

Effects of Silymarin on Reducing Liver Aminotransferases in Patients with Nonalcoholic Fatty Liver Diseases

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ABSTRACT

Background:

The hepatoprotective effects of silymarin have been confirmed by various researchers worldwide; however few studies are available about the therapeutic impact of silymarin on the level of aminotransferases in patients with nonalcoholic steatohepatitis (NASH). Our purpose is to determine whether silymarin improves the serum level of aminotransferases in patients with NASH.

Materials and Methods:

This was a double blind, randomized, placebo-controlled trial performed on 100 patients with NASH. Subjects were randomized to receive silymarin (140 mg/q12h) for three months or placebo, given in the same manner. A blood sample was drawn at baseline (before treatment) and after completion of the treatment schedule to assess serum aminotransferase levels. We measured body mass index (BMI) before and after administration of the treatments for both groups of patients.

Results:

There were insignificant changes in BMI for both groups. The mean serum alanine aminotransferase (ALT) level in the case group significantly changed from 84.06 to 68.54 IU/mL following treatment with silymarin ($p < 0.001$), however this change was not significant in the control group. The mean serum aspartate aminotransferase (AST) level in the case group significantly decreased from 71.94 to 54.70 IU/mL after treatment with silymarin. This change in the placebo group was not significant (from 62.94 to 61.56 IU/mL).

Conclusion:

Administration of silymarin can effectively reduce liver aminotransferases without any changes in BMI in patients with NASH disease.

Keywords: Silymarin; NASH; ALT; AST

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INTRODUCTION

Silymarin is a unique flavonoid complex derived from the milk thistle plant. This plant is the subject of decades of research into its beneficial properties that include liver protection and decongestant effects(1-3). Known beneficial effects include regenerating liver cells damaged by alcohol or drugs, decongestion of the liver, protection against industrial poisons such as carbon tetrachloride, protection of the liver against pharmaceuticals that stress the liver caused by some antibiotics and analgesics, treatment of viral hepatitis

as a complement, and increasing the survival rate of patients with cirrhosis(1,4-6). Silymarin can also protect liver cells from injuries caused by ischemia, radiation, and viral hepatitis(7-10). In addition, recent applications of this agent are highlighted by administration of nontraditional uses of this drug in order to protect other organs in addition to the liver(11). The hepatoprotective effects of silymarin have been confirmed by various studies of partial hepatectomy and toxic models in experimental animals. Some studies have shown that silymarin has multiple actions as a hepatoprotective agent, which are attributed to some of its antioxidant properties. Beneficial effects of this plant can be mediated by its triggering role on increasing protein synthesis that leads to cell-regenerating activities(12). However, controversy exists regarding the decreasing effects of this drug on aminotransferases. Although some studies have shown that the levels of serum liver enzymes were not significantly different for subjects on silymarin compared with placebo(13), others described a significant reduction in liver enzymes following administration of this agent(14).

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease that occurs in patients with no significant alcohol consumption. It is characterized by macrovesicular steatosis, hepatocellular necrosis, a mixed inflammatory infiltrate, various grades of fibrosis and Mallory bodies. The prevalence of this disease is unknown; however recent studies have indicated that the incidence is about 3%, although the rates are higher in some populations such as obesity and diabetes mellitus(15). Some recent studies have shown that NASH is probably the most common cause of liver disease in Iran(16), which is most likely attributed to the considerable high non-alcoholic feature of hepatitis in Iran compared with other countries.

To the best of our knowledge, there are few studies regarding the therapeutic impact of silymarin on the level of aminotransferases in patients with NASH. In this study, we intend to determine whether silymarin improves the serum level of aminotransferases in patients with NASH.

MATERIALS AND METHODS

This was a double blind, randomized, placebo-controlled trial performed on 100 consecutive patients with NASH who referred to the Gastrointestinal Ward of Shahid Mohammadi Hospital in Bandar Abbas to compare the effect of a standard recommended dose

of silymarin with a placebo on liver enzymes. We conducted this study in compliance with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board at Hormozgan University of Medical Sciences; all study participants provided informed consent. Eligibility criteria included the presence of NASH confirmed by sonography and elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). All tests and ultrasound processes were performed at the same center to avoid human error. Exclusion criteria included positive tests for hepatitis B or C infection; the presence of other advanced liver diseases such as autoimmune hepatitis, Wilson's disease, hemochromatosis, or alpha 1-antitrypsin deficiency; having taken known hepatotoxic drugs; history of alcohol consumption; or jejunal bypass surgery. At baseline, we obtained a detailed history that included demographics, medical history, and medications. Weight was measured using a single scale and standing height was measured using a microtoise. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

Eligible, consenting patients were randomly assigned by block randomization to one of the two groups. The case group received silymarin (two tablets that each contained 140 mg of silymarin per day). The control group was treated with an identical-appearing placebo. The treatment period was for three months. Both drugs were in the form of tablets. All patients were advised to consider a low-energy, low-fat daily dietary regimen and regular physical activity.

A blood sample was drawn at baseline (before treatment) as well as after the completion of the treatment schedule to assess serum levels of aminotransferases. BMI was measured before and after administration of the drug and placebo for both groups of patients.

Results were reported as mean \pm standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the student's t-test for continuous variables and the chi-square test (or Fisher's exact test if required) for the categorical variables. The changes in study parameters in each group were assessed by the paired t-test. This study was performed with a power of 80%. P-values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 100 subjects met our inclusion criteria and provided informed consent for enrollment. Subjects' mean age was 48.37 ± 6.01 years and 62.0% were males. Participants were randomly assigned to receive silymarin (n=50) or placebo (n=50). The mean age for the case group was 48.42 ± 6.57 years and for the control group, it was 48.32 ± 5.45 years. The age range for both groups was 35-60 years. The male to female ratio in both groups was 31:19 (Table 1). The case group mean BMI before drug administration was 29.04 kg/m^2 which decreased to 28.70 kg/m^2 following treatment ($p > 0.05$). For the control group, the mean BMI before drug administration was 29.18 kg/m^2 which reduced to 28.84 kg/m^2 after treatment ($p > 0.05$). The mean serum ALT level in the case group was 84.06 IU/mL before treatment, which declined to 68.54 IU/mL after treatment with silymarin ($p < 0.001$). The mean serum level of this enzyme in the control group was 74.48 IU/mL before the placebo treatment and 73.32 IU/mL after administration of placebo, which was insignificant ($p > 0.05$). The mean serum AST level in the case group significantly decreased from 71.94 to 54.70 IU/mL after treatment with silymarin ($p < 0.001$), while this change in the placebo group was not significant, and declined from 62.94 IU/mL before treatment to 61.56 IU/mL after treatment ($p > 0.05$). On the other hand, the decline in mean ALT and AST levels did not differ in the placebo

group, whereas these changes were significant in the silymarin group (Table 2). No serious adverse events were recorded; side-effects were similar in frequency and uncommon in both groups.

DISCUSSION

Experimental studies have identified a number of hepatoprotective mechanisms for silymarin. The cytoprotective effects of silymarin are attributable to its antioxidant and free radical scavenging properties as well as its interaction with cell membrane components to prevent any abnormalities in the lipid fractions responsible for maintenance of normal fluidity (17). Also, it can stimulate protein synthesis through acting RNA polymerase enzymes that result in increased ribosomal formation (18). Silymarin has anti-inflammatory and anti-fibrotic activities (19-23). Moreover, silymarin has a regulatory action on cellular and mitochondrial membrane permeability in association with an increase in membrane stability against xenobiotic injury (24). It can prevent the absorption of toxins into hepatocytes by occupying the binding sites as well as inhibiting many transport proteins at the membrane level (4).

Most clinical trials performed on the hepatoprotective effects of silymarin have mainly focused on its therapeutic effects on alcoholic liver diseases, liver cirrhosis, viral hepatitis, toxic and iatrogenic liver diseases, and liver related mortality due to hepatocellular carcinoma. Recent data have shown a

Table 1: Baseline characteristics and clinical data of the study population.

Characteristics	Case group (n=50)	Control group (n=50)
Male gender	31 (62%)	31 (62%)
Age (years)	48.42 ± 6.75	48.32 ± 5.45
Body mass index (BMI, kg/m^2)	29.04 ± 3.66	29.18 ± 3.32
Grade I fatty liver by sonography	30	28
Grade II fatty liver by sonography	16	17
Grade III fatty liver by sonography	4	5

Table 2: Results of silymarin and placebo effect on nonalcoholic steatohepatitis (NASH).

Indicator	Silymarin group (n=50)		Placebo group (n=50)	
	Before treatment	After treatment	Before treatment	After treatment
IBMI (kg/m^2)	29.04 ± 3.66	28.70 ± 2.56	29.18 ± 3.32	28.84 ± 2.89
ALT	84.06 ± 6.65 **	68.54 ± 5.54 **	74.48 ± 4.45	73.32 ± 5.58
AST	71.94 ± 4.56 **	54.70 ± 5.51 **	62.94 ± 4.45	61.56 ± 3.39

** $p < 0.001$

decreased incidence of this malignancy among silymarin treated patients(19).

In the present study, we could show that the administration of silymarin effectively reduced serum levels of liver enzymes. This reduction was not observed in the placebo group. Similar findings were reported by Hajaghamohammadi et al.(14) In another study by Hashemi et al., administration of silymarin effectively reduced hepatic biochemical parameters that included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. In their study, treatment with this drug resulted in considerable improvement in liver function(25).

The most appropriate method for differentiating NASH from fatty liver without inflammation is a liver biopsy. However the cost, risks and sampling error of performing a biopsy do not seem to be worth the information that could guide treatment decisions and imaging techniques such as sonography and computed tomography (CT) which are among the common imaging modalities for detection of lipids in the liver(14,26-30).

NASH is mainly characterized by active inflammation and hepatocyte damage, thus the protective role of silymarin on liver functions in this subgroup of patients can be explained by its inhibitory effects on the inflammatory processes and hepatocellular damage, which has been

previously described. Excess pro-inflammatory factors in these patients can inhibit hepatic fat disposal and thus promote lipid accumulation within hepatocytes. The latter induces sustained hepatic generation of pro-inflammatory cytokines(25,31). It seems that silymarin is able to inhibit pro-inflammatory cytokines that result in disposing lipid accumulation. It has been demonstrated that the elevations of liver enzymes are directly associated with higher concentrations of inflammatory markers such as C-reactive protein(28,32-35) and therefore it seems that the impact of silymarin on decreasing liver enzymes can be mediated by its suppressing effects on inflammatory biomarkers.

One of the limitation so four study is that we were unable to perform liver biopsies. However in a meta-analysis of 49 studies, we found that the specificity of ultrasound for diagnosis of fatty liver was 94% when using liver biopsy as the gold standard(36).

In conclusion, administration of silymarin can effectively reduce liver aminotransferases without any changes in BMI in patients with NASH disease.

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