ORGINAL ARTICLE

The Efficacy of Silymarin and Vitamin E in Non-Alcoholic Fatty Liver Disease: A Clinical Trial

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Abstract

Objective: Nowadays, lifestyle modification is the best treatment recommended to patients with the nonalcoholic fatty liver disease (NAFLD). The therapeutic effects of vitamin E and silybin on liver functions were documented. The present study was conducted to examine the effect of silymarin and vitamin E on patients with NAFLD.

Materials and Methods: From September 2014 to March 2015, clinical trial was conducted on 92 patients with NAFLD at 2 Shahid Sadoughi university clinical research centers. Sampling was based on convenient method. There were no randomization or blinding in this study, but two types of treatments were compared. The patients were divided in two groups of daily intake of vitamin E (400 IU) and Silymarin 280 mg for four months. Alanine aminotransferase (ALT) and liver ultrasonography were done at baseline and after four months.

Results: Eighty patients completed the course of treatment successfully .After 4 months, both groups had experienced a significant reduction in their serum ALT levels. The mean change in the ALT level from the baseline was -31.6 U/L in the silymarin group vs. -15.1 U/L in the vitamin E group (*P*-value= 0.07). Treatment with silymarin was more effective than vitamin E (*P*-value< 0.0001). The mean ALT level changed to normal was 55.0% (22 of 40 patients)in the silymarin group, while it was 45.0% (18 of 40 cases) in the vitamin E group (*P*-value= 0.04).

Conclusion: The treatment of NAFLD with silymarin appears to be significantly effective in biochemical improvement whereas treatment with vitamin E improves ultrasonographic parameters.

Keywords: Nonalcoholic fatty liver disease, Silymarin, Vitamin E, Clinical trial

Introduction

One of the most common liver disorders is fatty liver disease. For example, it is estimated about 25% of adults in America suffer from fatty livers, while they even do not drink excessive alcohol. This condition is known as nonalcoholic fatty liver

disease (NAFLD). Over 25% of adults NAFLD are presumed to have nonalcoholic steatohepatitis (NASH) on the basis of elevated serum aminotransferase levels and in the absence of other identifiable causes of liver injury (1).

A definitive diagnosis of nonalcoholic steatohepatitis is currently based on histologic evidence such as fat accumulation (steatosis) in hepatocytes, accumulation of inflammatory cells, and liver cell injury. NASH and damaged liver cells lead to progressive liver fibrosis and eventual liver-related illnesses and death (2-6). There is no definite drug approved for the treatment of NAFLD (7). Currently, the recommended treatment includes lowering the calorie intake, weight loss, and exercise. Drugs such as vitamin E, metformin, silymarin, and insulin-sensitizing drugs like pioglitazone have also been tried.

Silybummarianum is a herbal medicine that has been used to treat different liver disorders for centuries (8). So far, only a few studies have been done to evaluate the effect of silymarin on NAFLD. Therefore, this study evaluated the effect of silymarin in the treatment of the NAFLD. The assessmentwas done by comparing silymarin with vitamin E. Recently, vitamin E has been in focus to be used as a cytoprotectant and an anti-oxidative scavenger of free radicals in the treatment of liver damages caused by cirrhosis, viral infections and amanita phalloides poisoning (9).

Materials and Methods

This quasi experimental study was performed on 92 NAFLD patients who had referred to the Gastroenterology clinic of the Shahid Sadoughi University of Medical Sciences in Yazd, Iran, from September 2014 to March 2015.

Sampling was based on convenient method. There were no randomization or blinding in this study, but two types of treatments were compared. Out of 92 patients who entered the study, 12 patients were excluded due to lack of follow up.

The inclusion criteria were NAFLD confirmed through abdominal ultrasonography, persistent elevation in the level of alanine aminotransferase (ALT), fatty changes diagnosed through ultrasonography, and over 20 years of age. The exclusion criteria were autoimmune hepatitis, alpha-1 antitrypsin deficiency, chronic hepatitis B or C, hemochromatosis, and Wilson's disease. Patients with past history of diabetes, daily consumption ethanol, severe cardiac, pulmonary, renal, or psychological problems, positive pregnancy test, and the use of drugs such as statins, fibrates, anti-convulsants, NSAID, acetaminophen, warfarin, metronidazole, anti-depressants, or anti-psychotics were also excluded from the study.

The patients were categorized in two groups randomly and received daily vitamins E (400 IU) or silymarin 140 mg BID (with the brand name of Livergol from Goldaru Pharmaceutical Company, Iran) for four months. Additionally, they were all given consultation for standard weight-loss programs and persuaded to follow low-fat diets (< 30 fat g/day). ALT measurements and ultrasonographic (General Electric LOGIQ 400 CL ultrasound devices) evaluations of their liver was done at baseline and after four months. Fatty liver was diagnosed according to the defined criteria. In this regard, four parameters were taken into account, including blurredness of vessels, attenuation of echogenicity, brightness of the liver, and the contrast of the liver-to-kidney ratio (10). Those in the first group received vitamin E 400 UI /day, and those in the second group were given silymarin 140 mg BID (livergol-Goldaro Company). No patient had clinical evidence of cirrhosis or decompensated liver diseases or BMI above 40.

The sample size is calculated based on previous studies and statistical advice.

Before the study, informed written consent was taken from the patients. Statistical parameters were used to analyze the demographic data descriptively. Those parameters included standard deviation, mean, and 95% confidence interval. In addition, T-test was used to evaluate the quantitative variables. A

P-value of less than 0.05 would signify statistical significance.

Ethical considerations

The study was approved by the ethics committee of Yazd University of Medical Sciences, Yazd, Iran, (IR.SSU.MEDICINE. REC.1393.114) and the registration of clinical practice with the code (IRCT20081110001444 N6).

Results

In this study, 92 non-diabetic NAFLD patients were included but 80 patients completed the study and 12 patients' loss to follow up.

The data on the demographic features of the studied cases are presented in Table 1. The mean age for group one (i.e. vitamin E group) and group two (i.e. Silymarin group) was 44.2 and 43.7 years respectively. The mean BMI of group one before and after the treatment was 30.8 Kg/M2 and 29.8Kg/M2, and it was 29.3 Kg/M2 and 28.3Kg/M2 for group two. As Table 3 indicates, the two groups were not significantly different in terms of age and BMI.

According to Table 2, the mean serum ALT level was 109 IU/ mL in group one and 112 IU/mL in group two before the treatment (*P*-value= 0.70). As in Table 4, the mean change in the ALT level from the baseline up to the fourth month of the treatment was -15.9 U/L for the vitamin E group and -31.2 U/L for the Silymarin group (*P*-value= 0.071). Thus Silymarin was, more efficacious than vitamin E (*P*-value< 0.0001). The mean ALT level changed to normal in 45.0% of the patients (i.e. 18 out of 40) in the vitamin E group. For the Silymarin group, however, the rate was 55.0% (i.e. 22 out of 40) (*P*-value= 0.04). Based on the ultrasonography findings, after four months, only four of those who had taken vitamin E and two in the silymarin group were normalized. The adverse events (AEs) were mainly temporary and included pruritus, dysgeusia, and diarrhea. There were, indeed, no serious AEs to record.

At the baseline, there were no significant differences of BMI, gender, age, and ALT between the two groups. The mean level of the serum ALT was 109 IU/mL and 112 IU/mL in groups one and two before the treatment respectively (*P*-value= 0.70). At the end of a four-month treatment period, a significant decrease was observed in the ALT levels of both groups under treatment (table 2).

Table 3 presents the mean values of BMI in the NAFLD patients before and after the treatment. The mean decreased in both groups

Table 1. The baseline characteristics of NAFLD patients

Variable	Vitamin E	Silymarin	*P*-value
Mean of age	44.2 (±11)	43.7 (±9.8)	0.78*
Male	25 (62%)	27 (67%)	0.63**
Female	15 (38%)	13 (33%)	
Mean of BMI (kg/m^2	30.8 (±5.0)	29.3 (±6.8)	0.70
Mean of ALT	109 (±29)	112 (±38)	0.70

*T-test
**Chi-square

Table 2. Mean of ALT before and after the vitamin E and silymarin therapy in NAFLD

Group	ALT before treatment Mean (±SD)	ALT after treatment Mean (±SD)	*P*-value*
Vitamin E	109 (±30)	93 (±21)	0.032
Silymarin	112 (±38)	81 (±29)	0.025

*Paired sample T-test

Table 3. Mean of BMI before and after the vitamin E and silymarin therapy in of NAFLD

Group	BMI before treatment Mean (±SD)	BMI after treatment Mean (±SD)	*P*-value*
Vitamin E	30.8 (±5.0)	29.8 (±0.3)	0.42
Silymarin	29.3 (±6.8)	28.3 (±3.4)	0.32

*Paired sample T-test

a little, but there was no significant difference between them after the treatment (*P*-value= 0.425). The mean of the ALT levels changed to normal in 45.0% of the patients (i.e. 18 out of 40) in the vitamin E group and in 55.0% of the cases (i.e. 22 out of 40) in the silymarin group (*P*-value= 0.04).

The change in the mean of the ALT level from the baseline up to the fourth month was -15.9 U/L for the vitamin E group and -31.2 U/L for the Silymarin group (*P*-value=.071). In other words, Sylimarin was more efficacious than vitamin E (*P*-value< 0.0001).

Based on the ultrasonographic findings, after four months of treatment, four cases in the vitamin E group and two in the silymarin group were normalized.

Discussion

In this study, biochemical analyses and ultrasonographic examinations indicated that treatment with vitamin E and silymarin can be effective in the improvement of conditions in NAFLD patients. ALT improvement was higher in the silymarin-treated group than in the vitamin E-treated group, while the improvement of fatty livers scored better in the vitamin E group.

The results of this study are in agreement with those of Hajiani and Hashemi (11) whose patients received vitamin E 400U/day and Silybummarianum extract containing silymarin. Once the treatment period ended, the serum AST and ALT levels proved to have significantly decreased in both treatment groups. AST normalization was significant difference between the groups ,but AlT was not. This result of the mentioned study is same as that of our study. In comparison, however, our patients had a higher AlT level before the treatment.

In another case control study by Solhi et al. (12), silymarin (210 mg for 8 weeks) and a placebo were randomly assigned to NASH patients. Silymarin could decrease ALT and AST more significantly than the placebo, which is in agreement with our results.

Masoudi et al. (13) showed that silymarin can significantly decrease LFT and especially ALT in NASH patients, which is the same as our finding. In that study, silymarin was used as in ours, but the control group used a placebo instead of vitamin E.

At a tertiary care hospital in Kuala Lumpur, Malaysia, a randomized, placebo-controlled, double-blind study was conducted on a group of adults who suffered from biopsy-proven NASH and had an NAFLD activity score (NAS) of 4 or more. They took silymarin or placebo for 48 weeks. As this period ended, liver biopsy was repeated. a dose of 700 mg three times a day was chosen. While the enzyme and the fibrosis decreased, the NAS score did not decrease significantly (14). A more positive point about the study in Malaysia is that the patients underwent liver biopsy before and after the treatment so that the changes in liver histology could be clearly denoted. That was the first study in which was used to treat NASH through paired liver biopsies. Histologically, previous observations are confirmed in that silymarin may be of benefit in the treatment of NAFLD.

Silymarin (silybummarianum) is known as a natural ingredient of milk thistle that has experimentally proved to possess promising anti-fibrotic properties for liver injuries.Due to its specific structure; silymarin is classified as a flavonoid compound. A few of other such compounds are baicalein, quercetin, and baicalin. Owing to their anti-fibrogenic properties, they have attracted increasing attention (15). Silymarin is considered as an antioxidant which may alleviate hepatic injuries. This is thought to be done through cytoprotection and inhibition of Kupffer cell function. A related compound, silibinin, is also anti-fibrotic in cultured stellate cells (16).

However, despite the theoretical benefit of silymarin and its assumed efficacy in cultured cells, a systematic review of 14 pieces of research showed no clear evidence for the ability of this drug to reduce mortality or improve liver histology and the biochemical

markers of liver function in those suffering from chronic liver diseases (17).

Pharmacologic therapies have been conducted for the treatment of patients with NASH, but most of these attempts have not been sustained enough to yield definite patient-centered clinical evidence of efficacy (e.g. against decompensated cirrhosis). Some reports on surrogate outcomes, such as research about serum aminotransferase levels or histologic features, have even provided conflicting results (18).

Non-alcoholic fatty liver disease (NAFLD) patients who have elevated ALT levels typically undergo a liver biopsy so as to be checked against advanced fibrosis or possible nonalcoholic steatohepatitis (NASH). It is to be noted, however, that even individuals with normal ALT levels can be in advanced stages of NAFLD. In other words, there is currently no known optimal ALT level with which to predict NASH or advanced fibrosis. To confirm these diseases or to select patients for liver biopsy, metabolic risk factors have to be evaluated at first (19-25).

In a report published recently in the field of NASH treatment, a decade of clinical trials involving a diversity of pharmaceutical agents targeting the pathological concepts of NAFLD was reviewed, but no single intervention was found to convincingly improve all the important outcomes for all NASH patients. Therefore, in 2018, there was no single medication to recommend as a target-specific agent for routine clinical use by all NAFLD patients. Apparently, the best available treatment is to instruct patients to follow a reasonable dietary plan and a tailored exercise program. Together with this, they should be treated for any associated comorbid disease with a specific medicine from a list of medications (21).

Conclusions

In conclusion, no definite effect of silymarin on liver diseases was established. Biopsy is recommended before and after treatment for its diagnostic value. Also, ALT alone may not be a good surrogate for histopathologic responses; otherwise, many confounding factors such as weight, diet, diabetes, and physical activity may influence the efficacy of silymarin. A consistent research program to consolidate the existing evidence and explore new potential usages would be very welcome.

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Conflict of Interest

There is no conflict of interest.

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