REVIEW ARTICLE

Effects of Supplementation with Different Forms of Vitamin E on Liver Enzymes: A Systematic Review of Randomized Clinical Trials

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Abstract

Background: Obesity and non-alcoholic fatty liver disease (NAFLD) are considered as the main causes of liver-associated morbidity and mortality. Antioxidant administration was proposed as a remedy for liver problems such as steatohepatitis. This systematic review aimed to examine the effects of supplementation with various forms of Vitamin E on liver enzymes.

Methods: To find relevant articles, in our systematic review article, we searched PubMed, Scopus, Embase, Cochrane library, and Web of Science up to 20 MAY, 2021. Randomized controlled trials (RCTs) on the effects of vitamin E supplementation, in isolation or combined with other nutrients, on liver health were included. After excluding irrelevant records, 21 studies remained.

Results: According to the results of the included studies, vitamin E, especially α-Tocopherol or its co-supplementation with other antioxidants, at specific dosage could possibly have positive effects on improving liver functions and levels of Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes.

Conclusion: Vitamin E,could possibly have positive effects on improving the liver function and the levels of ALT and AST enzymes.

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Keywords: Vitamin E, Alanine transaminase, Aspartate aminotransferases, Non-alcoholic fatty liver disease, Liver enzymes

Introduction

Obesity and non-alcoholic fatty liver diseases (NAFLD) are the main causes of liver-associated morbidity and mortality up to 2030.[1] Regardless of diagnostic methods, 29.62% of the Asian population was reported to have NAFLD, which is increasing drastically, especially in the obese individuals.[2] Nonalcoholic fatty liver disease is defined as excessive fat accumulation in the liver cells. It is accompanied by obesity, increased blood pressure, and high cholesterol levels. The severity of symptoms varies in different people, ranging from mild to critical situations. The most important remedy for this illness is considered lifestyle change including weight loss and controlling the intake of simple carbohydrates and sweets. Another conspicuous remedy is considered antioxidant supplementation including vitamin E. It has been shown in various studies that vitamin E can reduce the complications associated with NAFLD.[3] However, the amount of vitamin E prescribed for each patient is ambiguous.[4]

Recent investigations have concluded that reactive oxygen species (ROS) plus reactive nitrogen species (RNS) could lead to the loss of liver function, reduction in bile synthesis, and production of harmful substances.[5] Inflammation is one of the mechanisms that could cause the generation of excessive free radicals which leads to cell damage. Peroxidation of DNA is another main

mechanism for the pathogenesis of liver damages.[6]

Vitamin E, a fat-soluble antioxidant, is critical in devastating free radicals in our body.[7] It represses the generation of isoprostanes (lipid peroxidation index). In humans and experimental animals,[8] it is used quickly for causing protection against peroxidation and meanwhile is reduced with other antioxidants like thiol (glutathione+lipoic acid) and vitamin C.[9] Vitamin E has also immense effects on gene expression as well as mediating cell signaling.[10] Some studies did not find any effect regarding vitamin E supplements and liver enzyme levels,[11-18] while some studies have shown positive effects.[19, 20] Meanwhile, different studies have indicated the negative effects of vitamin E supplementation on liver function.[21-29] Also, considering the fact that various forms of vitamin E have been used alone or in combination with other nutrients or supplements in different studies, it is recommended that the effectiveness of vitamin E supplementation should be compared in studies[13, 16-19, 21-23, 25-27, 30, 31] alone or in combination with other nutrients.[12, 15, 20] Therefore, the main purpose of this review was to investigate the role of different types of vitamin E in liver enzymes amelioration.

Methods

Search Strategy

Databases such as PubMed, Scopus, Embase, Cochrane library, and Web of Science were searched up to 20 MAY, 2021 to find relevant articles. Search strategy was prepared according to PRISMA guideline as follows: ("Vitamin E supplement*" OR Tocopherols OR "alpha-Tocopherol" OR "beta-Tocopherol" OR "gamma-Tocopherol" OR "tocotrienol" OR "Tocotrienols" OR "Vita E") AND ("liver enzyme" OR "SGPT" OR "SGOT" OR "AST" OR "ALT" OR "GGT" OR "gamma-Glutamyl transferase" OR "alanine aminotransferase" OR "Aspartate Aminotransferase" OR "Aspartate Apo aminotransferase" OR "Aspartate Transaminase" OR "Glutamic Oxaloacetic Transaminase" OR "L Aspartate 2 Oxoglutarate Aminotransferase" OR "Glutamate Aspartate Transaminase" OR "Serum Glutamic Oxaloacetic Transaminase" OR "Alanine Transaminase" OR "Glutamic Alanine Transaminase" OR "Alanine 2 Oxoglutarate Aminotransferase" OR "alanine aminotransferase" OR "Glutamic Pyruvic Transaminase") to retrieve randomized controlled trials (RCTs) assessing the effect of vitamin E supplementation on liver enzymes. Both vitamin E supplements in isolation or in combination with other supplements were included. Endnote X9 software was used for managing the references.

Screening, Inclusion, and Exclusion Criteria

Our inclusion criteria for the studies were treatment with vitamin E supplement in isolation or in combination with other nutrients, population of adults

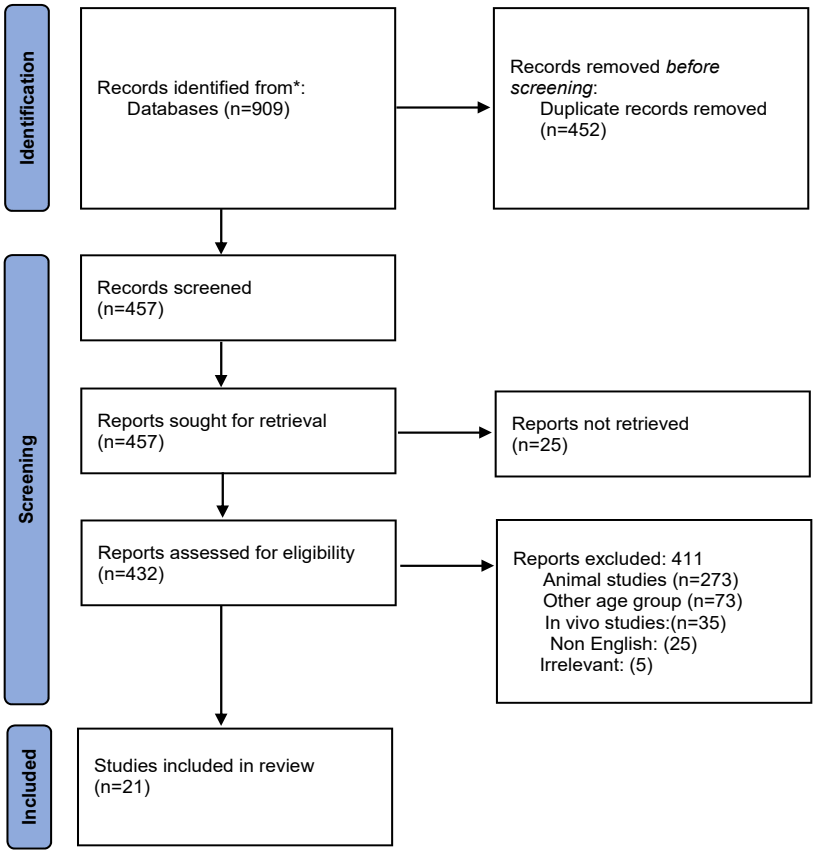

Figure 1: Flow chart of the study

over 18 years of age (healthy and unhealthy), measured outcome variables related to ALT and AST, and access to full-text articles in English. Non-RCTs composed of animal, observational studies with case-control, cross-sectional, or cohort design, also studies lacking adequate information on the baseline or follow-up of liver enzyme measurements were excluded.

The articles were screened by two individuals separately,TD and AHA. In the case of any disagreement, the opinion of the third person, Z.S, was applied. In the first step, 452 duplicate articles were removed; then, after screening based on the titles and abstracts, 381 records were excluded because of animal studies, in-vivo studies, and other age groups. After reading the full texts, 30 articles with irrelevant reports and non-English language ones were excluded; finally, 21 studies were included in the current systematic review (Figure 1).

Data Extraction

Data extraction was carried out by two independent researchers by including first author's name, publication year, study population, population age, study design, dosage of supplementations, and duration of the studies that are all reported in Table1.

Results

In this review, studies were categorized into three groups; 14 studies assessed the impact of tocopherol supplementation on laboratory parameters, 4 studies examined the effects of tocotrienol supplementation, and 8 studies evaluated adjuvant supplementation with a variety of dietary supplements.

Table 1: Characteristics of the included studies

Study	Country	Journal	Study population	Number	Age	Intervenition group	Control group	Duration	Result
France sco Marott a et al 2007	USA	Journal of Gastroent erology and Hepatology	50 patients with HCV-related cirrhosis	29 male, 21 female	Mean age 62 years (range 54-75 years)	a-tocopherol 900 IU/ day	Fermented papaya Preparation 9g/ day	6 months	Vitamin E supplementation almost normalized ALT only in the limited vitamin E-deficient subgroup
Simin Nikbin Meveda in et al 1998	USA.	American Society for Clinical Nutrition	88 healthy subjects		Aged>65y	Suplementation with 800 IU (60 IU,200IU, or 800 IU) all – rac – a – tocopherol/d	Placebo capsules contained soybean oil	4 mo	No significant adverse effects On liver enzyme function
Yasuko Ota, et al 2004	Japan	Elsevier Inc.,	(17member) Eight HCVINFECTED PATIENTS'a md9 control healthyadult	Seven female and one male	Average age, 57.3 8.9y	500mg/d of D-alphatocopherol – HCVINFECTED PATIENTS'and	500mg/d of D-alpha – tocopherol – healthy adult	12 wk	No significant difference between C,T In long term
Ying Han, et al 2013	China	Springer Intemational publishing switzerland	248 patients enrolled with NAFLD and IFG were equally randomized to two			Bicyclol 25 mg three times Daily Bicyclol: (4.40-dimethoxy – 5.6.50.60-dimethylene – dioxy – 2.20-dicarboxylate biphenyl)	(a-tocopherol) 100 mg three times daily	24-week	ALT levels showed greater improvement in the bicyclol group after 24 weeksbetween C;T
Jvotsna A. Patil, et al, 2012	India	Ind J Clin Biochem	Thirty subjects with occupational exposure to pesure ot pesticides i.e. sprayers of grape gardens	-	Between 20 to 45 years	Vitamin E supplementation (400 mg/ day) for	Before/ after	15 das.	ALT AST ↓
K. SAEIAN et al (2004)	USA	Alment Pharmacol Ther	Fifty - one naïve chronic hepatiitis C patients	9 females – 38 male	> 18 years	High – dose vitamin E supplementation – therapy plus vitamin E 800 IU b.d.	Interferon/ rib avirin therapy (control)	6 months	ALT AST ↓
Hashemian Z MDl, et al 2012	Iran.	Iranian Journal of Pediatric Hematology Oncology	45 beta – thalassemic patients	24 men – 21 females	3 to 45 years,	Vitamin E 400-600 unit/ day	Before supplementation	Three-months	ALT AST ↓
ALEXANDR A VON HERBAY et al (1997)	Germany	Amsterdam B.V. Published under license	23 patients suffering from chronic hepatitis C	12 male, 11 female		Vitamin E dose was 400 IU twice a day	Placebo	12 weeks	ALT AST ↓

Marcelo Kugelmas et al (2016)	Greece	Journal of Gastroenterology Hepatology	16 patients with biopsy – proven NASH	9 women and 7 men	54.8 2.3 – 41.5 2.6*	Effects of a step 1 American Heart Association diet plus aerobic exercise with 800 IU of vitamin E daily	Diet Alone	12 – week	No significant difference between C,T
Suzanne May Quinn Tan, et al , (2018)	Malaysia	Nutrients	45 patient with type 2 diabetes with stable glucose control	48 male 18 female	18 to 80 years old	Tocotrienol – rich vitamin E from palm oil (Tocovid) 200 mg twice a day	Received placebo twice a day	8 weeks	ALT AST ↑
Chwan – Li Shen et al (2018)	USA	Shen et al. BMC Complementary and Alternative Medicine	89 postmenopausal osteopenic women	89 female	Age 45 and older	-Low tocotrientol (430 mg) tocotrienol/ day - High tocotrienol (860 mg) tocotrienol/day	Placebo (430 mg olive oil/ day),	12 weeks	No significant difference between C;T
Muhammad Amjad Pervez1 et al (2018)	Pakistan	Turk J Gastroenterol	71 patients having ultrasound – proven fatty liver disease,	37 female – 34 male	> 20 years of age,	δ-tocotrienol 300 mg twice daily	Placebo.	12 weeks.	ALT AST ↓
GANYEE-LIN et al (2016)	Malaysia	Journal of oil palm research	31 subject with metabolic syndrome	16 female – 16 men	25-56 years	Tocotrienol – rich fraction (TRF) 200 mg twice daily	Placebo capsules	2 weeks	No significant difference between C;T
MAKOTO IKED et al (2004)	JAPAN	Tohoku J.Exp. Med	10 healthy male uniformed divers	10 MALE	Mean age: 32.8 years	Vit c (600mg), 150 mg a – tocoferol – Tea catechins (600mg)	Without supplimentation	40 ays	ALT AST ↑
CARLO CLERICI et al (2004)	Italy	ANTICANCER RESEARCH	Fifteen consecutive patients with advanced HCC	13 male, 2 females	Mean age: 71.1±5.7 years	All – trans retinoic acid 25 mg/ m2 per Os – tamoxifen 20 mg/ day per os – vitamin E (300) MG/ DAY PER OS.	No supplement therapy	20 months	ALT AST ↓
Chiara Cerletti et al (2020)	Italy	British Journal of Nutrition	113 adults with NAFLD	39 females – 74 male	18-80 years old	Mixture of different natural ingredients, namely, DHA, phosphatidylcholine silymarin. Choline, curcumin and D-α- tocopherol	Placebo	3 months	ALT: No significant difference between C;T AST ↓
Golnaz Ekhlasi 2016	Iran	Journal of research in medical sciences	Sixty NAFLD patients	48 men and 12 women	25 – 64 years,	(1) symbiotic twice daily + Vitamin E – 400 IU/d	Placebo capsule	-8 weeks	AST ALT ↓
Graham P. Butcher et al (1993)	Liverpool (UK)	Journal of Hepatology	28 alcoholic patients	17 male and 11 female	19-70 year	(Vitamin E 400 mg, beta carotene 40 mg, vitamin C 1000 mg and selenium 100 ~ g daily)	Take less than 40 mg alcohol perday	7 days	No significant difference between C;T
Sung – Hee Cho et al (2005)	Daegu	JOURNAL OF MEDICINAL FOOD	42 subjects were selected from type II diabetic patients	18 men and 24 women	Mean standard deviation age 56.6 2.7 ears	Cassia tora Fiber Supplementconsisting of 2 g of soluble fiber extracted from Cassia semen (C. tora L.), 200 mg of – tocopherol, 500 mg of ascorbic acid, and 300 mg of maltodextrin	Maltodextrin only with a little brown caramel color.	2 month	AST ALT ↓
Karin Groenbaeka et al (2006)	Denmark	European Journal of Gastroenterology & Hepatology	Patients with chronic HCV and elevated plasma ALT	12 men and 11 women	18 -75 years	Three daily tablets containing vitamin C and E and selenium	Placebo	6 month	No significant difference between C;T about ALT
Stephen A. Harrison et al (2003)	San Antonio, Texas	The American Journal of Gastroenter Ology	49 Patients with diagnosis of NASH	24 men and 25 women	18 yer of age or older	Combination of vitamin E 1000 IU and vitamin C 1000 mg per day	Before treatment	6 month	No significant difference between C;T

ALT: Alanine Transaminase; C: Control; T: Treatment; AST: Aspartate Aminotransferases; NFLD: Non-alcoholic Fatty Liver Disease; HCC: Hepatocellular Carcinoma; NASH: Nonalcoholic steatohepatitis; HCV: Hepatitis C virus

Most of the studies in the first group which assessed the effects of tocopherol illustrated that the levels of both ALT and AST enzymes were reduced after supplementation. Although in some studies such as that carried out by Giada Sebastiani, tocopherol supplementation only reduced the ALT level,[32] or Raul Bernal-Reyes could not find any significant changes in the liver enzymes after tocopherol supplementation.[33]

Nevertheless, in studies on the effects of tocotrienol, no significant change was observed in liver enzymes during the study phase. However, two studies had completely different results. Pervez et al. (2018) observed that both ALT and AST parameters reduced after supplementation with tocotrienol.[34] Further, Tan et al. (2018) reported increased levels of liver enzymes after supplementation with tocotrienol.[35]

Moreover, interventions which examined the effects of combined supplements containing vitamin E on liver enzymes found that sometimes, according to different interventions, it could possibly have significant effects on decreasing ALT and AST. However, Cerletti et al. (2020) found that supplementation with the mixture of different natural ingredients such as Silymarin, DHA, Curcumin, Phosphatidylcholine, choline, and D-α-Tocopherol had lowering effects only on AST.[36]

Discussion

In this systematic review, the effects of vitamin E supplementation in various forms or co-supplementations on liver enzymes were assessed. It was found that alpha-tocopherol supplementation had positive effects on liver enzymes, while tocotrienol supplementation did not have consistent positive effects. Also, co-supplementation of vitamin E and other compounds had positive effects on improving the liver function; however, it is difficult to justify the final effects due to the various supplements used in the combination form.

The current study showed that supplementation with tocopherol could have positive effects on the levels of liver enzymes, while tocotrienol supplementation did not have consistent positive effects.

The main reasons for high serum aminotransferase levels are alcohol-related liver damage, hepatitis B, C, autoimmune hepatitis, steatosis (NAFLD), non-alcoholic steatohepatitis, hemochromatosis, recent alpha1-antitrypsin deficiency known as sprue celiac. Elevated g-glutamyltransferase levels have been investigated in numerous clinical conditions, such as pancreatic disease, myocardial infarction, renal failure, COPD, diabetes, and alcoholism.[37]

Vitamin E is considered as the most effective antioxidant in human. It has intrinsic antioxidant activity because it can give hydrogen ions from its cromanol to scavenge peroxyl lipid radicals.[38] Moreover, vitamin E works with cellular components; meanwhile, it helps to increase the antioxidative environment Superoxide dismutase (SOD), a vital antioxidant enzyme, which can break down superoxide radicals into oxygen or hydrogen peroxide. Vitamin E also increases the activity of other antioxidant enzymes such as catalase and glutathione peroxidase.[39] This essential vitamin could also suppress the peroxidation process and prevent the expression of beta-converting growth factor, related to hepatic fibrosis and hepatic apoptosis through activating hepatocytes.[40] All the aforementioned mechanisms could possibly justify the hepato-protective effects of vitamin E.

Animal investigations have shown that α-tocopherol could scavenge ROSs.[41] Vitamin E meaningfully improved the levels of ALT, AST, inflammation, hepatocellular ballooning, and histological changes.[42] Overall, vitamin E could decrease blood cholesterol levels and may protect the body from inflammation; meanwhile, it has an important function in the negation of oxidant substances. All the beneficial effects of vitamin E could help improve the lipid profile and liver injuries.[43] In one study conducted in Canada in 2019, patients with AIDS and non-alcoholic steatohepatitis (NASH) consumed 800 IU of oral vitamin E (alpha-tocopherol) daily; as a result, it was suggested as a beneficial treatment for AIDS patients with fatty liver.[42] In the next study conducted in Germany in 1997 on patients with hepatitis C, they used high-dose vitamin E supplements (800 IU RRR-a-tocopherol); the results showed that in the intervention group who received short-term supplementation, reduction in the liver enzymes was observable, but, in long term, ALT levels returned to the initial level.[43] Therefore, for more reliable results, longer durations are essential to assess the real effects of vitamin E supplements on liver enzymes

Also, it was observed that vitamin E in the form of Tocotrienol did not affect the liver enzymes. However, in previous investigations, it was reported that Tocotrienol had more hypo-cholesterolemic and anti-sclerotic impacts on humans.[41] In patients with non-familial hypercholesterolemia, supplementation with palm oil which is rich in tocotrienol could reduce LDL-cholesterol, total serum cholesterol, apolipoprotein B, and triglyceride levels.[42] Also, consumption of appropriate dose of tocotrienol could decrease LDL-C and total cholesterol more significantly. The mechanism for cholesterol reduction is through down-regulation of peroxisome proliferator-activated. Meanwhile, the anti-inflammatory effect of vitamin E through decreasing pro-inflammatory and increasing anti-inflammatory effects could also mediate these effects.[43]

In other studies using combination therapy, it was demonstrated that the results were controversial; which seems to depend on the type of co-nutrient and its antioxidant properties and possibly their interactions with vitamin E. The first study in 1992 on alcoholics

applied a combined form of vitamin E, vitamin C, beta carotene, and selenium in the intervention group, and it did not have any desirable effect on the liver function.[23] However, another study that used vitamin E and silymarin showed significant improvements in ALT and AST, which may be related to rehabilitation of the hepatocytes membrane and decrease of enzyme scattering in extracellular medium.[44] Combination therapy of vitamin E, docosahexaenoic acid, and choline has been reported to improve ALT among pediatric patients with NASH.[45] Another study conducted in Texas on NASH patients compared the efficacy of a combination of vitamin E (1000 IU/day) plus vitamin C (1000 mg/day) supplements on the liver function. In addition, similar dietary recommendations were applied for all patients, including weight loss and reduction in fat consumption (less than 30g per day). Finally, ALT level did not change during the study period , but liver fibrosis in the intervention group and BMI in both groups decreased.[16]

The strong point in this study is investigation of different types of vitamin E supplements (tocopherol and tocotrienol) as well as co-supplementation, which was not performed in previous studies. Also, accurate and extensive search and screening were done; meanwhile, we considered the results of all relevant papers. However, one of our limitations was lack of access to the full text of some papers as well as non-English articles. Since different factors such as diet status, level of physical activity, supplement dose, and the duration of the intervention are important factors that can affect the function of the liver and its enzyme levels, it is necessary to conduct more extensive studies with longer durations for more reliable and accurate results. Moreover, due to the variations in the supplement dose, type, and study durations and co-supplementations, we could not conduct the meta-analysis and the data are presented only as a systematic review.

Conclusion

Vitamin E, especially α-Tocopherol, alone or in co-supplemention with other antioxidants, could possibly have positive effects on improving the liver function and the levels of ALT and AST enzymes. However, further studies are needed to find a definitive conclusion. It is recommended that further investigations should be conducted to better elucidate the exact mechanisms of actions regarding the effects of vitamin E supplement on liver enzymes to better define the specific dose or duration of supplementation.

Authors' Contributions

The authors' responsibilities were as follows: A.ASADI conceived the study. A. ASADI and T.DEHGHANcarried out the literature search. A.ASADI and T.DEHGHAN carried out data extraction and independent reviewing. M.AKBARZADEH and Z.SOHRABI conducted the quality of included studies. Z.SOHBABI and M.AKBARZADEH conducted data analysis and interpretation. A.ASADI and T.DEHGHAN wrote the manuscript. K.LEILAMI conducted critical revision. All authors approved the final manuscript.

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