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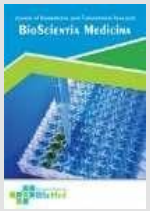

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The Effects of Vitamin E Administration in Non-Alcoholic Fatty Liver Disease

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A B S T R A C T

Non-alcoholic fatty liver disease (NAFLD) is a liver disease which has high prevalence in the society. There is no drug that is considered to be able to effectively treat this disease until today. The treatments has wide range from modifications to diet and exercise. The role of vitamin E in the treatment of NAFLD has been studied in many researches. It has high antioxidant capacity that have the ability to decrease the level of reactive oxygen species (ROS) and prevent oxidative damage that can cause cellular senescence and apoptosis. The antioxidant properties may inhibit the progression into liver damage and may even treat hepatic fibrosis in NAFLD. It also has an anti-inflammatory role that affects various inflammatory cytokines produced in NAFLD. The use of vitamin E in non-alcoholic steatohepatitis without diabetes is advised by recent guidelines from the American Association for Study of Liver Disease (AASLD) and the European Association for the Study of Liver Disease (EASLD). In patients with non-alcoholic steatohepatitis, vitamin E can decrease oxidative stress, inhibit the pathogenesis of the disease, and be used as a therapeutic option. However, new research on the safety and efficacy of vitamin E in treating diabetic non-alcoholic steatohepatitis patients is still deemed insufficient.

1. Introduction

The increasing prevalence of metabolic disorders such as diabetes mellitus, as advancements in farming technology that produce in abundance products like corn, which is converted into fructose syrup that is served in many processed foods ending on dinner plates, will eventually make NAFLD rank among the most significant chronic liver diseases in the world. Treatment of this disease has not provided satisfactory effectiveness despite many intensive studies regarding NAFLD. Until recently, there was no approved medication treatment for NAFLD. Instead, patients were primarily advised to increase their exercise and reduce their weight, which is likely difficult to achieve and even harder to maintain. However, suggestions to encourage physical activities and management of associated conditions such as obesity and the other components of metabolic syndrome are expected to reduce morbidity and mortality associated with liver damage and cardiovascular disorders in patients with NAFLD.[1,2]

The latest strategies for managing NAFLD include the use of antioxidant micronutrients such as vitamin E.[1] Various clinical trials for NAFLD have shown improvements in the biochemical and histological conditions of the liver induced by vitamin E administration. However, several limitations of these trials must be considered.[1,2]

Non-alcoholic fatty liver disease

Lipid uptake, synthesis, and oxidation occur in the liver prior to their distribution to peripheral tissues. The cell population in the liver is divided into 2 types: parenchymal, also called hepatocytes, and non-

parenchymal cells, consisting of liver sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), hepatic NK cells and Kupffer cells. Hepatocytes are associated with primary liver functions, such as lipid metabolism. Stellate cells react to lipotoxicity-induced hepatocyte damage and inflammation. Stellate cells are activated and turn into myofibroblast-like cells, which secrete collagen and cause fibrosis. Lipotoxicity in LSEC can result in oxidative stress and steatohepatitis by lowering nitric oxide levels and raising reactive oxygen species (ROS) levels. Kupffer cells are activated during liver injury by releasing inflammatory cytokines and chemokines that contribute to the formation of NAFLD.[2]

NAFLD is a metabolic syndrome hepatic manifestation. It is described as a build-up of hepatic fat in individuals who abstain from alcohol. NAFLD encompasses a broad range of conditions, from steatosis or a simple accumulation of fat in the liver to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis with various clinical consequences.[3,4]

Most patients with this disease have no symptoms at all, and it is linked to obesity as well as other metabolic syndrome conditions like dyslipidemia, central adiposity, hypertension, insulin resistance, and diabetes.[3] On the other hand, certain patients may experience symptoms such as lipomatosis, hepatomegaly, acanthosis nigricans, fatigue, and discomfort in the right upper quadrant. End-stage liver disease can coexist with cirrhosis in patients.[5] NAFLD is frequently diagnosed as a result of abnormal liver function tests or by chance upon radiologic findings of the abdomen. Hepatomegaly, which is brought on by the liver's fatty infiltration, may manifest physically.[5]

Pathogenesis of NAFLD

Two-hit hypothesis

NAFLD is caused by a complex web of interrelated factors that play a role in its development and progression. Numerous hypotheses have been proposed, which then lead to the “two-hit hypothesis”. According to this theory, a diet heavy in fat, obesity, insulin resistance, and a sedentary lifestyle all contribute to the buildup of lipid in the liver, which serves as a "first hit" that sensitizes the liver to activate a "second hit." The second hit will activate the inflammatory process which can be followed by the process of fibrogenesis.[4,6] According to an experimental study, a "second insult" is necessary to start inflammation and fibrosis in obese animals, such as ob/ob mice with leptin deficiency, who exhibit increased hepatic lipid accumulation.[4]

However, this view was later considered too simple to be applied to humans with NAFLD, where parallel factors act synergistically in genetically predisposed individuals who are experiencing the development and progression of NAFLD. As a consequence, “multiple hit hypothesis” is proposed to replace the “two hit hypothesis” in the pathogenesis of NAFLD.[4,6]

Multiple-hit hypothesis

Changes in the gut microbiota, obesity with adipocyte proliferation, and insulin resistance can be caused by dietary practices, environmental factors, and genetics.[3,7–10] Triglyceride and free fatty acid (FFA) accumulation in NAFLD is linked to obesity and insulin resistance. NAFLD's pathogenesis is intricate and multifaceted, and there are several competing theories in the literature. The onset of NAFLD is attributed to a number of risk factors. The development of steatosis or steatohepatitis, which causes increased adipose tissue lipolysis and de novo lipogenesis (DNL), ultimately leads to an increase in fatty acids in the liver and is largely dependent on insulin resistance. Insulin resistance leads to adipose tissue dysfunction, which in turn causes changes in adipokine and inflammatory cytokine production and secretion.[6] Triglycerides are the form of fat that builds up in the liver. Elevated levels of lipid metabolites, free fatty acids, and free cholesterol are the causes of the increased lipotoxicity.[11] Reactive oxygen species production and endoplasmic reticulum (ER) stress, along with mitochondrial dysfunction, occur as a result of fat accumulation in the liver, mainly in the form of triglycerides. Excessive nutrients will burden

the ER, which will then activate unfolded protein response and, as a consequence, will stimulate the progression of insulin resistance by means of various mechanisms, including inflammation and activation of c-jun N-terminal kinase.[6]

The pathogenesis of NAFLD is significantly influenced by the gut microbiota. By providing toll-like receptors (TLR) ligands, which are able to stimulate the production of proinflammatory cytokines by liver cells, the gut microbiota not only affects how nutrients are absorbed and eliminated by the liver but it also affects inflammation within the organ. Adipose tissue dysfunction in obesity, type 2 diabetes mellitus, and NAFLD affects the metabolism of fat and glucose by two different mechanisms: first, it functions as an endocrine organ, releasing cytokines derived from fat, and second, it causes ectopic fat deposition due to lipotoxicity and free fatty acid.[6]

Genetic predispositions and epigenetic modifications can influence the fat content of hepatocytes and the inflammatory environment in the liver. This can result in the development of long-term liver inflammatory conditions through a variety of heterogeneous hepatocellular damage pathways, which may eventually lead to hepatocellular death, stellate cell activation, and the deposition of connective tissue matrix.[11–13]

Histopathology

The histologic manifestations of NAFLD are diverse, ranging from moderate to more severe cases of steatosis exhibiting portal and lobular inflammation, ballooning hepatocytes, fibrosis, and cirrhosis. Steatosis has several morphological appearances. Macrovesicular steatosis appears when large lipid droplets fill the cytoplasm and displace the nucleus. Meanwhile, microvesicular steatosis occurs when there is an accumulation of large amounts of lipid droplets, but the nucleus remains in place. Lipid droplets are formed from a triacylglycerol core with or without cholesterol esters and phospholipids peripheral monolayer.[6]

Structure of vitamin E

The identification of vitamin E occurred in 1922 when Herbert Evans et al. were observing the fat-soluble component of green leafy vegetables needed for the reproductive process of mice. At that time, this component was called tocopherol (Greek: ol = alcohol, pheros = giving birth, and tocos = childbirth). Currently, the term vitamin E refers to a group of 8 compounds produced by various homogentisic acid plants. This group of molecules consists of 4 tocopherols and 4 tocotrienols. The saturated form of vitamin E is called tocopherols, whereas the unsaturated form, called tocotrienols, has isoprenoid side chains. Based on hydroxyl and methyl substitutions within the phenolic rings, tocopherols and tocotrienols are classified as alpha, beta, gamma, and delta forms, respectively. The most prevalent form of vitamin E found in nature is alpha-tocopherol. Its form of vitamin E is the most researched. Various plant oils like corn oil, peanut oil, and soybean oil have high alpha-tocopherol content. In contrast, tocotrienols are rarely found in food but can be found in barley, oats, rice bran, and palm oil. Today, the synthetic form of vitamin E consists mainly of α-tocopherol, which was initially synthesized in 1938.[14,15]

Metabolism of vitamin E

In line with other vitamins that are fat-soluble, the formation of micellar structures, bile secretion, pancreatic activity, and intestinal membrane penetration all affect vitamin E's bioavailability.[16] Following their breakdown by intestinal wall esterase enzymes and partial digestion by gastric lipase, the isoforms of vitamin E are transported to the enterocytes' basolateral side. Triacylglycerols, phospholipids, cholesterol, and vitamin E tocotrienols and tocopherols from food are absorbed in the intestinal lumen Together with fat derived from food and distributed as chylomicron particles. Vitamin E isoforms bound to chylomicrons are transferred to peripheral tissues such as adipose tissue, bone, skin, muscle, lung, and brain via the lymphatic system.

During transport, the endothelial-bound enzymes catabolize chylomicrons in the circulation. The catabolized chylomicrons then hydrolyze triglycerides and release FFA after being absorbed by the liver through a receptor. The remnant of the resulting chylomicrons that contain absorbed E vitamins will be incorporated with high-density lipoprotein (HDL) and very low-density lipoprotein (VLDL) and released into the bloodstream. The process of bio-discrimination, which emphasizes the selective recession of alpha-tocopherol from the liver to the plasma, is carried out by α-Tocopherol transfer protein (α-TTP), a cytoplasmic protein found in the liver that has different affinities for each form of vitamin E. α-TTP exhibits a 100% affinity for alpha-tocopherol, but its affinity for other isoforms is comparatively lower. It only has a 50% affinity for β-tocopherol, a 10%–30% affinity for γ-tocopherol, and a 1% affinity for δ-tocopherol. Vitamin E isoforms that are not attached to α-TTP can be catabolized in the liver by cytochrome P450 (CYP4F2), initiating ω-hydroxylation and oxidizing it with ω-hydroxylase. Subsequently, the isoforms of vitamin E are converted into derivatives such as carboxyromanol, hydroxychromanol, and carboxylhydroxychroman. In addition to catabolism, it is considered that the isoforms of vitamin E that metabolized are also eliminated by biliary excretion.[16–18]

The activity of vitamin E

An imbalance between reactive species formation and antioxidant defenses is known as oxidative stress. It will cause DNA damage and cellular biological disturbances. One of the strongest antioxidants in nature is vitamin E. Its antioxidant properties are due to the presence of the hydroxyl component of the tocochromanol aromatic ring, which provides hydrogen atoms to neutralize ROS or unbound radicals. Additionally, there has been an increase in interest lately in the antioxidant role of vitamin E on reactive nitrogen species (RNS). RNS consists of peroxynitrite (ONOO-), nitrogen dioxide (NO_2), and nitric oxide (NO).[19–21]

However, under some circumstances—such as persistently low levels of radical flux and the lack of co-antioxidants like vitamin C—vitamin E can become a pro-oxidant, according to in vitro studies. Furthermore, the findings of multiple in vivo investigations indicate that vitamin E may have pro-oxidant effects when taken in high doses or in smokers who consume diets high in polyunsaturated fats.[22]

Vitamin E's biological activity extends beyond its capacity as an antioxidant. Indeed, the regulation of inflammatory responses, gene expression, membrane-bound enzymes, cellular signaling modulation, and proliferation of cells are all affected by vitamin E. A variety of other enzymes that are involved in signal transduction are also affected by vitamin E, both directly and indirectly. These enzymes include diacylglycerol kinase (DAGK), protein kinase C (PKC), protein phosphatase 2A (PP2A), protein tyrosine phosphatase (PTP), protein tyrosine kinase (PTK), 5-, 12-, and 15-lipoxygenases (5-, 12-, and 15-LOX), cyclooxygenase-2 (COX-2), phospholipase A2 (PLA2) and the mitogen-activated protein kinase (MAPK) signal transduction pathway.[15]

Experimental studies of vitamin E and NAFLD

The methionine and choline-deficient (MCD) diet is the diet used in non-alcoholic steatohepatitis studies on experimental animals. The MCD diet is low in choline and methionine, which are crucial for the synthesis of VLDL and hepatic beta-oxidation, and high in fat (10%) and sucrose (40%). Research conducted with rats given an MCD diet demonstrated that vitamin E markedly decreased oxidative stress. Depletion of liver glutathione storage, decreased steatosis, inflammation, activation of hepatic stellate cells, expression of collagen mRNA, and improvement of fibrosis were observed in the control group.[23]

Larter et al. conducted research using mice fed an MCD diet containing 20% fat and 5% fat for 3 weeks. As a result, administration of the MCD diet raised serum ALT levels and caused lobular inflammation, balloon degeneration, and hepatic steatosis in hepatocytes. The mice in the high-fat diet MCD group

and the mice in the low-fat diet MCD group accumulated triglycerides in their livers nearly equally, but the high-fat MCD group had three times higher levels of lipoperoxide. The increase in lipid intake in this study did not affect the severity of steatohepatitis. However, the steatohepatitis that occurred was associated with impaired hepatic adiponectin activity and hepatocyte adipogenic transformation in both mouse groups.[24]

Research conducted by Nan et al. in mice fed the MCD diet showed an increase in serum levels of ALT and AST as well as steatosis and inflammatory infiltrates in the liver. Administering vitamin E and/or aminobenzotriazole can reduce alanine aminotransferase and aspartate aminotransferase levels and improve hepatic steatosis and necroinflammation.[25] Research conducted by Karimian et al. showed that mice underwent partial hepatectomy could accelerate the progression of NAFLD, but this progression could be inhibited by vitamin E.[26] While Chung et al. found that elevating hepatic α or γ-tocopherol provided protection against lipopolysaccharide-induced NASH through the reduction of liver damage, lipid peroxidation, as well as inflammation without altering hepatic steatosis or body mass.[27]

Studies of vitamin E and NAFLD in human

Vitamin E has been utilized as monotherapy or in combination with other drugs in several clinical trials to manage NAFLD, with improvements in liver histology and biochemistry. The length of these clinical trials ranged from 24 weeks to 2 years, and the daily doses were between 100 and 1200 IU.[28]

There are 2 well-known studies regarding the vitamin E's effects on NAFLD, namely the Pioglitazone, Vitamin E or Placebo for Nonalcoholic Steatohepatitis (PIVENS) and the Treatment of NAFLD in Children (TONIC) tests.[29,30]

Vitamin E was investigated as a treatment for nonalcoholic steatohepatitis in the PIVENS trial. The results were significantly higher in the group of patients who were given high-dose of vitamin E (800 IU/day) in ninety-six weeks of treatment compared to placebo (43% vs 19%, p = 0.001), while pioglitazone did not produce a statistically significant difference. Histopathological examination revealed that there was a decrease in the ballooning of the hepatocyte and lobular inflammation, which reflects the expected effect of antioxidants leading to reduced oxidative stress-mediated damage. Interestingly, the administration of vitamin E also significantly decreased hepatic steatosis and alanine aminotransferase levels but had no significant effect in the occurrence of fibrosis.[29]

In response to these findings, Lavine et al. carried out a multicenter, double-blind, double-placebo randomized clinical trial in children. In the TONIC trial, 173 pediatric patients, who were on average age of 13 years old, were given either a placebo, 400 IU of vitamin E, or 500 mg of metformin twice a day for 96 weeks. A reduction in ALT levels (≤50% baseline or ≤40 U/L from 48 weeks to 96 weeks of treatment) was the primary outcome. The histological picture that improves in non-alcoholic steatohepatitis after treatment with these two treatments is hepatocellular ballooning. However, neither metformin nor vitamin E was better than the placebo in reducing ALT levels or improving the scores of steatosis, lobular inflammation, or fibrosis.[30]

Previously, Lavine et al. also conducted research aimed at determining whether oral vitamin E supplementation could reduce aminotransferase and alkaline phosphatase levels in children with obesity-related non-alcoholic steatohepatitis. This study involved children aged less than 16 years who were diagnosed with non-alcoholic steatohepatitis with increased serum aminotransferase concentrations for more than 3 months. These patients were given oral vitamin E between 400 and 1200 IU per day. This study concluded that daily oral administration of vitamin E can normalize serum aminotransferase and alkaline phosphatase levels in pediatric patients with non-alcoholic steatohepatitis.[31]

After four years of therapy, studies using vitamin E in combination with atorvastatin and vitamin C

showed that it was effective in lowering hepatic steatosis among individuals with NAFLD diagnosed by computed tomography (CT). In a small-scale trial, the efficacy of ursodeoxycholic acid (UDCA) combined with vitamin E was assessed in comparison to either UDCA or placebo alone. Improvements in steatosis and transaminase levels occurred only in the group receiving combination therapy. With long-term (>2 years) evaluation of the effectiveness of co-combination (UDCA and vitamin E) among patients who have non-alcoholic steatohepatitis, Piettu et al. found improved histologic lesions in most patients.[32,33]

In a study by Nobili et al., 90 children diagnosed with NAFLD were given a workout plan and diet low in calories. The children were divided into 2 groups: 45 children were given vitamin E therapy (600IU/day) with a combination of 500 mg/day of ascorbic acid, and 45 children were given a placebo. Twenty-four months later, both groups experienced improvements in steatosis, lobular inflammation, and hepatocyte ballooning states. When compared to placebo, ascorbic acid and alpha-tocopherol additions did not, however, show any improvement in histology or biochemistry.[34]

Currently, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) provide guidance on the use of vitamin E as a potential short-term therapy for adult patients who biopsy-diagnosed non-alcoholic steatohepatitis without diabetes. Vitamin E is not suggested for use in treating non-alcoholic steatohepatitis in diabetic NAFLD without a liver biopsy, cirrhosis, or cryptogenic cirrhosis patients until adequate evidence of its efficacy is available.[15]

2. Conclusion

The pathogenesis of NAFLD is very complex and is associated with obesity, type 2 diabetes mellitus, insulin resistance, hepatitis, and fibrosis. A better understanding of the mechanisms of NAFLD pathogenesis is necessary for the development of preventive and therapeutic strategies. The development of NAFLD begins with an increase in ROS production and changes in the production of adipokines, chemokines, and various cytokines. The latest strategies in managing NAFLD include the use of antioxidant micronutrients such as vitamin E.

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