

Therapeutic Effects of Vitamin E Supplementation in Liver Diseases and Transplantation

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INTRODUCTION

The prevalence of malnutrition in end-stage liver disease is well known. Less is known about the health implications of fat-soluble vitamin deficiencies in advanced liver disease. Oxidative stress is commonly associated with liver disease and thought to be involved in the pathogenesis. Oxidative stress is mediated by reactive oxygen species (ROS), which is generated in the liver. Vitamin E is of particular interest as an antioxidant due its potential to reduce or control the effects of ROS contributing to liver disease progression. The limited availability of organs in the donor network and risk of premature death as disease severity worsens creates an urgent need for alternative interventions in this population. This review analyzes the therapeutic efficacy of vitamin E supplementation and its components in various states of chronic liver disease, including uses pre and post liver transplantation.

Oxidative stress has been detected in almost all clinical and experimental conditions of chronic liver disease studied^[1]. Pathways controlling cell death, gene transcription, inflammation, and cell activation are all under redox dependent control^[2]. Low intake of antioxidant nutrients can contribute to increased oxidative stress^[3]. When increased hepatic oxidative stress overcomes an individual's antioxidant defenses, pro-inflammatory cytokines are activated. This inflammation can progress to cell death, fibrosis and eventually cirrhosis. Patients with cirrhosis and liver damage undergoing elective transplantation face additional generation of ROS related to graft ischemia from the donated liver and insult of reperfusion injury when the transplanted liver is re-oxygenated^[4]. The mechanisms involved in pathogenesis and the potential for response to antioxidant therapy vary between the forms of liver disease^[2]. It is important for the medical and research community to recognize the increasing incidence rates and indication for liver transplantation

ABSTRACT

Oxidative stress is commonly associated with liver disease. It is thought to play a role in non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease and chronic hepatitis C. This review evaluates antioxidant therapy through vitamin E supplementation as an alternative or supplemental treatment in liver disease management. PubMed and CINAHL databases were searched for research studies on vitamin E supplementation in various states of chronic liver disease, including applications for pre and post liver transplantation. The findings from the clinical studies reviewed were mixed. Timing between vitamin E supplementation, diagnosis, and staging of liver disease varied between subjects compared against each other within studies. Research findings demonstrated the beneficial effects of tocotrienol supplementation over alpha-tocopherol supplementation through a greater reduction in Model for End-Stage Liver Disease scores. The risk of adverse outcome or no benefit from vitamin E supplementation was common in alcoholics and hepatitis C patients. Four post transplant patients consuming doses of vitamin E >1 g/day had elevations in aminotransferase levels. Although the evidence of oxidative stress in chronic liver disease is clear, limited data do not support vitamin E supplementation in all forms of chronic liver disease. Investigating the differences between the two vitamin E compounds, tocopherols and tocotrienols, is an important area for future research.

consequently affecting allocation and availability of organs in the United States^[5]. The time interval between listing and transplantation may last several months, which provides the medical team with an uncommon opportunity to initiate long-term preoperative nutritional therapy, monitor disease progression and evaluate postoperative complications^[6,7].

It is the structure of vitamin E that makes it effective as an antioxidant. Vitamin E is a fat-soluble vitamin. Its major biological role is protecting polyunsaturated fats and other components of the cell membrane from oxidation by free radicals^[8]. In a study of non-alcoholic fatty liver disease (NAFLD) patients^[5], 16 out of the 52 subjects were found to have deficient vitamin E levels. The subjects deficient in vitamin E also had higher triglyceride levels and increased steatosis on ultrasound results in comparison to patients with adequate vitamin E levels. The term vitamin E encompasses 8 compounds divided into two classes: tocopherols and tocotrienols, each with its own biological effects^[9]. The majority of research studies investigate vitamin E referring to tocopherols, specifically alpha-tocopherol^[7,10]. Equally important to note, several studies refer to vitamin E as a generic term without specifying the particular compound or presume it to be synonymous with alpha-tocopherol. Many studies also fail to mention if the form of vitamin E supplementation is natural versus synthetic. It should be recognized that tocotrienols have powerful neuro-protective, anticancer, and cholesterol-lowering properties that may not be shared by tocopherols^[8,10,11]. Alpha-tocopherol is the major chain breaking lipid soluble antioxidant preventing lipid peroxidation^[3]. It is widely researched because it has the highest biological activity and is the predominant form of vitamin E in the plasma regardless of dietary intake^[12]. Dietary tocopherols are present largely in corn, wheat and soybeans, while tocotrienols are found primarily in barley, oats, palm, and rice bran^[11]. However, in all population studies caution should be taken with dosing of alpha-tocopherol supplementation. Current research does suggest a risk of cardiovascular events and

hemorrhagic stroke with alpha-tocopherol supplementation dosing >400 IU/day^[8,10].

A literature review was conducted using PubMed database and CINAHL databases. The search was limited to English and included both animal and human studies of all ages and parts of the world. The search terms used included vitamin E, supplementation, tocotrienols, antioxidants, cirrhosis, liver disease, and liver transplantation. Studies were also identified through screening the reference lists of the selected articles.

REVIEW OF CURRENT LITERATURE

Animal studies investigating the effect of tocotrienols on liver function

There have been interesting properties of tocotrienols found in animal models. Studies demonstrating promising effects of tocotrienols with regard to liver function can be found in table 1. One study evaluated the effect of tocotrienols on metabolic syndrome and liver function. Palm tocotrienol-rich fraction (TRF) was supplemented in rats fed a high carbohydrate, high fat diet over 16 weeks. TRF was found to improve liver structure and function with reduced plasma liver enzymes, inflammatory cell infiltration, fat vacuoles and balloon hepatocytes. The results suggested that tocotrienols protect the heart and liver in the study's model of human metabolic syndrome^[13]. It is yet to be found if these benefits can be expected in humans, specifically humans diagnosed with NAFLD. One major limitation in tocotrienol research is the dosage regimen. Oral consumption of tocotrienols may not provide the most suitable pharmacokinetic profile for each indication^[14].

Chronic and excessive alcohol consumption accelerates reactive oxygen species (ROS). Kaur *et al*^[15] evaluated vitamin E supplementation in mice treated with ethanol. The mice were randomly divided into three groups: control, (*n*=6) alcohol-treated, (*n*=6) and alcohol+vitamin E treated over a period of 15 days.

Table 1 Animal studies investigating the effect of tocotrienols on liver function.

Study	Objectives	Sample	Treatment	Control	Duration	Results
Wong <i>et al</i> ^[13]	To measure the changes following intervention with a mixture of vitamin E compounds in a rat model of chronic diet-induced cardiovascular, metabolic and liver changes.	N=32 Wistar rats	Alpha-tocopherol, alpha-tocotrienol & delta-tocotrienol mixture (TRF); Corn starch (C) or high carbohydrate, high fat (H) diets. C+TRF, n=8 H+TRF, n=8	C, n= 8 H, n=8	8 weeks control followed by 8 weeks treatment	H rats had 1.8x greater plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels vs C rats (<i>p</i> <0.05) H+TRF caused plasma AST and ALT to decrease by 41.2% and 40%, respectively (<i>p</i> <0.05).
Kaur <i>et al</i> ^[15]	To evaluate the molecular mechanism associated with alcohol-induced oxidative stress and its prevention with vitamin E supplementation.	N=18 Male balb/c mice	Group III: 8% ethanol + .2ml of 5IU/kg body weight of vitamin E in olive oil (n=6)	Group I: control (n= 6) Group II: 8% ethanol in tap water (n=6)	15 days	There was a significant (<i>p</i> <0.05) difference in serum malondialdehyde levels, catalase, glutathione S-transferase, superoxide dismutase, total glutathione, reduced glutathione, oxidized glutathione, and the redox ratio from group I to group II and Group II to group III. Livers and serum were collected for histological measures at various time points after CCl ₄ injection. The results from histology and serum ALT and AST showed that the intervention reduced liver damage during acute liver injury, increased collagen synthesis, & a positive repairing response to hepatocyte injury.
Shen <i>et al</i> ^[17]	To evaluate effects of vitamin E & selenium on proliferation & apoptosis of hepatic stellate cells in acute liver injury induced by carbon tetrachloride (CCl ₄)	N=156 Sprague Dawley rats	Intervention: Injected with CCl ₄ and fed chow supplemented with vitamin E and selenium (n=52)	Control: Fed standard chow (n=52) Pathological: Injected with CCl ₄ (n= 52)	Injections 2x/ week over 8 weeks; analysis after 3, 7, 14 and 28 days from the last injection	

Alcohol ingestion promoted oxidative stress. The mice that received vitamin E supplementation had restored redox status, reduced apoptosis and reduced indicators of oxidative stress. Evidence of reduced oxidative stress was shown by analysis of lipid peroxidation, catalase, glutathione S-transferase, superoxide dismutase, total glutathione, oxidized glutathione, and reduced glutathione. The authors concluded that vitamin E was a potential therapeutic agent for alcohol-induced oxidative damage in the liver.

Hepatic stellate cells (HSCs) are known to play a key role in liver fibrogenesis. The activation of HSCs is a major source of collagen to produce fibrosis. Thus, the resolution is associated with a net loss of activated HSCs via apoptosis^[16]. Previous studies have provided evidence to support the idea that fibrosis is driven by oxidative damage. Antioxidative nutrients, such as vitamin E, can protect hepatocytes to prevent fibrosis induced by carbon tetrachloride. In a study conducted by Shen *et al*^[17], 156 rats were randomly divided into 3 groups: normal control, pathological and intervention. The rats in the intervention group were given standard chow supplemented with vitamin E and selenium; the other two groups were given standard chow. The rat livers were evaluated at various points after the last injection of carbon tetrachloride, and at each point the number of activated HSCs was less in the intervention group compared to the pathological group. The animals were receiving vitamin E supplementation throughout the duration of injections that were harming the liver. In real-life situations with humans, medical teams are seeing the damage after it has already occurred and they are trying to reverse hepatocyte damage or liver fibrosis. Therefore, human research in the area is needed.

The effect of vitamin E supplementation on NAFLD

Studies on the effect of vitamin E supplementation on NAFLD have been conducted. Non-alcoholic steatohepatitis histologically resembles alcohol-induced liver damage. It is primarily associated with obesity, type II diabetes, and hyperlipidemia^[18]. Oxidative stress, changes in metabolic parameters, and endotoxin-induced cytokine release contribute to the nature of this disease. Under normal conditions, antioxidants balance the rate of ROS produced^[18]. One study investigated the effect of increased oxidative stress in the liver of NAFLD patients. The study included 43 subjects: 12 healthy controls, 15 with steatosis, and 16 with steatohepatitis. Hepatic and plasma oxidative stress parameters were measured and compared between the groups. There were no significant changes in clinical and biochemical parameters between the groups beyond a slight increase in body mass index. Most of the patients were asymptomatic with normal or mild alterations of lipid profiles and liver function test results. However, parameters related to oxidative stress in the liver and plasma samples revealed significant increases in pro-oxidant conditions in the NAFLD patients compared to the control subjects. Disease progression from steatosis to steatohepatitis involved a further systemic reduction in the antioxidant capacity of the liver, shown by a decrease in the activity of catalase and superoxide dismutase. These data suggest that nutritional support

with antioxidants could be promising in balancing the ROS produced and possibly even reducing disease progression^[18]. There were limitations that were found in the study design. A clinical and nutritional history was reported but could not be found in the methods section. In addition, there was variability in the length of dietary treatment. Prior to liver biopsies, patients were fed a diet containing 25 kcal/kg, with 30% of kcal from lipids and 15% kcal from proteins. A limitation was that some subjects followed this diet for as few as 2 days prior to the procedure. Finally, the average body mass index (BMI) of healthy subjects was a normal 22 in comparison to the much higher average BMIs of 35 in steatosis and 47 in steatohepatitis. The evidence for the therapeutic effect of vitamin E would have been more convincing if the average BMI in the healthy control group for this study was closer in comparison to the average BMI in the treatment group.

Pharmacological interventions with vitamin E for the treatment of NAFLD

Pharmacological interventions with vitamin E for the treatment of NAFLD have been studied. A study by Socha *et al*^[19] consisted of 15 randomized control trials (RCT). A meta-analysis was performed on 3 RCTs of particular interest that investigated vitamin E therapy in comparison to placebo or no treatment. The meta-analysis revealed no difference in the percentage of patients with a normal serum alanine transaminase (ALT) level in those treated with vitamin E compared to those who were administered the placebo. Differences in vitamin E doses (400-800 mg/day) and weight changes in the control subjects limited the value of the meta-analysis^[19]. Details of study design and limitations are summarized for the 3 studies can be found in table 2. Although risk factors and mechanisms of disease progression are similar in children and adults, caution should be taken in applying results to children. The age range of the children who participated in the studies referenced was not available in the review. Details of the dietary therapy were not provided, which was another limitation of this study. A pilot study conducted by Magosso *et al*^[20] investigated tocotrienols supplementation in 64 patients with confirmed NAFLD. Results indicated those in the treatment group did benefit in terms of normalization of the hepatic echogenic response in NAFLD compared to placebo. Worsening of NAFLD grade was recorded in only two patients in the placebo group. No adverse events were reported for either group. The effectiveness of tocotrienols could be partially explained by their preferential distribution to the liver. These findings encouraged larger cohort studies to confirm the positive results of tocotrienols in this population and supported the need to manage this disease in its early stages since disease progression can be hard to predict^[20].

Vitamin E supplementation in the treatment of nonalcoholic steato hepatitis (NASH)

Clinical trials have investigated the effects of vitamin E supplementation in the treatment of NASH. These results are

Table 2 Characteristics of the vitamin E pharmacological intervention trials for the treatment of non-alcoholic fatty liver disease investigated in a meta-analysis (Socha *et al*^[19]).

Study	Randomized	Blinding	Follow-up	Population	Intervention	Control	Duration
Vajro <i>et al</i> ^[21]	Yes	Yes	Yes 28/28	Children	Vit E (n= 14) 400 mg (2 mo)+100 mg (3 mo)	Placebo (n = 14)	5 months
Nobili <i>et al</i> ^[22]	Yes	Yes	Yes 88/90	Children	Vit E (n=45) 600 IU + Vit C 500mg/day	Placebo (n= 43)	12 months
Bugianesi <i>et al</i> ^[23]	Yes	No	Yes 105/110	Adults	Metformin 2g/ day (n= 29) 2gm/ day N= 26	Vit E 800 IU/ day (n= 28) No treatment N= 27	12 months

shown in table 3. Hyperinsulinemia and hyperglycemia have been linked to oxidative stress in the pathogenesis of NASH^[24,25]. A RCT of 20 subjects was conducted to evaluate the correlation of insulin resistance, vitamin E status, and NASH. The researchers compared vitamin E supplementation (400 IU/day) alone versus vitamin E (400 IU/day) and 30 mg/day of pioglitazone, an insulin sensitizer, in non-diabetic, non-cirrhotic subjects with NASH. The combination treatment improved all histological lesions of NAFLD, producing a significant decrease in steatosis, cytologic ballooning, Mallory's hyaline, and inflammation. Between 2005 and 2007 a large-scale multicenter trial, PIVENS trial, was carried out based on the findings from the pilot study^[24,25]. The PIVENS trial compared pioglitazone (30mg/day) versus vitamin E (800 IU/day) versus placebo for the treatment of adults without diabetes who had biopsy-confirmed NASH. The results published in 2010 found that vitamin E supplementation was superior to the placebo for the treatment of NASH in adults who did not have diabetes. There was no benefit of pioglitazone over placebo for the primary outcome. The primary outcome was considered to be an improvement in histologic findings, which required improvement by one or more points in the hepatocellular ballooning score. No increase in the fibrosis score and either a decrease in the activity score for NAFLD to a score of 3 points or less with at least a point decrease in the lobular inflammation or steatosis score. Significant benefits of pioglitazone were observed for some of the secondary outcomes. These secondary outcomes referred to body weight, insulin resistance, serum enzyme levels, and quality of life^[25].

Treatment with antioxidants in patients with alcoholic liver hepatitis

Studies evaluating the treatment with antioxidants in patients with

alcoholic liver hepatitis have been conducted. These are shown in table 4. Alcohol can enhance ROS formation through induction of cytochrome P-4502E1 in the brain and liver. Chronic alcohol abuse and accelerated ROS production can decrease the body's antioxidant defense mechanisms^[26-28]. These changes in the body's redox status produce serious effects on cellular function and pathogenesis of alcohol induced liver injury^[26,29]. The median intake of vitamin E was found to be low in patients with alcoholic cirrhosis^[25]. Only glucocorticoid steroid treatment has been shown to have any benefit on survival, but known contraindications limit their use. The theoretical benefit of antioxidant therapy in acute alcoholic hepatitis has inspired further research to evaluate the efficacy of antioxidant therapy versus corticosteroid therapy or in combination^[27,29]. Based on findings that hospitalized alcoholics had lower serum alpha-tocopherol levels compared to control subjects, Mezey *et al*^[30] conducted a randomized controlled trial to evaluate the effects of vitamin E supplementation (1,000 IU/day) on patients with mild to moderate alcoholic hepatitis. This study measured the effect of a 3 month daily oral administration of vitamin E on clinical and laboratory parameters of liver function. Patients were also followed for one year after the trial was completed. Vitamin E supplementation did not show beneficial effects on liver function tests, nor did it display significant influence on one-year survival rates. No adverse events were observed from vitamin E administration in comparison to placebo administration. The short 3-month duration of vitamin E supplementation was a limitation in this study, and the benefits of a longer supplementation period should be considered for future research. A randomized control trial by Phillips *et al*^[27] hypothesized the survival advantage in acute alcoholic hepatitis with antioxidant therapy compared to traditional corticosteroid treatment (CD). This study evaluated changes in 30-day mortality of patients diagnosed

Table 3 Clinical trials investigating the effects of vitamin E supplementation in the treatment of nonalcoholic steatohepatitis (NASH).

Reference	Sample	Intervention	Control	Duration	ALT levels	Results
Sanyal <i>et al</i> ^[24]	n=20	400 IU /day vitamin E plus 30 mg/day pioglitazone vs 400IU vitamin E/day	None	6 months	Levels normalized in all patients regardless of treatment arm	2 patients in the combination therapy group did not complete the study. Combination therapy was significantly superior to vitamin E alone. Inflammation disappeared altogether in 4 of the 8 patients who completed treatment.
Sanyal <i>et al</i> ^[25]	n=247	800IU/day Vitamin E	30mg/day pioglitazone or placebo	96 weeks	Vitamin E -37.0 U/liter Pioglitazone -40.8 U/liter Placebo -20.1 U/liter	Both agents associated with reductions in hepatic steatosis ($p=0.0005$) for vitamin E and pioglitazone $p<0.001$). Average 4.7 kg weight gain in subjects who received pioglitazone compared to vitamin E or placebo

Table 4 Clinical trials investigating the effects of antioxidant therapy in the treatment of alcoholic hepatitis.

Reference	Sample size & population	Control	Treatment	Duration	ALT	Oxidative stress markers	Survival
Mezey <i>et al</i> ^[30]	51 mild to moderate alcoholic hepatitis	Placebo n =26	Vitamin E (1000 IU/day) n= 25	3 months	No change	Decrease in hyaluronic acid with Vitamin E	At 1 year follow up: 85% w/ treatment vs 77% w/ placebo p=Not significant
Phillips <i>et al</i> ^[27]	101 acute alcoholic hepatitis	*Corticosteroids (CS) n=53	*Anti-oxidant cocktail (AO) n=48	4 weeks	NA	NA	30 Day survival= 70%w/ CS vs 54% w/ AO ($p=0.05$); 2.4 greater odds of death in AO group at 30 days. At 1 year survival= 50% in CS vs 40% in AO; ($p=0.43$)
Stewart <i>et al</i> ^[29]	70 severe alcoholic hepatitis	Active drug n=36	Placebo n=34	6 months	NA	NA	180 day survival 53% w/ active drug vs 56% placebo; ($p=0.699$). Incidence of encephalopathy, GI bleeding and sepsis was similar between the 2 groups

with acute alcoholic hepatitis. The antioxidant cocktail (AO) used in this study used the oral route for the following ingredients: an oral dose of 12 mg β -carotene, 1,100 mg vitamin C, 388 mg vitamin E, 300 μ g selenium, 1600mg methionine, 300 mg allopurinol; and 30mg/kg parenteral desferrioxamine, and 150 mg/kg intravenous N-acetylcysteine. After adjusting for baseline bilirubin, white cell count, and presence of encephalopathy, the odds of dying within 30 days while on antioxidant therapy alone was 3-fold higher than those on traditional corticosteroid treatment. The trial was terminated early because of these negative results. The survival advantage in the corticosteroid group was lost at one-year follow up. This study supported previous findings that the benefits of corticosteroids are limited to short-term effects that act as a bridge to more extensive treatment options such as liver transplantation^[27]. A study conducted by Stewart *et al*^[29] was a double blinded and placebo controlled trial of 70 patients with severe alcoholic hepatitis. It was conducted to investigate whether there was an additional benefit to antioxidant therapy alone or in combination with corticosteroids. Survival at 6 months did not improve in either group. The antioxidant therapy used in this study was a loading intravenous dose N-acetylcysteine of 150mg/kg, followed by a 100mg/kg daily dose for one week. Daily oral supplements of vitamin A, vitamin E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid, and coenzyme Q were also administered for 6 months. The study design did not exclude the potential role for antioxidants to delay the onset of disease among heavy drinkers. Additional limitations were that the drug doses prescribed in this study were insufficient or that the antioxidant cocktail used did not perform an antioxidant function. The number of limitations seen in this study suggests the need for further research in this patient population.

Vitamin E supplementation in the treatment of chronic hepatitis C

The effect of vitamin E supplementation on chronic hepatitis C has been studied. Evidence of oxidative stress has been detected in almost all clinical conditions of chronic liver disease, yet the mechanisms by which hepatitis C virus (HCV) produces liver damage are still unclear. One study conducted on markers of lipid peroxidation, antioxidant status, hepatic fibrogenesis, and liver function in 42 chronic hepatitis C patients in an effort to confirm the role of oxidant stress on HCV liver damage^[1]. The antioxidants glutathione, selenium, and vitamins A, C, and E were found to be significantly decreased in these patients compared to matched controls. These findings supported a mechanism of oxidant stress in causing HCV liver damage. Oxidant stress was reflected in blood and urine through a variety of pro- and antioxidant markers tested in both cirrhotic and non-cirrhotic groups. These results suggest that antioxidant therapy could slow liver disease progression in the HCV population when used in combination with alpha-interferon and ribavirin treatment^[1]. Another study evaluated HCV positive liver recipients 6 months post transplant without recurrence to assess levels of oxidative stress compared to HCV positive non-transplant patients and standard controls. Micronutrient antioxidants, nutritional intake and anthropometry were included as criteria assessed in each group. Hepatic levels of liver lipid peroxidation were significantly higher in HCV-OLTs compared with controls or HCV non-transplant. Waist-hip ratios were higher in HCV patients compared with controls but age, gender distribution, nutrition status and proportion of patients with diabetes were similar between transplant and non-transplant groups. HCV liver transplant recipients with biopsy proven increases in oxidative stress and inflammation displayed suboptimal intake of antioxidant micronutrients suggesting that they may benefit

from increased antioxidant intake. Plasma vitamin E assays indicated levels were within normal range although all patients failed to meet their daily required intake^[1]. More research in relation to HCV infection and vitamin E treatment post transplant is covered in the section on liver transplantation.

Vitamin E supplementation in liver transplantation

Pre-operative effects of vitamin E supplementation in liver transplantation have been investigated. The 2 classes of vitamin E, tocopherols (TCP) and tocotrienols (TE), possess different biological activity and may have unique effects in liver transplantation. A study assessed the concentrations of TE and TCP in vital tissues and organs in subjects supplemented with 400 mg TE or TCP daily. The participants were split into two groups: a non-surgical healthy control group and a pre-surgical group. The groups were supplemented over a mean duration of 20 weeks. In the prospective liver transplantation patients, oral TE was found to have lowered the model for the end-stage liver disease (MELD) score in 50% (7 out of 14) of patients supplemented, whereas only 20% of TCP supplemented liver patients demonstrated a reduction in MELD score. Because the MELD score quantified the prognosis of cirrhotic patients after transjugular intrahepatic portosystemic shunt, these results suggest that oral TE may be more effective than TCP. Four out of the 7 patients in the study who experienced a reduction in MELD score had hepatitis C cirrhosis. This work highlights a need for more research to describe or identify individual constituents of the vitamin E family, tocopherols or tocotrienols and their effects on liver disease^[7]. More research is needed to find an alternative since traditional treatment in hepatitis C is frequently ineffective and has many adverse side-effects. Vitamin E may be promising alternative due to the adverse side-effects of traditional treatment in hepatitis C cirrhosis and the number of non responders, this outcome encourages more research in the efficacy of TE against end-stage liver disease^[9]. In another study of prospective liver transplant patients, the relationship between blood levels of fat-soluble vitamins, specifically vitamin E levels, were compared with disease type (22 cholestatic disease, 74 hepatocellular disease) while controlling for MELD scores. Reduced oral intake, malabsorption, and hepatic changes involving reduced synthesis of carrier proteins are factors that affect vitamin E status in liver disease patients. In this prospective analysis of pre-transplant patients, no differences between disease groups were found for vitamin E status. Plasma vitamin E levels were negatively correlated with MELD scores. The prevalence of vitamin E deficiency in the study was very low, with only 3 patients being deficient. A limitation was that lipoproteins were not measured in this study, so it is possible the actual number of vitamin E deficiencies were greater^[31]. Other research evaluating fat-soluble vitamin deficiencies in liver transplant candidates indicated a low incidence of vitamin E deficiency in this population. Interestingly there was only one case of post-transplant reperfusion injury which occurred in a patient with vitamin E deficiency^[32]. Another study investigated whether patients with lower fat-soluble vitamin levels exhibited depleted antioxidant levels and increased lipid peroxidation prior to transplant. This study also assessed whether the inevitable ischemia and reperfusion injury on the graft encountered during transplant surgery affected antioxidant levels and lipid peroxidation post reperfusion. Twelve patients undergoing liver transplantation were matched with an equal number healthy control subjects. The study found lowered antioxidant defenses and evidence of free radical damage in transplant patients' pre-reperfusion, during reperfusion and post-reperfusion compared to the control subjects. The researchers concluded that the imbalance

between antioxidant capacity and free radical damage experienced during reperfusion would support the use of antioxidants in liver transplantation in attempt to reduce the severity of reperfusion injury. It was also suggested that this would improve short-term allograft function and survival^[4]. There was no elaboration on dose, duration, or possibility of adverse effects with regard to the researcher's antioxidant supplementation recommendation.

A previous work conducted by Bartels *et al*^[33] investigated the effect of vitamin E infusions on 68 patients scheduled to undergo elective, tumor-related, partial liver resection. This was a placebo-controlled double-blind study. It was hypothesized that antioxidant protection would prevent damage to the liver and improve postoperative clinical outcome in transplanted patients. The findings indicated that preoperative administration of vitamin E is safe. Supplementation of vitamin E may reduce ICU stay, prevent vitamin E (alpha-tocopherol) depletion after ischemic reperfusion injury and could reduce the impact of ischemic reperfusion injury in liver surgery. One major strength of this study was that short-term supplementation is more feasible in practice since the time frame from getting listed for an organ to undergoing surgery in the transplant population is so variable. A similar study completed by Goode *et al*^[34] associated the drop in antioxidant levels during reperfusion with hemodynamic changes. They suggested a multifaceted strategy for both the donor and recipient to ameliorate reperfusion injury through use of a free radical quenching agent in organ preservation via rinse solutions. Oral vitamin supplementation was not referenced as a possible recommendation for antioxidant repletion therapy.

The effects of vitamin E supplementation while on post-transplant immunosuppression medications has been examined. Hepatitis C virus reinfection after liver transplantation results from immunosuppression medications and affects survival rates post transplantation. Oxidative stress is thought to be involved because of its role in the pathogenesis of HCV pre-transplantation. Risk factors for oxidative stress include immunosuppression, which is required after transplantation in order to prevent graft rejection. A study of HCV positive organ recipients evaluated liver lipid peroxidation, antioxidant potential, and plasma vitamin E, vitamin C, and retinol levels at 6 and 12 months post transplant. A significant relationship was found between liver lipid peroxidation and HCV recurrence at both assessment times. Researchers determined that oxidative stress was independently associated with HCV recurrence^[35]. All micronutrient levels within the two groups were within reference ranges. More work is needed evaluating antioxidant supplementation in HCV liver transplant recipients with HCV disease recurrence.

The transplant population is unique in that certain supplements found to be beneficial to the general public can be detrimental to the post-transplant patient. This due to the lifelong immunosuppression regimen required to prevent allograft rejection. The use of alternative medicine products and large dose vitamin supplements are becoming increasingly popular since many agents are advertised as immune stimulants. A study of 290 post-liver transplantation patients assessed dietary supplement use through a questionnaire. Thirty five percent of patients admitted to continuous use of vitamins. Four of these patients reported consuming high doses of vitamin E >1 g/day, which resulted in elevations in aminotransferase levels. Upon discontinuing the vitamin E supplements, the liver enzymes and graft function returned to normal within 4-8 weeks. Excessive supplementation of vitamin E is currently discouraged post-liver transplant because it may disrupt the immunosuppression required to prevent graft rejection. It is important to recognize that most research done on

vitamin supplementation does not include transplant recipient subjects^[36]. This is an area for future research.

DISCUSSION

Although numerous studies have examined the role of oxidative stress in various forms of liver disease, more research is needed before antioxidant supplementation can be recommended to the pre-liver transplant population. Despite encouraging work in the field, results from clinical studies have been mixed. High dose vitamin E supplements have been linked with an increased risk of abnormal bleeding^[37]. Patients diagnosed with liver disease are already at risk for clotting disorders, which surprisingly is not consistently mentioned in the studies reviewed. In one study, researchers experienced a loss to follow-up in the vitamin E treatment group due to patient death from bleeding esophageal varices^[30]. Prothrombin time was monitored in this study, and it remained unchanged between patients receiving vitamin E supplementation versus placebo. Timing between vitamin E supplementation, diagnosis, and staging of liver disease varied between subjects compared against each other within studies. Failure to acknowledge differences in disease stages within a treatment group could have skewed adverse reactions or proof of significance. Disease staging proves to be complicated because of the invasive nature of completing a liver biopsy when liver disease is suspected. Many patients with the disease can be asymptomatic, or symptoms may not correlate with severity of histology or atypical blood work^[38,39]. Lastly, while studies implied the patient population was at risk for vitamin E deficiency, none of the studies actually recruited subjects diagnosed with vitamin E deficiency nor investigated correcting deficiency levels without supplementing beyond standardized normal ranges.

A common theme among the studies reviewed was that they evaluated either alpha-tocopherol or vitamin E within an antioxidant blend. Variations in the composition and formulation of tocotrienol-rich fraction limit applications of research^[14]. Failure to acknowledge the differences between the two vitamin E compounds, tocopherols and tocotrienols, is another major limitation in this area of research^[7,9,13]. There was only one human study that recognized the differences between the two forms. This study actually used tocotrienols rather than alpha-tocopherols and supported the growing body of evidence suggesting that the biological activity differs between the different forms of vitamin E^[7,9,10]. These findings support the need for a double blinded, prospective clinical trial to test tocotrienols in patients who cannot tolerate standardized drug therapy. To date, vitamin E supplementation has not shown to be a noteworthy treatment compared to standardized treatment methods for liver disease. The Proud trial underway proposed by Nickkholgh *et al*^[6] is a double blind multi-center trial with two parallel groups of patients listed for liver transplantation to evaluate the effects of enriched formulas on nutrition status. This study design is promising and the results may address several unanswered questions of preceding work in this area.

In addition to distinguishing tocotrienols from tocopherol supplementation, dosage, sampling times, bioavailability, study population and endpoints of supplementation are current limitations to research^[8-10]. With regard to dosage, it is still unclear whether there is more risk or benefit to supplement liver disease patients above the recommended daily value^[40]. Establishing differences in natural versus synthetic forms of vitamin E supplementation should also be specified.

Finally, the impact of overall nutrition status of subjects remains

a weakness in current research. With the known prevalence of malnutrition in various forms of liver disease, is it ever appropriate to compare interventions to healthy control populations^[31]? Dietary sources of vitamin E are not always prevalent in the diet of liver disease patients^[9]. The evidence for vitamin E supplementation might be more convincing if preliminary vitamin E levels and nutrition status were assessed at baseline. A more critical comparison of vitamin E food sources versus vitamin supplementation in healthy and diseased subjects could also be meaningful to this area of research.

CONCLUSION

The diverse types of liver disease and variables of disease progression made the comparison of vitamin E supplementation on prognosis and disease progression difficult to evaluate. Until biopsy confirmation is made, it is not always possible to accurately classify liver disease in the early stages. The impact of timing with regard to antioxidant and vitamin E supplementation complicate recommendations derived from these studies for use in clinical practice. Excessive supplementation of vitamin E is currently discouraged post-liver transplant because it may disrupt the immunosuppression required to prevent graft rejection. Increasing vitamin E intakes through natural sources in the diet may be a safer and more effective way to impact oxidative fibrosis and rates of liver disease progression. There are many foods that provide vitamin E. Vegetable oils, seeds and nuts contain the best sources of alpha-tocopherol. Appreciable amounts are also found in green leafy vegetables and fortified cereals. A detailed list of the content of vitamin E in foods is available^[41]. Tocotrienols were found to be more effective than tocopherols in reducing liver disease. However, the low abundance of tocotrienols in food sources make higher intake of tocotrienols difficult for most people. Professionals working with chronic liver disease patients should promote optimal nutrition status throughout all stages of treatment. Emphasis on adequate micro-nutrient and antioxidant intake derived from food sources opposed to supplementation is recommended until more conclusive findings are published.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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