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Effect of 8 Weeks milk thistle powder (silymarin extract) supplementation on fatty liver disease in patients candidates for bariatric surgery

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ABSTRACT

Introduction: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and is becoming the most frequent indication of liver transplantation. At present, since no Food and Drug Association (FDA) approved medication exists for NAFLD patients, bariatric surgery is indicated for the significant improvement in obesity-related comorbidities, such as NAFLD. However, alternative therapy is emerging to manage NAFLD. Problematically, many patients taking herbal remedies, such as Silymarin (milk thistle), with little/no understanding of its purported properties.

Methods: Fifty-two morbidly-obese (47.84 ± 6.48 kg m^{-2}) patient candidates (mean age: 38.90 ± 10.28 years; n = 41 women and 11 men) for bariatric surgery with NAFLD were randomly assigned to determine the efficacy of eight weeks of Silymarin supplementation (140 mg four times daily for a total of 560 mg) on the aspartate transaminase (AST)/alanine transaminase (ALT) (AST/ALT) ratio, Fibrosis-4 (Fib-4) score, NAFLD score, sonographic grading, and fibroscan stages of NAFLD.

Results: Significant ($p \leq 0.05$) improvements were found in AST/ALT ratio, BMI and sonographic grading. No significant change was found for fibroscan staging, Fib-4, and NAFLD scores.

Conclusion: Silymarin improved ultrasound fatty liver grading and liver enzymes morbidly-obese patient candidates for bariatric surgery with NAFLD after only eight weeks, without any adverse effects.

1. Introduction

Obesity, a public health problem around the world, is defined as body mass index (BMI) above 30 kg/m2 [1]. Obesity is associated with various chronic diseases such as hypertension, diabetes, atherosclerosis, fatty liver and metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with a prevalence in the general population ranging from 20 to 30% [2]. The prevalence of NAFLD in the obese population increases to 90% [3]. Concurrent with the global obesity epidemic, the prevalence of NAFLD continues to rise in many countries [4,5]. NAFLD is defined as the presence of liver steatosis in histology or on an imaging after excluding secondary causes such as medications, excess alcohol consumption, and chronic hepatitis C. According to a large study of patients with non-alcoholic fatty liver, weight loss of ≥10 kg through a comprehensive lifestyle program resulted in a marked improvement in NAFLD and hepatic fibrosis [6]. However, only a small number of patients are able to achieve the desired amount of weight loss. In previous clinical trials, NAFLD is often diagnosed and staged in a non-invasive manner using imaging, scanning, and laboratory techniques [7,8]. While bariatric surgery plays an important role in the treatment of obesity and its subsequent improvement in NAFLD, performing the surgery in patients with undiagnosed NAFLD before surgery leads to severe consequences such as sepsis, portal vein thrombosis, anastomotic leakage, and even surgical failure and death [1,3]. Careful evaluation of NAFLD, before and after surgery, is important in following up patients who are candidates for bariatric surgery, not only in terms of preventing the progression of NAFLD disease but also preventing cirrhosis of the liver [5].

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In morbid obese patients with BMI above 35–40 kg/m2, the liver may have additional stores of glycogen, water, and fatty deposits [3]. Therefore, technical difficulties in liver retraction are expected during the operation in these patients [5]. In previous studies, by following calorie restricted diets before surgery, the amount of glycogen, water, and fatty deposits were reduced, allowing the surgeon to safely retract the liver and expose the stomach and intestines [9]. While the blood biomarker test for liver function is used as a screening tool to identify patients at risk for NAFLD, normal values do not rule out severe liver disease such as varicose veins or advanced liver disease, even if there is no complaint of liver disease [10,11]. Therefore, the use of aspartate transaminase/alanine transaminase ratio (AST/ALT ratio) along with other scoring systems such as Fib 4 score and NAFLD score is increasingly used in NAFLD patients at risk of liver fibrosis to determine the stage of the disease [3]. The main treatment method of NAFLD is improving lifestyle with the aim of losing weight and increasing physical activity to reduce insulin resistance to date and overall weight loss is the key to improving the histopathological features of NASH [10]. Therefore, the general recommendation is to follow relatively low-calorie diets (with a caloric content commensurate with energy intake), use carbohydrates mainly with low glycemic index, and minimize the consumption of fructose, alcohol, saturated and unsaturated fats in patients with NAFLD [10]. Increasing evidence suggests that prescribing specific supplements or nutrients with shown hepatic protection function may help accelerate the improvement of changes in liver enzymes and perhaps hepatic steatosis, or at least slow its progression [12]. Silymarin is a powerful antioxidant agent extracted from milk thistle (Silybum marianum) with a specific liver tropism and is actually a set of antioxidant substances of which the most concentrated are six flavolignans (silibine A and B and a flavonoid (taxifolin) [13]. By reducing oxidative stress and consequent cytotoxicity, silymarin protects intact liver cells or cells not yet irreversibly damaged and thus may be considered to be hepatoprotective [14]. Based on previous studies, silymarin should be initiated as early as possible in patients with fatty liver disease when the regenerative potential of the liver is still high [9,15]. Therefore, we decided to study the effectiveness of milk thistle extract (Silymarin) in improving or reducing the severity of NAFLD among obese people before bariatric surgery. Because if the positive effect of this drug is proven, it can prevent the complications of this disease on surgery by reducing the severity of liver disease in the preoperative period. Also, if the fat content is reduced and the severity of fatty liver disease is reduced, it will probably reduce the size of the liver, which will facilitate bariatric surgery in the upper abdomen.

2. Methods

2.1. Participants

In this double-blinded randomized clinical trial, 60 morbid obese patients with NAFLD identified by ultrasound and at different stages of the disease who were candidate for bariatric surgery in Loghman Hakim Hospital were selected and recruited to the study. We conducted this study to determine the efficacy of Silymarin on AST/ALT ratio, Fib 4, NAFLD scores, sonographic grading and fibroscan stages of NAFLD. Thirty participants were randomly divided to experimental group and LS (lifestyle modification + Silymarin) (n = 30) or control group, LP (lifestyle modification + Placebo) (n = 30) equally. After initial assessments, 3 participants of LS group and 5 patients from LP were dropped out of the study because of not returning at follow-ups and the study was conducted to 52 aforementioned participants. Participants signed consent forms before participating in the study and they were aware of the study aims [16]. This study was confirmed by the ethics committee of Shahid Beheshti University of Medical Sciences (ID: IR.SBMU.MSP.REC.1399.771) and was registered in Iranian Registry of Clinical Trials website with number IRCT20210817052218N1. Consecutive patients aged between 18 and 65 years who were morbid obese and candidate for bariatric surgery with a probable diagnosis of NAFLD in liver sonography (grades II and III steatosis) with or without increased levels of liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT) (above 20 mg/dl for women and 30 mg/dl for men) were enrolled in the study. Secondary causes of hepatic steatosis were excluded. Allocation to groups was achieved by a block randomization method (LS vs. LP group). The allocation was concealed by using opaque, sealed envelopes that were consecutively numbered. Apart from the project coordinator, the patients, attending physicians, staff involved in the obesity surgery clinics, and members collecting and analyzing data were blinded to the intervention allocation. LS group took 560 mg of Silymarin for 8 weeks, 140 mg four times a day. and the LP group took the same tablet as a placebo and did the same lifestyle modification method. Exclusion criteria included a history of alcohol consumption, DM, chronic liver disease, use of drugs such as statin, fibrate, NSAID, and those with positive results for tests of autoimmune hepatitis and virus markers (hepatitis B surface antigen, hepatitis C virus antibody).

2.2. Intervention protocol

52 patients were allocated randomly to study groups: LP (n = 25) was treated with only lifestyle modification (500 kcal/day deficit from weight-maintaining caloric intake) and placebo. Group LS (n = 27) was treated by the same lifestyle modification and administration of 560 mg of Silymarin, 140 mg four times a day. Treatment courses were considered for 8 weeks. The shape and packing of the pills were similar in both groups. Patients were called regularly (every 2 weeks) to insure taking pills and considering lifestyle modification.

2.3. Measurements

Baseline characteristics of the participants including age, sex, height, weight, BMI, FBS (fasting blood sugar) and platelet count were obtained. The primary outcomes were biomarker changes including AST, ALT, AST/ALT ratio, FIB 4 score which is a non-invasive liver fibrosis assessment tool based on patient age, platelet count, AST and ALT values and also we measured NAFLD score which includes additional variables such as body mass index, albumin and presence of glucose intolerance. Applying an AST/ALT ratio of >1 facilitates categorizing patients between high risk vs low risk, with previous studies reported an association between AST/ALT ratio >1 and advanced fibrosis on liver biopsy. Normal FIB-4 score is defined <1.45, and abnormal NAFLD score is >0.676 [1]. All measurements were done at baseline and 2 months after intervention. In addition, we considered BMI, grading of fatty liver on ultrasound and according to fibroscan-Metavir as the secondary outcomes. Patients were called regularly (every 2 weeks) to insure compliance with taking pills and lifestyle modification.

2.4. Statistical analysis

Statistical analyses were performed by IBM SPSS statistics ver. 26.0 (IBM Co., Armonk, NY, USA). Prior to data analysis, all variables were tested for normality. Descriptive statistics of the variables were presented in means and standard deviations. The effects of intervention between the groups were tested with T-test for continuous variables and the chi-square test (or Fisher's exact test if required) for the categorical variables. That being said, the significance level was set at two-sided $P<0.05$. Subsequently, the quantitative data are expressed as the mean ± standard deviation.

3. Results

Of the 60 patients candidate for bariatric surgery, eight did not come back for the follow up lab data tests. There were no adverse events during the treatment period. Assessing the distribution of variables

Table 1
Demographic and baseline characteristics of participants in each group (N = 52).

Variable	All (N = 52)	LS (n = 27)	LP (n = 25)	Between-group comparison
Age (years)	38.90 ± 10.28	37.81 ± 9.93	38.08 ± 10.01	0.70
Height (cm)	165.55 ± 7.40	166 ± 7.65	165.5 ± 6.95	0.43
Weight (kg)	133.25 ± 25.08	134.96 ± 26.90	132.40 ± 25.20	0.62
BMI (kg/m2)	47.84 ± 6.48	47.20 ± 6.98	48.24 ± 6.95	0.09
FBS	98.13 ± 16.25	97.55 ± 15.68	98.76 ± 16.10	0.12

Values are presented as the mean ± standard deviation. All values are in physiological range and are not significantly different from each other.
LS, lifestyle modification + silymarin; LP, lifestyle modification + placebo; BMI, body mass index; FBS fasting plasma sugar.

before carrying out parametric analyses and results, showed that all of them were normal (Table 1). The mean age of patients was 38.90 ± 10.28 years and sex distribution showed 41 (75.9%) female and 11 (20.4%) male participants. We compared the primary and secondary aforementioned outcomes after 2 months within each study group and between groups (Table 2). Although participants in both groups were checked for daily calorie restriction, patients in LS group showed a significant improvement in BMI. Serum level of AST, ALT and risk ration of AST/ALT decreased in all case groups, but was not significant in patients who were treated by lifestyle modification and placebo. FIB 4 score and NAFLD score did not show any significantly change within groups and also there was no difference between groups. A significant decrease in number of patients with high sonographic grading of fatty liver were observed in LS group (P = 0.004) (Table 3) but the number of patients in category of Fibroscan-Metavir stages did not change significantly after 2 months of treatment with Silymarine and calorie restriction (Table 4).

4. Discussion

This randomized controlled clinical trial suggested a significant benefit of Silymarin and carolie restriction in improving liver aminotransferases in patients candidate for bariatric surgery with NAFLD after only two months, without having any specific side effects. Liver enzymes levels and BMI were significantly less decreased in those receiving only weight reduction recommendation. Even though liver enzymes reduction were significantly less in group LS after two months we did not observe a decline in the aminotransferase levels in group only receiving lifestyle modification, (0.12 and 0.11 for AST and ALT, respectively). Therefore, we assumed that the differences observed in each group were probably because of the specific medication administered. Our study was designed as randomized, and placebo-controlled to eliminate the confounding potentials of lifestyle modifications and other biases that might be observed in open-labeled, uncontrolled studies. Loguercio et al. in a recent multicenter randomized double-blind study conducted on 180 patients with histological diagnosis of NAFLD/NASH, the administration of silybin and vitamin E (silibine 188 mg, phosphatidylcholine 388 mg, vitamin E 180 mg) for 12 months determined the normalisation of transaminase, a significant reduction of gamma-glutamyl transferase levels and the significant decrease of liver steatosis measured with ultrasound scan [17]. Solomon et al. report showed that supplementation with 420 mg/day of silymarin reduced the 4-years risk of mortality in patients' cirrhosis [18].Based on previous studies overall tolerability of Silymarin is usually good, even for high doses and long-term administration. For these reasons, the guidelines of the Mayo Clinic on food supplements classifies the use of silymarin for hepatoprotection as Grade B ("Good scientific evidence for use") [19]. We prescribed 560 mg Silymarine in this study. Anushiravani et al. in a randomized double-blinded, placebo-controlled trial on 150 consecutive patients with NAFLD who were assigned to five groups: lifestyle plus placebo, metformin 500 mg/day, silymarin 140 mg/day, pioglithasone 15

Table 3
Results of Silymarin effect on NASH according to sonography results.

Variable	Group	No. Before treatment	No. After treatment	P-value between groups
Grade I fatty liver by sonography	LS	6 (22.2%)	9 (33.3%)	0.004
	LP	5 (20%)	6 (24%)	
Grade II fatty liver by sonography	LS	9 (33.3%)	15 (55.5%)	
	LP	10 (40%)	12 (48%)	
Grade III fatty liver by sonography	LS	12 (45.5%)	3 (11.2%)	
	LP	10 (40%)	7 (28%)	

Table 4
Results of Silymarin effect on NASH according to Fibrosan-Metavir Score.

Variable	Group	No. Before treatment	No. After treatment	P-value between groups
F0–F1[a]	LS	5 (18.5%)	6 (22.2%)	0.057
	LP	6 (24%)	6 (24%)	
F2	LS	10 (37%)	13 (48.1%)	
	LP	9 (36%)	10 (40%)	
F3	LS	8 (29.6%)	6 (22.2%)	
	LP	7 (28%)	6 (24%)	
F4	LS	4 (14.9%)	2 (7.5%)	
	LP	3 (12%)	3 (12%)	

[a] F: Fibrosan-Metavir Score.

Table 2
Baseline and changes in outcome measurements after 8 weeks (N = 52).

Variable	Group	Mean (SD) Before	Mean (SD) After	Mean difference (after-before)	95% Confidence Interval of the Difference	P-value within groups	P-value between groups
BMI(kg/m2)	LS	46.23 ± 4.57	45.01 ± 4.44	−1.21	−1.79)-(-0.63))	0.00	0.02
	LP	46.42 ± 3.67	46.32 ± 3.91	−0.10	−1.95)-(1.73))	0.90	
AST	LS	35.81 ± 16.57	30.22 ± 15.94	−5.59	−6.90)-(-4.19))	0.00	0.00
	LP	41.24 ± 12.29	40.04 ± 13.39	−1.20	−2.70)-(0.30))	0.12	
ALT	LS	39.64 ± 17.98	34.59 ± 17.44	−5.05	−6.72)-(-3.38))	0.00	0.01
	LP	43.84 ± 11.99	47.68 ± 10.88	3.84	−1.05)-(8.73))	0.11	
AST/ALT ratio	LS	0.96 ± 0.20	0.85 ± 0.29	−0.10	−0.19)-(-0.03))	0.04	0.04
	LP	0.93 ± 0.33	0.92 ± 0.41	−0.07	−0.57)-(0.42))	0.76	
NAFLD Score	LS	−0.72 ± 1.63	−0.67 ± 1.15	0.05	−0.37)-(0.49))	0.78	0.75
	LP	−0.34 ± 1.63	−0.34 ± 1.64	−0.009	−0.09)-(0.00))	0.17	
Fib4 Score	LS	0.71 ± 0.32	0.69 ± 0.30	0.20-	−0.07)-(0.03))	0.42	0.90
	LP	0.66 ± 0.32	0.63 ± 0.33	−0.20	−0.46)-(0.00))	0.42	

LS, lifestyle modification + silymarin; LP, lifestyle modification + placebo.

mg/day, and vitamin E 400 IU/day, all for 3 months showed significant benefit of silymarin, pioglitazone, and vitamin E in improving liver aminotransferases in patients with NAFLD after only 3 months, without exerting any specific side effects [6]. NAFLD is a common condition among morbidly obese patients candidate for bariatric surgery. NAFLD is associated with hepatomegaly and may lead to some technical challenges in liver retraction and adequate access to the gastro-esophageal junction in laparoscopic bariatric surgery. Supplementation with Silymarin before surgery may be appropriate in these cases.

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Authors' contribution

S.H.M developed the original idea and the protocol, F.E.Y abstracted and searched data, S.P.R wrote the manuscript, and is a guarantor. B.O. and contributed to the development of the protocol, abstracted data, and prepared the manuscript. A.H. double checked and did the final edition.

Research Location

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CRediT authorship contribution statement

Seyed Hadi Mirhashemi: Conceptualization, Methodology, Software. **Azadeh Hakakzadeh:** Data curation, Writing – original draft. **Farbod Emami Yeganeh:** Visualization, Investigation. **Bahador Oshidari:** Supervision. **Seyed Parviz Rezaee:** Writing – review & editing.

Declaration of competing interest

No potential conflict of interest relevant to this article was reported.

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