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Vitamin E and Non-alcoholic Fatty Liver Disease

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Abstract

Purpose of review—Oxidative stress plays a central role in the transition from simple steatosis to nonalcoholic steatohepatitis (NASH). An effective therapeutic strategy is to target reduction in oxidative stress in NASH patients. The aim of this review is to discuss the role of oxidative stress in NASH and biological activities of vitamin E and present available evidence on the therapeutic efficacy of vitamin E in NASH.

Recent findings—In Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, vitamin E therapy demonstrated a significant improvement in steatosis, inflammation, ballooning, and resolution of steatohepatitis in adult patients with aggressive NASH who do not have diabetes or cirrhosis. Although vitamin E showed a significant resolution of NASH in children, a sustained reduction of alanine aminotransferase was not attained in The Treatment of NAFLD in Children (TONIC) trial.

Summary—The prevalence of nonalcoholic fatty liver disease (NAFLD) is likely to increase over time due to the epidemics of obesity and diabetes. Presently, there is no definitive treatment for NAFLD. Based on available evidence, vitamin E (RRR- α -tocopherol) is only recommended in NASH adults without diabetes or cirrhosis and with aggressive histology. Validation is needed in children before its use can be recommended. Longer follow-up of randomized controlled trials are needed to assess long-term vitamin E safety.

Keywords

Vitamin E; α -Tocopherol; Oxidative Stress; Nonalcoholic Fatty Liver Disease; Nonalcoholic Steatohepatitis

Introduction

Nonalcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease in the western world, encompasses a histological spectrum of liver diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and liver cancer (1). In the United States, the prevalence of NAFLD is estimated to be 17–33% and 5.7–17% for NASH (2). The disease is closely associated with obesity and diabetes and, due to their ongoing epidemics, the prevalence of NAFLD both in adults and children is likely to increase over time and continue to become a serious public health burden.

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Currently, there is no definitive treatment for this disease. NASH is characterized histologically by the presence of hepatic steatosis, lobular inflammation, and hepatocyte ballooning (3). Although the precise mechanism underlying disease progression from steatosis alone to NASH remains poorly understood, it is believed that oxidative stress plays a central role contributing to hepatocellular injury. Thus, an effective therapeutic strategy is to target reduction in oxidative stress in patients with this disease. This aim of this review is to discuss briefly the role of oxidative stress in NASH and biological activities of vitamin E and present available evidence on the therapeutic efficacy of vitamin E in NASH.

Oxidative Stress in Nonalcoholic Steatohepatitis

Oxidative stress results from an imbalance between excessive production of reactive oxygen species (ROS) and decreased antioxidant defenses. Important endogenous sources of ROS are the mitochondria, microsomes, and peroxisomes. Oxidative stress is considered a second “hit,” playing a critical role in the transition from steatosis to NASH. Experimental and human studies indicate a strong association between the severity of NASH and degree of oxidative stress (4, 5).

Increased hepatic uptake and synthesis of free fatty acids (FFA) are compensated by an increase in the ability of the mitochondria to oxidize FFA (6). Consequently, the increased delivery of electrons to the electron transport chain creates a state of over reduction of some respiratory chain components, which react abnormally with oxygen to form the superoxide anion radical, thus increasing the generation of ROS (7). In patients with NASH, an increase in fatty acid oxidation as well as a decrease in the activity of mitochondrial respiratory chain complexes has been demonstrated in the liver (8, 9). Hepatic ATP depletion is also present in NASH (10). Furthermore, structural abnormalities in the mitochondria have been observed, consisting of enlargement (megamitochondria), loss of cristae, and paracrystalline inclusions (11).

The increased activity of cytochrome P450 system, particularly CYP2E1 and CYP4A, is involved in the lipo oxygenation of long chain fatty acids with concomitant production of ROS (12). In NASH patients, higher hepatic CYP2E1 expression and activity associated with mitochondrial dysfunction have been observed (13, 14). Microsomal CYP4A metabolizes long chain and very long chain fatty acids with resultant production of dicarboxylic acids that serve as substrates for peroxisomal β -oxidation (15). Proliferation and enlargement of hepatic peroxisomes are found in patients with hepatic steatosis (16). Microsomal and peroxisomal oxidation are relatively minor pathways of fatty acid disposal but become significant when CYP2E1 levels are low and long chain fatty acids accumulate. In Cyp2e1^{-/-} mice with NASH, CYP4A enzymes are upregulated, thus playing an important role as alternative initiators of oxidative stress in the liver (17).

Insufficient antioxidant defenses are also a major factor promoting oxidative stress in NASH, as evidenced by decreased hepatic glutathione and diminished superoxide dismutase, catalase, glutathione peroxidase, and glutathione transferase activities that correlate with disease severity (4, 7). The presence of single nucleotide polymorphism of superoxide dismutase has also been found in NASH (18). As a result, ROS overproduction enhances

lipid peroxidation that leads to the formation of aldehyde by-products, such as 4-hydroxynonenal and malondialdehyde (MDA), and increases the production of several cytokines, such as tumor necrosis factor- α (TNF- α), transforming growth factor- β (TGF- β), Fas ligand, and interleukin-8 (19). Both lipid peroxidation products and cytokines, in turn, damage the mitochondrial DNA and respiratory chain polypeptides and further generate more ROS production, thus triggering a vicious cycle. These events have the potential to induce apoptosis, inflammation, and liver fibrosis by impairing nucleotide and protein synthesis, promoting inflammatory cytokine production, and activating hepatic stellate cells.

Vitamin E Chemical Structure

Vitamin E is a lipid-soluble, chain-breaking antioxidant that prevents the propagation of free radicals. Synthesized by plants alone, vitamin E exists in 8 different forms, four tocopherols and four tocotrienols. The positions and numbers of the methyl groups attached to the chromanol ring designate each form as α , β , γ , or δ . Natural tocopherols have a saturated phytyl tail with three chiral centers in the RRR configuration (i.e. RRR- α -tocopherol) whereas tocotrienols contain an unsaturated side chain. The antioxidant properties of vitamin E are due entirely to the chromanol head while the phytyl tail largely determines mobility. The structure of each form governs its biological activity.

Vitamin E Pharmacokinetics

Dietary vitamin E is solubilized into mixed micelles in the intestinal lumen, absorbed in the small intestine via passive diffusion, and packaged into chylomicrons. A recent study, however, has suggested the role of scavenger receptor class B type 1 (SR-BI) in mediating vitamin E transport across the enterocytes (20). On entry into the circulation via the lymphatic system, chylomicrons are hydrolyzed by lipoprotein lipase (LPL) and, as a result, a fraction of vitamin E is released and taken up by extrahepatic tissues via the postulated LPL-dependent bridging mechanism (21). The transformed chylomicron remnant is taken up by the liver mainly via receptor-mediated endocytosis. In the hepatocytes, the α -tocopherol form of vitamin E is preferentially bound to α -tocopherol transfer protein (α -TTP) for resecretion into the circulation (22). Defects in human α -TTP gene leads to decreased circulating vitamin E levels and neurological symptoms (23). Similar findings have also been demonstrated in mice with deletion of α -TTP gene (23). Hence, α -TTP essentially maintains the levels of α -tocopherol in plasma and tissues whereas other vitamin E forms are preferentially metabolized by microsomal P450 or excreted into the bile (22).

It has been proposed previously that secretion of α -tocopherol from the hepatocytes is dependent on VLDL assembly and secretion. However, a Golgi-independent mechanism not directly coupled to VLDL secretion has been indicated to facilitate α -tocopherol secretion into the plasma (21). This is supported by a recent study in mice that showed no reduction in α -tocopherol content in peripheral tissues in the absence of VLDL due to lack of microsomal triglyceride transfer protein (24). α -tocopherol has been shown to be acquired from endosomes by α -TTP and transferred to the plasma membrane, where it is secreted from the cell through ATP-binding cassette protein A1 (ABCA 1) transporter and acquired by lipoproteins (23, 25).

In the plasma, lipoproteins are considered to be major carriers of α -tocopherol, serving as efficient sources for peripheral tissue uptake. The plasma phospholipid transfer protein and, recently, cholesteryl ester transfer protein enhance the transfer of vitamin E between lipoproteins and cells (26, 27). Although LDL receptor may modulate uptake of α -tocopherol to tissues, it has been found to be nonessential in maintaining steady-state tissue levels of vitamin E in vivo (21). Interestingly, the role of SR-BI, a cell surface receptor, in the peripheral distribution of HDL-associated α -tocopherol has been increasingly recognized. In vivo studies in SR-BI-deficient mice have shown decreased α -tocopherol levels in several peripheral organs (28).

Vitamin E Pharmacodynamics

During the initiation phase of lipid peroxidation, free radicals extract a hydrogen atom from the susceptible polyunsaturated fatty acid (PUFA) within biological membranes resulting in the formation of a lipid radical (ROOH). Oxygen then reacts with the unstable lipid radical forming a peroxy radical (ROO•), a chain-carrying radical that is able to attack another PUFA, thus propagating a chain reaction. Vitamin E intercepts propagation of peroxy radical more rapidly than PUFA by donating its phenolic hydrogen to the radical and converts it to a hydroperoxide product. Consequently, the formation of tocopheroxyl radical reacts with another peroxy radical, thereby forming non radical products. In humans and experimental animals, vitamin E suppresses the production of isoprostanes, an index of lipid peroxidation (29, 30). By protecting against peroxidation, vitamin E becomes consumed rapidly and regenerated back to its reduced form by the cytoplasmic antioxidant cycling network that includes vitamin C and thiol antioxidants, such as glutathione and lipoic acid (31). The antioxidant defence interaction of vitamin E and other micronutrients against free radicals is illustrated in Figure 1.

Vitamin E has also been characterized to mediate cell signaling and regulate gene expression independent of the antioxidant properties. In vascular smooth muscle cells, α -tocopherol inhibits protein kinase C via activation of protein phosphatase 2A (32). Other major effects of α -tocopherol on signal transduction include activation of mitogen-activated protein kinase and phosphatidylinositol 3-kinase and inhibition of phospholipase A2, cyclooxygenase, lipoxygenase, and NADPH-oxidase activities (32, 33). In effect, the molecular events lead to inhibition of cell proliferation, platelet adhesion and aggregation, monocyte-endothelial adhesions, and cytokine release. These mechanisms are thought to be independent of the antioxidant properties of α -tocopherol as other forms of vitamin E, which have relatively equal antioxidant potency, do not share many of these cellular functions. The cellular activities and regulation of gene expression by various forms of vitamin E have been extensively reviewed elsewhere (31, 32, 34).

It has been suggested, however, that oxidative stress, rather than α -tocopherol regulation, is directly responsible to the cell signaling pathways described previously, as various prooxidants and antioxidants are able to manipulate their responses (35). This is coupled mainly to the antioxidant role of vitamin E in protecting long-chain polyunsaturated fatty acids and therefore maintaining membrane stability for important signaling events. Whether

signal transduction is regulated by a specific role or antioxidant phenomenon of vitamin E in the membrane remains to be fully elucidated.

Vitamin E in Experimental Models of NAFLD

The effects of vitamin E have been evaluated in several experimental nutritional models of NAFLD. In mice fed with methionine-choline-deficient (MCD) diet, vitamin E attenuated steatohepatitis, as evidenced by decreased liver enzymes and diminished histological steatosis and necroinflammation (36). This was associated with reduction in MDA, enhanced superoxide dismutase activity, and downregulation of genes related to inflammation, apoptosis, and fibrosis. Another study using MCD diet-induced model of steatohepatitis demonstrated repletion of hepatic glutathione and reduction in oxidative stress markers, hepatic stellate cell activation, and histologic fibrosis in mice supplemented with vitamin E (37). A diet-induced obesity model in rats also showed amelioration of oxidative stress in addition to improvement of antioxidant activity after vitamin E intervention (38). In obese (ob/ob) mice, α - or γ -tocopherol showed protection against lipopolysaccharide-induced liver injury as shown by decreased alanine aminotransferase levels with accompanying reduction in hepatic MDA and TNF- α (39). Vitamin E treatment also provided protection against bile acid-induced hepatocyte injury in leptin-receptor deficient Zucker rat (fa/fa) by improving portal and lobular inflammation and hepatocellular necrosis (40). Moreover, when carbon tetrachloride was administered to rats, vitamin E ameliorated liver necrosis (41). Interestingly, vitamin E downregulated the expression of TGF- β 1, a cytokine implicated in the development of liver fibrosis (36). Results of these in vivo studies reflect the potential therapeutic role of vitamin E in human NASH.

Vitamin E in Clinical Trials of NAFLD

In addition to the protective role of vitamin E as an antioxidant and beyond its antioxidant potential, levels of plasma α -tocopherol are also found to be decreased in NASH patients compared to healthy controls, forming a theoretical basis for its use in the treatment of NASH (42). Published studies that assess the efficacy of Vitamin E in NAFLD or NASH as monotherapy and combination therapy are summarized in Table 1 and Table 2, respectively. Contrasting outcomes of earlier studies are mainly due to small sample sizes and differences in primary end points and vitamin E formulations. Pre supplementation levels of vitamin E or other antioxidant micronutrients were not available in most of these studies.

More recently, two large multicenter randomized controlled trials (RCT) were conducted by NASH Clinical Research Network to evaluate the efficacy of vitamin E for ameliorating NASH in adults [Pioglitazone versus Vitamin E versus Placebo for the Treatment of Non diabetic Patients with Nonalcoholic Steatohepatitis (PIVENS)] and children [The Treatment of NAFLD in Children (TONIC)], respectively. The PIVENS trial included 247 nondiabetic and noncirrhotic adults with NASH who received vitamin E (800 IU/day), pioglitazone (30 mg/day), or placebo for 96 weeks (44). The primary outcome was improvement in histological features, as assessed by standardized scores for steatosis, inflammation, hepatocellular ballooning, and fibrosis. The study design was to compare the treatment group (vitamin E or pioglitazone) versus the placebo group with less than 0.025 considered

as statistical significance for multiple comparisons. Compared with placebo, vitamin E therapy demonstrated a robust improvement in NASH (43% vs 19%, $P=0.001$) while pioglitazone did not reach statistical significance (34% vs 19%, $P=0.04$). Although a significant reduction in hepatic steatosis, lobular inflammation, and hepatocellular ballooning was observed, no significant improvement in fibrosis score was associated in both treatment groups. Interestingly, combination therapy of vitamin E and pioglitazone in a small pilot study was superior to vitamin E alone by demonstrating not only a significant decrease in steatosis, cytologic ballooning, Mallory's hyaline, and inflammation but also a significant reduction in pericellular fibrosis compared to baseline histology (55).

In the TONIC trial, 173 children were randomized to receive vitamin E (400 IU twice daily), metformin (500 mg twice daily), or placebo for 96 weeks (43). Neither agent was superior to placebo in attaining the primary outcome, a reduction in ALT level 50% or less of the baseline or 40 U/L or less at each visit from 48 to 96 weeks. Resolution of NASH was significantly greater for vitamin E treatment group, as compared to placebo, that was attributed mainly by significant improvement in hepatocellular ballooning. Baseline α -tocopherol levels were relatively similar between the vitamin E and placebo groups. Unlike in PIVENS, no significant reduction in steatosis and inflammation was observed. Similarly, both trials showed no improvement in fibrosis.

Vitamin E Safety

Concerns about the safety of vitamin E supplementation have been raised because of its implications in increased overall mortality and the development of hemorrhagic stroke and prostate cancer. Although some meta-analyses suggested that the use of high-dose vitamin E (>400 IU/day) increased all-cause mortality, others failed to show such an association (57–60). Another meta-analysis that included nine trials indicated that vitamin E might increase the risk for hemorrhagic stroke (61). More recently, an extended follow-up of a large RCT observed an increased prostate cancer incidence in healthy men taking vitamin E (400 IU/day) over 7 years (62).

Conclusion

Vitamin E (RRR- α -tocopherol) at a dose of 800 IU/day is beneficial only in non-diabetic or non-cirrhotic adults with active NASH. Validation is needed in children before its use can be recommended. The histologic diagnosis of aggressive steatohepatitis must be established prior to vitamin E therapy. Balancing the potential risks and benefits is warranted before starting treatment while aggressive monitoring of cardiovascular disease complications should also be addressed while on therapy. Importantly, longer follow-up RCTs are needed to assess the long-term safety and therapeutic value of vitamin E on clinical outcomes, particularly liver-related and cardiovascular outcomes, in NASH patients. Assessment of vitamin E or antioxidant micronutrient status must also be emphasized.

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Key Points

- Vitamin E (RRR- α -tocopherol) at a dose of 800 IU/day is only recommended in non-diabetic and non-cirrhotic adults with active NASH on histology.
- The role of vitamin E therapy in children needs further validation.
- The potential risks and benefits of vitamin E must be balanced before starting treatment.
- Large RCTs with longer follow-up in NASH patients are needed to assess the long-term safety and therapeutic value of vitamin E on patient-oriented clinical outcomes.

Figure 1.

The antioxidant defence interaction of vitamin E and other micronutrients against free radicals. (Cu, copper; FA, folic acid; Fe, iron; γ -Glutamyl A.A., gamma-glutamyl amino acid; GSH, glutathione; GSSG, glutathione disulfide; GSH Px, glutathione peroxidase; GSH Rx, glutathione reductase; MS, methionine synthase; Mn, manganese; NA, nicotinic acid; PUFA, polyunsaturated fatty acid; S-AdoMet, S-adenosylmethionine; Se, selenium; Zn, Zinc)

Table 1
Published studies on the effects of vitamin E monotherapy in patients with NAFLD

Author	Study Population and Design	Vitamin E Dosage	Duration	ALT	Steatosis	Inflammation	Ballooning	Fibrosis
Lavine et al. 2011 (43)	173 children with biopsy-proven NAFLD and persistent ALT elevation randomized to vitamin E, metformin <i>versus</i> placebo	400 IU twice daily	96 weeks	–	–	–	↓	–
Sanyal et al. 2010 (44)	247 non-diabetic and non-cirrhotic adults with NASH randomized to vitamin E, pioglitazone <i>versus</i> placebo	800 IU daily	96 weeks	↓	↓	↓	↓	–
Yakaryılmaz et al. 2007 (45)	9 consecutive patients with NASH given vitamin E	800 mg daily	24 weeks	↓	↓	–	NA	–
Bugianesi et al. 2005 (46)	110 patients with biopsy-proven NAFLD or NASH randomized to vitamin E, metformin <i>versus</i> placebo	400 IU twice daily	1 year	↓	NA	NA	NA	NA
Vajro et al. 2004 (47)	28 children with ultrasound-diagnosed NAFLD and elevation of transaminases randomized to vitamin E and low calorie diet <i>versus</i> low calorie diet alone	400 mg/day × 2 months, then 100 mg/day × 3 months	5 months	↓	↓ (based on ultrasound)	NA	NA	NA
Kugelmas et al. 2003 (48)	16 patients with NASH randomized to vitamin E and diet/exercise <i>versus</i> diet/exercise alone	800 IU daily	12 weeks	↓	NA	NA	NA	NA
Hasegawa et al. 2001 (49)	12 NASH and 10 NAFLD patients given dietary instruction for 6 months, followed by vitamin E	300 mg daily	1 year	↓ (NASH group)	↓ (6/9 NASH patients)	↓ (5/9 NASH patients)	NA	↓ (5/9 NASH patients)
Lavine et al. 2000 (50)	11 children with ultrasound-diagnosed NAFLD and elevation of transaminases given vitamin E	400 IU – 1200 IU daily	4–10 months	↓	– (based on ultrasound)	NA	NA	NA

Abbreviations: alanine aminotransferase (ALT), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH)

Table 2

Published studies on the effects of vitamin E combination therapy in patients with NAFLD

Author	Study Population and Design	Vitamin E Dosage	Duration	ALT	Steatosis	Inflammation	Ballooning	Fibrosis
Pietu et al. 2012 (51)	110 patients with NASH given vitamin E plus UDCA	500 IU daily	4 years	↓	↓ (3/10 patients)	↓ (3/10 patients)	↓ (3/10 patients)	↓ (4/10 patients)
Foster et al. 2011 (52)	1,005 healthy subjects (80 with CT-diagnosed NAFLD and transaminases < 1.5 times the upper limit of normal) randomized to vitamin E, vitamin C, and atorvastatin <i>versus</i> placebo	1000 IU daily	4 years	NA	↓ (based on CT)	NA	NA	NA
Nobili et al. 2006 (53)	90 children with biopsy-proven NAFLD randomized to vitamin E plus vitamin C and diet/exercise <i>versus</i> diet/exercise and placebo	600 IU daily	1 year	–	↓ (based on ultrasound)	NA	NA	NA
Dufour et al. 2006 (54)	48 patients with NASH randomized to vitamin E plus UDCA, UDCA <i>versus</i> placebo	400 IU twice daily	2 years	↓	↓	–	NA	–
Sanyal et al. 2004 (55)	20 patients with NASH randomized to vitamin E plus pioglitazone <i>versus</i> vitamin E alone	400 IU daily	6 months	↓	–	↓	↓	–
Harrison et al. 2003 (56)	49 patients with NASH randomized to vitamin E and C <i>versus</i> placebo	1000 IU daily	6 months	–	NA	–	NA	↓

Abbreviations: alanine aminotransferase (ALT), computed tomography scan (CT), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), ursodeoxycholic acid (UDCA)