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ORIGINAL ARTICLE

The Efficacy of Silymarin in Decreasing Transaminase Activities in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Clinical Trial

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Background and Aims: **Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of increased liver enzymes. According to statistical reports, 20%-40% of Western population and 5%-30% of the population of Pacific and Asian countries are afflicted with this disease. The prevalence of NAFLD is higher in hyperlipidemic, diabetic and obese people. Considering the high prevalence of NAFLD and its complications and lack of consensus on its treatment, we were motivated to study the efficacy of silymarin on this disease.**

Methods: **In this randomized clinical trial, 50 patients including 32 men (64%) and 18 women (36%) were divided into case and control groups. The mean age of case group was 40.3 and for control group was 39.9 years. All patients had elevated liver enzymes and had increased liver echogenicity (lipid accumulation) on sonography. The case group was treated with one tablet containing 140 mg silymarin per day for two months and the control group was treated in the same manner with placebo. Before and after the study, weight, body mass index (BMI) and liver transaminases levels were measured for each patient.**

Results: **The difference between the mean weight and BMI measured before and after the study was not statistically significant in both case and control groups. But the mean ALT and AST levels deceased from 103.1 to 41.4 and 53.7 to 29.1 IU/mL, respectively in case group which was statistically significant (P<0.001 & P<0.001). In the control group, the decrease in mean ALT and AST, with decrease of 7.8 and 2.2 IU/mL, respectively, was not statistically significant.**

Conclusions: **Considering the significant drop in liver enzymes following administration of silymarin, it seems that after conducting similar studies in order to determine the appropriate doses and treatment periods, this cheap and easy to access drug can be prescribed for treatment of NAFLD.**

Keywords: **Non-alcoholic Fatty Liver Disease, Non-Alcoholic Steatohepatitis, Silymarin**

Introduction

Non-alcoholic fatty liver disease (NAFLD) is considered as the most common cause of chronic liver diseases worldwide. One type of progressive NAFLD is known as non-alcoholic steatohepatitis (NASH) which can lead to cirrhosis, hepatocellular carcinoma (HCC), liver dysfunction and ultimately to death [1, 2]. From the histological point of view, the characteristic of NAFLD is accumulation of macrovesicular lipids. There are two histological types of NAFLD including isolated fatty liver and fatty liver together with evidence of inflammation (NASH). Histology of the liver in NAFLD is indistinguishable from alcoholic hepatitis and includes balloon degeneration, hepatocyte necrosis, and fibrosis.

Currently, there is no consensus for staging and grading of NAFLD. It has been shown that there is no relationship between the disease grade and serum level of alanine aminotransferase (ALT) [3]. Incidence of NAFLD is not accurately determined based on the published reports. NAFLD is the most common disorder relating to liver in developed

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countries and it is estimated that 20%-40% of Western population and 5%-35% of the population of Pacific and Asian countries are afflicted with NAFLD. The highest incidence is in 40-49 age group [2, 4, 5]. This disease may appear at any age (even in childhood) and its probability increases with hyperlipidemia. Risk factors in NAFLD are obesity, sudden weight loss, diabetes and hyperlipidemia [4, 6, 7].

Considering the treatment of NAFLD, like other aspects of the disease, there are no definite treatments. Proven by conducting controlled studies, one of the treatments proposed is exploiting from active extracts, "silymarin" and "silibone" being obtained from the plant *Silybum marianum*, both are some mixtures of flavonolignans. Among the properties of these extracts, anti-oxidant activity, stimulating synthesis of proteins, antidote effects against α-amanitine, effect on the metabolism of the membrane phospholipids and protective effect on hepatocytes shown in both *in vivo* and *in vitro* studied, can be mentioned. Silymarin acts via two mechanisms: The first mechanism consists of protective effect on the cell membrane because of the direct interference with cellular components and the second mechanism is the antioxidant effect. Indeed, it seems that the cell membrane is the target for silymarin and silibone activities. These two mixtures can prevent membrane absorption of phalloidine and α-amanitine via avoiding phalloidine binding to the cell surface and suppressing the membrane transporting system for these toxins. Silibone not only has effect on the cell membrane but also affects the cell nucleus and increases the ribosomal synthesis of proteins by simulating the polymerases and RNA transcription process. Stimulating the protein synthesis is an important stage in liver lesions repair and is necessary for substituting the structural proteins and the enzymes damaged by liver toxins.

Materials and Methods

In this randomized clinical trial, after approval of the ethics committee and informing the subjects regarding the project and also to assure them regarding privacy of their information, 50 persons including 30 men (64%) and 18 women (36%) were studied. The inclusion criteria were presence of NAFLD confirmed by sonography and presence of elevated levels of aspartate aminotransferase (AST) and ALT. All tests, and ultrasound processes were performed at the same center to avoid personal errors. In addition to taking a complete history in relation to alcohol consumption and using drugs, tests for autoimmune hepatitis and viral markers were requested for all patients. Patients with history of diabetes, alcohol abuse, and those positive for autoimmune hepatitis and viral markers were excluded from the study. The patients were then divided into two groups so that the effect of silymarin on NAFLD can be evaluated.

Patients were randomly assigned to each group. One group was treated with "Livergol" tablet containing 140 mg of silymarin active extract and another group was treated with placebo. Both drugs were in the form of tablets. Placebo was completely similar to the active drug respecting the shape, color and package and all its ingredients were identical to the main drug except for silymarin active extract which did not exist in the placebo. Patients of each group took one tablet/day for two months. To study the efficacy of silymarin, weight, AST, ALT and body mass index (BMI) were measured before and after administration of the drug and placebo for both groups of patients. Data were analyzed by SPSS® (v 11.5) for Windows®.

Results

No patients in the two groups were excluded from the study during the research period. Sixteen men (64%) and nine women (36%) in the control group and 16 men (64%) and nine women (36%) in the case group were studied. The mean age for the case group was 40.3 and for control group was 39.9 years. The age range for both groups was 15-60 years. The mean weights for the case and control groups was 83.7 and 815.0 kg, respectively (P>0.05). For the case group, the mean BMI before administration of the drug was 30 kg/m^2 which decreased to 29.03 after the treatment (P>0.05). For the control group, the mean BMI before drug administration was 29.01 kg/m^2 which increased to 29.03 after the treatment (P>0.05).

The mean serum ALT level in the case group was 1031.1 and 41.4 IU/mL before and after treatment with silymarin (P<0.001) (Fig. 1). The mean serum ALT level in the control group was 96.6 and 88.8 IU/mL before and after administration of placebo

Table 1. Demographic characteristics of the case and control groups.

Group	N	Age (yr)	Sex		Weight (kg)	BMI
			Male	Female		
Case	25	40.3	16 (64%)	9 (36%)	83.72	30
Control	25	39.9	16 (64%)	9 (36%)	81.96	29.1

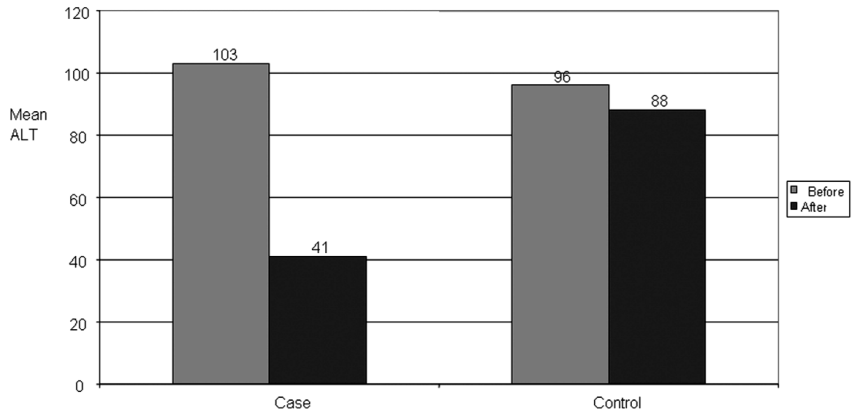

Figure 1. ALT levels before and after treatment with silymarin in the case and control groups.

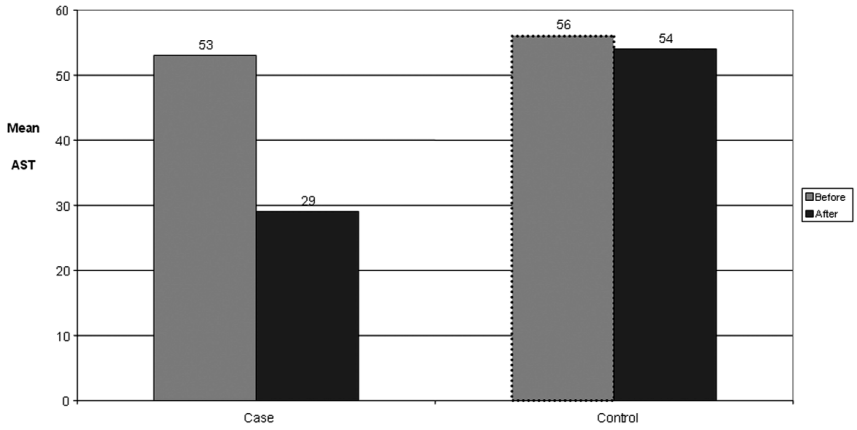

Figure 2. AST levels before and after treatment with silymarin in the case and control groups.

(P>0.05) (Fig. 1). The mean serum AST level in the case group was 53.07 and 29.1 IU/mL before and after treatment with silymarin (P<0.001) (Fig. 2). The mean serum AST level in the control group was 56.3 and 54.1 IU/mL before and after treatment with placebo (P>0.05) (Fig. 2).

Discussion

In recent studies, there is increasing evidence for considering NAFLD as part of metabolic syndrome including obesity, hyperinsulinemia, insulin resistance, hypertriglyceridemia and hypertension. People with truncal obesity have more chance of afflicting with NAFLD. However, the molecular mechanisms by which obesity and diabetes can lead to NAFLD have not still been known. Recently, presence of insulin resistance, increase in free fatty acids, increase in fatty acids β-oxidation and increased peroxidation of lipids in liver were observed in those with NAFLD. From the symptomatologic point of view, most patients are asymptomatic. Liver disease is diagnosed either by routine tests or following an examination for diabetes, hypertension and obesity.

NAFLD is the most common cause of unexplained continuous increase in serum ALT level [6]. When there are clear symptoms, they are mostly non-specific. Tiredness is the most common complaint from and is not related to the severity of the disease. Another common complaint is about discomfort which is usually as a vague discomfort in the right upper quadrant of the abdomen. A small number of patients have more serious symptoms of liver diseases such as nausea and itching, ascites, hemorrhage from the esophageal varices or hepatic encephalopathy subsequent to liver cirrhosis. There are no pathognomonic physical signs relating to NAFLD, but obesity is the most common sign being observed in 30%-100% of patients. The most common finding in relation to the liver is hepatomegaly which has been reported in half of the patients. In a lower percentage of patients, symptoms and signs of chronic liver disease appear; spider angiomas and plantar erythema are the most common signs among others.

In 50%-90% of the patients, there is an elevated level of serum aminotransferases [1, 6, 8, 9]. This elevated level is 1-4 times the normal level; in most cases, the ALT level is higher than AST so that AST/ALT ratio is never >2. Diagnosis of NAFLD is made based on a series of clinical signs and symptoms and paraclinical findings. Paraclinical methods being used in relation to this disease are divided into two groups: Invasive and noninvasive. Biopsy is one example of invasive methods and measuring the serum level of aminotransferases and imaging techniques are examples of noninvasive methods. Serum level of aminotransferases cannot be a criterion for distinguishing NAFLD from NASH by itself. Presence of lipids in the liver is detected by imaging techniques; Sonography, magnetic resonance imaging (MRI) and computed tomography (CT) are among common imaging

modalities used to detect presence of fatty liver. Sonography is the cheapest one. In a study by Mishra and Younossi [10] a new grading system on the basis of sonography images has been reported, being used in confirming the diagnosis of NAFLD. This grading system can however not be used for NASH and liver fibrosis. Based on the same study, sonography is one of the most important techniques in qualitative study of lipid infiltration in the liver. Abdominal sonography is extensively used in screening asymptomatic patients with fatty liver disease with accidentally-diagnosed raised aminotransaminase levels. Sonography is very sensitive but it cannot detect little amounts of liver steatotic lipids [11, 12].

There have not been any published data regarding treatment with silymarin in NAFLD so our trial was compared with other drugs used in treatment of NAFLD. In Caldwell *et al.* study [13], thiazolidindions were used in 10 patients; in nine improvements in serum transaminase level were detected. Among those 10 patients, three were diabetics and one had hepatitis C [5]. In Laurin *et al.* study [14], clofibrate had not had any effect on liver function. Regarding the effect of vitamin E, one study was performed in children and only in one patent, the liver function was improved. The study had however not had any control group. The value of UDCA, a hydrophilic bile acid with hepatoprotective properties, on NASH was examined in a controlled trial [14]. 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. The usual dose of UDCA is 10-15 mg/kg/day orally. In another single uncontrolled series, 10 children treated with taurine supplements orally had radiologic resolution of their fatty liver [15]. Radiologic improvement was accompanied by a decrease in glycine/taurine-conjugated bile acids.

In two recent studies [16, 17], betaine supplements were given for the treatment of patients with NASH. Betaine is a precursor of S-adenosyl methionine, a hepatoprotective factor. In one study [16], 10 subjects received betaine anhydrous for 12 months in two daily divided doses. Seven of 10 subjects completed one year of treatment. In this group, an improvement in aminotransferase activity as well as liver histology was noted. Similarly, a 25% improvement in hepatic steatosis was reported in a randomized controlled trial in which betaine was administered along with diethanolamine glucuronate and nicotinamide ascorbate for eight weeks [17]. These findings now require confirmation in large scale, long-term trials.

The silymarin active extract is one of the drugs used in treatment of chronic liver diseases which has not had any serious side effects. In our study, silymarin extract caused apparent improvement in liver function and also leaded to drop in serum aminotransferase levels, and in a two-month period caused a significant drop of 41% in serum ALT level ($P<0.001$). Serum AST level was also decreased from 53.07 to 29.1 IU/mL which ($P<0.001$). Nonetheless, in the control group, placebo did not caused any significant decrease in serum aminotransferase level. Considering our findings and taking into account the importance of liver disease and availability of herbal medicines in Iran, usage of this drug in patient with NAFLD might be feasible. The duration and the recommended dosage should be studied in the future research. In our study, the effect of silymarin on patient's prognosis was not studied which should be studied later.

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