

Vitamin E Therapy in Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is closely related to oxidative stress. Vitamin E (VE) is an effective antioxidant, which could relieve NAFLD symptoms by improving the balance of oxidation and anti-oxidation. However, recent researches indicate that the functional mechanisms of VE are not only limited to anti-oxidation, but also include adjusting the metabolism disorders of glucose and lipid. Furthermore, the efficacy of VE remains controversial in the treatment of NAFLD by far, and the suitable condition of patient, drug dosage, drug safety and course of treatment during clinical application still need to be discussed. Therefore, this paper reviewed the recent study progresses of clinical application of VE alone and VE and other drugs.

KEYWORDS

Vitamin E; Nonalcoholic Fatty Liver; Therapy

1. Introduction

NAFLD is a clinic oopathological diagnosis in which more than 5% of hepatocytes demonstrate macrovesicular steatosis in an individual without the history of alcohol intake. NASH is characterized by steatosis with hepatocellular ballooning and lobular inflammation, accompanied by perisinusoidal fibrosis [1,2]. With the global epidemic tendency of obesity and Type 2 diabetes, NAFLD has become the most common chronic liver disease. The incidence rate of NAFLD is 17% - 33%, and NASH is 5.7% - 17% in the United States [3]. Therefore, a lot of researches focus on the problem of the treatment of NASH. Insulin resistance and oxidative stress are considered the main pathogenesis of NAFLD [4], and then reducing the level of oxidative stress is an effective strategy. VE is recommended to treat NASH patients without Type 2 diabetes.

VE is a powerful antioxidant, which can improve the impact of free radicals on the body in the normal process of metabolism and oxidative stress [5]. Studies have shown that VE can interrupt the radical chain reaction,

prevent free radicals into the cell membrane, and maintain the stability of cell membranes [6]. VE inhibits the generation of mitochondrial ROS, through increasing the mitochondrial membrane potential and improving mitochondrial function [7]. Meanwhile, it can protect polyunsaturated fatty acids in the cell membrane, and inhibit lipid peroxidation [8]. Clinical trials also showed that VE (300 mg daily) can improve the extent of oxidative stress in patients with NASH [9]. In addition, VE also has non-antioxidant function including regulating cell signaling and gene expression, improving liver inflammation and fibrosis through the regulation of inflammatory signaling by reducing the expression of TNF- α , TGF- β 1, IL-6 and other inflammatory cytokines [10]. VE seems to become a promising treatment of NASH, so we tried to perform a systematic review of VE in clinical trials of the treatment of NASH.

2. Therapeutic Effect of VE Alone

Although a series of experiments present the potential role of VE in the treatment of NAFLD, early clinical results of VE present conflicting results. Lavine investigated 11 pediatric patients with ultrasound diagnosed

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NAFLD, and they found that VE significantly decreases ALT levels, but not liver histology (steatosis, inflammation, fibrosis) after 4 - 10 months of treatment with VE (400 - 1000 IU per day) under the condition of the constant BMI [11].

Kawanaka *et al.* [9] found VE (300 mg daily) improved the clinical symptoms and the histopathological parameters on patients with NASH. Bugianesi *et al.* [12] has randomized 110 NASH cases (liver biopsy proven) into VE (400 IU twice daily) VS metformin (2 g/d) VS life intervention for one year, they also found that VE can not improve steatosis, inflammation and fibrosis level except ALT levels. They did not show the effect of VE.

However Hasegawa *et al.* [13] has treated 12 NASH patients and 10 NAFLD patients respectively with VE (300 mg/day) for one year, which showed significantly ALT reduction, improved steatosis, inflammation and fibrosis levels, as well as decreased TGF- β 1 levels. Yakaryilmaz gave VE (800 mg daily) on 9 patients with biopsy-proven NASH for 24 weeks, both the ALT levels and fatty degeneration were significantly improved [14]. The above studies show that VE treatment for NAFLD is beneficial, but for the reasons of small sample size, single-center and different endpoints, they are not able to provide enough evidence to assess the effectiveness of VE.

Recently two large clinical trials PIVENS and TONIC have encouraging results. Sanyal *et al.* [15] investigated 247 non-diabetic biopsy-proven NASH patients. Patients were randomized to receive VE (800 IU daily, 84), pioglitazone (30 mg/d, 80) or placebo (83) for 96 weeks. Compared with placebo, VE significantly improved the primary endpoint (at least two points reduction on NAS score and a grading reduction on ballooning degeneration) (43% vs. 19%; $P = 0.001$), but pioglitazone was not significantly improved (34% vs. 19%; $P = 0.04$) ($P \leq 0.025$ was considered statistically significant). Meanwhile drugs could improve ALT levels, steatosis, lobular inflammation in patients with NASH, but could not improve fibrosis level and the portal area inflammation. Subsequently Lavine [1] investigated 173 pediatric patients with biopsy-proven NAFLD. Patients were randomized into VE (400 IU twice daily, 58), metformin (500 mg twice daily, 57), or placebo (58) for 96 weeks. Although VE can significantly improve ALT levels at 24 weeks, at 72 and 96 weeks, metformin and VE are not able to significantly improve the primary endpoint compared with placebo (at 48 and 96 weeks, ALT levels continued to decline to half baseline or below 40 U/L). However VE can inhibit the development of NASH through improving the hyaline degeneration (58% VS 28%, $P = 0.006$), and significantly improve NAS score. Compared with PIVENS experiments, VE did not signif-

icantly reduce hepatic steatosis and lobular inflammation [10]. But these two experiments presented VE are not able to improve the further development of NASH including the level of fibrosis and portal area inflammation, which seems to be the insufficiency of VE on treatment of NASH. Meanwhile, although a series of experimental and clinical studies confirmed VE could improve insulin sensitivity [16-19], these two experiments did not find. These results showed that in the early stages of NAFLD, VE monotherapy can improve liver function and certain pathological changes of liver tissue at least. Interestingly, Sanyal *et al.* [20] found that VE (400 IU/day) and pioglitazone (30 mg/day) combination therapy for six months in patients with NASH, ALT levels, ballooning degeneration, hyaline degeneration and fibrosis level were significantly improved compared to VE, as well as the fasting glucose and FFA. But unfortunately there is no any large controlled studies on treating NASH combined VE with insulin-sensitive drugs to assess its efficacy so far.

3. Combination with VE and Other Drugs

3.1. Combination with VE and Lifestyle Intervention

Unreasonable lifestyle plays a very important role in the pathogenesis of NAFLD, studies have shown that lifestyle interventions (including diet, exercise and low-calorie diet) can significantly improve ALT levels and insulin resistance in NAFLD patients [21,22]. Kugelmas [23] performed a clinical study on 16 biopsy-proven NASH patients, and found that VE (800 IU daily) and lifestyle intervention (diet and exercise) for 12 weeks improved ALT, cholesterol and hyaluronic acid, however, short-term VE complement showed no significant increase in efficacy. Subsequently Vajro *et al.* [24] studied 28 pediatric NAFLD patients diagnosed by ultrasound, with VE (400 mg/dx 2 months and then 100 mg/dx 3 months) and a low calorie diet VS a low calorie diet therapy for five months. VE can improve ALT and steatosis level, subgroup analysis also shows that VE can improve ALT levels on those who do not follow the diet guide. Meanwhile Hoofnagle [25] also shows VE can improve ALT levels and NAS score of weight gain patients based on PIVENS experimental analysis, indicating that VE can be used for those obese children with NAFLD who can not adhere to a low-calorie diet. D'Adamo [26] studied 24 obese prepubertal children which followed a 6-month lifestyle intervention combined with Vitamin E supplementation (600 mg/day) and they were compared with 21 age and sex-matched obese peers who underwent lifestyle intervention only. After 6-month treatment, levels of PGF2- α , ALT, lipid profile and HOMA-IR significantly decreased and esRAGE significantly increased in children treated with Vitamin E. In

contrast, no significant change in any of these markers was detected in the lifestyle only group. Vitamin E supplementation was associated with a significant reduction in oxidative stress and improved cardio-metabolic alterations.

3.2. Combination VE with VC

VC is a powerful antioxidant, which can not only clear the ROS in order to inhibit lipid peroxidation, but also enhance the regeneration of VE [5]. 49 patients with NASH were randomized to receive high-dose (VE 1000 IU and VC 1000 mg/day) for 6 months, Harrison [27] found that the level of fibrosis was significantly improved compared with placebo, but the level of ALT and inflammation did not. Different from Harrison, Nobili [28] detected that VE and VC complement did not significantly enhance the efficacy. They randomized 90 pediatric NAFLD patients into VE (600 IU/day) and VC (500 mg/Day) plus (diet and exercise) group, and living intervention group. The two groups did not improve the level of fibrosis, although the NAS score, transaminase levels, triglycerides, cholesterol, fasting glucose, insulin sensitivity index and lipid metabolism were improved. 57 NAFLD patients were randomized to receive vitamin E (600 IU/day) and vitamin C (500 mg/day) or ursodeoxycholic acid (10 mg/kg/day) after 6 months, VE plus VC group can improve the ALT and AST levels more effectively, although the difference is not obvious [29]. Foster [30] evaluated the effective of simvastatin (20 mg/day) plus antioxidants VE (1000 IU daily) VC (1 g daily) for four years on 80 NAFLD patients diagnosed by CT, and found it significantly improved steatosis compared with placebo, but ALT, inflammation and liver fibrosis levels were not evaluated.

3.3. Combination with VE and UDCA

UDCA prevent the further development of NAFLD through its anti-apoptotic and immune function [31]. However, it is still controversial of UDCA on steatosis and inflammation and improving ALT levels [32,33]. But it can be used as a targeted adjuvant drug. Madan *et al.* [13] found that VE (400 mg daily) combined ursodeoxycholic acid (300 mg twice daily) and life interventions can significantly reduce the ALT levels on NAFLD patients. Dufour *et al.* [34] also found that vitamin E (400 IU twice a day) and UDCA (12 - 15 mg/kg/day) combination therapy for 2 years significantly improved ALT levels and hepatic steatosis in patients with NASH, in the case that BMI did not improve. However, Taeshik *et al.* [35] have found VE (800 IU/day) and UDCA (5 - 10 mg/day) combination therapy can significantly improve ALT, AST, total bilirubin, alkaline phosphatase, γ -glutamyl GGT, and clinical symptoms of pediatric NAFLD

patients with decreased BMI. But it showed no significant effect on those patients without decreased BMI, indicating that the decrease of BMI was the basis of the treatment of pediatric NAFLD patients with BIM pediatric patients. Balmer *et al.* [36] found that the combination of VE and UDCA increased adiponectin levels and decreased hepatocyte apoptosis, suggesting that the joint VE and UDCA can improve body metabolism. Recently Pietu [37] found four years' VE (500 IU/day) and UDCA treatment significantly improved ALT levels on 110 NASH patients, meanwhile about 33% patients have been improved on steatosis, inflammation, ballooning degeneration and fibrosis levels. Among 10 patients with liver biopsy during follow-up period, seven patients has improved NAS score, one patient deteriorated and no significant side effects were found.

3.4. VE Application and Drug Safety

The US guidelines about Non-alcoholic fatty liver disease treatment, show that VE (800 IU/d) can improve the histological damage on liver biopsy proven NASH and suspicious NASH children. VE (800 IU/d) can reduce liver histological damage of non-diabetes adult NASH patients, therefore VE can be used as a prefer choice on adult NASH patients without diabetes. It is not recommended for the treatment of NASH with diabetes, NAFLD without liver biopsy data, NASH cirrhosis or cryptogenic cirrhosis. Because its efficacy remains to identity, they will not be recommended for routine treatment of pediatric NASH patients [38].

Two clinical studies including PIVENS and TONIC, presented VE did not produce serious side effects, but these studies did not have enough evidence to assess the possible side effects of VE treatment. While series of meta-analysis also shows that the VE (400 or 800 IU) is not able to produce serious side effects [39-41], Bjelakovic *et al.* [42] performed systematic review and found that single VE application or combination with other antioxidant drugs can increase the risk of death. Miller's meta-analysis [43] also shows that the VE (≥ 400 IU daily) may increase all-cause mortality, another large randomized controlled trial showed total mortality is not significantly affected VE (400 IU, every other day), but it increased the risk of hemorrhagic stroke [44]. In addition, a recent randomized controlled trial showed that healthy men supplemented VE (400 IU/d) over seven years will increase the risk of prostate cancer [45]. Given that most NASH patients have the risk of metabolic factors, the VE drug safety still need to pay more attention.

4. Summary

Lifestyle interventions are currently the basis in the treatment of NAFLD. Simple life intervention is not

enough because of its limited efficacy and few patients can adhere to exercise and weight loss and other life intervention. Due to the multifactor pathogenesis of NAFLD, combinations with lifestyle change and drug may be a more appropriate treatment strategy.

Although the long-term efficacy of VE is not very clear, VE still need be paid more attention by many researchers as the most promising treatment of NASH drug. Considering our daily intake of VE is less than the recommended dose, and VE is cheaper than any other medication, it is necessary of proper VE supplement and the related risk factors treatment in addition to lifestyle changes. However, due to the potential safety of VE, treatment benefits and potential side effects of VE need assessment before treatment.

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