

# Effect of silymarin on liver size and nonalcoholic fatty liver disease in morbidly obese patients: A randomized double-blind clinical trial

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**Background:** A large liver size is a factor that may increase the difficulty of bariatric surgery (BS) and unwanted complications. Some agents have been used to decrease the liver size before BS. Silymarin has been used as an antioxidant agent to improve liver function tests. This study was designed to evaluate the effects of silymarin on liver dimensions, function, and lipid profile. **Materials and Methods:** A double-blind randomized clinical trial was performed on 56 patients. The patients were divided into silymarin and placebo groups. Blood samples and sonographic examinations were taken from the patients before and 4 weeks after the administration of the silymarin or placebo. In the first group, 140 mg silymarin was prescribed every 8 h for 4 weeks, and the other group received placebo in the same way with the same tablet shape. After the completion of the 4-week treatment, laboratory tests and ultrasonography were carried out again. **Results:** Thirty-nine (69.6%) patients were female with a mean body mass index (BMI) of 46.2 kg/m<sup>2</sup> and a mean age of 36.8 years. Most of the patients had a compliance of 80% and higher. The analysis did not show any significant difference in aspartate transaminase, alkaline transaminase, liver size, cholesterol, and triglyceride changes among the silymarin and placebo groups. BMI loss was slightly higher in the silymarin group although the difference was not statistically significant. **Conclusion:** The present findings show that silymarin administration for 4 weeks does not affect liver size and function, but further evaluations should be carried out on the subject.

**Key words:** Clinical trial, liver size, morbid obesity, nonalcoholic fatty liver disease, silymarin, ultrasound

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## INTRODUCTION

Obesity has become one of the most significant health concerns in developed and developing countries; in 2016, more than 1.9 billion adults worldwide were overweight, including more than 650 million obese cases, a number that has tripled in the last 50 years.<sup>[1]</sup> Bariatric surgery (BS) is the strongest

weapon for long-term weight loss and improvement of obesity-related comorbidities compared to the most effective nonsurgical therapies.<sup>[2]</sup> It has become the mainstay treatment of morbid obesity in the long term. A large liver size is a factor that may increase the difficulty of operation and unwanted complications.<sup>[3]</sup> In patients with morbid obesity, some factors such as large amount of intra-abdominal fat, large fatty left liver lobe, male gender, and body mass index (BMI)

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>50 can increase the technical difficulties of performing this surgery.<sup>[3,4]</sup> Liver enlargement due to nonalcoholic steatohepatitis, especially the lateral segment of the left lobe, can cause poor access to the gastroesophageal junction during BS in morbidly obese patients and can limit the surgeon's dominance over the upper abdomen anatomy and technically affect the procedure. Allegorically, this limitation can lead to an increase in liver injury and elevate the risk of unintentional bleeding during traction.<sup>[4-6]</sup> Morbid obesity, type-2 diabetes mellitus (DM), and hyperlipidemia are the most important risk factors for nonalcoholic fatty liver disease (NAFLD).<sup>[7-10]</sup> NAFLD consists of a spectrum of liver diseases ranging from simple steatosis, fibrosis, and cirrhosis, which can even progress toward hepatocellular carcinoma.<sup>[11-13]</sup>

NAFLD has been reported in about 84% to 96% of the liver biopsies of patients who have undergone BS.<sup>[14-16]</sup> Nonetheless, calorie-restricted diets before BS have been able to reduce the size and intrahepatic fat of the liver and there is a strong relationship between changes in liver volume and fat content,<sup>[4,17-20]</sup> but studies on the effects of weight loss on NAFLD have shown inconsistent results and there are also some reports showing that weight loss may increase inflammation<sup>[21]</sup> and worsen fibrosis.<sup>[16,22]</sup> Furthermore, there are some concerns about the patients' degree of compliance with their low-calorie diets before the surgery. It is because of these problems that other methods should be used to decrease liver size and improve its function before BS.

Silymarin milk thistle (MT) is an antioxidant agent that has been used by physicians to treat liver and gallbladder disease for several years. The active complex of MT is a lipophilic extract from its seeds that contains three flavonolignan isomers, collectively known as silymarin. This herbal drug not only reduces free radical production and lipid peroxidation but also protects the cell membrane against radical-induced damage with the stimulation of polymerase and RNA transcription. Silymarin has antifibrotic properties, induces hepatic stellate cell apoptosis, evokes the degradation of collagen deposits, and decreases insulin resistance, fasting insulin levels, alkaline transaminase (ALT), and aspartate transaminase (AST).<sup>[23,24]</sup>

This study was designed to evaluate the effects of silymarin on liver dimensions and liver enzymes and lipid profile and may help facilitate any subsequent surgical procedures and reduce intraoperative complications.

## MATERIALS AND METHODS

This study was conducted as a randomized, double-blind, placebo-controlled, clinical trial on patients with morbid

obesity referred to our tertiary center from May to July 2019. The protocol of this study was approved by the Ethics Committee of Iran University of Medical Sciences with this number (IR.IUMS.REC.1397.1173). The registration number in the Iranian Registry of Clinical Trials is IRCT20190128042520N1. The inclusion criteria were 18–60-year-old patients who were candidates of BS with Class III morbid obesity or higher (BMI  $\geq 40$  kg/m<sup>2</sup>). The exclusion criteria included allergy to herbal drugs, consumption of chicory or MT, omega-3 or warfarin or midazolam intake, alcohol addiction, following a low- or very low-calorie diet, extreme physical activity, cirrhosis or hepatitis, and serum glutamic pyruvic transaminase >5-fold higher than normal. Patients who did not have compliance for using the prescribed tablets or did not return the tablets cans, were excluded from the study. All the patients underwent our bariatric clinic protocol, including psychologic evaluation/ treatment and nutritional consultation for the detection and treatment of unhealthy eating habits before starting this study. After signing an informed written consent form, the qualified patients were allocated into two groups of silymarin or placebo, each with 30 patients, using permuted block randomization with four letters in each block. The basic characteristics of the patients who received silymarin or placebo are shown in Table 1. Blood sample collection and ultrasonographic examination were performed before and 4 weeks after the administration of the silymarin or placebo. To ensure a double-blind study protocol, the participants, radiologist, and laboratory technician were blinded to the type of drugs received by each patient.

The blood samples collected were examined to check the fasting blood sugar (FBS), to perform a liver function test (LFT), and to check the lipid profile, blood urea nitrogen (BUN), and creatinine (Cr) concentration. In the sonographic examination, which checked the liver span and fatty liver grade, the volume of the second segment

**Table 1: The basic characteristics of the patients who received silymarin or placebo**

| Variable                          | Silymarin (n=27) | Placebo (n=29) | P     |
|-----------------------------------|------------------|----------------|-------|
| Weight (kg), mean±SD              | 130.03±17.63     | 128.51±15.39   | 0.71  |
| BMI (kg/m <sup>2</sup> ), mean±SD | 46.6±4.8         | 45.8±5.0       | 0.87  |
| Female sex, n (%)                 | 18 (69.2)        | 21 (72.4)      | 0.64  |
| Age (years), mean±SD              | 36.46±10.00      | 37.52±8.94     | 0.88  |
| DM, n (%)                         | 6 (23.1)         | 2 (6.9)        | 0.137 |
| Alcohol, n (%)                    |                  |                |       |
| Nondrinker                        | 21 (80.8)        | 24 (82.8)      | 0.90  |
| Rare-drinker                      | 5 (19.2)         | 5 (17.2)       |       |
| Smoking, n (%)                    |                  |                |       |
| Never smoke                       | 21 (80.8)        | 25 (86)        | 0.57  |
| EX-smoker                         | 1 (3.8)          | 2 (7)          |       |
| Smoker                            | 4 (15.4)         | 2 (7)          |       |

SD=Standard deviation; BMI=Body mass index; DM=Diabetes mellitus

of the liver was also measured by a single radiologist after 8 h fasting. This segment has the most coverage on the proximal part of the stomach anatomically and limits the exposure of the gastroesophageal junction. The second liver segment has specific anatomical limits (the inferior margin is the left branch of portal vein and the lateral margin is the left hepatic vein), which can increase the accuracy of the ultrasonography. To estimate segment II of the liver volume, the largest anteroposterior (AP), transverse (T), and craniocaudal (CC) diameters were measured above the left branch of the portal vein and medial to the left hepatic vein. The volume was then calculated for all the patients by this formula:

$$\text{Volume of segment II (cc)} = \text{AP (cm)} \times \text{CC (cm)} \times \text{T (cm)} \times 0.523$$

### Intervention

In the silymarin group, 140 mg silymarin was administered every 8 h for 4 weeks (tablet Livergol, silymarin 140 mg, Goldaru Pharma Co., Isfahan, Iran), and in the placebo group, 1 tablet of the placebo (with identical shape and packing as the silymarin tablets) was administered every 8 h for 4 weeks. The patients were contacted every week after taking the drug to check their medication compliance and possible side effects. Then, the patients were requested to return the capsule cans to the researchers. After 4 weeks, abdominal ultrasonography and laboratory tests were carried out again the same way as in the preintervention step.

### Statistical analysis

The collected data were analyzed by SPSS version 22 (Chicago, Illinois, USA). A *P* value lower than 0.05 was considered statistically significant. The analyses were performed using the Chi-square test, independent *t*-test, and paired *t*-test.

## RESULTS

Sixty morbidly obese patients who were candidates of BS were enrolled in this study after submitting their informed consent forms. About 87.5% of the subjects had a compliance rate of 80% and higher. Three patients had a compliance <70% and was excluded from the study. One patient discontinued drug due to diarrhea and was excluded from the study. Finally, 29 patients were included in the placebo group and 27 patients in the silymarin group. Thirty-nine (69.6%) patients were female. The mean  $\pm$  standard deviation (SD) of age and BMI was  $36.8 \pm 9.4$  (range: 20–56) years and  $46.2 \pm 4.9$  (range: 40.3–58.1) kg/m<sup>2</sup>, respectively. There was no difference between the groups who received either silymarin or placebo in terms of gender, age, and BMI. The prevalence of DM was 23.1% and 6.9% in the

silymarin and placebo groups, respectively. Rare alcohol consumers made up 19.2% of the silymarin group and 17.2% of the placebo group. In the silymarin group, 15% of the patients were smokers versus 7% in the placebo group. The analysis showed no statistically significant differences in terms of DM, smoking, and alcohol consumption between the two groups in the beginning of the study (*P* > 0.05). According to the ultrasonography data, the baseline and postintervention volume of segment II was  $66.04 \pm 41.74$  and  $55.85 \pm 40.94$  (mean  $\pm$  SD) in the silymarin group, respectively, which did not show significant changes in comparison with the placebo group. Grade-3 fatty liver had the highest prevalence (42.3%) in the silymarin group and a prevalence of 34.5% in the placebo group. The analysis did not reveal any significant changes in fatty liver grading following the silymarin treatment.

The distribution of the volume-related variables (superior inferior; anterior posterior; and transverse diameter of segment II, volume of segment II, liver span, and grade of fatty liver) was mostly normal in both the groups. Both the groups were similar in liver size and laboratory tests (AST, ALT, ALP, Bili T, Bili D, FBS, cholesterol, TG, HDL, LDL, BUN, and Cr) at baseline [Tables 2 and 3]. Since the two groups were easily comparable, their liver size and laboratory test results were compared after the administration of silymarin and placebo, and the results showed no statistically significant differences between them [Tables 2 and 3]. The difference in BMI loss between the silymarin and placebo groups was not significant, but it was borderline (*P* = 0.065), being slightly higher in the silymarin group. Moreover, the differences in liver size and laboratory test results before and after the intervention were calculated in each group and compared with each other to find any probable residual confounding effects. This analysis also did not show any statistically significant difference between the two groups.

## DISCUSSION

The factors contributing to BS difficulty include fat content and size of the left liver lobe, especially segments II and III, which can affect operative procedures on the proximal part of the stomach and decrease hepatic fragility, when the liver is retracted during surgery.<sup>[3,4,25]</sup> Various studies have demonstrated the reducing effects of diet and nutritional regimen on the volume and fat content of the liver, but none of these studies have been randomized clinical trials or contained a low sample size.<sup>[4,17-19]</sup> Furthermore, the dietary approach is relatively expensive and has been associated with a failure rate of 13% to 20% in patients' compliance.<sup>[17,19]</sup> Furthermore, pharmacologic agents have been used to reduce the size of liver before performing bariatric surgery. Iannelli *et al.* concluded that the consumption of omega-3

**Table 2: The size of different segments/lobes of the liver and fatty liver grade before and after receiving silymarin or placebo**

| Size   | Silymarin   |             | Placebo     |              |
|--|-------------|-------------|-------------|--------------|
|  | Before      | After       | Before      | After        |
| Superior inferior (craniocaudal) diameter of lateral segment of left lobe (cm) |             |             |             |              |
| Mean±SD*   | 3.65±1.08   | 2.98±0.94   | 3.23±0.85   | 2.90±0.8565  |
| P  |             | 0.76        |             | 0.63         |
| Anterior posterior lateral segment of left lobe (cm)                           |             |             |             |              |
| Mean±SD  | 4.80±1.10   | 4.88±1.17   | 4.96±1.14   | 4.79±1.04    |
| P  |             | 0.77        |             | 0.88         |
| Transverse lateral segment of left lobe diameter (cm)                          |             |             |             |              |
| Mean±SD  | 6.58±2.18   | 6.41±1.97   | 6.45±1.56   | 6.14±1.43    |
| P  |             | 0.57        |             | 0.81         |
| Transverse diameter (span) of right lobe (cm)                                  |             |             |             |              |
| Mean±SD  | 13.58±1.93  | 13.358±1.90 | 13.79±1.59  | 13.43±1.4859 |
| P  |             | 0.87        |             | 0.82         |
| Volume of segment II (cc)  |             |             |             |              |
| Mean±SD  | 66.04±41.74 | 55.85±40.94 | 56.38±29.09 | 48.52±27.08  |
| P  |             | 0.43        |             | 0.54         |
| Fatty liver grade, n (%)   |             |             |             |              |
| 0  | 1 (3.8)     | 5 (19.2)    | 0 (0)       | 3 (10.3)     |
| 1  | 8 (30.8)    | 7 (26.9)    | 11 (37.9)   | 13 (44.8)    |
| 2  | 6 (23.1)    | 6 (23.1)    | 8 (27.6)    | 7 (24.1)     |
| 3  | 11 (42.3)   | 8 (30.8)    | 10 (34.5)   | 6 (20.7)     |
| P  |             |             | 0.47        |              |

SD=Standard deviation; \*=P value

daily for 4 weeks decreases the left liver lobe size up to 20%, but they did not clarify whether this size reduction is directly induced by omega-3 or if it is a secondary effect of weight loss.<sup>[26]</sup> According to the review of literature, to date, there have been no studies about the effect of silymarin on liver size; therefore, this study was designed to overcome this gap and assess this effect. The active extract of MT (silymarin) has anti-inflammatory, antifibrotic, and antioxidant properties that work by stabilizing the hepatocyte membrane structure. Based on silymarin's capacity to promote liver regeneration by stimulating nuclear polymerase A and increasing ribosomal protein synthesis and also the transformation of stellate hepatocytes to myofibroblasts and subsequently the prevention of collagen fibers deposition, it seems that silymarin can decrease the liver size.<sup>[27]</sup>

A randomized clinical trial demonstrated the efficacy of silymarin in 50 NAFLD patients. The patients were treated with one silymarin tablet 140 µg daily for 2 months, and their mean ALT and AST levels decreased from 103.1–41.4 U/L to 53.7–29.1 IU/ml, respectively ( $P < 0.001$ ).<sup>[24]</sup> Another study also confirmed the effect of silymarin on transaminase level changes.<sup>[28]</sup> These results are in contrast with the present findings, which did not demonstrate significant changes in transaminase level, although it should be noted that baseline levels of transaminases stood in the normal range. As shown in Table 2, transaminase levels raised in the silymarin group in comparison with their baseline levels after the treatment, although the change was not significant. These changes may

be induced by the unknown effects of this agent on liver function; therefore, this potential effect should be evaluated in other studies with larger sample sizes. According to the demographic data, there were no significant differences between the two groups at baseline and the two groups seemed easily comparable; it can therefore be argued that silymarin does not affect liver size and fatty liver grade significantly in comparison with placebo, although the lack of this effect may be due to the relatively small sample size and short duration of silymarin usage. There were some changes in indicators such as TG and total bilirubin, which decreased in the silymarin group and increased in the placebo group, but the difference was not statistically significant, maybe as a result of the low sample size in each group [Table 3].

The present study had several limitations. First, the sample size was small. Second, the treatment duration with silymarin was 1 month, three times a day, which is probably considered short. The researchers recommend further studies with larger sample sizes and a longer duration of silymarin treatment. It should be noted that the patients' compliance with silymarin consumption was about 80%, which is a remarkable strength for the study.

## CONCLUSION

The findings of the present study show that silymarin administration for 4 weeks does not affect liver size and function, but further evaluations should be carried out



**Table 3: The laboratory findings and body mass index before and after receiving silymarin or placebo**

| Laboratory findings       | Silymarin    |              | Placebo      |              |
|---------------------------|--------------|--------------|--------------|--------------|
|                           | Before       | After        | Before       | After        |
| AST (U/L)                 | 35.12±17.16  | 44.84±24.87  | 33.76±17.37  | 45.54±17.29  |
| <i>P</i>                  |              | 0.91         |              | 0.66         |
| ALT (U/L)                 | 40.24±30.54  | 47.16±30.82  | 38.03±20.65  | 47.14±21.23  |
| <i>P</i>                  |              | 0.99         |              | 0.50         |
| ALP (U/L)                 | 228.20±68.24 | 216.12±57.98 | 225.07±66.29 | 222.04±64.25 |
| <i>P</i>                  |              | 0.73         |              | 0.89         |
| Bilirubin total (μmol/L)  | 0.63±0.27    | 0.58±0.17    | 0.54±0.10    | 0.55±0.08    |
| <i>P</i>                  |              | 0.32         |              | 0.87         |
| Bilirubin direct (μmol/L) | 0.26±0.11    | 0.26±0.10    | 0.23±0.07    | 0.25±0.07    |
| <i>P</i>                  |              | 0.46         |              | 0.79         |
| FBS (mmol/L)              | 114.28±32.38 | 112.72±20.86 | 113.41±24.57 | 114.46±38.10 |
| <i>P</i>                  |              | 0.84         |              | 0.90         |
| Cholesterol (mmol/L)      | 214.68±34.41 | 205.20±31.16 | 197.79±35.42 | 196.25±31.44 |
| <i>P</i>                  |              | 0.30         |              | 0.88         |
| Triglyceride (mmol/L)     | 159.88±73.55 | 144.36±44.21 | 137.28±66.46 | 167.93±80.25 |
| <i>P</i>                  |              | 0.18         |              | 0.24         |
| HDL (mmol/L)              | 46.12±12.52  | 45.80±5.80   | 41.86±3.91   | 46.79±14.27  |
| <i>P</i>                  |              | 0.75         |              | 0.30         |
| LDL (mmol/L)              | 130.48±25.16 | 130.20±15.62 | 128.24±21.73 | 123.61±19.55 |
| <i>P</i>                  |              | 0.18         |              | 0.77         |
| BUN (mmol/L)              | 22.88±4.02   | 23.20±5.30   | 24.68±6.44   | 25.89±6.76   |
| <i>P</i>                  |              | 0.12         |              | 0.29         |
| Creatinine (mg/dL)        | 0.85±0.13    | 0.89±0.13    | 0.89±0.12    | 0.89±0.13    |
| <i>P</i>                  |              | 0.89         |              | 0.91         |
| BMI (kg/m <sup>2</sup> )  | 46.6±4.8     | 46.0±4.5     | 45.8±5.0     | 45.1±4.9     |
| <i>P</i>                  |              | 0.06         |              | 0.09         |

AST=Aspartate transaminase; ALT=Alkaline transaminase; ALP=Alkaline phosphatase; FBS=Fasting blood sugar; HDL=High density lipoprotein; LDL=Low density lipoprotein; BUN=Blood urea nitrogen; BMI=Body mass index

on the subject. Liver size can contribute to the technical difficulty of BS. A preoperative diet or drug consumption may be necessary to reduce probable intraoperative complications. This study found that using silymarin 140 μg three times daily for 4 weeks cannot make a significant change in liver size, LFT, and lipid profile and the substance may need a longer duration of administration for it to prove effective. Further studies should be carried out with larger sample sizes and a longer duration of silymarin treatment.

#### Informed consent

Informed consent to participate in the study was obtained from the participants.

#### Ethical approval statement

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

#### Availability of data and material

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 restrictions of their containing information that could compromise the privacy of research participants.

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#### Conflicts of interest

There are no conflicts of interest.

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