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ORIGINAL ARTICLE

A Placebo-Controlled Trial of Silymarin in Patients with Nonalcoholic Fatty Liver Disease

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Background and Aims: **Nonalcoholic fatty liver disease (NAFLD) is a chronic liver condition that is characterized by significant hepatic lipid deposition with or without necroinflammation and fibrosis. Researchers have proposed that oxidative stress may play a role in pathogenesis of NAFLD, and there is challenging evidence for the efficacy of antioxidant agents in its treatment. Therefore, we tried silymarin as an antioxidant in a randomized controlled trial for a group of patients with NAFLD.**

Methods: **During an 18-month period, a placebo-controlled study was conducted among patients with nonalcoholic steatohepatitis (NASH) referred to the Ahvaz Jundishapur University Hospital (AJSUH) and Hepatitis Clinic from 2007 to 2008. Based on sonography findings and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels or liver biopsy, we selected 100 NASH patients who were referred to our center for management of liver disease. Patients who had positive viral markers and other hepatic diseases and patients who had ingested ethanol or drugs known to produce fatty liver disease within the previous 6 months were excluded from the study. Patients were randomized to two groups: Group A received a placebo, and Group B received treatment with 280 mg of silymarin. Treatment was continued for 24 weeks, and cases were evaluated every 4 weeks in the outpatient clinic.**

Results: **A total of 100 subjects who met the inclusion and exclusion criteria were included in the analysis. Group A (50 cases, 29 males and 21 females) and Group B (50 cases, 28 males and 22 females). The mean age was 39.0 ± 10.70 years for Group A and 39.28 ± 11.117 years for Group B. The age range for both groups was 20 to 50 years. The mean serum ALT levels in the silymarin group were 113.03 and 73.14 IU/mL before and after treatment, respectively (P = 0.001). ALT normalization (ALT < 40) was observed in 18% and 52% of patients in Groups A and B, respectively (P = 0.001). AST normalization (AST < 40) was observed in 20% of cases in the placebo group and 62% of cases in the silymarin-treated group (P = 0.0001). No significant side effects were reported in our cases.**

Conclusions: **Silymarin treatment appears to be significantly effective in biochemical improvement and decreasing transaminases levels in patients with NAFLD.**

Keywords: **Nonalcoholic Fatty Liver Disease, Milk Thistle, Vitamin E, Silymarin**

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of conditions ranging from simple fatty infiltration of the liver to steatohepatitis, fibrosis, and cirrhosis. Nonalcoholic steatohepatitis (NASH) is histologically characterized by significant accumulation of hepatic lipid and predominantly lobular necroinflammation, with or without centrilobular fibrosis. NASH is histologically similar to alcoholic liver disease, but without a history of ingesting significant amounts of ethanol [1]. The disorder may be progressive, causing chronic liver

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disease, including liver cirrhosis. Because of the increase in the incidence of its predisposing conditions such as obesity and type 2 diabetes mellitus, NASH is a common disorder. NAFLD is the most common liver disorder in developed countries, and it is estimated that 20%-40% of the Western population and 5%-35% of the population of Pacific and Asian countries are afflicted with the disease [2, 3].

Insulin resistance plays an important role in the pathogenesis of NASH, but oxidative stress is also an important issue. Consequently, the exact pathophysiology of the disease is not clear, and because of that, the management of this condition is empirical so various drug treatments have been attempted with variable success, including vitamin E, ursodeoxycholic acid, gemfibrozil, metformin pioglitazone, and orlistat [4-7].

Because no single pharmacologic therapy has completely proven to be effective for the treatment of this disorder, weight loss is generally suggested as the standard therapy; however, studies on the benefits of weight loss have shown inconsistent results, and there are some reports that weight loss may increase inflammation [8] and worsen fibrosis [9, 10]. Given that a considerable number of patients with NAFLD are not obese or would not benefit from weight loss, use of medication that can directly reduce the severity of liver damage independent of weight loss is a reasonable alternative.

There are few challenging evidences for efficacy of antioxidant agents such as vitamin E and silymarin in the management of NASH.

Despite a proposed role of oxidant stress in the pathogenesis of NAFLD, antioxidant approaches have not been investigated sufficiently in NAFLD therapy [11, 12].

Milk thistle (*silybum marianum* or silymarin), an antioxidant and a regulator of immune functions by modulating cytokine production, was used in classical Greece to treat liver and gallbladder diseases to protect the liver against toxins [13-15]. There are some challenging reports about silymarin efficacy for treatment of NASH [16, 17] but few randomized, placebo-controlled studies provide support for silymarin, so we tried to evaluate the efficacy and safety of oral silymarin in a placebo-controlled study of subjects with NASH.

Materials and Methods

After approval of the ethics committee during an 18-month period, we conducted a random clinical trial of patients with NAFLD referred to the Ahvaz JundiShapur University Hospitals (AJSUH) and Hepatitis Clinic from 2007 to 2008.

The study included 100 NASH patients who attended our center for management of liver disease. The criteria used for diagnosis of NASH include (a) sonographic evidence of fatty liver, (b) elevated ALT more than 1.2 times of the normal (c) excluding other chronic liver conditions, (d) suggestive histological evidence of NASH, or (e) the presence of strong risk factors such as type 2 diabetes or obesity (BMI ≥ 30 kg/m2).

Patients were excluded if they had an intake of ethanol (more than 20 g/day) or if they had ingested drugs known to produce fatty liver disease, such as steroids, estrogens, amiodarone, tamoxifen, or other chemotherapeutic agents in the previous 6 months.

Patients were screened for viral hepatitis B and C using HBsAg and anti-HCV antibody and for other hepatic diseases including autoimmune hepatitis, Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency. Patients with severe comorbid medical conditions (such as severe cardiac, pulmonary, renal, or psychological problems) or those not consenting to participate in the study were also excluded. The patients were followed up with a weight-reducing diet at least three months by checking ALT levels. After this screening period, liver biopsies were performed in nonresponders to rule out other causes of liver diseases and to prove the histologic diagnosis of NAFLD in patients without obesity or diabetes. At the end of this period, the patients having ALT levels of at least 1.2 times the upper normal limit and risk factors of NAFLD or histological evidence of the disease, were included in the study.

Ultrasonographic evaluations of liver were performed at the entry of the study and at the end of the treatment. In the ultrasonographic examination, fatty liver was diagnosed according to the modified criteria [18]. The four parameters used in this criteria were brightness of the liver, attenuation of echogenicity, blurred vessels, and the contrast ratio of the liver-to-kidney in an ultrasonography (US; General Electric LOGIQ 400 CL).

Patients were randomized to two groups, which received a placebo (Group A, 50 patients) or silymarin treatment (Group B, 50 patients).

In Group B, the patients were treated with Livergol tablets containing 140 mg of silymarin active extract. Group A served as a control group, and the participants were treated with a placebo. Both drugs were in the form of tablets. The placebo tablet had the same shape, color, and packaging as the active drug. Patients of each group took two tablets per day for 6 months.

Treatment was continued for 24 weeks, and cases

were evaluated every 4 weeks in the outpatient clinic for a 6-month period. Serum levels of ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), fasting plasma glucose (FPG), serum triglycerides, and cholesterol were monitored at each visit during treatment.

Statistical analysis

Sample size calculations were based on the comparison of paired data. With a sample size of 71 subjects (36 cases for each arm), this study had an 95% power to detect a difference in ALT levels equivalent to one standard deviation with a two-sided $\alpha = 0.05$. Considering the possibility of non-adherent cases to therapy we included 100 patients in the study. Statistical analysis was performed using a repeat-measures analysis of variance and Pearson's correlation, with baseline and population comparisons made using student's *t* tests and chi-squared tests for equal proportion where appropriate. For all comparisons, a two sided $\alpha = 0.05$ was considered statistically significant.

All calculations were made using SAS, version 8.2 (SAS Institute,Cary, NC, USA).

Results

Basal characteristics were similar in the two groups. Twenty-nine men (58%) and 21 women (42%) in Group A and 28 men (56%) and 22 women (44%) in Group B were studied (P = 0.8). The mean age for Group A was 39.0 ± 10.70 and for Group B was 39.28 ± 11.117 years. The age range for both groups was 20 to 50 years. For Group A, the mean BMI before administration of the drug was 27.80 kg/m^2, which decreased to 27.42 after the treatment (P = 0.99). For Group B, the mean BMI before drug administration was 26.75 kg/m^2, which decreased to 26.60 after the treatment (P = 0.609; see Table 1).

The mean serum ALT levels in Group B were 113.54 and 73.14 IU/mL before and after treatment with silymarin, respectively (P = 0.001; see Fig. 1). The mean serum ALT levels in Group A were 104.54 and 89.92 IU/mL before and after administration of placebo, respectively (P = 0.237; see Fig. 1).

The percentage of patients with ALT normalization (ALT < 40) in Group A was 12% (6 patients) after 3 months of therapy which increased to 18% (9 cases) after 6 months. In the sylimarin-treated group, the figures were 32% (16 patients) after 3 months and 52% (26 cases) after 6 months. The difference between the two groups was significant (P = 0.001).

The mean serum AST level in Group A was 73.02 and 66.16 IU/mL before and after treatment with the placebo, respectively (P = 0.343; see Fig. 2). The mean serum AST level in Group B was 71.42 and 49.66 IU/mL before and after treatment with silymarin, respectively (P = 0.006; see Fig. 2).

The percentage of patients with AST normalization (AST < 40) was 22% (11cases) after 3 months and 20% (10 patients) after 6 month in Group A. The figures were 46% (23 cases) after 3 month and 62% (31 patients) after 6 month in the sylimarin-treated group. The difference between the two groups at the

Table 1. Baseline characteristics of the subjects and outcome at 6 months.

Variable	Placebo(n:50)			Sillymarin(n:50)			P-value Sillymarin vs. Placebo	
	Before Treatment	After Treatment	P-value	Before Treatment	After Treatment	P-value	Baseline	After Treatment
Age (yr)	39.0±10.70			39.28±11.117			NS	
Sex (m/f)	29/21			28/22			0.8	
BMI	27.80±3.75	27.42±3.35	0.99	26.75 ±2.65	26.60 ±2.53	0.609	0. 098	0.169
Fasting plasma glucose (mg/dl)	106.80±44.97	107.0±45.178	0.97	105.96±35.84	108.34±53.12	0.978	0.920	0.892
2hpp	158.92±64.56	165.60 ±60.63	0.087	161.32±63.72	165.78±64.24	0.986	0.852	0.989
Triglyceride (mg/dl)	261.32±102.02	268.52±102.68	0.66	281.48±116.66	260.16±102.18	0.915	0.360	0.694
Total Cholesterol (mg/dl)	216.18±52.12	220.82±53.79	0.196	235.18±59.25	238.42±59.94	0.999	0.092	0.126
LDL(mg/dl)	135.36±47.45	142.96±47.45	0.941	163.30±49.69	160.42±48.47	0.476	0.005	0.073
HDL(mg/dl)	41.06±6.00	39.40±5.33	0.458	40.58±5.19	40.90±5.75	0.589	0.670	0.179
ALT(U/liter)	104.54±41.82	89.92±41.83	0.237	113.54±50.92	73.14±62.44	0.001	0.363	0.118
AST (U/liter)	73.02±39.62	66.16±27.44	0.343	71.42±66.50	49.66±33.26	0.006	0.884	0.008
ALT<40 number`(%)	0.00	9 (18%)		0.00	26(52%)			0.001
AST<40 number`(%)	0.00	10 (20%)		0.00	31(62%)			0.0001

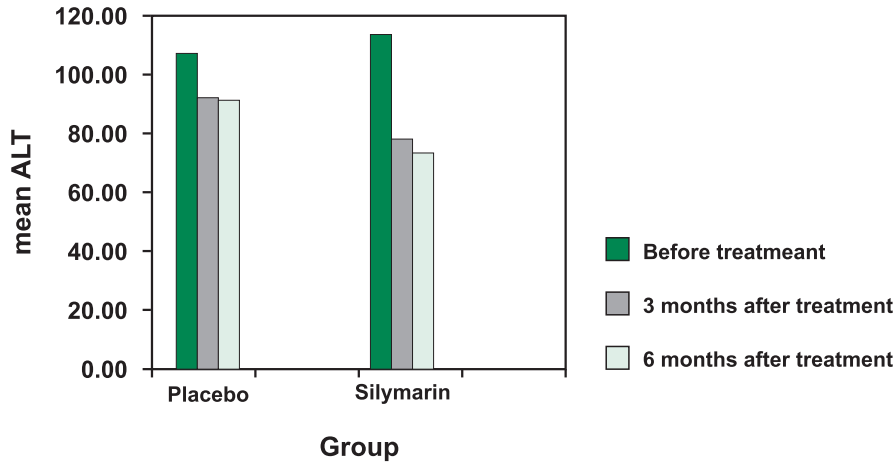

Figure 1. ALT levels before and after treatment with silymarin.

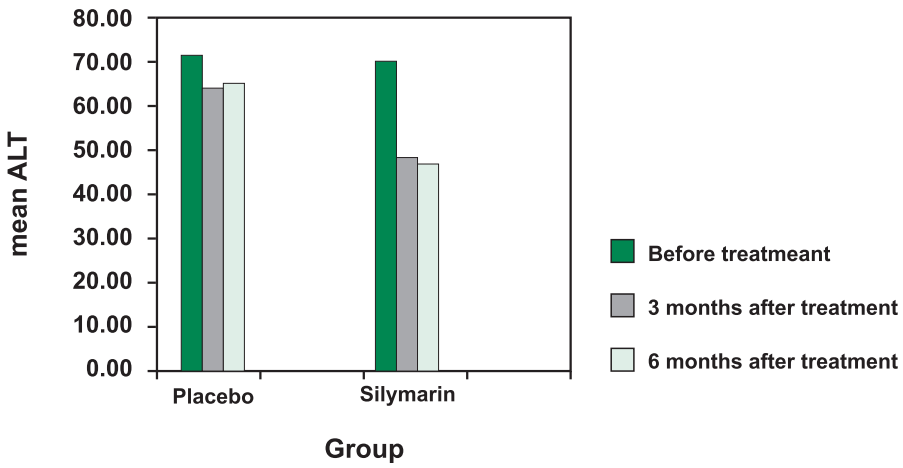

Figure 2. AST levels before and after treatment with silymarin.

end of therapy was significant (P = 0.0001).

Discussion

NAFLD is a disease with genetic, environmental, metabolic, and stress-related components; the prevalence of NAFLD has consistently increased with changes in lifestyle. NAFLD is associated with a potential risk of progression to cirrhosis, hepatocarcinoma, and liver failure (19).

Therefore, treatment of NAFLD has drawn wide attention. In recent studies, there has been increasing evidence for considering NAFLD as part of a metabolic syndrome including obesity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, and hypertension [20].

However, the molecular mechanisms by which obesity and diabetes can lead to NAFLD are still not known. In a recent study, the presence of insulin resistance and increases in free fatty acids, fatty acids beta oxidation, and peroxidation of lipids in the liver were observed in those with NAFLD [21].

There is no strong evidence supporting any effective therapeutic agents for reducing inflammation and fibrosis or preventing the progression of NASH. Nonetheless, weight reduction and the drugs that overcome oxidative stress may be appropriate to slow the disease process.

Silybum marianum has been used as an anti-

oxidant to protect the liver against toxin in several studies. The substance has been investigated for use as a cytoprotectant, an anticarcinogen, and a supportive treatment for liver damage from Amanita phalloides poisoning [22, 23].

The active component of the silymarin complex is silybin, and the main mechanism of its action is not completely understood, but a variety of mechanisms have been proposed. For instance, silymarin is reported to have antioxidant properties, such as by increasing superoxide dismutase activity in erythrocytes and lymphocytes [24].

Silymarin has also been reported to stabilize the hepatocyte membrane structure, thereby preventing toxins from entering the cell through entero-hepatic recirculation, and to promote liver regeneration by stimulating nucleolar polymerase A and increasing ribosomal protein synthesis [25].

Silybin selectively inhibits leukotriene formation by Kupffer cells and is a mild chelator of iron. It also prevents glutathione depletion in human hepatocyte, protecting cells from damage *in vitro* [26, 27].

There is a lack of studies about the treatment of NAFLD in our area, so our trial was compared with other drugs used in the treatment of NAFLD.

Previous studies that have suggested a therapeutic role for *silybum marianum* in NAFLD have either been uncontrolled and/or were conducted in a heterogeneous group of patients with fatty livers.

In Caldwell *et al.* study [28], thiazolidindions were used in 10 patients; in nine improvements in serum transaminase level were detected.

In a recent double-blind, randomized controlled study in Tehran, Merat *et al.* [29] compared a placebo with Probucol, which is a lipid-lowering agent with strong antioxidant properties. In this study liver tests normalized or were significantly improved after 6 months of treatment with Probucol. The authors concluded that the antioxidant effect of probucol regardless of its lipid-lowering effect was the responsible mechanism for the normalization of ALT levels.

In another study, treatment of NASH patients with vitamin E resulted in significant improvement in hepatic steatosis and ALP, ALT, and GGT levels [4].

The effects of ursodeoxycholic acid (UDCA), a hydrophilic bile acid with hepatoprotective properties, on NASH were examined in a controlled trial [5]. Use of UDCA was associated with improved liver enzyme levels and a decrease in hepatic steatosis. However, the long-term effects and optimal dose of UDCA have not been established.

Although promising results have been obtained with silymarin in patients with alcoholic liver disease, clinical trials have produced conflicting results.

Trails of silymarin in patients with NASH are limited, but in one study, silymarin treatment in patients affected by cirrhosis and diabetes was associated with a reduction of insulin resistance and a significant decrease in fasting insulin levels, suggesting an improvement of the activity of endogenous and exogenous insulin. Given these findings, this substance presents an interesting option for the treatment of NAFLD [6].

In one study of 85 consecutive cases of NAFLD treated with 4 pieces per day of the complex silymarin-vitamin E-phospholipids for 6 months followed by another 6 months of follow-up, they found an improvement in treated individuals, including insulinaemia, liver enzyme levels, and degree of steatosis ($P < 0.01$) [30].

Finally, in a recent study from Iran of 50 NAFLD patients who were treated with 140 mg of silymarin for 8 weeks followed by another 2 months of follow up, the researchers found an improvement in the liver enzyme levels of the treated individuals [17]. In this study, silymarin extract caused apparent improvement in serum ALT levels (41%). Additionally, serum AST levels decreased from 53.07 to 29.1 IU/mL ($P < 0.001$) [17].

In two groups of NAFLD patients with elevated liver enzymes, we investigated the effects of a placebo and silymarin on biochemical tests with higher doses and longer durations of treatment than previous studies. Although there were no significant differences between silymarin and the placebo in decreasing the mean ALT level after therapy, we found a significantly greater number of patients with normal ALT at the end of treatment with silymarin: 32% *vs.* 12 % after 3 months and 52% *vs.* 18% after 6 months ($P = 0.001$)

Compared to ALT, silymarin treatment had a greater impact on the changes in AST level, not only because AST normalization was more significant in the silymarin group (62% *vs.* 20% in the placebo group; $P = 0.0001$), but also the decrease in mean AST level in the silymarin group was significantly higher than the AST level of the placebo group ($P=0.008$).

There were no significant changes in the variables related to metabolic syndrome, including glucose metabolism, hyperlipidemia, and BMI before and after treatment with placebo or silymarin (Table1).

Another finding of the study was that treatment with s*ilybum marianum* in subjects with NAFLD was safe and well tolerated. Patient compliance with medication was good in both groups, and all cases completed the study.

We could not reach a conclusion about the

histological change because we did not biopsy the patients after the treatment period. In conclusion, in terms of biochemical improvement, silymarin treatment is effective in the treatment of NAFLD, particularly when other drugs have failed or as a complementary treatment associated with other therapeutic modalities.

Treatment with silymarin costs less than any other treatment, and there are negligible side effects. In the future, our findings must be confirmed in larger scale studies with pre- and post-treatment biopsies. Fallow-up of cases to clarify persistent or temporary effects of the drug on NASH is very important.

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