Vitamin E Treatment for Patients with Nonalcoholic Steatohepatitis

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Received: 12-02-14
Accepted: 05-11-14

Abstract

Nonalcoholic Steatohepatitis (NASH) is characterized histologically by the ballooning of hepatocytes, lobular inflammation and steatosis. If this diagnosis is suspected, it is important to exclude other causes of liver damage, especially excessive consumption of alcohol. Nevertheless, to date, a biopsy is the only method available to confirm the diagnosis. Vitamin E should be considered a first-line therapy for treatment of this disease because several clinical studies have shown that a dose of 800 UI/day improves the histology of non-diabetic adults suffering from NASH even when there is no significant impact on fibrosis. These results were confirmed by biopsies. Despite the proven benefits of the use of this drug, it is important to be aware that its use cannot replace changes in diet and exercise but rather should be seen as a complement to these measures.

Keywords

Nonalcoholic steatohepatitis, vitamin E, oxidative stress.

INTRODUCTION

NASH is characterized histologically by the ballooning of hepatocytes, lobular inflammation and steatosis (1, 2). Currently, NASH can only be diagnosed through a liver biopsy which is the diagnostic gold standard. It also provides information concerning the presence and degree of inflammation, necrosis and fibrosis which are all important for establishing the patient's prognosis (2-5). The differences between NASH and alcoholic steatohepatitis are microscopically small which make it difficult to histologically differentiate between them. For this reason, it is important to obtain information from the patient about his or her drinking habits (4).

NASH is part of a much broader entity called NAFLD (nonalcoholic fatty liver disease) which includes the early stages of hepatic steatosis: steatosis without inflammation, and steatosis with mild inflammation. Ultimately, NAFLD develops into the characteristic inflammatory condition of NASH that progress to fibrosis and finally cirrhosis (1, 2, 5). It is not yet completely clear that individuals progress from simple steatosis to the inflammatory state. Interactions between genetic susceptibility, metabolic disorders and oxidative stress are the most important factors (6, 7).

NAFLD is the most prevalent liver disease worldwide (2, 4, 6). The prevalence of NAFLD is estimated to be from 20% to 30%, and the prevalence of NASH is thought to be from 2% to 3% in the general population of the western world (8).

Because of its antioxidant qualities, vitamin E has been recommended in current American guidelines for treating NASH. "Vitamin E (α -tocopherol) administered at daily dose of 800 IU / day improves liver histology in non-diabetic adults with biopsy-proven NASH…" This does not obviate the importance of intervention in patient lifestyle and diet as part basic treatment for patients with NASH (9, 10). In this article we review the pathophysiology of NASH with emphasis on the role of vitamin E in the treatment of patients with this disease.

PATHOPHYSIOLOGY

While the pathogenesis of NASH is not yet completely clear, the best accepted hypothesis proposed to date to explain the events leading up to steatosis and subsequently to steatohepatitis is the "two-hit" theory. The first hit in the onset of this disease is fat overload (11, 12). A sedentary lifestyle, genetic factors and increased calorie intake makes individuals more susceptible to the development of insulin resistance and hyperinsulinemia which leads to an increase in hepatic lipid synthesis and release of free fatty acids from adipose tissue. If the liver is maintained in this state, it becomes incapable of metabolizing all of the fatty acids it produces and that are removed from circulation. This condition eventually leads to the second hit which is hepatic steatosis and oxidative stress (4, 5, 13).

Oxidative stress is an imbalance favoring pro-oxidants over antioxidants (3). During hepatic steatosis, hepatocytes enter a hypermetabolic state that leads to increased production of free radicals in cell organelles (13). Increasing amounts of reactive oxygen species (ROS) in hepatocytes lead to lipid peroxidation which is a reaction which provides a continuous supply of additional free radicals with potentially devastating effects (14, 15).

One antioxidant is vitamin E (tocopherol) which reacts with lipid peroxides to reduce them towards fatty acids. They form the relatively stable radical tocopheroxyl that persists long enough to pass back to tocopherol by way of a reaction with vitamin C on the cell surface (12). Because of this feature, vitamin E has been considered for use as a treatment for patients with NASH (13, 16).

MANIFESTATIONS AND DIAGNOSIS

NAFLD is a common syndrome that ranges from simple steatosis to steatohepatitis (NASH) with subsequent fibrosis and cirrhosis (5). Although at diagnosis most patients are asymptomatic, some patients, especially children, may complain of fatigue and discomfort. Discomfort in the right upper quadrant of the abdomen, suspicion due to increased levels of aminotransferases, and an abdominal ultrasound with a bright liver disease are all signs of this disease. Obesity, diabetes and dyslipidemia should also be taken into account during the evaluation of conditions that might be associated with NAFLD and NASH (5, 17).

During the diagnostic evaluation other common causes of liver disease should be excluded, but ultimately a liver biopsy is the only method available to confirm the diagnosis. It is also important for defining the patient's prognosis (Table 1) (3, 4). Despite its great clinical value, a biopsy is expensive and leads to a slight increase in morbidity and, on rare occasions, results in mortality. This tool should only be considered for patients for whom the presence of non-alcoholic hepatic steatosis is suspected who are at high risk of steatohepatitis and advanced fibrosis (obesity, type II diabetes mellitus, dyslipidemia and metabolic syndrome) and in cases of uncertain diagnosis (3, 9).

Table 1. Brunt System of Classification of NASH

Degrees of NASH
Grade 1 Mild
Steatosis: Macrovesicular, 33% up to 66% Ballooning: Minimum Inflammation: L: diffuse chronic mild acute (PMN) and (Mn) Q: none or mild
Grade 2. Moderate
Steatosis: Any degree from 33% to over 66%, mixed * Ballooning: In zone 3 Inflammation: L: mild chronic, PMN, ballooning, pericellular fibrosis Q: mild to moderate
Grade 3. Severe
Steatosis: typically> 66% (panacinar); mixed Inflammation L: Acute and chronic diffuse PMN, perisinusitis, ballooning and fibrosis.may appear concentrated in Zone 3 areas Q: mild to moderate.
Staging (fibrosis) Step 1: In area 3 perivenular, perisinusitis, focal or extensive fibrosis Step 2: As above plus focal or extensive periportal fibrosis Stage 3: Bridging fibrosis, focal or extensive Step 4: Cirrhosis

PMN: polymorphonuclear, Mn: mononuclear cells L: lobular, P: portal * macrovesicular and microvesicular steatosis. Adapted from reference (2).

ROLE OF VITAMIN E IN THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS

At present there is no effective treatment for NASH. Nevertheless, considering the important role of vitamin E as an antioxidant factor there have been several clinical trials in order to demonstrate its benefits in the clinical and histopathological evolution of this disease (Table 2).

Among these is the PIVENS trial (Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis). This was a multicenter, double-blind, placebo-controlled study in which histological improvement was evaluated in 247 non-diabetic and non-cirrhotic patients who had NASH. Patients were randomly assigned to receive a daily dose of pioglitazone (80 patients), vitamin E (84 patients) or a

Table 2. Published Studies on Vitamin E Therapy in Patients with NASH

Author	Patients	Dosage	Duration	Results
Sanyalet, et al (2010) (16, 17)	247 adults with NASH who were not diabetic or cirrhotic	800UI/d	96 Weeks	↓ Steatosis ↓ Ballooning ↓ Inflammation ↓ ALT Fibrosis (no improvement)
Lavine, et al (2011) (19, 20)	173 patients between 8 and 17 years with biopsy-proven NAFLD	800UI/d	96 Weeks	↓ ALT (not higher than with placebo) ↓ Ballooning
Yakaryilmaz, et al (2007) (21)	9 patients with biopsy-confirmed NASH	800mg/d	24 Weeks	↓ ALT ↓ AST ↓ Steatosis Inflammation (no improvement) Fibrosis (no improvement)
Vajro, et al (2004) (22)	28 children diagnosed with NAFLD by ultrasound who had elevated transaminases	400 mg/d	5 M	↓ ALT ↓ Steatosis (diagnosed with ultrasound)

NAFLD: Nonalcoholic fatty liver disease, IU: international units, mg: milligrams, M: months, ALT: alanine aminotransferase, AST: aspartate aminotransferase

placebo (83 patients) for ninety-six weeks (18). The daily dosages were 30mg for pioglitazone and 800U for vitamin E. This study found that 43% of the patients who received vitamin E (P = 0.001) improved vs. 34% of those who received pioglitazone (P = 0.04) and 19% of those who received placebos. The difference in the rates of improvement between pioglitazone and placebos was not statistically significant while the difference between the improvement rates of Vitamin E and placebos was. Nevertheless, both drugs were associated with improvement in aminotransferase levels, reduction in steatosis and lobular inflammation, but neither resulted in an improvement in fibrosis. The same study showed that after treatment with vitamin E was suspended aminotransferase levels increased indicating that indefinite administration of the treatment may be necessary. In addition, no significant differences were found between the adverse effects of vitamin E and the adverse effects of placebos (19).

A reassessment of the PIVENS trial by Hoofnagle et al. focused on the response of serum ALT in patients who received vitamin E or placebos and on the association of this response with the initial clinical, histological changes and interactions with changes in body weight. They found that changes in ALT were more common among those who received vitamin E (48%) than in those who received placebos (16%; p <0.001). Among the group receiving vitamin E, ALT responses were associated with decreased activity of nonalcoholic fatty liver disease (NAFLD), but there was no improvement in fibrosis after the end of treatment at 96 weeks. ALT levels increased in the vitamin E group after administration ended but did not increase in the placebo group after administration ended. Both treatment groups had almost identical ALT levels at week 120. These results are similar to those shown in the full cohort of the main publication of the PIVENS trial. Moreover, the results showed that weight loss (2 kg or more) is also associated with ALT response, with improved NAFLD (<0.001) and improved fibrosis (p <0.02), but vitamin E had greater effects on NAFLD independent of changes in body weight. Finally it should be noted that the effects of vitamin E and weight loss on ALT response and histology are independent, meaning that even those patients who lose weight would benefit from therapy with vitamin E (20).

The TONIC (Treatment of nonalcoholic fatty liver disease in children) trial was another multicenter, double-blind, placebo-controlled study. It included 173 patients who were between the ages of eight and seventeen years of age. Patients were randomly assigned to receive vitamin E (58 patients), metformin (57 patients) or placebos (58 patients) for 96 weeks. Dosages were 400 IU twice daily for vitamin E and 500 mg twice daily for metformin (21). Neither agent was superior to placebos for achieving either sustained reductions of at least 50% in baseline ALT levels or sustained ALT levels of 40 U/L or less. Measurements were taken every 12 weeks from week 48 until week 96. This study also found that the resolution of NASH was significantly higher in the group of patients treated with vitamin E than in the placebo group. This result was attributed to the significant decrease in hepatocellular ballooning that was found in patients treated with vitamin E. This is similar to PIVENS' results even though the TONIC trial did not look at decreased hepatocellular ballooning as a primary out-

come because of the histopathological differences between NALFD in pediatric patients and adults. The TONIC study found no improvement in fibrosis (22).

Previous to these two large studies there had been other smaller studies which had results with major differences in the primary outcomes evaluated. In addition to much smaller populations, these studies had less monitoring time, and some of them were not controlled with placebo groups.

A 2007 study by Yakaryilmaz et al. looked at the effect of vitamin E on nine patients whose diagnoses of NASH had been verified by biopsy. The study evaluated the effect of vitamin E on the peroxisome proliferator-activated receptor gamma (PPARG) and on insulin resistance. Patients were give 800 mg of vitamin E daily for 24 weeks. Before treatment began patients' livers were evaluated biochemically and histologically. These evaluations were repeated after treatment ended. At the end of the 24 weeks, statistically significant decreases of AST, ALT and steatosis were found, but no histological changes were found in the level of inflammation and fibrosis. No patient experienced adverse effects at this dosage of vitamin E (23).

Vajro, et al. (2004) conducted a study of a group of 28 children with obesity related liver dysfunction. The patients were divided into two groups. The average age of group one was 9.88 (+/- 3.97) years, and of group two was 10.7 (+/- 3.45). The patients were evaluated to determine whether there were any beneficial effects of vitamin E treatment on weight loss, transaminase levels and steatosis measured by ultrasound. The children included in this study all had chronic hypertransaminasemia (AST or ALT levels 1.5 times above the normal value for more than 6 months) and signs of steatosis in ultrasound. The study had a single-blind design in which patients were randomized into one of two groups: Group 1 (placebo plus diet) and Group 2 (vitamin E + diet). Later each group was subdivided depending on patient compliance with treatment. Group 1 was divided into Subgroup 1A for those who complied with the diet and Subgroup 1B for those who had not complied. Group 2 was divided into Subgroup 2A for those who had complied with vitamin E therapy and Subgroup 2B for those who had not complied with vitamin E therapy. Subgroup 2A was further divided into Subgroup 2A1 for those who did not comply with the diet and Subgroup 2A2 for those who did comply with the diet. The study found that the 400 mg/day dosage of Vitamin E produced significant decreases in ALT values for patients in Subgroup 2A who approached normalization independent of any changes in weight. On the other hand, those patients who achieved high serum levels of vitamin E and also lost weight achieved ALT normalization and remission of steatosis. Furthermore, a comparison between Subgroup 1A who complied only with diet and Subgroup 2A1 who complied only with vitamin E therapy found that both groups of patients had decreased levels of ALT at two months of monitoring, but that there was a greater decrease in Subgroup 1A (complied only with diet) than in Subgroup 2A1 (complied only with vitamin E) at five months of monitoring. All signs of steatosis disappeared from ultrasound images in Subgroup 2A2 group who lost weight during treatment with 400mg of vitamin E. These results highlight the importance of promoting healthy eating as one of the major treatment interventions for patients with NASH, but we must also note that many patients fail to comply with dietary regimes leading to the failure of the intervention. This underlines the importance of using antioxidants such as vitamin E as a good alternative therapy for these patients (24).

A pilot study by Kugelmas, et al. (2003) evaluated the effects of Step 1 of the American Heart Association diet combined with increased aerobic exercise with and without daily administration of vitamin E on the profiles of cytokines (TNF alpha, IL-8, IL -6) and levels of liver enzymes in 16 patients between 18 and 65 years of age with biopsy proven NASH. This was a single-blind study in which patients were randomly assigned to receive 800 IU of vitamin E daily. Patients who did not receive vitamin E received placebos. The test was carried out over a period of 12 weeks. Cytokine values did not significantly diminish with weight loss with or without administration of vitamin E during the study. The lifestyle changes were associated with improvements in liver enzymes and plasma cholesterol in patients with NASH, while the dosage of vitamin E used in this study showed no additional benefit. This result may be due to small sample size, the short follow-up time, or the dosage of vitamin E used (25, 26).

A review published in November 2013 about currently available options for treatment of patients with NASH recognized the current recommendation for the use of vitamin E as first-line therapy in patients with NASH confirmed by biopsy who are not cirrhotic and who do not have diabetes but also highlighted the fact that this therapy has only shown a significant benefit in less than half the patients. For this reason, the review concluded that future treatment strategies should be based on pathogenic disease pathways if an effective treatment for patients with NASH is ever going to be developed (27).

Ji H-F et al. conducted a meta-analysis to evaluate the effect of vitamin E on decreasing aminotransferases in patients with NAFLD, NASH and chronic hepatitis C (CHC). The four studies they looked at included patients with NASH who received vitamin E supplements. The studies included the TONIC and PIVENS trials. They found that vitamin E could optimize levels of AST and ALT in these patients. However, it should be noted that this meta-analysis was limited by an inability to exclude the an inability to exclude

effects of interventions involving lifestyle changes, exercise and the use of other antioxidants and an inability to exclude the effects of other risk factors for chronic liver disease such as alcohol and drug use, Added to this, the heterogeneity of the studies must be taken into account as it limits the overall analysis as well as having less specificity for aminotransferase levels than biopsies taken at the time of diagnosis and assessment of liver disease (28).

Although among the major studies to assess the effect of the use of vitamin E in patients with NASH we have not found statistically significant differences with the use of placebos and other therapeutic options over the short term, there is concern about possible adverse effects of prolonged use of Vitamin E.

A systematic review of nine randomized included new randomized placebo-controlled trials in order to evaluate the effects of vitamin E for a period of at least one year on the overall incidence of cerebrovascular accidents as well as subtypes of cerebrovascular accidents. It found an increased risk of hemorrhagic stroke (RR = 1.22, 95% CI: 1.0 to 1.48, p = 0.045). Due to the results obtained from their review, the researchers recommend avoiding indiscriminate use of vitamin E because of the serious consequences of hemorrhagic strokes in morbidity and mortality (29).

A randomized placebo-controlled study which included 35,533 patients followed for a minimum of seven years has studied the risks of Vitamin E related to prostate cancer. It compared a placebo group with a group receiving vitamin E at a daily dose of 400 IU. There was a significant increase in the risk of prostate cancer among those who took Vitamin E (HR 1.17; 99% CI, 1.004-1.360; p = 0.008). The absolute increase in risk was 1.6 per 1000 person years (30).

Another meta-analysis has looked at the dose-response relationship of vitamin E supplementation and total mortality in adults. It showed that patients who receive high doses of vitamin E (greater than or equal to 400 IU/day) had increased mortality from all causes. This meta-analysis limited its search to randomized controlled trials whose patient samples consisted of adults who received treatment with vitamin E alone or in combination with other vitamins or minerals and which excluded pregnant women and which had a minimum of 1 year of treatment and monitoring. The results provided by this meta-analysis should be considered with caution because several of the studies have small sample sizes and were performed among patients with several chronic diseases. This limits the study's ability to generalize results to the healthy adult population (31).

CONCLUSION

Although there is currently no effective drug therapy for patients with NASH, the evidence shown by the PIVENS study suggests that proper administration of vitamin E improves liver histology in adult non-cirrhotic patients with NASH who do not have diabetes. Nevertheless, more studies are needed before this recommendation can be extended to diabetic patients or to patients who have cirrhosis with NASH. Studies conducted on pediatric patients with NASH have not found sufficient evidence to support the use of vitamin E. In addition to administration of Vitamin E, it has been shown that weight loss reduces steatosis and liver inflammation. Weight loss through a low calorie diet combined with increased physical activity should be recommended for all patients. As for side effects, we have not found statistically significant differences in short-term use of vitamin E with placebos and other treatment options. Still, indiscriminate use of Vitamin E is not recommended for long periods of time as there is evidence suggesting increased risks of prostate cancer, hemorrhagic stroke and death from all the causes.

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