

Anti-Oxidants for NAFLD: a concise review

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Abstract: This review is done to briefly highlight the therapeutic options available for NAFLD (Non-Alcoholic Fatty Liver Disease), and the role of anti-oxidants in support of NAFLD. PubMed and Google Scholar search was done using the keywords such as NAFLD, Liver cirrhosis, fibrosis, steatosis, anti-oxidants, inflammatory markers, apoptosis. This review article contains precise data from a few crucial recent articles that throw light on the current situation and treatment options available for NAFLD patients. NAFLD was recently re-termed as MAFLD (Metabolic Associated fatty Liver Disease) and has started affecting a significant proportion of the population mainly due to the incidence of metabolic syndrome as one of the greatest risk factors of NAFLD. Therapeutic options for the same have been studied for a long time but no single effective option has been discovered yet. Understanding the mechanism of NAFLD has led to the use of vitamins especially vitamin E and other substances such as polyphenols which are the emerging new options included for the treatment. These targets the reactive oxygen species, inflammatory markers, modulate fatty acid oxidation, and insulin resistance. Recent guidelines have recommended the use of Vitamin E in biopsy-proven NAFLD patients without diabetes. On the contrary, vitamin E has side effects seen at certain doses due to which the therapeutic ability although most effective, is limited in such patients. Despite the risk profile, vitamin E is still considered one of the safest options due to patient tolerability and improvement in NAFLD stages that has been proven histologically as well but in non-diabetic patients. This article also provides a brief insight into other therapeutic options available in the category of nutrients. There is a need for research to look into more options available as treatment and also to identify the risk and benefits of vitamin E to find a more permanent therapeutic solution for NAFLD patients.

Key words: NAFLD, steatosis, liver fibrosis, vitamin E, anti-oxidants, liver inflammation.

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Abbreviations: NAFLD, Non-Alcoholic Fatty Liver Disease; MAFLD, Metabolic Associated fatty Liver Disease; NASH, non-alcoholic steatohepatitis; AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of the Liver; ROS, reactive oxygen species; TGF β -1, Transforming growth factor Beta-1; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; COX-2, Cyclooxygenase; ALT, Alanine aminotransferase; UDCA, Ursodeoxycholic acid.

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Introduction

Primary prevention and lifestyle changes have been the center for the treatment of Metabolic Associated Fatty Liver Disease (MAFLD) ((initially termed as Non-alcoholic fatty liver disease (NAFLD))) [1]. NAFLD is one of the most common liver diseases that affect significantly a huge proportion of the population mainly due to the already existing risk factors present in a certain type of elderly population. On the other hand, young individuals are at high risk too due to obesity and consumption of foods depleted in fiber and vitamins. NAFLD comprises four stages namely, hepatic steatosis, non-alcoholic steatohepatitis (NASH), leading to fibrosis, and non-reversible cirrhosis [2].

NAFLD is said to be associated with obesity, hypertension, insulin resistance, and lipid abnormalities that comprise the spectrum of metabolic syndrome [3]. It is said that 90% of NAFLD patients have at least one of the above metabolic syndrome components while 33% may have three or more [4]. Oxidative stress and insulin resistance play a vital role in the progression towards NAFLD [5]. There are several causes due which oxidative stress occurs that are mediated by reactive oxygen species in the hepatic environment. An increase in the number of fatty acids results in increased oxidative stress levels that further cause the formation of reactive oxygen species promoting hepatocyte injury [6]. Due to these reasons, vitamin E with antioxidant properties shows a potential benefit in treating NAFLD [6]. Apart from vitamin E offering anti-oxidant effects, it also has anti-inflammatory effects that drastically reduce the inflammatory markers and cytokines which in turn reduces inflammation and steatosis in NAFLD [6].

There are no approved medications particularly for NAFLD [7]. Therapeutic options targeting each of the components of metabolic syndrome is the mainstay of the treatment today that has shown results in slowing down the progression to cirrhosis in NAFLD patients. According to previous researches, vitamins with antioxidant properties have been shown to offer health benefits especially in cases of NAFLD by decreasing reactive oxygen levels and preventing oxidative damage that can slow down the progression of hepatic injury [6].

Currently, available data regarding the efficacy of vitamin E is not enough to provide support in the therapeutic options in NAFLD patients with diabetes. The guidelines by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) have also recommended vitamin E in patients with biopsy-proven steatohepatitis in those patients without diabetes [7,8]. Apart from vitamin E, other nutrients such as vitamin C, micronutrients, and polyphenols have shown some beneficial effects in a few of the

studies undertaken to test their efficacy [9-12]. Improvements have been demonstrated by biopsy results, decrease in liver enzymes, and anthropometric measurements. Some of the research has been carried out on animals and have not been tested on humans [9-11].

The focus of this article is to highlight the role and efficacy of anti-oxidants in the treatment of NAFLD that slows down the progression to steatohepatitis and cirrhosis. Because of the ability of Vitamins to reduce oxidative stress, they are considered as one of the promising therapeutic options in the treatment of NAFLD.

Role of Anti-Oxidants

Vitamin E

Antioxidant and Anti-inflammatory properties

Due to its antioxidant properties, vitamin E is effective against the reactive oxygen species (ROS) and also the cytokine TGF β -1 (Transforming growth factor Beta-1) related liver fibrosis that occurs in NAFLD by repressing the peroxidation which decreases hepatocyte apoptosis [13,14]. Oxidative changes, cytokine release, and metabolic demands play a major role in the progression of the disease. Out of all the forms of vitamin E, alpha-tocopherol is the most powerful and active in fighting off the disease, and hence vitamin E is considered the powerful chain-breaking antioxidant in the human body [15]. Vitamin E has also been shown to increase the actions of other antioxidants such as superoxide dismutase, catalase, and glutathione dismutase [15-18]. Researches have shown that Vitamin E supplementation can cause changes in gene expression that can decrease c-myc and TGF β -1 leading to decreased production of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) which is a major contributor to oxidative stress [19]. Vitamin E is a powerful anti-inflammatory agent and it works by increasing Adiponectin and Nuclear localization of NF- κ B, and decreasing the levels of TNF- α IL-1,2,4,6,8 and COX-2 (Cyclooxygenase). These mediators are the main culprit in increasing the inflammation in liver causing liver steatosis and hepatitis [3,13,16,18].

Anti-Apoptotic properties

Anti-inflammatory and anti-apoptotic properties of vitamin E also provide benefits in treating NAFLD. Adiponectin mRNA and protein levels are increased with vitamin E supplementation that suppresses hepatic fatty acid synthesis and reduces inflammation in patients with NAFLD. Vitamin E increases levels of BCL-2 which is an anti-apoptotic protein and decreases levels of BAX and p53 which are pro-apoptotic proteins as well as Caspases-8,9 and 3 and cytochrome C in the apoptotic pathway [20]. Cell

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signaling and cellular proliferation are hence modulated due to which the chances of cellular injury are drastically reduced [21,22].

Therapeutic and Risk profile of Vitamin E

A study from Japan by researchers Nagashimada and Ota has stressed vitamin E as a therapeutic option for NAFLD but has pointed out the fact that still significant research is required in the pathogenesis of NAFLD to assign a proper treatment. Vitamin E is said to regulate hepatic homeostasis that halts progression to fibrosis [23]. Research by Schurks, et al, have shown concern regarding the amount of vitamin E supplementation that can do more harm than benefit in cases with NAFLD [24]. According to the research, an amount more than or equal to 400 IU/day can significantly increase the mortality due to hemorrhagic stroke or prostate cancer [25,26]. It is still under debate whether Vitamin E is associated with all-cause mortality when used for long periods or in increased amounts in patients with steatohepatitis and fibrosis in NAFLD. Vitamin E is the only antioxidant with anti-inflammatory and anti-apoptotic properties [27].

Other major studies by Nobili, et al, Ersoz, et al, Wang, et al, Zohrer, et al, etc, combined vitamin E therapy with diet, exercise, and lifestyle changes and showed only biochemical improvement in decrement of ALT (Alanine aminotransferase) levels [37-40]. Combination therapy of vitamin E with vitamin C, UDCA (Ursodeoxycholic acid) and have not only demonstrated a decrease in ALT levels but also showed signs of improvement histologically [32,34,35]. There is no such exact dose at which vitamin E is prescribed, the dose and duration depend upon the patient's profile, etiology of NAFLD, the degree of liver damage as evidenced by imaging, and other risk factors.

Role of other Nutrients in NAFLD

Vitamin D

Much has been debated about vitamin D in NAFLD. Despite a deficiency of vitamin D in NAFLD, there is a risk in supplementing vitamin D to these patients due to hypercalcemia [41]. Increased calcium has been shown to harm rather than benefit patients with NAFLD as stated earlier [42]. According to researchers such as Sheriff, Nobili, and Reif, Vitamin D carries the ability to reduce the anti-inflammatory markers and act as an anti-fibrotic to reduce hepatic proliferation in patients with NAFLD [43,44]. Despite these beneficial effects, strong pieces of evidence in terms of improved histopathology are lacking in support and research needs to be carried to understand the pathophysiology in these cases.

Other Vitamins

Vitamin C is often given in combination with Vitamin E to enhance the anti-oxidant property [38,45].

Vitamin A on the other hand has not been studied extensively but researchers have found its deficiency along with vitamin D in patients with NAFLD [46,47]. Enough research has not been done on vitamin A and its relation to NAFLD.

Micronutrients

Researcher Perumpail also highlighted information about other micronutrients that have useful or harmful effects on NAFLD [27]. Such as iron has shown an inverse relation with NAFLD treatment as it worsens steatohepatitis and liver enzymes but this has only been proven in animal studies [9]. Other micronutrients like Zinc, Selenium, Calcium, Magnesium, and Phosphorus have shown no benefit as well in improving the liver enzyme levels and are associated with increased incidence of NAFLD. Only Zinc supplementation with selenium decreases the AST ALT levels in these patients. All these findings are a result of animal research and still, a lot needs to be done in this field to come up with reliable treatment options concerning micronutrients [10,11].

Role of Polyphenols

Polyphenols are plant-derived compounds that have been associated with a promising therapeutic option for NAFLD [48]. Rodriguez-Ramiro et al, found out that polyphenols not only reduce fatty acid oxidation but also modulate insulin resistance and lowers oxidative stress [49]. Polyphenols are not as essential as vitamins but recently some research has been done on the same to find out more about its therapeutic effect in patients developing steatohepatitis and fibrosis in NAFLD [49]. Some clinical trials and in-vitro studies have reported promising hepatoprotective results that can slow down the progression to permanent damage in NAFLD patients [12, 49, 50].

Doses of polyphenols and Resveratrol (a stilbenoid polyphenol) ranging from 150mg up to 3000mg have been tried and tested for 4 weeks, 8 weeks, and 12 weeks by different researchers in patients with NAFLD [51-56]. Studies also substituted pomegranate juice with a hypocaloric diet for 12 weeks in such patients [56]. These studies by eminent researchers clarified the fact that polyphenols did have weightage in reducing the progression by changing the anthropometric measurements significantly such as waist circumference, body mass, weight, and also the degree of steatosis [54-56]. Resveratrol on the other hand showed improvement in the lifestyle changes associated with physical activity [50]. Chen, et al and Ekhlasi, et al experimented with Resveratrol and pomegranate juice respectively, and discovered

Table 1. Liver Injury in NAFLD and Therapeutic Action of Vitamin E

Mode of Liver Injury	Final Hit	Result of Injury	Mechanism of action of Vitamin E
Oxidative Stress			↑ SOD, Glutathione Peroxidase, Catalase, Lipid Peroxyl Radical Scavenging ↓ C-myc, TGF- α , TGF- β , NADPH Oxidase
Inflammation	Lipid Peroxidation and FFA	MAFLD → Cirrhosis	↑ Adiponectin ↓ TNF- α IL-1,2,4,6,8 ↓ COX-2 ↑ Nuclear localization of NF- κ B
Apoptosis			↑ BCL-2 ↑ BAX, P53 ↑ Cytochrome C ↑ Caspases 9,8,3

Abbreviations: FFA = Free Fatty Acids; MAFLD = Metabolic Associated Liver Disease; SOD = Superoxide Dismutase; NADPH = Nicotinamide adenine dinucleotide phosphate; COX = Cyclooxygenase.

Table 2. Vitamin E therapy in NAFLD – Review of Major studies

Reference/Author	Vitamin E Dose	Treatment Duration	Type of Therapy (Monotherapy or Combination)	Beneficial Effects
Lavine et al. 2011[5]. (TONIC TRIAL)	400 IU Twice Daily	96 weeks	Monotherapy	Decrease in Hepatic Ballooning
Sanyal et al. 2010 [28]. (PIVENS TRIAL)	800 IU Once daily	96 weeks	Monotherapy	Decrease in ALT, steatosis, Inflammation
Bugianesi et al. 2005 [29].	400 IU Once Daily	1 year	Monotherapy	Decrease in ALT
Kugelmas et al. 2003 [30].	800 IU Once daily	12 weeks	Monotherapy	Decrease in ALT
Hasegawa et al. 2001 [31].	300mg Once Daily	1 year	Monotherapy	Decrease in ALT, Steatosis, Inflammation, Fibrosis.
Pietu et al. 2012 [32].	500 IU Once Daily	4 years	Combination with UDCA	Decrease in ALT, steatosis, Inflammation, fibrosis
Foster et al. 2011 [33].	1000 IU Daily	4 years	Combination with vitamin C and Atorvastatin	Decrease in steatosis based on CT findings.
Dufour et al. 2006 [34].	400 IU Twice Daily	2 years	Combination with UDCA	Decrease in ALT and Steatosis
Sanyal et al. 2004 [35].	400 IU Once Daily	6 months	Combination with Pioglitazone	Decrease in ALT, Inflammation and Ballooning
Harrison et al. 2003 [36].	1000 IU daily	6 months	Combination with vitamin C	Decrease in Fibrosis

Abbreviations: ALT = Alanine aminotransferase; CT = Computed Tomography Scan; NAFLD = Non-Alcoholic Associated Fatty Liver Disease; UDCA = Ursodeoxycholic acid

that these had a significant effect in NAFLD patients by the reduction in the liver enzymes and decreasing the insulin resistance [50, 52]. Similarly, reduction in the cytokines and interleukins have also been noticed [12, 49, 50]. As of now, polyphenols' effectiveness has been proven by liver ultrasound and clinical studies but not by actual biopsy results. Nevertheless, polyphenols have not shown any harmful effects and are still considered beneficial in patients with metabolic-associated fatty liver disease or NAFLD that could aid in improving the life of such patients.

Role of Diet

There is no specific diet assigned for NAFLD patients but as the name suggests, the dietary changes about reducing the fat and decreasing insulin resistance are preferred to slow down the progression to permanent liver damage. Diabetes, dyslipidemia, obesity is the major risk factors that need to be looked out for when suggesting any treatments and lifestyle modifications in NAFLD patients [57]. Some studies have reported low mortality risk and reduced incidence of chronic metabolic diseases with the Mediterranean diet. It is not specifically designed for NAFLD patients but it has been shown to reduce the incidence of risk factors and modify eating habits that are beneficial in NAFLD patients mainly due to the enhancement of anti-oxidation present in the dietary foods [58, 59].

Novel Therapeutic Options

As stated earlier, researches are being carried out to gain further insight into the pathophysiology and related treatment options for NAFLD. Certain drugs are still in the clinical trial phase and are being tested for further approval. Drugs like Selonsertib and Cenicriviroc have shown anti-inflammatory and anti-fibrotic effects in patients with NAFLD [60]. Nevertheless, it is still imperative to prescribe anti-oxidants and other treatment options available for NAFLD to prolong the prevalence and reduce the progression of the disease to cirrhosis and hepatocellular carcinoma.

Conclusion

This review was written to concisely highlight the crucial aspects and profile regarding the treatment of NAFLD with anti-oxidants and vitamins. Although other options as treatment are available for metabolic syndrome in NAFLD this article mainly focuses on the role of vitamins and anti-oxidants for NAFLD. Researches and clinical trials are still going on to identify the best

therapeutic options apart from vitamins and lifestyle changes as these just slow down the progression but do not halt the disease. Present therapeutic options are effective due to their antioxidant and anti-inflammatory properties as these targets the main mechanism of occurrence of NAFLD. Improvement in the liver enzyme levels and degree of steatosis only prolongs the prevalence but does not prevent the final stage of cirrhosis. On the other hand, vitamin E carries side effects as well that needs to be studied extensively as it is one of the promising therapeutic options available today for NAFLD.

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