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Vitamin E Supplementation for Treatment of Statin Induced Hepatocellular Damage: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Statin treatment can cause elevation of the liver aminotransferase levels in 1-3% of the patients with hypercholesterolemia. Previous studies indicate that vitamin E plays a role in declining the increased levels of liver enzymes caused by fatty liver disease.
Objectives: We conducted this study to determine the effect of vitamin E on liver aminotransferase levels in patients with elevated aminotransferase levels due to statin consumption.
Materials and Methods: This study was a randomized, double-blind, placebo-controlled trials. Eligible patients were those who developed elevated aminotransferase levels after initiation of statin. They were randomized into the intervention group (vitamin E capsules, 400 units/day for one month) and placebo group. Randomization was done with permuted block sampling method with a 2:1 enrolment ratio. Study capsules were allocated in separate packs blinded and labeled using a four-digit code. Alanine aminotransferase (ALT) and asparate aminotransferase (AST) levels were checked in the beginning and one month after the intervention. Comparison of the levels before and after the intervention was done by paired sample T-test, and between group difference was checked by independent sample T-test.
Results: A final number of 23 patients enrolled in this study (15 in the intervention and 8 in the control parallel groups). Baseline ALT and AST levels in both groups showed no difference (74.3 ± 9.1 vs. 77.6 ± 17.5, P = 0.9; and 50 ± 8.2 vs. 43.3 ± 9.3, P = 0.34, respectively). With consumption of vitamin E, ALT level was decreased from 77.6 ± 17.5 to 40.9 ± 13.4, showing a significant difference with placebo (treatment difference = -25.7, P = 0.04). However, the reduction of asparate aminotransferase level from 43.3 ± 9.3 to 29.8 ± 5.9 was not significant compared to placebo (treatment difference = -1.5, P = 0.12).
Conclusions: Vitamin E therapy in patients with moderately elevated aminotransferase levels (1.5-3 times than basal levels) due to statin consumption may be beneficial and can reduce the asymptomatic hepatocellular damages.

1. Background

High cholesterol levels (also called hypercholesterolemia) have been associated with cardiovascular disease (CVD) (1-4). Statins (or HMG-CoA reductase inhibitors) are a group of medications that decrease the lipid level via inhibition of HMG-CoA reductase, an enzyme which plays a central role in the production of cholesterol. In addition to their lipid lowering effects, statins are suggested to have antithrombotic, anti-inflammatory and antioxidant properties that could stabilize the atherosclerosis plaques (5, 6). Although the benefits of statins in prevention of cardiovascular events are undeniable, it can increase the liver aminotransferase levels, generally less than 3 folds the upper limit of normal range (ULN) (7-9). The incidence

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of asymptomatic hepatocellular dysfunction (manifested by Asparate aminotransfersae [AST] and Alanine 2 aminotransfersae [ALT]) ranges from about 3% for any elevation to less than 1% for elevations greater than 3 times the ULN. If levels of aminotransferase increase three times higher than the normal range, continuing statin lead to problems (10, 11).

An exogenous vitamin E supplement can improve the liver function due to antioxidant properties in fatty liver disease and non-alcoholic steatohepatitis (NASH) (12-15). However, vitamin E has not been used for treatment of statin induced asymptomatic hepatocellular damaged revealed by abnormal liver enzymes.

2. Objectives

The aim of this study was to determine the effect of vitamin E in patients with elevated aminotransferase levels due to consumption of statin.

3. Materials and Methods

3.1. Trial Design

This study was a randomized, double-blind, single center, placebo-controlled trial conducted from February 2014 to December 2015. 802 patients were enrolled to see if they meet inclusion criteria; the data from twenty three participants were used in the final analysis. Figure 1 shows the CONSORT flow diagram of the study. The protocol of this study was approved by the Vice Chancellor for Research of Faculty of Medicine, Shiraz University of Medical Sciences and written informed consent was obtained from all patients. The trial was registered at Iranian registry of clinical trials (www.IRCT.IR) under the registration number of IRCT2014042817470N1.

3.2. Patients

Eligible patients referred to Imam Reza Clinic, affiliated to the Shiraz University of Medical Sciences in Shiraz, Southern Iran received atorvastatin based on the accepted guidelines. Patients were admitted to the study based on the following inclusion criteria: (i) consumption of atorvastatin, (ii) increased aminotransferase levels equal or more than 1.5 and less than 3 folds the upper limit of normal range. Exclusion criteria included any of the following: (i) consumption of any drug other than atorvastatin that could increase the liver aminotransferases, (ii) past medical history of liver disease or elevated aminotransferase before atorvastatin initiation, (iii) increased aminotransferase levels equal or more than 3 folds.

3.3. Interventions and Outcomes

The patients were randomized into two study groups. They received once daily vitamin E supplement (400 units, 30 capsules/person) manufactured by the 21st century, USA as the intervention group or indistinguishable placebo capsules containing starch as the control group. The eligible patients were asked to continue unchanged dose of atorvastatin during one month period of treatment. The primary outcomes were liver aminotransferase levels including alanine transaminase and asparate transaminase at baseline and one month after the intervention. Collection and analysis of all clinical and laboratory data were performed by the study team blinded to group assignment.

3.4. Randomization and Blinding

Patient were randomized in a permuted block scheme according to age, and sex and allocated into two groups in 2:1 manner, intervention group (n = 15) and controlled parallel group (n = 8). Study capsules were allocated in separate packs blinded and labeled using a four-digit code. The information regarding which codes correspond to what treatment was maintained by the project coordinator. Apart from the project coordinator, the patients, the staff involved

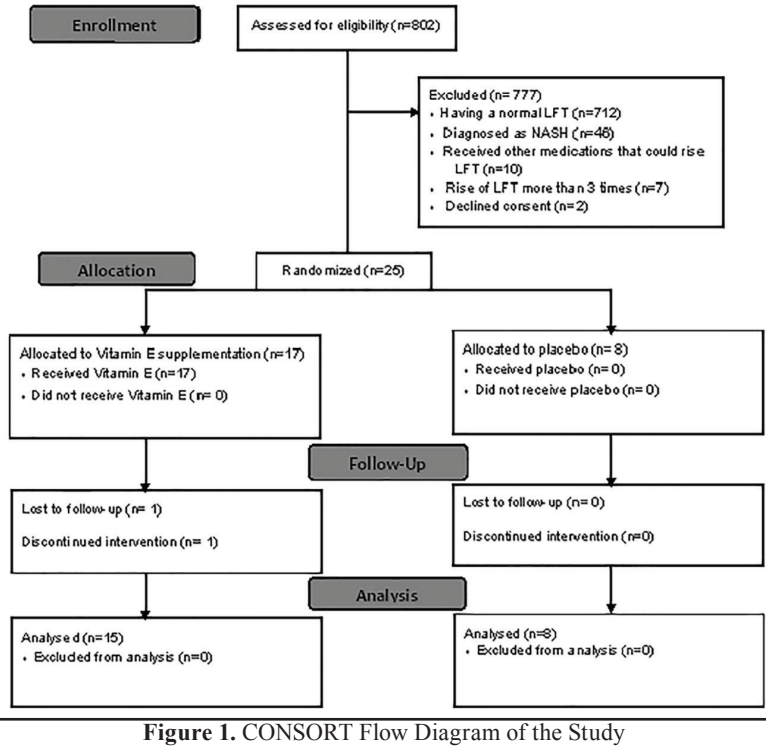

Figure 1. CONSORT Flow Diagram of the Study

in clinical center, and members collecting and analyzing data were blinded to the intervention allocation.

3.5. Statistical Analysis

Data were entered into Statistical Package for Social Sciences (SPSS), version 20. Descriptive data were presented as mean, standard deviation, frequency and percentage. Baseline categorical variables were analyzed by independent t-test or Chi-square tests. The significance of the differences between measurements before and after the intervention was assessed using paired t-tests and the between group difference by independent sample T-test. A two-sided P value < 0.05 was considered statistically significantly.

4. Results

A total of 23 patients were enrolled in the study; 15 patients in the intervention group and 8 in the control group. The mean ± SD age of the participants in both groups was 40 ± 11.8 years; the majority of them were men (61%). The characteristics of the participants are summarized in Table 1. There was no statistically significant difference between the two groups regarding baseline ALT and AST levels.

Consumption of vitamin E 400 units for one month in the intervention group decreased the ALT levels from 77.6 ± 17.5 to 40.9 ± 13.4 (P < 0.001) and AST level from 43.3 ± 9.3 to 29.8 ± 5.9 (P = 0.024), while consumption of placebo did not alter the level of these enzyme significantly (P = 0.39 and 0.072 for ALT and AST, respectively.) The comparison between vitamin E and placebo groups also showed statistically significant changes in the mean level of ALT and a trend toward reduction of AST after the intervention, as shown in Table 2.

5. Discussion

The results of our trial showed that daily supplementation with 400 unit vitamin E can reduce the statin-induced elevated liver transaminase levels. Statins are effective in reducing cardiovascular events and are safe for almost all patients, but elevation of hepatic aminotransferases occurs in approximately 3% of patients during statin therapy. The exact mechanism by which statins may induce hepatocellular injury is yet unclear.

An animal study by Kornbrust et al. suggested that the depletion of mevalonate or one of its sterol metabolites caused by the inhibition of 3-hydroxyl, 3-methyl-glutaryl-CoA reductase (HMG-CoA) enzyme might account for the elevated liver enzymes (16-18).

In addition to HMG-CoA reductase inhibitors, fatty liver disease and NASH are common causes of asymptomatic aminotransferase increase. It is currently believed that oxidative stress plays an important role in the hepatic damage in these patients (19-21). Effects of vitamin E alone or combined with other vitamins on elevated liver aminotransferase, especially in NASH, were reported recently. The use of exogenous antioxidants is thought to minimize the oxidative stress in NASH (22, 23). As a possible mechanism of action, antioxidant role of vitamin E

Table 1. Baseline Characteristics of Participants

Characteristics	Vitamin E Group	Control Group	P value
Age	40.5 ± 10.7	39.5 ± 11.7	0.45
Sex			
Male (%)	9 (60%)	5 (62.5%)	0.38
Female (%)	6 (40%)	3 (37.5%)	
Cause of statin therapy			
Primary prevention	8 (53.3%)	4 (50%)	0.78
Secondary Prevention	7 (46.6%)	4 (50%)	0.22
Asparate Aminotransferase (AST)	43.3 ± 9.3	50 ± 8.2	0.34
Alanine Aminotransferase (ALT)	77.6 ± 17.5	74.3 ± 9.1	0.90
Concomitant medications			
Asprin	8 (53.3%)	4 (50%)	0.76
Clopidogrel	5 (33.3%)	2 (25%)	0.12
ACE inhibitor	8 (53.3%)	5 (62.5%)	0.08
Ca channel blocker	3 (20%)	1 (12.5%)	0.07
B-Blocker	2 (13.3%)	2 (25%)	0.23
Angiotensin receptor blocker 1	(6.6%)	0 (0%)	0.09
Ejection Fraction (%)	58.6 ± 4.5	59.6 ± 6.5	0.67
Concomitant Hypertension	7 (46.6%)	3 (37.5%)	0.08
Concomitant Diabetes	2 (13.3%)	1 (12.5%)	0.23
Baseline Creatinine	0.8 5± 0.24	0.79 ± 0.32	0.12
Baseline GFR	89 ± 12	91 ± 15	0.11

Table 2. Liver Transaminase Levels before and after the Intervention

Characteristics	Placebo Group (n = 8)				Vitamin E Group (n = 15)				Difference of	P value
	Baseline	1 months	Difference	P value	Baseline	1 months	Difference	P value	difference	
AST	50 ± 8.2	38 ± 15.4	12	0.072	43.3 ± 9.3	29.8 ± 5.9	13.5	0.029	-1.5	0.12
ALT	74.3 ± 9.1	63.3 ± 34.3	11	0.39	77.6 ± 17.5	40.9 ± 13.4	36.7	< 0.001	-25.7	0.04

Abbreviations: ALT, Alanine Aminotransferase; AST, Asparate Aminotransferase

can improve the liver function (24). A trial by Yakaryilmaz et al. evaluated the effects of vitamin E therapy in a group of 9 patients with biopsy-proven NASH. They were given vitamin E 800 mg daily for 24 weeks. Histologically, necroin ammation and peroxisome proliferator-activated receptor-a (PPAR-a) staining index were improved in seven patients. These results were in favor of hepatocytes inflammation reduction (25). Another study in children with NASH revealed that daily oral vitamin E administration (400 - 1200 IU) normalized the serum aminotransferase and alkaline phosphatase levels (26). A meta-analysis of randomized controlled trials (RCTs) conducted on role of vitamin E in the treatment of NASH showed obvious reductions in aminotransferases, inflammation and liver fibrosis (27). However, in a study by Harrison and colleagues, treatment of forty five NASH patients with vitamins E and C (1000 IU and 1000 mg, respectively) daily for 6 months showed no change in the inflammation, but it resulted in a statistically significant improvement in the liver brosis score (28). In another randomized study, oral Vitamin E (600 IU/day) and vitamin C (500 mg/day) combination in patients with fatty liver disease was more efficacious on serum aminotransferase levels than ursodeoxycholic acid (10 mg/kg/day), but the difference was not significant (29).

To the best of our knowledge, this is the first study that has reported the beneficial effect of addition of vitamin E to statins in reduction of aminotransferase levels. However, the effects of this combination have been evaluated in some other studies. In a study by De Caterina et al., combining vitamin E with statins added nothing to statin anti-lipid effects (5) although we know that both statins and vitamin E may interfere with oxidative stress by reducing lipid peroxidation.

Leonardo et al. reached the same finding (30). Napoli and colleagues revealed that pravastatin reduced the activity of cholesteryl ester transfer protein (CETP), but not that of lecithin-cholesterol acyltransferase (LCAT). Addition of vitamin E prevented the decrease in CETP activity and had no effect on LCAT activity in the hypercholesterolemia patients (31).

One of the limitations of our study was that we could not show the direct evidence of changes in the hepatocyte and liver structure; instead, we used aminotransferase levels as an indirect evidence of hepatocellular damage and recovery. In fact, depiction of such changes has some ethical and technical issues, so using surrogate end point seems reasonable.

5.1. Conclusion

In conclusion, vitamin E therapy in patients with moderately elevated the aminotransferase levels (1.5 - 3 times than basal levels) since statin consumption is beneficial and can reduce the asymptomatic hepatocellular damages. This intervention may be suggested as a new approach for treatment of liver enzymes elevation due to statins. Future studies are required to see if this treatment can also be helpful in patients with statin induced severe elevations of aminotransferase levels (more than 3 times the basal levels). Furthermore, clinical trials with pre-specified clinical end points are needed to see whether this reduction in aminotransferase levels can result in clinical benefits or not.

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Authors' Contribution

Study concept and design: Aghasadeghi, Attar. Acquisition of data: Nabavi, Amirmoezi. Analysis and interpretation of data: Nabavi, Attar. Drafting of the manuscript: Amirmoezi. Critical revision of the manuscript for important intellectual content: Aghasadeghi, Attar, Amirmoezi. Statistical analysis: Aghasadeghi, Attar.

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The authors have no financial interests related to the material in this manuscript.

References

1. Attar A, Aghasadeghi K, Parsanezhad ME, Namavar Jahromi B, Habibagahi M. Absence of Correlation between Changes in the Number of Endothelial Progenitor Cell Subsets. *Korean Circ J*. 2015;**45**(4):325-32.
2. Attar A, Khosravi Maharlooi M, Khoshkhou S, Hosseini A, Jaberipour M, Dehghan A*, et al*. Colony forming unit endothelial cells do not exhibit telomerase alternative splicing variants and activity. *Iran Biomed J*. 2013;**17**(3):146-51.
3. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *The Lancet*. 2007;**370**(9602):1829-39.
4. Zibaeenezhad MJ, Farhadi P, Attar A, Mosleh A, Amirmoezi F, Azimi A. Effects of walnut oil on lipid profiles in hyperlipidemic type 2 diabetic patients: a randomized, double-blind, placebo-controlled trial. *Nutr Diabetes*. 2017;**7**(4):e259.
5. De Caterina R, Cipollone F, Filardo FP, Zimarino M, Bernini W, Lazzerini G*, et al*. Low-density lipoprotein level reduction by the 3-hydroxy-3-methylglutaryl coenzyme-A inhibitor simvastatin is accompanied by a related reduction of F2-isoprostane formation in hypercholesterolemic subjects: no further effect of vitamin E. *Circulation*. 2002;**106**(20):2543-9.
6. Hadaegh Y, Niknam M, Attar A, Maharlooei MK, Tavangar MS, Aarabi AM*, et al*. Characterization of stem cells from the pulp of unerupted third molar tooth. *Indian J Dent Res*. 2014;**25**(1):14-21.
7. Attar A, Eslaminejad MB, Tavangar MS, Karamzadeh R, Dehghani-Nazhvani A, Ghahramani Y*, et al*. Dental pulp polyps contain stem cells comparable to the normal dental pulps. *J Clin Exp Dent*. 2014;**6**(1):e53-9.
8. Iman A, Akbar MA, Mohsen KM, Ali F, Armin A, Sajjad A*, et al*. Comparison of intradermal injection of autologous epidermal cell suspension vs. spraying of these cells on dermabraded surface of skin of patients with post-burn hypopigmentation. *Indian J Dermatol*. 2013;**58**(3):240.
9. O'Sullivan S. Statins: A review of benefits and risks. *TSMJ*. 2007;**8**:52-6.
10. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ*, et al*. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med*. 2002;**137**(7):581-5.
11. Shafiei F, Tavangar MS, Razmkhah M, Attar A, Alavi AA. Cytotoxic effect of silorane and methacrylate based composites on the human

dental pulp stem cells and fibroblasts. *Med Oral Patol Oral Cir Bucal*. 2014;**19**(4):e350-8.
12. Akcam M, Boyaci A, Pirgon O, Kaya S, Uysal S, Dundar BN. Therapeutic effect of metformin and vitamin E versus prescriptive diet in obese adolescents with fatty liver. *Int J Vitam Nutr Res*. 2011;**81**(6):398-406.
13. Alborzi A, Pouladfar GR, Moghadam AG, Attar A, Drakhshan N, Maharlooei MK, *et al*. First molecular-based detection of mucocutaneous leishmaniasis caused by Leishmania major in Iran. *The Journal of Infection in Developing Countries*. 2013;**7**(05):413-6.
14. Venditti P, Napolitano G, Di Stefano L, Di Meo S. Effect of vitamin E on characteristics of liver mitochondrial fractions from cold-exposed rats. *J Bioenerg Biomembr*. 2011;**43**(4):387-97.
15. Zhang W, Shu X-O, Li H, Yang G, Cai H, Ji B-T, *et al*. Vitamin intake and liver cancer risk: a report from two cohort studies in China. *Journal of the National Cancer Institute*. 2012;**104**(15):1174-82.
16. Arca M, Pigna G. Treating statin-intolerant patients. *Diabetes Metab Syndr Obes*. 2011;**4**:155-66.
17. Kornbrust DJ, MacDonald JS, Peter CP, Duchai DM, Stubbs RJ, Germershausen JI, *et al*. Toxicity of the HMG-coenzyme A reductase inhibitor, lovastatin, to rabbits. *J Pharmacol Exp Ther*. 1989;**248**(2):498-505.
18. Parsanezhad ME, Attar A, Namavar-Jahromi B, Khoshkhou S, Khosravi-Maharlooei M, Monabati A, *et al*. Changes in endothelial progenitor cell subsets in normal pregnancy compared with preeclampsia. *J Chin Med Assoc*. 2015;**78**(6):345-52.
19. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;**114**(4):842-5.
20. Merat S, Malekzadeh R, Sohrabi MR, Hormazdi M, Naserimoghadam S, Mikaeli J, *et al*. Probucol in the treatment of nonalcoholic steatohepatitis: an open-labeled study. *J Clin Gastroenterol*. 2003;**36**(3):266-8.
21. Merat S, Malekzadeh R, Sohrabi MR, Sotoudeh M, Rakhshani N, Sohrabpour AA, *et al*. Probucol in the treatment of non-alcoholic steatohepatitis: a double-blind randomized controlled study. *J Hepatol*. 2003;**38**(4):414-8.
22. Mehta K, Van Thiel DH, Shah N, Mobarhan S. Nonalcoholic fatty liver disease: pathogenesis and the role of antioxidants. *Nutr Rev*. 2002;**60**(9):289-93.
23. Phung N, Farrell G, Robertson G, George J, editors. Vitamin E but not glutathione precursors inhibits hepatic fibrosis in experimental NASH exhibiting oxidative stress and mitochondrial abnormalities. Hepatology; 2001. WB SAUNDERS CO INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
24. Bjelakovic G, Gluud LL, Nikolova D, Bjelakovic M, Nagorni A, Gluud C. Antioxidant supplements for liver diseases. *Cochrane Database Syst Rev*. 2011(3):CD007749.
25. Yakaryilmaz F, Guliter S, Savas B, Erdem O, Ersoy R, Erden E, *et al*. Effects of vitamin E treatment on peroxisome proliferator-activated receptor-alpha expression and insulin resistance in patients with non-alcoholic steatohepatitis: results of a pilot study. *Intern Med J*. 2007;**37**(4):229-35.
26. Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. *J Pediatr*. 2000;**136**(6):734-8.
27. Sato K, Gosho M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, *et al*. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Nutrition*. 2015;**31**(7-8):923-30.
28. Harrison S, Torgerson S, Hayashi P. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Alternative Medicine Review*. 2004;**9**(1):100-1.
29. Ersoz G, Gunsar F, Karasu Z, Akay S, Batur Y, Akarca US. Management of fatty liver disease with vitamin E and C compared to ursodeoxycholic acid treatment. *Turk J Gastroenterol*. 2005;**16**(3):124-8.
30. Leonard SW, Joss JD, Mustacich DJ, Blatt DH, Lee YS, Traber MG. Effects of vitamin E on cholesterol levels of hypercholesterolemic patients receiving statins. *Am J Health Syst Pharm*. 2007;**64**(21):2257-66.
31. Napoli C, Leccese M, Palumbo G, de Nigris F, Chiariello P, Zuliani P, *et al*. Effects of vitamin E and HMG-CoA reductase inhibition on cholesteryl ester transfer protein and lecithin-cholesterol acyltransferase in hypercholesterolemia. *Coronary artery disease*. 1998;**9**(5):257-64.