible adverse events of the drug with special emphasis on diarrhoea, abdominal pain, abdominal cramps, headache, myalgias and any history suggestive of liver toxicity such as jaundice, lower limb edema, abdominal distention or bleeding tendency, as well as history suggestive of renal toxicity including changes in urine output, puffy eyes or pruritus.

At the week 12 visit, in addition to collecting the previous data, body mass index (BMI) was calculated, and physical examination was performed. At week 24, patients were assessed again for BMI calculation, physical examination, inquiry about possible adverse events of the drug, and laboratory testing including CBC, liver function tests and liver enzymes. At week 36, patients were assessed for safety confirmation similar to the week 12 visit. At the end of the study (48 weeks), patients were evaluated with the same panel as the week 24 visit, in addition to a FibroScan with CAP and MRI-PDFF. At all visits, the patient's

compliance to medication was checked. Study medications were to be stopped if intractable adverse events (such as diarrhoea or abdominal pain) or pregnancy occurred.

2.4 | Study Outcomes

The primary efficacy outcome was a change in liver fat content as quantified by MRI-PDFF at baseline and at 48 weeks of treatment. Although the main statistical analysis was intended as intention-to-treat, this proved impossible because a relatively large number of patients in both groups dropped out before week 48, and thus no second MRI was available. Therefore, only 40 patients in each group were analysed per protocol.

Secondary outcomes included change from baseline to week 48 in serum transaminase levels and fat quantification by CAP. Safety and tolerability were assessed by the incidence and severity of adverse events and changes in physical examination findings, vital signs and standard laboratory safety parameters (including CBC, liver profile and kidney functions).

2.5 | Study Tools

FibroScan and CAP were performed using TE FibroScan 502 (Echosens, Paris, France) by trained operators. The examinations were performed according to the manufacturer's recommendations, which included at least 4 h of fasting and applying an M or XL probe on the right liver lobe through the intercostal spaces. Steatosis stage was decided according to a mean of different cut-off points as proposed by the manufacturer and assigned a stage: non-steatosis, S1, S2 or S3. Fat quantification was done using MRI-PDFF (Ingenia 1.5 Tesla, Philips, Eindhoven, the Netherlands).

TABLE 1 | Demographics and baseline clinical characteristics.

	Placebo group, $N=59$	Lubiprostone group, $N=57$	p
Male	10 (16.9%)	5 (8.8%)	NS
Female	49 (83.1%)	52 (91.2%)	NS
Age, years	47.0 ± 10.2	43.3 ± 9.1	< 0.05
Diabetes	16 (27.1%)	21 (36.8%)	NS
Hyperlipidemia	43 (72.9%)	39 (68.4%)	NS
Hypertension	7 (11.9%)	7 (12.3%)	NS
BMI	35.7 ± 5.0	38.2 ± 4.9	< 0.01
Body weight (kg)	58 (98.3%)	56 (98.2%)	NS
HbA1c	5.9 ± 1.3	6.2 ± 1.7	NS
Fasting plasma glucose	104.5 ± 34.4	108.2 ± 35.8	NS
Creatinine	0.97 ± 0.21	0.89 ± 0.2	< 0.05
Fibrosis/KPa	5.05 ± 1.44	4.84 ± 1.50	NS
Triglycerides	193.6 ± 89.5	165.8 ± 103.6	NS
Total cholesterol	219.7 ± 45.9	194.1 ± 36.4	< 0.01
HDL	47.7 ± 9.4	43.3 ± 8.1	NS
LDL	133.5 ± 37.7	115.6 ± 33.9	< 0.05
Liver chemistries			
ALT (U/L)	21.5 ± 7.9	21.5 ± 7.7	NS
AST	21.5 ± 5.2	19.6 ± 10.2	NS
Serum albumin (g/L)	42.7 ± 3.9	41.0 ± 3.6	NS
Total Bil, mg/dL, median (IQR)	0.8 (0.6–0.9)	0.7 (0.5–0.9)	NS
Blood exam			
Haemoglobin (g/L)	123 ± 11	122 ± 11	NS
White blood cell (10^9/L)	6.8 ± 1.4	6.6 ± 1.3	NS
Platelets (10^9/L)	271 ± 50	264 ± 44	NS
CAP	302.5 ± 42.6	313.8 ± 48.2	NS
MRI-PDFF, median % (IQR)	11.37 (7.8–15.45)	14.97 (11.2–19.96)	< 0.01

MRI-PDFF is an optimised MRI-based biomarker independent of the scanner's manufacture, platform and field strength. We used MRI-PDFF to minimise or correct the confounding factors (T1 bias, T2* bias and multifrequency interference effects of fat and eddy currents) that can induce errors in fat fraction estimations with conventional MRI-based techniques [12].

2.6 | Ethical Considerations

All study procedures were carried out according to the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee for human subject research at the Faculty of Medicine, Helwan University (serial number 11–2020) on 11 February 2020. All participants signed a written informed consent before inclusion in the study.

2.7 | Statistical Analysis

Qualitative variables were analysed using the Chi-squared test, while quantitative variables were analysed using independent Student *t*-tests. In all tests, the *p*-value was considered significant when <0.05.

3 | Results

Between November 2020 and February 2023, 176 patients were screened, and 60 were excluded due to either declining participation or not meeting the enrollment criteria. Thus, 116 eligible patients were randomly assigned to either the placebo control group ($n=59$) or lubiprostone treatment group ($n=57$), the demographics and baseline clinical and laboratory characteristics of these patients are shown in Table 1. Nineteen patients in the placebo-control group did not complete the protocol due to loss to follow-up or technical difficulties with MRI-PDFF. Seventeen patients in the lubiprostone group did not complete the protocol due to loss to follow-up, discontinuing treatment, diarrhoea, or pregnancy. Thus, 40 patients in each group had complete data and were analysed (Figure 1).

Although there was no intentional gender bias in selection, females predominated in our cohort (83% in control and 91% in lubiprostone groups were females). The average age was 47.0 ± 10.2 in the placebo group and 43.3 ± 9.1 in the lubiprostone group ($p<0.05$). The baseline characteristics were similar between the two groups except for age, BMI, creatinine, total cholesterol, LDL and MRI-PDFF (all $p<0.05$, Table 1). After 24 weeks of treatment, the changes of the lab parameters showed significant differences for platelets and ALT; the only significant difference

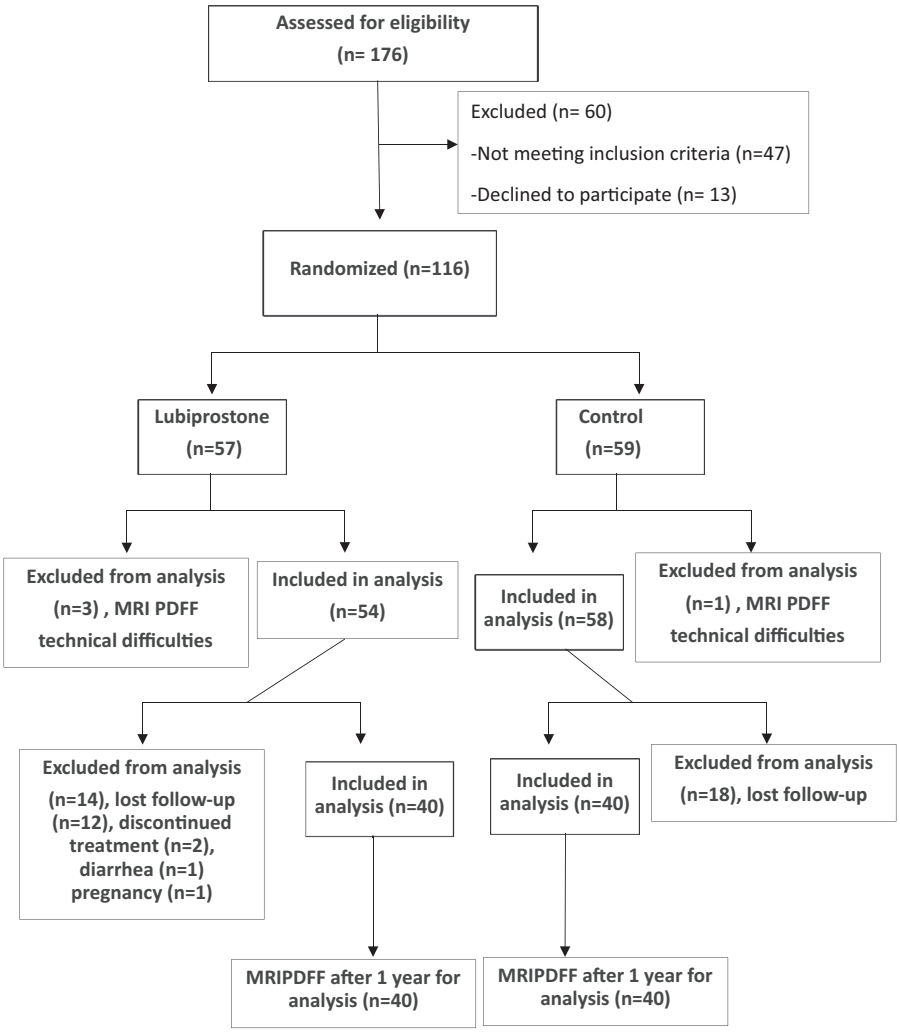

FIGURE 1 | Flow chart of patient recruitment and study procedure.

was total leukocyte counts after 48-week treatments (Table 2). Two (5%) patients in the lubiprostone group and 4 (10%) in the placebo group had ALT decreases more than 17 IU/L (p = NS) after 48 weeks treatment. The imaging examinations showed that after 48-weeks treatment, lubiprostone significantly decreased MRI-PDFF value (Figure 2 and Table 3). Further analysis revealed that 47.5% (19/40) patients in the lubiprostone and 40% (16/40) in the placebo group had more than 30% decrease of MRI-PDFF (p = NS) after 48 weeks.

Forty-eight weeks treatment did not change lipid profiles and fasting plasma glucose levels (Table 4). However, HbA1c was significantly decreased in the lubiprostone group. This might be due to the decreased intestinal absorption of glucose.

Adverse events are shown in Table 5. Only 1 serious AE, severe diarrhoea, occurred in the lubiprostone group, at 2 months, and this patient discontinued medication and removed herself from the study. A non-serious AE, mild diarrhoea, was reported at 3 months, but spontaneously resolved after only 1 week, and did not require dose modification. No AEs occurred in the placebo group.

TABLE 2 | Comparisons between group I and group II regarding laboratory data differences after 24 and 48 weeks.

	Placebo group, $N=40$	Lubiprostone group, $N=40$	p
Difference at 24 weeks			
HB	−0.2 (−0.55 to 0.15	−0.1 (−0.7 to 0)	NS
TLC	−0.59 (−1.85 to 1.55)	0.5 (−0.7 to 2.9)	NS
Platelets	−0.5 (−10 to 6)	8 (−7 to 20)	<0.05
ALT	0 (−6 to 7)	0 (−10 to 6)	NS
AST	−2 (−4 to 6)	4 (−1 to 13)	<0.05
Total Bil.	0.04 (−0.01 to 0.09)	0.02 (−0.01 to 0.06)	NS
Direct Bil.	0.03 (0.01 to 0.06)	0.02 (−0.02 to 0.08)	NS
Serum Alb.	0 (−0.12 to 0.2)	0 (−0.16 to 0.09)	NS
Difference at 48 weeks			
HB	0.2 (−0.1 to 0.4)	0 (−0.6 to 0.3)	NS
TLC	−0.7 (−1.49 to 0.7)	1.35 (−0.4 to 2.05)	<0.05
Platelets	13 (−24 to 23)	19 (−12 to 30)	NS
ALT	−3 (−8.5 to 4)	−2 (−9 to 1)	NS
AST	2.5 (−4.5 to 4.5)	3 (−3 to 8)	NS
Total Bil.	0.03 (−0.01 to 0.08)	0.02 (−0.02 to 0.12)	NS
Direct Bil.	0 (−0.01 to 0.1)	0.01 (−0.03 to 0.06)	NS
Serum Alb.	−0.01 (−0.15 to 0.1)	0 (−0.1 to 0.12)	NS

Note: Mann–Whitney test.

4 | Discussion

The present randomised controlled trial is the first to evaluate the long-term therapeutic effect of lubiprostone in unselected MASLD patients without constipation, regardless of liver enzyme levels. We found that compared with the placebo group, lubiprostone significantly decreased fat content as measured by MRI-PDFF, a non-invasive, quantitative and accurate method for quantifying fat in the liver. This implies the efficacy of the drug in decreasing hepatic steatosis in patients with MASLD. Furthermore, long-term treatment with lubiprostone was safe; in this regard, our study is consistent with other studies in constipated patients without liver disease [13, 14].

MASLD is a heterogeneous disease; its pathogenesis includes metabolic abnormalities [15], inflammation [9], oxidative stress [16], hormonal imbalances [17], and mitochondrial dysfunction [4, 18]. MASLD is now the most common cause of chronic liver disease in most global regions [19]. The progressive form of MASLD is MASH, which can progress to liver fibrosis, cirrhosis and HCC [20]. MASLD has become one of the leading indications for liver transplantation [21]. The complexity of MASLD pathogeneses allows for a wide array of potential therapeutic targets [22]. Resmetirom has recently been approved by the FDA, but at an annual list cost of approximately $47,000 USD [23]. Moreover, a phase 3 randomised controlled trial demonstrated that diarrhoea (27% vs. 16%) and nausea (22% vs. 12%) were more frequent with resmetirom than with placebo [24]. Thus, its widespread use and availability in many global regions is uncertain.

Although the pathogenesis of MASLD is a multi-hit event [25], an increase in intestinal permeability is considered an important factor in the pathogenesis, and a potential therapeutic target to treat patients [26]. Lubiprostone attenuates intestinal permeability [27] and therefore has therapeutic potential. It is a bicyclic

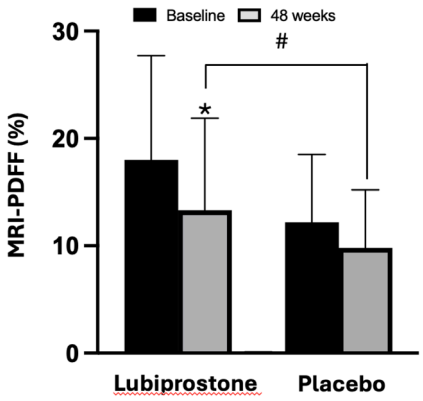

FIGURE 2 | Fat fraction in liver.*Significant difference between baseline and 48 weeks treatment with lubiprostone; # significant difference of the MRI-PDFF changes after 48 weeks treatment between lubiprostone and placebo groups (−4.2% vs −2.3%).

TABLE 3 | Comparisons of CAP, fibroscan and MRI-PDFF changes between the two groups after 48-week treatments.

Difference		Group I (placebo) No. = 40	Group II (lubiprostone) No. = 40	*p*
CAP	Median (IQR)	−31 (−50 to 2) −26.5 (−59 to 40)	-26.5 (−59 to 40)	0.956
	Range	−93 to 78	−136 to 88	
Fibrosis/KPa	Median (IQR)	0.1 (−0.9 to 0.5)	−0.3 (−0.8 to 1.1)	0.718
	Range	−3.6—4.7	−2.9 to 1.9	
MRI-PDFF %	Median (IQR)	−2.32 (−3.47 to 1.09)	−4.17 (−7.1 to −0.98)	0.044
	Range	−15.5 to 3.73	−27 to 8.57	

Note: Mann–Whitney test.

TABLE 4 | Comparisons of the changes of lipid profiles and diabetes-related parameters between the two groups after 48-week treatments.

Parameters median (IQR)	Placebo group (*N* = 40)	Lubiprostone group (*N* = 40)	*p*
Total cholesterol	−5.5 (−26–23)	−26 (−36 to 16)	NS
Triglycerides	−18.5 (−56–15)	−39 (−52 to 11)	NS
HDL	3.5 (−3.5–6.5)	3 (−5 to 5)	NS
LDL	−8 (−18.5–15.5)	−6 (−29 to 9)	NS
HbA1c	0.17 (9–3-0.4)	−0.3 (−0.4 to 0.1)	< 0.05
Fasting plasma glucose	5 (−4.5–13)	−4 (−13 to 9)	NS

fatty acid derived from a prostone metabolite of prostaglandin E1. Hayashi et al. [28] demonstrated that lubiprostone prevents small bowel injury induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in rats. Unlike many laxative products, lubiprostone does not show signs of drug tolerance or chemical dependency, nor does it impact serum electrolyte concentrations [29], which makes it virtually worry-free for long-term application. In a mouse study, Kim et al. [7] found that high-fat diet (HFD) significantly increased intestinal permeability, and lubiprostone reversed the intestinal permeability back to normal control levels. In parallel with the changes in intestinal permeability, the elevated portal venous endotoxin levels in the HFD mice reverted to normal values after lubiprostone treatment. A human study using lactose-mannitol ratio to evaluate intestinal permeability [9] showed that lubiprostone significantly decreased intestinal permeability in patients with MASLD.

Lubiprostone has recently been shown to be effective in a selected subset of patients with MASLD, in a pioneering study by Kessoku and colleagues [9]. This randomised, double-blind, placebo-controlled, phase 2a controlled trial demonstrated that lubiprostone significantly decreased MRI-PDFF. Furthermore, lubiprostone also decreased liver enzymes. The main difference between our study and that of Kessoku et al. is that their study limited the cohort to those with constipation and elevated liver enzymes, whereas our study did not have these restrictions. Thus, we believe that our cohort is more likely to reflect the real-world scenario in clinical practice. To compare further, the primary endpoint of the RCT by Kessoku and coworkers was the absolute changes of ALT at 12 weeks of lubiprostone treatment; our RCT aimed to investigate the effect of lubiprostone on hepatic steatosis over 48 weeks. Thus, our 48-week study also aimed to evaluate the safety of long-term lubiprostone administration. Although it is well known that lubiprostone is generally well tolerated [30], to our knowledge, our study is the first to test the safety of long-term lubiprostone therapy in patients with MASLD. Our findings implied that lubiprostone treatment could be a therapeutic strategy to treat MASLD, and that long-term administration is safe and well tolerated.

A decrease of > 30% in MRI-PDFF [31] and ALT decrease > 17 IU/L [32] have been suggested to be useful indices to quantify therapeutic responses in MASLD studies. Our study did not show differences in the two groups in the proportion of patients achieving these endpoints, for unclear reasons. However, one possible explanation for the lack of difference in ALT responses is that the vast majority of our patients had baseline ALT values in the normal range.

There were some limitations of the present study. First, although we did not set any value of ALT in recruitment, there were only two and three patients with ALT > 40 IU/L in groups I and II, respectively, which indicated that in our Egyptian real-world experience, the majority of MASLD patients have normal liver chemistry. Lubiprostone is poorly absorbed when administrated orally and therefore displays a low systemic bioavailability, which suggests that it only acts on the gut lumen [29]. Since endotoxin in circulation is an important pathogenic factor of MASLD, we speculate that lubiprostone decreases the endotoxin concentration in the portal vein, attenuating the fat accumulation in the liver. Second, we did not measure systemic or portal venous endotoxin and inflammatory cytokine levels because of technical difficulties. Moreover, we did not measure gut permeability. Therefore, we cannot provide direct evidence for or against the hypothesis that lubiprostone exerts its effect by decreasing gut permeability and reducing endotoxin/cytokine levels to decrease the inflammatory insult to the liver.

Another limitation was the significant number of patient dropouts, in both groups (approximately 30% of the randomised cohorts),

TABLE 5 | Adverse events.

Group	AEs in included patients ($n = 40$ each group)	AEs in patients excluded from analysis (placebo group, $n = 19$; lubiprostome group, $n = 17$)
Placebo	No adverse events	No adverse events
Lubiprostone	one patient developed mild transient diarrhoea not requiring dose modification	one patient discontinued treatment due to severe diarrhoea

almost all due to loss to follow-up. This made it unfeasible to perform the intended intention-to-treat analysis of the study results because the primary measured outcome was the MRI-PDFF result and the wk-48 value was missing in so many patients. Thus in the end, only 40 subjects in each group remained for per-protocol analysis. We believe that the major reason for such a relatively large dropout rate was the COVID pandemic. The study ran from November 2020 to February 2023, and during most of this time, the pandemic restrictions discouraged unfettered movement. Thus, as our patients were asymptomatic and believed they did not have serious or life-threatening liver disease, their enthusiasm for repeat visits, especially to a medical facility, solely for the sake of research, was likely to have been extremely low.

5 | Conclusion

Long-term lubiprostone treatment (over 48 weeks) was effective in reducing fat content in patients with MASLD; this effect was not influenced by constipation and liver enzyme status. Furthermore, lubiprostone-treated patients generally did not show serious adverse effects.

Author Contributions

Mohamed El-Kassas: conceptualization, investigation, writing – original draft, methodology, validation, writing – review and editing. **Hala Mostafa:** conceptualization, methodology, data curation, writing – review and editing. **Wessam Abdellatif:** investigation, methodology, formal analysis, data curation, writing – review and editing. **Sohier Shoman:** methodology, data curation, investigation, writing – review and editing. **Gamal Esmat:** investigation, methodology, writing – review and editing, formal analysis, data curation. **Mayur Brahmania:** investigation, methodology, writing – original draft, writing – review and editing, formal analysis, visualization. **Hongqun Liu:** investigation, writing – original draft, writing – review and editing, methodology, data curation. **Samuel S. Lee:** conceptualization, writing – original draft, writing – review and editing, validation, supervision.

Conflicts of Interest

M.E.-K.: investigator/speaker/advisory board member: AstraZeneca, Roche, MSD, AbbVie, Eva, Mash Premier, Takeda, Organon, AUG, Inspire, HSO, Gilead, Janssen, Intercept, Rameda, Ipsen, Onxeo, MinaPharm, Pharco, Zeta, Alfa Cure, Bayer, Oncoustics, PDC, and Spimaco. S.S.L. speaker/advisory board member: Abbvie, Gilead, Jazz, Oncoustics, and Sobi. M.B.: investigator/speaker/advisory board member: Roche, Merck, Gilead, Abbvie. All other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.