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Silymarin in treatment of non-alcoholic steatohepatitis: A randomized clinical trial

Abstract

Background: No pharmacologic agents have been approved for the treatment of non-alcoholic steatohepatitis (NASH) that is common in our region. The present study was designed to evaluate the efficacy of silymarin, a known herbal drug, in the treatment of NASH.

Methods: This clinical-trial study was conducted on 64 patients with NASH who were randomly divided as case group (33) and control group (31). Abdominal sonography and persistent elevation in levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) more than 1.2 times of the upper normal limit within the last six months were selected as inclusion criteria. They were advised to take low-fat, low carbohydrate diet, do regular sport activity to lose weight up to 4 Kg. Patients in the case group received 210 mg/day silymarin orally for 8 weeks and those in the control group received placebo. After 8 weeks, the patients were reevaluated and their AST and ALT levels were measured. This study was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with registration number ID: IRCT201202159018N1.

Results: The mean age of patients in case and control groups was 43.6 ± 8.3 and 39.4 ± 10.5 years, respectively. Their BMI were 27.4 ± 1.7 and 27.5 ± 1.9 , respectively. Their weights were also 79 ± 9.2 and 76.9 ± 9.5 kg, respectively. Serum concentrations of ALT were 91.3 ± 21.3 and 38.4 ± 11.8 in case group before and after the study respectively, while the figures were 84.6 ± 23.3 and 52.3 ± 29 in the control group ($P=0.026$). The same trend was seen for AST ($P=0.038$).

Conclusion: The patients who had taken silymarin experienced more notable fall in hepatic enzymes.

Keywords: Silymarin, NAFLD, NASH, treatment, AST, ALT.

Citation:

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Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by predominantly macrovesicular hepatic steatosis occurring in individuals in the absence of significant alcohol consumption. Non-alcoholic steatohepatitis (NASH) is often regarded as the hepatic manifestation of the metabolic syndrome, which is a variable constellation of obesity, diabetes, hyperlipidemia, and hypertension (1, 2). The prevalence of fatty liver in the general population of industrialized North American and European countries has been reported up to 45% (3). The patients with NASH may not only suffer the hepatic consequences of an altered metabolic environment but indeed NASH may contribute for atherosclerosis development (4). Various factors have suggested for etiology of NASH, including body fat, insulin resistance, oxidative stress, cytokine/adipokine interplay, apoptosis, and small intestinal bacterial overgrowth (5).

Lifestyle modification, dietary changes, and exercise are recommended for control of NASH (6). Furthermore, several groups of drugs have been suggested according to the pathomechanisms of liver injury in NASH; including antioxidants, carnitine, and insulin sensitizers (7). Nevertheless, while some agents show modest improvements in LFTs and even histologic parameters, the agents mentioned above are generally used to modify risk factor profiles rather than as primary therapy for NASH (8). Complementary therapy, such as herbal drug may receive attention for the treatment of NASH (9). There are some reports on the utility of silymarin, the extracts of the flowers and leaves of silybum marianum (milk thistle) in liver diseases (10).

Experiences of using silymarin alone or in combination with other agents in patients with NASH are limited in the medical literature (11-15). The present study was conducted to evaluate the efficacy of silymarin in the treatment of NASH.

Methods

This randomized clinical trial study was conducted on eighty patients with NASH who had referred to the hepatology clinic of the Medical University in Arak, Iran. The inclusion criteria were the presence of NASH confirmed by abdominal sonography and persistent elevation in levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) more than 1.2 times of the upper normal limit within the last six months (11, 12). Those who had autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, and chronic hepatitis B or C were excluded from the study. Patients with history of diabetes, severe cardiac, pulmonary, renal, or psychological problems, positive pregnancy test, daily ethanol consumption ≥ 20 g, substance abuse, use of drugs such as statins, fibrates, NSAID, acetaminophen, warfarin, metronidazol, anti-convulsants, anti-depressants, anti-psychotics and antihistamines also were excluded from the study.

Clinical history, physical examination, and lab tests were recorded at baseline. The patients were randomly divided into case and control group with random block design method. All the patients have been recommended to take low-fat, low carbohydrate diet (through a consultation with a defined nutritionist), do regular sport activity to lose weight

up to 4 Kg during 8 weeks. Moreover, the patients in case group received 70 mg tablet of silymarin 3 times a day (with trade name of Livergol from Goldaru pharmaceutical company, Iran) for 8 weeks, while the patients in control group received placebo in same shape and schedule produced by the same pharmaceutical company. After 8 weeks, the patients were reevaluated and their AST and ALT levels were measured. This study was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with registration number ID: IRCT201202159018N1

The study was approved by the local Ethics Committee of Arak University of Medical Sciences, Iran. All patients gave informed written consent. Demographic data were analyzed by descriptive statistics including mean, standard deviation and 95% confidence interval. Statistical analysis was performed by t-test for quantitative variables.

Results

During the study period, 7 cases in the case group and 9 subjects from the control group did not participate in the follow-up and were excluded from the study. So, sixty-four subjects completed the study (33 in case group and 31 in control group) and the data from these patients were analyzed. The general characteristics of the patients were shown in table 1.

The mean ALT levels were 91.3 ± 21.3 and 38.4 ± 11.8 IU/l, in the case group before and after treatment respectively. In the control group, the mean values were 84.6 ± 52 and 33 ± 29.9 IU/L, before and after treatment respectively (table 2). The mean AST levels before and after treatment in the case and the control groups are shown in table 2.

Table 1. General characteristics of the patients enrolled in case and control group (mean \pm SD)

Group	Case (n=33)	Control (n=31)	P-value
Mean age (yr)	43.6 \pm 8.3	39.36 \pm 10.5	NS
Sex (M/F ratio)	1.3	1.5	NS
Weight (Kg)	77 \pm 9.2	76.9 \pm 9.5	NS
BMI (kg/m ²)	27.4 \pm 1.7	27.5 \pm 1.9	NS
TG (mg/dl)	252.2 \pm 52.8	248.4 \pm 53.2	NS
Cholesterol (mg/dl)	195.7 \pm 34.4	193 \pm 35.7	NS
BMI, body mass index	M, male F, female	NS, not significant	

Table 2. Serum concentrations of AST and ALT, before and after the study in case and control groups (mean±SD)

Group	Case		Control		P-value (case vs. control)
	Before intervention	After intervention	Before intervention	After intervention	
ALT (IU/l)	91.3±21.3	38.4±11.8	84.6±23.3	52.3±29.9	0.026
AST (IU/l)	62.8±10.5	30.5±8.2	70.4±18.9	36.2±12.4	0.038

AST: Aspartate aminotransferase ALT: Alanine aminotransferase

Discussion

Sixty four patients with NASH were treated by either silymarin or placebo in the present study, while all were recommended to change diet, loss weight, and have daily activities. The results confirmed that silymarin could help the patients with NASH in lowering their hepatic enzymes particularly ALT. so, it is useful for the treatment of NASH. NASH is an increasingly common cause of chronic liver disease worldwide with potential for substantial impact on healthcare costs from its morbidity and mortality (6). Only a limited number of studies are available in pharmacological and dietary supplement interventions for NAFLD/NASH (7). Currently, no pharmacologic agents are approved for NAFLD or NASH treatment (15). While some agents show modest improvements in LFTs and even histologic parameters, studies performed to date are limited by small sample sizes and short follow-up periods (8). The most researched herbal treatment for liver diseases is silybum or milk thistle. Its active constituents are collectively known as silymarin (9). It has been used for centuries to treat liver, spleen and gallbladder disorders (16). One of the important issues about plant *S. marianum* is that it may be accepted as a safe herbal product, since no health hazards or side effects are known in conjunction with the proper administration of designed therapeutic dosages (16).

Hajaghamohammadi et al. used silymarin (140 mg/day orally) for the treatment of NASH in 25 patients for 2 months (11). They concluded that the drug lowers elevated serum level of hepatic enzymes, especially ALT. The author repeated his experiment with silymarin in another study and compared it with 2 other drugs, metformin and pioglitazone, with the same results (13). Hashemi et al. used silymarin (280 mg/day orally) for the treatment of NASH for 6 months (12). They concluded that silymarin treatment appears to be significantly effective in biochemical improvement and decreased transaminases levels in patients with NASH. The results of the present study are consistent with all the above

mentioned studies; though a different dose of silymarin had been used. In these studies, the effect of silymarin was compared with control group which had received no other treatment except the placebo. It seems unethical to deprive the patients from some form of potentially useful treatments, while in our study, the control group had received a number of treatment on lifestyle.

Loguercio et al. used silbin one of flavonolignan isomers of silymarin in the treatment of NASH in combination with vitamin E and phospholipid. They concluded that silybin conjugated with vitamin E and phospholipids could be used as a complementary approach for the treatment of patients with chronic liver damage (14). The authors have also conducted a multi-center clinical trial to evaluate the efficacy of silybin conjugated with phosphatidyl choline and vitamin E in the treatment of NASH with promising results (15). These combinations seem smart, however, in the present study; we only used silymarin to evaluate the solely effect of the drug. The results of the present study confirmed that silymarin could be used in NASH, at least as a complementary therapy to other proposed treatment modalities. However, we did not evaluate the patients for some other variables such as sonographic findings, biopsy changes, or insulin resistance. Furthermore, extending the treatment duration may help more comprehensive evaluation of the effect of the drug. Increase in sample size or multicenter studies also appear to be more conclusive.

In summary, silymarin is a useful herbal drug for the treatment of NASH. Its use for the patients should be taken into account, if feasible. Further studies could elucidate the true effect of the drug in NASH.

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