

## ORIGINAL ARTICLE

# Comparison of Efficacy of Glycyrrhiza Glabra (Licorice Extract) and Vitamin E in Decreasing Fibrosis Score in patients with Non-Alcoholic Fatty Liver Disease

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## ABSTRACT

**Aim:** To compare the efficacy of Glycyrrhiza glabra and vitamin E in decreasing fibrosis score in patients with non-alcoholic fatty liver disease (NAFLD).

**Method:** This randomized controlled trial was carried out in the Medical Wards of Mayo Hospital/King Edward Medical University, Lahore. Two hundred and twelve patients with NAFLD were divided via random assignment into Group A that was given 800IU of vitamin E per day and Group B that received Glycyrrhiza Glabra in a dose of 10 mg per day. Both groups received treatment for 3 months and were re-evaluated monthly for improvement in fibrosis scores and liver transaminases. Data was analyzed using version 26.0 of SPSS.

**Results:** Out of 212 patients, 53.4% were male and 46.6% were female. Mean age of patients in Group A was 35.8±14.26 and 41.93±14.2 in Group B. Fibrosis score in Group A decreased from 0.19± 1.02 to -0.14± 1.09 while reduction in Group B was from 0.29± 0.93 to -0.67± 0.97 (p-value <0.000). Only patients in Group B showed significant reduction in alanine transaminase (ALT 62.3± 15.3 to 57.2± 14.58, p-value <0.000). In lowering fibrosis score, vitamin E was effective in 11.3% of patients, whereas Glycyrrhiza glabra was effective in 34% patients (p-value 0.000).

**Practical Implication:** With the global increase in the cases of NAFLD, it has become imperative to devise new treatment strategies to overcome this burden. No definitive treatment modality provides an ultimate cure for these patients. This study proves a superior role of Glycyrrhiza glabra (licorice extract) in terms of lowering fibrosis score and reduction of ALT levels.

**Conclusion:** Both Glycyrrhiza glabra and vitamin E were effective in lowering fibrosis scores in patients with NAFLD, however, Glycyrrhiza glabra was more superior in terms of efficacy than vitamin E and also caused a considerable decrease in ALT levels.

**Keywords:** Glycyrrhiza glabra, Vitamin E, Fibrosis Score, Non-alcoholic fatty liver disease

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) can be defined by the presence of hepatic steatosis, seen either on imaging or histopathology, with moderate or no alcohol consumption, and without a secondary cause of fat deposition (including viral hepatitis, drugs or lipodystrophy) <sup>(1)</sup>. The term "NAFLD" has developed into an umbrella term for a variety of fatty liver diseases. It comprises non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) that involves accumulation of fat and concurrent infla<sup>1</sup>.

NAFLD is found to be the leading source of hepatic disease worldwide<sup>3</sup>. In different parts of the world, the incidence of NAFLD varies from 9- 36.9%<sup>4</sup> and about 5-20% Asians are affected with it<sup>5</sup>. Factors posing significant risk for the development of NAFLD consist of metabolic syndrome, hyperlipidemia, diabetes mellitus type 2 and central obesity<sup>6</sup>.

Despite the present understanding of the epidemiology and etiology of NAFLD, no particular pharmacological interventions have been licensed for this condition and only general management approach has been recommended. These include prevention of modifiable risk factors and management of hepatic and extra-hepatic complications. Several possible treatments for NAFLD have undergone extensive research in the past few years. These include anti-diabetic agents like pioglitazone, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, statins and other lipid altering medications, Farnesoid X activated receptor (FXR) agonists and few more<sup>7</sup>.

One of the newer treatment modalities is the utilization of agents with antioxidant properties. Promising results have been shown by antioxidants like Vitamin E, when compared with other therapeutic options<sup>8,9</sup>. Based on the recommendations of the

American Association for the study of Liver Diseases (AASLD), vitamin E must be administered at a dose of 800 IU/day on daily basis in patients who are not diabetic and have NASH proven on biopsy and is labeled as first line pharmacological agent for individuals belonging to this category<sup>1</sup>.

The significant factors in the development from hepatic steatosis to steatohepatitis are lipid peroxidation, reactive oxygen species and pro-inflammatory cytokines<sup>10</sup>. Keeping this mechanism in view, there is basis behind utilising micronutrients that have antioxidant, anti-inflammatory and immunomodulatory properties. The management of patients with NAFLD might potentially be accelerated with complementary therapy such as licorice. Glycyrrhizic acid, a triterpenoid found in the root of licorice, enhances fat metabolism and reduces lipid peroxidation to produce anti-inflammatory and antioxidant effects<sup>11</sup>. A number of studies on rat models with NAFLD showed reduced hepatic steatosis as well as decrease in transaminases with the use of Glycyrrhiza glabra <sup>(12, 13)</sup>. Similarly a study conducted by Haji Agha Mohammadi et al. found that daily 2g of aqueous licorice root extract containing 20% glycyrrhizic acid resulted in significant reduction in liver transaminases in NAFLD patients<sup>14</sup>.

To date, there are no large randomized controlled trials comparing these two agents and there is no conclusive data on the optimal management of NAFLD. This study was designed to compare the effectiveness of Vitamin E and Glycyrrhiza glabra in the management of NAFLD.

## MATERIALS AND METHODS

This randomized controlled trial was carried out in the Medical Wards of Mayo Hospital/King Edward Medical University, Lahore from 15th May, 2020 to 14th November, 2020. After getting approval after from the Advanced Studies Research Board (ASRB), a sample size of 212 patients (106 patients in each group) was calculated taking level of significance as 5%, power of test as 90%, with estimated percentage of Vitamin E as 48.1%<sup>8</sup> and

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Glycyrrhiza glabra as 87%<sup>15</sup>. Simple random sampling was employed in patient enrollment.

**Inclusion Criteria:** Patients of either sex, greater than 18 years of age, with NAFLD diagnosed on the basis of ultrasound, showing vascular blurring of portal or hepatic vein, enhanced echogenicity of liver and bright echoes, were recruited for the study. NAFLD fibrosis score was calculated by the formula<sup>16,17</sup>.

$-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets (}\times 10^9/\text{l)} - 0.66 \times \text{albumin (g/dl)}$ . The score was classified as low (F0-F2 < -1.455), intermediate (-1.455 – 0.675) or high (F3-F4 > 0.675).

Patients with high or intermediate scores were included in the study.

**Exclusion Criteria:** Secondary causes of hepatic steatosis, three fold or greater increase in transaminases, history of Ischemic heart disease and use of digoxin/ steroid therapy resulted in exclusion from the study.

**Sample Collection Procedure:** Informed written and verbal consent was obtained from the participants or their first degree relatives. Subjects were assigned to two groups, A and B, by computer generated randomization. All patients' complete biodata and clinical history was obtained. Clinical examination (including vital signs, weight and BMI), baseline investigations and ultrasound abdomen were done prior to the study. Treatment was then started on outpatient basis. Group A received 800 IU of vitamin E per day while Group B was given 10mg Glycyrrhizic acid (Glycyrrhiza glabra extract) as a single morning dose. Both groups were treated for 3 months. Patients were followed on monthly basis. Clinical examination and laboratory investigations were done at each visit. Efficacy was assessed by reduction in fibrosis score as calculated by non-invasive NAFLD fibrosis scoring system, with conversion from higher to lower fibrosis score (i.e. F3-4 to Intermediate score, or intermediate score to F0-2). In case of adverse events like hypersensitivity, hypertension, electrolyte imbalance, etc. treatment was discontinued.

**Data analysis:** Data analysis was done using Statistical Package for Social Science (SPSS) Version 26.0. Quantitative variable like age, weight, BMI, liver function tests (LFTs), fibrosis score were addressed as Mean±SD. Frequency and percentages were used to represent qualitative variables. Chi-square test was applied to compare efficacy of the two drugs. P-value ≤ 0.05 was taken as significant

**RESULTS**

Out of 212 patients with 106 participants in each group, 53.4% were male and 46.6% were female. Mean age of patients in Vitamin E group (Group A) was 35.8±14.26 and the mean age of patients in the Glycyrrhiza glabra group (Group B) was 41.93±14.2. The mean weight, BMI, alanine transaminase (ALT), aspartate aminotransferase (AST) and fibrosis score before and after treatment for vitamin E and Glycyrrhiza glabra group are shown in tables 1 and 2 respectively. The reduction in fibrosis score in Group A was statistically significant (p value of 0.000) while the decrease in both ALT levels and fibrosis score was statistically

significant in Group B (p value of 0.000). When efficacy in lowering fibrosis score was compared between the two groups, vitamin E was effective in 11.3% of patients, whereas Glycyrrhiza glabra was effective in 34% patients in lowering down the fibrosis scores (p-value 0.000). Thus Glycyrrhiza glabra was more effective in reducing fibrosis score in patients of NAFLD

Fig. 1: Efficacy of vitamin e and glycyrrhiza glabra in reducing fibrosis score

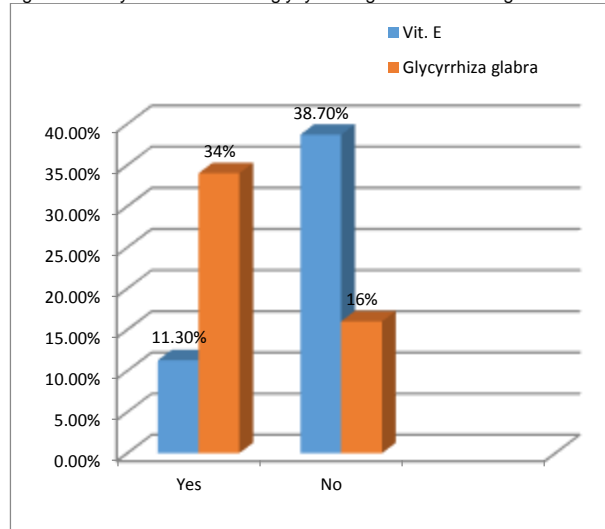


Fig. 2: Efficacy of vitamin e and glycyrrhiza glabra in reducing alt and ast

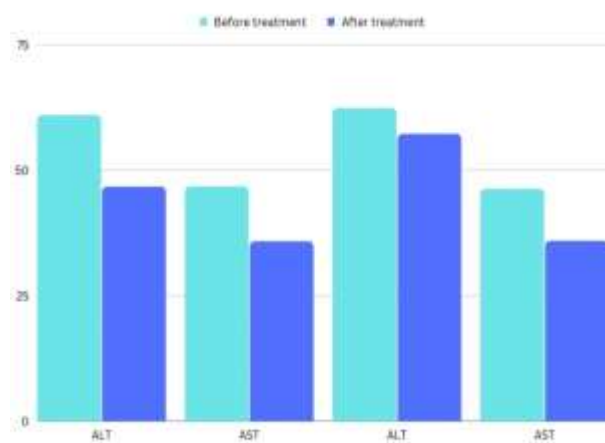


Table 1: mean bmi, weight, alt, ast, fibrosis score of patients before and after treatment in group a (vitamin E)

|                  | BMI        | Weight      | ALT        | AST        | Fibrosis Score |
|------------------|------------|-------------|------------|------------|----------------|
| Before treatment | 27.2± 3.69 | 94.8± 14.19 | 60.9±12.2  | 46.7± 5.24 | 0.19± 1.02     |
| After treatment  | 27.1± 3.51 | 94± 14.1    | 46.7± 5.25 | 35.8± 1.75 | -0.14± 1.09    |
| P-value          | 0.975      | 0.996       | 0.993      | 0.989      | 0.000          |

Table 2: mean BMI, weight, ALT, AST, fibrosis score of patients before and after treatment in Group B (Glycyrrhiza Glabra)

|                  | BMI        | Weight      | ALT         | AST        | Fibrosis Score |
|------------------|------------|-------------|-------------|------------|----------------|
| Before treatment | 26.9± 3.45 | 100.4± 14.2 | 62.3± 15.3  | 46.2± 8.35 | 0.299± 0.939   |
| After treatment  | 26.1± 3.43 | 98± 12.3    | 57.2± 14.58 | 35.9± 1.84 | -0.676± 0.97   |
| P-value          | 0.89       | 0.871       | 0.000       | 0.932      | 0.000          |

Table 3: Comparison of efficacy between both groups in terms of chi square test

| Groups             | Efficacy  |            | Total                             |
|--------------------|-----------|------------|-----------------------------------|
|                    | Yes       | No         |                                   |
| A                  | 24(11.3%) | 82(38.7%)  | 106(50%)                          |
| B                  | 72(34%)   | 34(16%)    | 106(50%)                          |
| TOTAL              | 96(45.3%) | 116(54.7%) | 212(100%)                         |
| Pearson Chi-Square | Value     | df         | Asymptotic Significance (2-sided) |
|                    | 43.862    | 1          | .000                              |

## DISCUSSION

This study compared the effect of *Glycyrrhiza glabra* and vitamin E in reducing fibrosis score in patients of NAFLD. The results showed that both drugs were effective in reducing the fibrosis score however, *Glycyrrhiza glabra* had superior efficacy as compared to Vitamin E (p value 0.000). This study also revealed that *Glycyrrhiza glabra* helped in reducing the mean values of ALT along with fibrosis score in patients with NAFLD, whereas, vitamin E only reduced the fibrosis score and did not have any effect on liver function tests. Isbrucker et al in his study revealed that in patients with NAFLD, giving *Glycyrrhiza glabra* extract in combination with lifestyle modification resulted in a notable reduction in the severity of steatosis, inflammation and NAFLD activity score<sup>18</sup>. Furthermore, another study by Li C showed that *Glycyrrhiza glabra* extract was able to achieve significant improvement biochemically by normalizing alanine transaminase in patients with NAFLD<sup>19</sup>. Similar results were shown by our study revealing the effectiveness of *Glycyrrhiza glabra* in not only reducing fibrosis score but significantly decreasing the levels of alanine transaminase as well. No side effects were seen with *Glycyrrhiza glabra* either clinically or on laboratory testing, which was also consistent with trials conducted previously.

Similarly, a study conducted by Ashraf MS, et al. in 2017, compared the effectiveness of Viucid (a nutritional supplement containing *Glycyrrhiza glabra*) with vitamin E in decreasing steatosis and liver fibrosis<sup>20</sup>. A total of 52 patients with fibrotic non-alcoholic steatohepatitis took part in the study and were randomly split into two groups. One group was given three sachets of Viucid daily and the other group was given 800 IU Vitamin E on daily basis. The results showed that after three months of treatment, the Viucid group showed significant decline in mean score of fibrosis in comparison to vitamin E group (reduction in fibrosis score from  $6.8 \pm 0.5$  to  $5.1 \pm 0.7$  kPa in Viucid group vs.  $6.9 \pm 0.5$  to  $6.5 \pm 0.4$  kPa in Vitamin E group; p-value <0.00001). Significant decline was also seen in steatosis and mean levels of alanine transaminase with Viucid when compared with vitamin E. The authors concluded that *Glycyrrhiza glabra* was superior in efficacy to vitamin E with regards to reduction in ALT, steatosis and fibrosis score. These findings concurred with those of our study.

In another study by Levine JE, et al., 66 patients with NAFLD who had raised levels of serum ALT and AST were randomized into two groups, one of which received licorice root extract (containing Glycyrrhizic acid) in aqueous form of about 2g and the other group received placebo i.e. 2g starch per day for two months<sup>21</sup>. The results showed that considerable reduction in serum ALT and AST was found only in the group receiving licorice root extract. Our study also showed that *Glycyrrhiza glabra* was effective in lowering down the levels of both transaminases i.e. ALT and AST. However, only the levels of ALT were statistically significant. Vitamin E also reduced the levels of ALT and AST, but this decrease was of no statistical significance.

Till now *Glycyrrhiza glabra* has shown promising results in improving fibrosis and transaminases in patients of NAFLD. However, further large multi-centered trials are required to validate this efficacy and to establish routine use of *Glycyrrhiza glabra* in treatment of NAFLD. Moreover, synergistic effect of *Glycyrrhiza*

*glabra* in combination with lifestyle modifications and pharmacological therapy needs to be explored further.

## CONCLUSION

This study concluded that both *Glycyrrhiza glabra* and vitamin E were effective in reducing the fibrosis score in patients with NAFLD however, *Glycyrrhiza glabra* had superior efficacy when compared to Vitamin E. This study also revealed that *Glycyrrhiza glabra* helped in reducing the mean values of ALT along with fibrosis score, whereas, vitamin E only reduced the fibrosis score and did not have any effect on liver function tests. The current study may provide useful information regarding a treatment strategy that is effective and has a better safety profile compared to conventional drugs used for NAFLD.

**Conflict of interest:** Nil

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