Medical Principles and Practice

Original Paper

Med Princ Pract 2022;31:254–261
DOI: 10.1159/000524805

Received: January 16, 2022
Accepted: April 26, 2022
Published online: May 6, 2022

Effect of Phentermine on Hepatic Steatosis in Bariatric Surgery: A Pilot Study

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Highlights of the Study

- Administration of short-time phentermine decreased the proportion of individuals with hepatic steatosis by 19%.
- Phentermine promoted a more significant loss of weight and fat mass among candidates for bariatric surgery.
- No differences in surgical complications were observed.
- Phentermine could be a reasonable treatment option in preoperative intervention.

Keywords
Obesity · Phentermine · Hepatic steatosis · Bariatric surgery

Abstract
Objective: Hepatic steatosis is associated with increased surgical complications in bariatric surgery patients. We aimed to evaluate the effect of phentermine in reducing hepatic steatosis, adipose tissue, and surgical complications in patients undergoing bariatric surgery. ***Methods:*** This was a two-arm, double-blind, randomized, controlled pilot trial of 64 adult subjects with BMI >35 kg/m^2 selected for bariatric surgery randomized into phentermine group (15 mg once daily) or placebo group for 8 weeks. Both groups adhered to a hypocaloric diet (500 calories/day) and an individualized exercise program. The primary endpoint was reducing the frequency of hepatic steatosis measured by ultrasound and reducing adipose tissue through fat mass in total kilograms or percentage. Key secondary points were the prevalence of surgical complications. Baseline and final biochemical parameters and blood pressure too were assessments. ***Results:*** In the phentermine group, the frequency of hepatic steatosis decreased by 19%, and the percentage of patients with a normal ultrasound increased from 9% to 28% ($p = 0.05$). Likewise, the decrease in fat mass in kilograms was more significant in the phentermine group (56.1 kg vs. 51.8 kg, $p = 0.02$). A significant reduction in the HOMA-IR index was observed regardless of weight loss. No differences in surgical complications were observed between groups. Phentermine was well-tolerated; no differences were observed in the frequen-

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cy of adverse events between the groups. ***Conclusions:*** Phentermine decreased the proportion of individuals with hepatic steatosis by 19% and promoted a more significant fat mass loss in kilograms among candidates for bariatric surgery.

Introduction

Severe obesity is a growing global problem with an increasing prevalence. In the USA, the age-adjusted prevalence of obesity increased from 30.5% to 42.4%, and severe obesity increased from 4.7% to 9.2% from 1999–2000 through 2017–2018 [1]. Such patients usually undergo bariatric surgery as part of comprehensive treatment to achieve weight loss. Laparoscopic Roux-en-Y gastric bypass is the gold standard of bariatric surgery, it promotes successful weight reduction and a lower nutritional risk of complications [2]. Candidates for bariatric surgery often have enlarged liver and hepatic steatosis, having a prevalence of 52–90% and 33–89%, respectively [3–6]. In addition to the inherent technical difficulties presented by the presence of a large adipose panicle, an enlarged fatty liver may further complicate surgery, for instance, increasing surgical time and increasing the risk of bleeding during surgical manipulation and conversion from laparoscopic surgery to open surgery [7, 8].

The use of pharmacological measures in conjunction with diet, exercise, and psychological interventions to achieve behavioral modification in patients with obesity has been documented as an alternative to bariatric surgery. A low-calorie diet is recommended to manage candidate bariatric surgery patients to reduce hepatic fatty infiltration and the adipose panicle and facilitate surgery [9–12]. Studies investigating the effect of low-calorie diets on the liver in candidates for bariatric surgery have reported a reduction in hepatic steatosis and fat infiltration of 5–20% [8, 13]; however, it is associated with low adherence and common side effects. Additionally, this type of diet can induce a catabolic state, favoring the loss of muscle mass, which could be detrimental to recovery after surgery [14, 15].

Combining dietary strategies with pharmacotherapy could be a promising approach to improve diet adherence and achieve the goals set in weight loss therapy. Phentermine is used as an appetite suppressant to aid weight loss in programs that include diet and exercise [16]. Currently, there are no specific pharmacological recommendations in the preoperative period for patients with obesity who are candidates for bariatric surgery. Thus, the main objective of this study was to evaluate the effect of phentermine in reducing hepatic steatosis and adipose tissue. Surgical complications in patients undergoing bariatric surgery were assessed as a secondary outcome.

Methods

Study Design and Participants

This is a two-arm, double-blind, randomized, controlled pilot trial: placebo versus phentermine 15 mg/day for 8 weeks. It was carried out at a specialized obesity clinic by an interdisciplinary team of healthcare professionals. Various hospital services referred patients, and those programmed for bariatric surgery within 3–6 months who met the inclusion criteria were invited to participate in the protocol. Both sex's patients, between 18 and 55 years old, with either a BMI ≥35 kg/m^2 with comorbidities or a BMI ≥40 kg/m^2 with and without comorbidities; and with the approbation of the Obesity Clinic Committee for bariatric surgery were eligible for inclusion in the study [17]. We excluded patients with severe lung disease, mental illness, giant hiatal hernia, gastric or duodenal ulcer, portal hypertension or esophageal varices, unstable coronary artery disease, high surgical risk, active substance use, intolerance to phentermine, or inability to implement lifestyle changes. The Research and Ethics Committee approved this study of the Hospital under identifier HJM0367/17-IQF. Written informed consent was obtained from the participants. This study was registered on Clinicaltrials.gov under the identifier NCT03849729.

Randomization

The patients were randomized by a computer-generated random number table. The placebo and the drug were indistinguishable in shape and appearance from each other; random codes were assigned, so neither the researchers nor the patients knew which treatment had been assigned. A third party performed treatment allocation and delivery. After providing informed consent, participants were assigned to a lifestyle intervention program that included an individualized exercise program and a daily diet plan that reduced 500 kcal below resting energy expenditure measured by indirect calorimetry (CCM Express indirect calorimeter, Minnesota, USA). The diet had the following macronutrient distribution: 45% carbohydrates, 25% proteins, and 30% lipids. All patients received a sufficient supply of medication or placebo during the preoperative period study and were instructed to take it once a day before breakfast. Within the program, psychological intervention was also provided to both groups. Participants were asked to avoid drinking alcohol and smoking during the study.

Intervention

Treatments were provided in capsules coated with polyvinyl chloride aluminum; the drug contained 15 mg of phentermine pellets and excipient q.s. The placebo had 15 mg of microcrystalline cellulose, anhydrous lactose, magnesium stearate, and hydrogenated vegetable oil. The dosage of phentermine was based on the amount required to achieve weight loss and beneficial effects based on previous studies and considering that patients usually have various comorbidities. A dose of 15 mg is the lowest dose suggested in a short time accordingly to the Food and Drug Administration

[16, 18, 19]. The capsules were packaged in blister packs, and both the drug and the placebo pellets were identical to enable a double-blind study. Treatment compliance was evaluated by counting the number of blister packs and capsules returned at each visit; appointments were every 2 weeks. Diet compliance was assessed by a 24-h recall and a 3-day food record (food log). The data were processed and converted into gram equivalents following the equivalent food system and were subsequently analyzed using Microsoft Excel 2010 software.

Measurements

A trained health professional determined anthropometric measurements; waist circumference (WC) and hip circumference were measured using a flexible tap (SECA, Hamburg, Germany). Body composition and weight were determined using a body composition analyzer to perform bioelectrical impedance (Tanita BC-418 Body Composition Analyzer) [20].

Blood samples were collected after overnight fasting for 8–12 h. The parameters evaluated were glucose, total cholesterol, HDL cholesterol (HDL-c), LDL cholesterol, triglycerides, insulin, alanine aminotransferase and aspartate aminotransferase, and creatinine levels. Insulin levels were determined by a chemiluminescence assay (IMMULITE 2000), while the other parameters were measured by the ADVIA 1800 Clinical Chemistry System, both devices from Siemens Healthcare Diagnostics (Deerfield, IL, USA).

The same trained and specialized radiologist performed baseline and final ultrasound liver ultrasound using a Samsung Medison Accuvix A30 ultrasound system with a 4.5-MHz sector transducer. The technical parameters, including gain adjustment, placement of the focal zone, and the optimum location of the transducer, were optimized for each patient. Ultrasound results were interpreted by one of the researchers who had previous experience in performing and interpreting hepatic ultrasound [21, 22]. The frequency of hepatic steatosis was assessed according to a 4-point scale: grade 0; normal ultrasound; grade 1–3; hepatic steatosis [23].

Study Endpoints

The primary endpoint was to evaluate whether phentermine could reduce the frequency of hepatic steatosis and adipose tissue through fat mass in total kilograms or percentage in patients undergoing bariatric surgery. Key secondary points were the prevalence of surgical complications, such as shorter surgical times, reduced intraoperative bleeding, and shorter hospital stay length.

Statistical Analysis

The sample size, calculated based on similar previous studies, was 23 considering a power of 80% and an alpha error of 0.05. Continuous variables are expressed as mean ± standard deviation (SD), median, and 25–75th percentile. Dichotomous variables are expressed as frequencies and percentages. Normal distribution was evaluated using the Kolmogorov-Smirnov test; variables without a normal distribution were log-transformed before the analysis. All analyses included only patients who completed the study (per protocol). Independent samples *t* test was used to compare the baseline variables between groups. Paired samples *t* test was used to compare the responses between groups based on different parameters. McNemar's χ^2 test compared categorical variables before and after the treatment. Differences were considered statistically significant when $p < 0.05$. The data were analyzed using SPSS for Windows (version 21.00; SPSS Inc.).

Results

Participants

A total of 64 participants met the inclusion criteria and were selected to be assigned to one of the two treatments, as presented in Figure 1. Of these, 60 participants completed the study. Of the withdrawals, one belonged to the phentermine group (PhG) and left due to SARS-CoV-2 infection. The remaining three were in the placebo group (PG). One participant withdrew from the study due to financial issues, another voluntarily declined to participate in the study, and one subject was restricted by the lockdown due to COVID-19 pandemic and could not attend the final measurement. The baseline characteristics of the participants were similar between the two groups (Table 1).

Comorbidities

20.3% of the participants had a diagnosis of type 2 diabetes, 35.9% had hypertension, and 7.8% had dyslipidemia at the time of the intervention.

Energy and Nutrient Intake

Baseline energy and macronutrient intake were similar between groups. Baseline and final energy intake in median and 25–75th percentile was 1,963 kcal (1,811, 2,091) and 1,290 kcal (1,158, 1,600) ($p < 0.0001$) for the PG versus 1,914 kcal (1,722, 2,100) and 1,285 kcal (1,025, 1,520) ($p < 0.0001$) for the PhG. Macronutrient distribution was preserved at 50% carbohydrates, 20% proteins, and 30% lipids throughout the study. Compliance with drug treatment was 95% for the PhG and 90.5% for the PG.

Effect of the Intervention

Hepatic Steatosis

In the PhG, the frequency of hepatic steatosis decreased from 91% to 72% ($p = 0.053$), and the percentage of patients with a normal ultrasound result increased from 9% to 28%. Such changes were not observed in the PG, where the percentage of patients with hepatic steatosis was similar at baseline and the end of the intervention (Fig. 2).

Anthropometric and Body Composition Measures

Bodyweight decreased in both groups by an average of −2.4 kg (95% CI: −3.30 to 0.21) in the PhG and −1.1 kg (95% CI: −3.21 to 0.26) in the PG. The baseline and final body weight analysis showed that both groups had a significant decrease in weight. Likewise, BMI showed

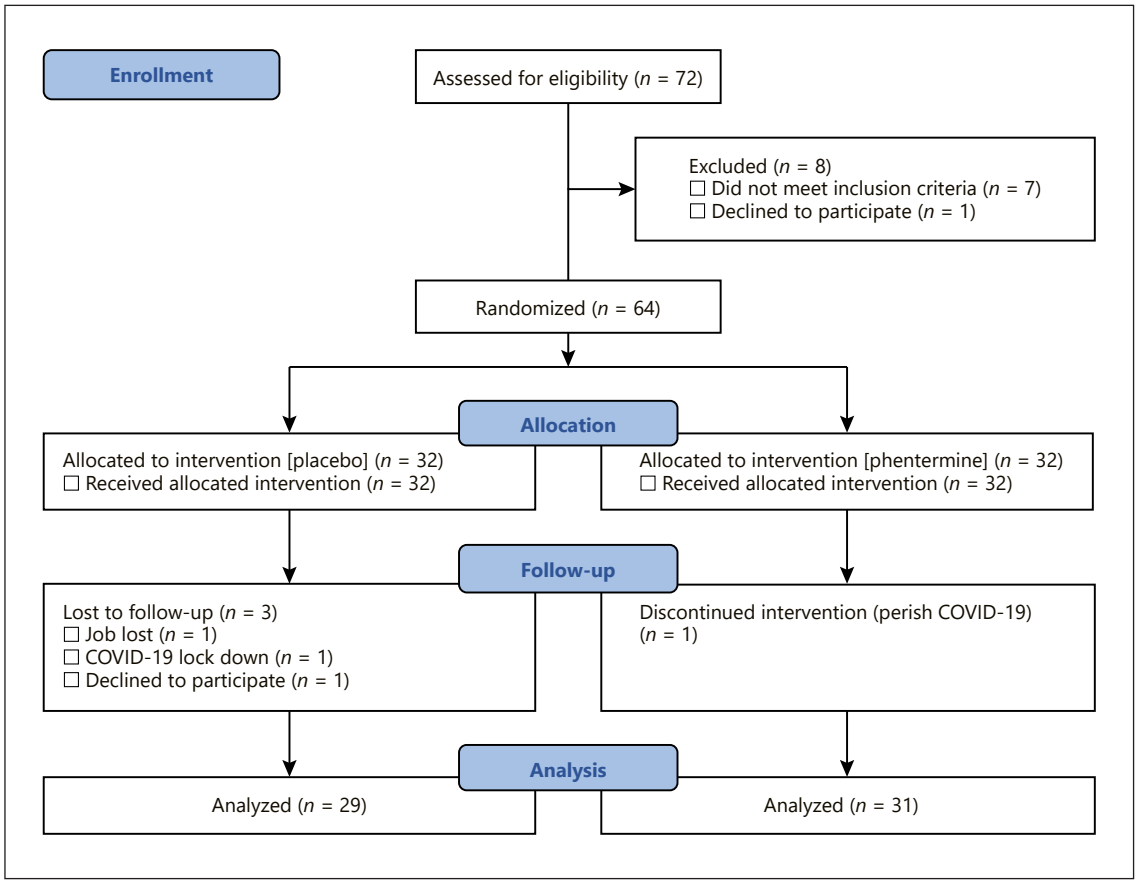

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

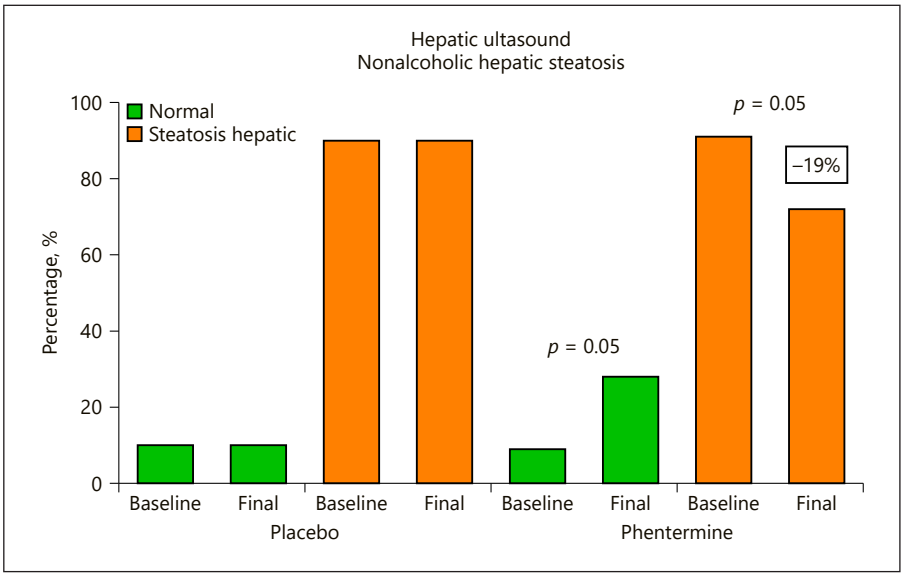

Fig. 2. Changes in the percentage of patients with hepatic steatosis at baseline and at final of the intervention.

Table 1. Baseline demographic and clinical characteristics

Parameter	Placebo (n = 32) Median (25–75th percentile) Frequency, %	Phentermine (n = 32) Median (25–75th percentile) Frequency, %	p value*
Gender female/male	17 (53)/15 (47)	22 (69)/10 (31)	0.200
Ultrasound normal/with hepatic steatosis	3 (10)/27 (90)	3 (9)/29 (91)	0.633
Age, years	35.5 (29.2, 43.7)	38.5 (31.0, 46.5)	0.275
Weight, kg	113.7 (98.6, 134.2)	118 (101, 139)	0.557
BMI, kg/m^2	41.2 (35.7, 50.7)	44.3 (39.7, 49.0)	0.559
Fat mass, kg	51.6 (37.0, 61.5)	56.1 (43.5, 61.6)	0.032
Fat mass, %	42.9 (36.5, 51.4)	48.6 (41.5, 52.0)	0.247
Fat free mass, %	57.0 (48.4, 63.4)	51.4 (47.9, 58.4)	0.277
Waist, cm	116 (104, 135)	121 (112, 131)	0.676
SBP, mm Hg	129 (118, 149)	133 (124, 141)	0.951
DBP, mm Hg	80.0 (75.0, 90.7)	83.5 (71.0, 90.7)	0.830
Glucose, mg/dL	82.5 (73.0, 91.0)	82.5 (75.0, 90.5)	0.513
Cholesterol, mg/dL	170 (152, 192)	171 (153, 192)	0.905
HDL-C, mg/dL	43.0 (36.9, 50.4)	42.0 (35.8, 46.0)	0.404
LDL-C, mg/dL	115 (102, 129)	116 (89.7, 134)	0.671
TG, mg/dL	127 (95.5, 175)	147 (114, 250)	0.196
Insulin, µUI/mL	20.6 (15.5, 29.9)	23.4 (20.0, 33.2)	0.937
HOMA-IR	4.21 (3.12, 7.03)	5.00 (3.42, 7.89)	0.911
AST, U/L	22.5 (20.0, 29.5)	24.0 (19.9, 28.0)	0.682
ALT, U/L	26.0 (21.0, 32.7)	29.0 (20.0, 35.0)	0.806
Creatinine, mg/dL	0.62 (0.58, 0.79)	0.76 (0.61, 0.85)	0.305

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
* Statistical analysis was performed with t test of independent samples t tests, and data were log-transformed before statistical analyses; categorical variables were analyzed with the χ^2 test.

a significant reduction in both groups, as shown in Table 2. Regarding weight loss percentage, 32.3% of the subjects in the PhG had a weight loss greater than 3%, while 24% of the subjects in the PG achieved such weight loss, as shown in Table 3. Otherwise, the fat mass in kilograms after the intervention the PhG decreased from 56.1 kg to 51.8 kg; p = 0.02; while in the PG, no change in fat mass in kilograms was observed (p = 0.07) (Table 2).

Biochemical and Clinical Parameters

After treatment, patients in the PhG or PG showed an increase in total cholesterol and HDL-C. Likewise, insulin concentrations decreased (p = 0.007), and the HOMA-IR index improved (p = 0.008) in the PhG (Table 2).

Surgical Complications

There were no significant differences in surgical time (126.8 ± 25.7 min vs. 142.7 ± 20.4 min; p = 0.17), bleeding volume (60.0 ± 41.0 mL vs. 56.1 ± 16.9 mL; p = 0.86), or duration of hospital stay between the PhG and PG.

Adverse Effects

There were no significant differences in adverse effects between groups, and no serious adverse effects were reported during the study (Table 4).

Discussion

This pilot study evaluated whether phentermine could reduce the frequency of hepatic steatosis and adipose tissue through fat mass in total kilograms or percentage in candidate patients undergoing bariatric surgery. This study showed that phentermine reduced the frequency of hepatic steatosis by 19%; it is probable that the impact on weight loss may indirectly influence the course of hepatic steatosis. Considering the "multiple hit" hypothesis [24], phentermine is associated with decreased leptin and increased leptin sensitivity secondary to weight reduction. Leptin has well-described effects on fatty liver reduction, promotion of fatty acid oxidation, and lipogenesis, as well as to reduce ectopic fat deposits in the liver and muscle [25]. It is possible to explain the reduction

Table 2. Anthropometric, clinical, and biochemical characteristics at baseline and final according to treatment

Parameter	Placebo (n = 29) Median (25–75th percentile)			Phentermine (n = 31) Median (25–75th percentile)		
	baseline	final	p value*	baseline	final	p value*
Weight, kg	113.7 (98.6, 134)	112.6 (98.9, 135.5)	0.021	118 (101, 139)	115.6 (98.7, 140.6)	0.012
BMI, kg/m^2	41.2 (35.7, 50.7)	40.5 (34.9, 48.9)	0.013	44.3 (39.7, 49)	43.0 (39.2, 47.9)	0.017
Waist, cm	116 (104, 135)	113 (104, 132)	0.12	121 (112, 131)	119 (107, 129)	0.20
Fat mass, kg	51.6 (37.0, 61.5)	49.1 (35.6, 62.0)	0.07	56.1 (43.5, 62)	51.8 (42.1, 62)	0.024
Fat mass, %	42.9 (36.5, 51.4)	44.5 (35.9, 52.0)	0.41	48.6 (41.5, 52)	48.2 (41.6, 51.4)	0.30
Fat free, mass, %	57.0 (48.4, 63.4)	55.5 (47.9, 64.1)	0.68	51.4 (48, 58.4)	51.8 (48.5, 58.4)	0.32
SBP, mm Hg	129 (118, 149)	135 (119, 144)	0.53	133 (124, 141)	129 (120, 136)	0.49
DBP, mm Hg	80.0 (75.0, 90.7)	80.0 (71.5, 87.5)	0.41	83.5 (71, 90.7)	82.0 (70.0, 85.0)	0.57
Glucose, mg/dL	82.5 (73.0, 91.0)	83.0 (74.0, 89.0)	0.75	82.5 (75, 90.5)	84.0 (76.0, 91.0)	0.98
Cholesterol, mg/dL	170 (152, 192)	175 (151, 205)	0.24	171 (153, 192)	172 (162, 196)	0.047
HDL-C, mg/dL	43.0 (36.9, 50.4)	45.8 (41.3, 53.6)	0.021	42.0 (35.8, 46)	42.4 (38.9, 49.7)	0.032
TG, mg/dL	127 (95.5, 175)	126 (90.0, 170)	0.14	147 (114, 250)	144 (106, 197)	0.41
Insulin, µUI/mL	20.6 (15.5, 29.9)	18.0 (11.2, 34.9)	0.14	23.4 (20, 33.2)	20.6 (14.2, 29.2)	0.007
HOMA index	4.21 (3.12, 7.03)	3.18 (2.03, 7.43)	0.17	5.00 (3.42, 7.8)	4.00 (2.78, 7.84)	0.008
AST, U/L	22.5 (20.0, 29.5)	22.0 (19.5, 30.5)	0.76	24.0 (19.9, 28)	25.0 (19.0, 28.0)	0.73
ALT, U/L	26.0 (21.0, 32.7)	23.0 (19.0, 30.5)	0.14	29.0 (20, 35)	27.0 (19.0, 37.0)	0.85

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. *Statistical analysis was performed with paired samples t tests, and data were log-transformed before statistical analyses.

Table 3. Percent weight loss among subjects

Percent weight loss among subjects	Placebo (n = 29) Frequency, %	Phentermine (n = 31) Frequency, %	p value*
Without weight loss	11 (38)	9 (29)	0.32
Less than 3% weight loss	11 (38)	12 (38.7)	0.58
More than 3% weight	7 (24)	10 (32.3)	0.34

* Statistical analysis performed with Pearson's χ^2 test.

in hepatic steatosis by improving the lipid profile in obese individuals with excessive lipid accumulation in the liver, a derangement of the gut-liver axis acts on the progression of liver damage, inflammation, and subsequent fibrosis.

Phentermine has appetite-suppressant effects through interaction with biogenic amine transporters, which mainly enhance norepinephrine, dopamine, and serotonin release in the central nervous system [26]. In this study, the PhG resulted in a more significant weight loss percentage, where 32.3% of the subjects in the PhG had a weight loss greater than 3%; in comparison, 24% of the subjects in the PG had this weight loss. Additionally, the fat mass in kilograms after the intervention in the PhG decreased, while in the PG, there was no change. To avoid a methodological bias, both groups received the same diet and an individualized exercise program, making the consumption of phentermine the main difference between groups. A hypocaloric diet, a deficit of at least 500 calories/day, and high protein diets are associated with improved weight maintenance and may benefit hepatic steatosis. In some animal studies, phentermine has also achieved greater fat loss. Visceral fat is metabolically more active and therefore more susceptible to fat depot loss than subcutaneous fat; this could be because it has more cellularity, greater vascularization, innervation, and susceptibility to certain hormones [27].

On the other hand, we observed that phentermine consumption slightly improves insulin resistance. Phentermine has been used as an adjuvant medication for weight loss and improves specific related biochemical parameters [28]. Elhag et al. [29] obtained similar results in a comparative study of the use of phentermine versus lorcaserin for 3 months. They concluded that the effects of both drugs on biochemical parameters could be the result of a long-term rather than a short-term intervention. Both groups showed an insulin decrease concentration in their study, but the decrease in the HOMA-IR index was more significant in the PhG. These findings are similar to our observations and previously published results showing

Table 4. Adverse effects of the interventions

Adverse effects of the interventions	Placebo ($n = 29$) Frequency, %	Phentermine ($n = 31$) Frequency, %	p value*
Headache	6 (20.6)	3 (9.6)	0.23
Dry mouth	12 (41.3)	10 (32.2)	0.46
Diarrhea	2 (6.8)	1 (3.2)	0.51
Constipation	3 (10.3)	1 (3.2)	0.26
Euphoria	1 (3.4)	1 (3.2)	0.96
Anxiety	3 (10.3)	2 (6.4)	0.58
Tachycardia, insomnia, SAH	0 (0)	0 (0)	0.99

SAH, systemic arterial hypertension. * Statistical analysis performed with Pearson's χ^2 test.

that weight loss can improve insulin sensitivity even in the absence of a change in glucose [30]. Interestingly short-term phentermine administration is sufficient to reduce hepatic steatosis fat mass and improve insulin sensitivity.

There are no studies examining the use of phentermine on the prevalence of surgical complications; our findings show no difference with the PG in the rates of surgical complications among PhG patients undergoing bariatric surgery. Moreover, it was observed that in addition to the presence of fatty liver, the participants had comorbidities associated with obesity, such as arterial hypertension, type 2 diabetes, and dyslipidemia. However, these comorbidities were controlled before surgery in both groups.

This study has a few limitations. The duration of the study was not enough to identify long-term changes. The primary endpoint was selected to assess hepatic steatosis and adipose tissue; thus, the sample size is inadequate to evaluate biochemical changes. The ultrasound was chosen to diagnose hepatic steatosis because it is a noninvasive technique but has limitations in terms of accurate differentiation between fibrosis and steatosis and quantifying the exact fat content. Finally, the SARS-CoV-2 pandemic negatively affected the follow-up of some participants due to lockdown issues, especially given that these patients have a high risk of severe illness due to COVID-19. Studies with larger populations and longer duration are needed to determine the overall effects of phentermine on hepatic steatosis, adipose tissue, and surgical complications in patients undergoing bariatric surgery.

Conclusions

This pilot study shows that 8-week treatment with a daily dose of 15 mg of phentermine joint with a lifestyle intervention program induced a 19% reduction of hepatic steatosis, promoted a greater loss of fat mass in kilograms in patients who were candidates for bariatric surgery. We suggest that phentermine could be a reasonable treatment option in preoperative intervention.

Acknowledgments

We thank Dr. Sánchez-Conde, R. of the Department of Radiology for providing his input and expertise in performing and evaluating ultrasound. Additionally, we acknowledge the help and dedication of Dr. Sosa-Duran, E.E., Aboharp-Hassan, Z., and we thank all the members of the Obesity Clinic who participated in the care of our patients or have otherwise supported us in the conduct of this study.

Statement of Ethics

This study was approved by the Research and Ethics Committee of the Hospital (HJM0367/17-IQF). Clinical trial registration NCT03849729. Written informed consent was obtained from the participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Medix SA de CV supported the preparation of the manuscript.

Author Contributions

Elizabeth Pérez-Cruz conceived and designed the study, analyzed, interpreted, and collected patient data, and was a major contributor to the writing of the manuscript. Martha Guevara-Cruz

designed the study, analyzed and interpreted patient data, and was a major contributor to the writing of the manuscript. Salvador Ortiz-Gutiérrez collected, analyzed, interpreted the patient data, and contributed to the writing of the manuscript. Yuritzy Luna-Camacho, Rafael Guzmán-Aguilar, and Giuseppe Briceño-Sáenz collected patient data and contributed to writing the manuscript. Luis E. González-Salazar and Adriana Flores-López analyzed and interpreted patient data and contributed to the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data are not publicly available due to privacy or ethical restrictions. The protocol and data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Please contact the corresponding author to complete a use agreement to access these resources.

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