Review paper

The role of vitamin and microelement supplementation in the treatment of ethanol-induced liver disease

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Abstract

High alcohol intake leads to an inadequate diet and impaired absorption, transport, and utilization of nutrients in the body, which results in malnutrition. Micronutrient supplementation, such as vitamins A, E, group B vitamins, folic acid zinc, and selenium may have a positive effect on those patients. In this article, the actual supplementation recommendations for vitamins and microelements in ethanol-induced liver disease patients are presented.

Introduction

Alcohol consumption is linked to more than 200 diseases and injury-related health conditions [1]. It is the third most common cause of preventable diseases worldwide after smoking and hypertension [2]. Ethanol-induced liver disease comprises a heterogenous group of diseases, including alcoholic fatty liver, alcoholic hepatitis, steatohepatitis, liver fibrosis, cirrhosis, and hepatic cell carcinoma (HCC) [3]. It is a significant burden to healthcare systems; it is one of the leading causes of mortality worldwide, and in the US it has become the most common indication to perform a liver transplant [1]. In 2010 alcoholic cirrhosis was responsible for almost 500,000 deaths globally, which translates to 0.9% of all deaths, and all alcohol-related deaths may translate to up to 6% of all global deaths [4]. Excessive alcohol consumption leads to inadequate diet [5]. Low to moderate alcohol consumption also increases food intake in both the short (after one portion) and long term. However, in high-dose alcohol intake, loss of appetite and early satiety may occur, as well as lowering of muscle mass and loss of body weight [6, 7]. These effects may originate from alcohol's high energy concentration, which may result in displacing other nutrient-dense meals, and lead to primary malnutrition [8]. In patients consuming more than 30% of their calories as alcohol, their intake of vitamins might not meet the minimal dietary recommendations [8, 9], whereas in ethanol-induced liver disease often more than 50% of calories come from the intake of alcohol. Alcohol toxicity impairs the absorption, transport, and utilization of essential nutrients, which leads to secondary malnutrition [8, 9]. Long-term ethanol consumption also increases small bowel transit, making the absorption of nutrients more difficult. Consumption of more than 100 g of ethanol per day increases the risk of alcoholic chronic pancreatitis 11-fold, which can cause severe maldigestion and further worsen the undernutrition of those patients, although it must be stated that the prevalence of alcoholic chronic pancreatitis amongst alcoholics is low and does not exceed 3% [10]. In ethanol-induced liver disease micronutrient depletion is common [11]. Micronutrient supplementation, such as vitamins A, E, group B vitamins, zinc, and selenium, may have a positive effect on those patients [12]. In this review we analyse the current literature to assess the need to provide adequate supplementation to the patients.

Vitamin A

Ethanol-induced liver disease is associated with lower levels of hepatic retinoid contents, and the degree of this reduction is correlated with disease severity [12]. Among alcoholic cirrhotic patients, the prevalence of vitamin A deficiency may be as high as 50% [13]. In patients evaluated for liver transplantation, regardless of the indication, the prevalence of vitamin A deficiency is 69.8% [14]. To date, there is a scarcity of evidence of vitamin A supplementation in ethanol-induced liver disease patients – oral supplementation of 2500 UI/day of vitamin A orally for 5 days given to 25 chronic alcoholics increased the serum levels in all but 2 patients [15]. Larger studies considering long-term outcomes in those patients are still lacking. If supplementation is considered, one must remember that because of the impaired hepatic metabolism in ethanol-induced liver disease, and because of potentiating the retinol toxicity by ethanol, the usual doses of vitamin A may be toxic to ethanol-induced liver disease patients [16].

Vitamin B_6 – pyridoxine

Vitamin B6 deficiency is very uncommon in the general population [17]. It mostly occurs as a part of mixed vitamin B hypovitaminosis with alcoholism as the main cause [17]. Supplementation with a daily dose of 100 mg is recommended when levels of plasma PLP are below < 20 nmol/l with hypovitaminosis symptoms [18]. Pyridoxine, when administered at 1000 mg or more daily for more than 12 months may lead to an overdose that results in peripheral sensory neuropathy [19].

Vitamin B_1 – thiamine

The main form of vitamin B1 in the human body is thiamine pyrophosphate. Hypovitaminosis B1 causes beriberi syndrome [20]. There are 2 forms of this condition: wet beriberi, in which the cardiovascular system is affected, and dry beriberi, which affects the nervous system [20]. In 12.5% of alcoholics, B1 deficiency may result in dry beriberi- possibly reversible Wernicke encephalopathy [21]. Alcoholics with uncomplicated alcohol dependence (low risk of severe thiamine deficiency) should take 250–500 mg of thiamine orally for 3–5 days, with a maintenance dose of 100–250 mg orally for as long as alcohol consumption continues. Alcohol addicts with malnutrition (severe risk of thiamine deficiency) should be given 250–500 mg of thiamine IM or IV for 3–5 days with a maintenance dose of 250–300 mg orally. For patients with diagnosed Wernicke encephalopathy, it is recommended to give parenteral thiamine 200–500 mg 3 times a day for 3–5 days, followed by oral thiamine 250–1000 mg/day [22].

Vitamin B_2 – riboflavin

Riboflavin deficiency is correlated with alcohol abuse. Alcohol diminishes the bioavailability of riboflavin and impairs the transport of flavin adenine dinucleotide across the epithelial layer within the small intestine [23]. Hypovitaminosis B_2 is not common [24]. To date, there are no clear recommendations for its supplementation in alcoholics. The recommended daily dose in healthy adults is 1.4 mg/day, and according to the Summary of Product Characteristics the recommended supply of vitamin B_2 is 15–25 mg/day orally as prophylaxis in alcoholics [25].

Vitamin B_3 – niacin

Niacin most frequently occurs in the form of nicotinic acid and nicotinamide. Alcohol use can impair the conversion of tryptophan to niacin [26]. Recommended daily dose for healthy adults is 15–20 mg of vitamin B_3 a day. For treatment purposes, the daily recommended dose is 250–300 mg of nicotinamide in split doses [26]. Because niacin deficiency is often seen together with depletion of other group B vitamins, supplementation is recommended in the form of vitamin b-complex formulas. High levels of niacin (3000 mg/day) may cause overdose symptoms, and prolonged exposition can cause hepatotoxicity [27].

Vitamin B_5 – pantothenic acid

B_5 deficiency occurs as a part of combined vitamin B deficiency. Sole supplementation is not recommended. As a part of vitamin B complex it is suggested for alcoholics to be administered 15–25 mg daily in split doses [28]. In alcohol-related peripheral neuropathy administering pantothenic acid as a component of vitamin B complex preparations resulted in partial remission of symptoms [28].

B_{12} – cyanocobalamin and B_9 folate

Up to 80% of hospitalized alcohol abusers suffer from folate deficiency and over 25% have vitamin B_{12} hypovitaminosis [29]. Alcoholics suffer from cyanocobalamin deficiency due to low intake, impaired absorption, and impaired release of vitamin B_{12} from food proteins. Impaired intestinal absorption also causes folate deficiency, as well as decreased hepatic storage and reduced renal reabsorption [18]. According to researchers, when low plasma concentrations are recognized, B_{12} deficiency is treated by intramuscular injections of 1000 µg every other day for 3 weeks. The maintenance dose can be administered IM (1000 µg once a month) or orally (1000–2000 µg once a day); both strategies are equally effective [18]. For folic acid deficiency, the

first line of treatment is intravenous supplementation in doses of 0.4–1.0 mg for 3 days; then, daily intake of 400 µg orally is recommended. Studies show that supplementation of over 1 mg of folic acid per day can be unsafe for the nervous system and can also mask the B_{12} deficiency, so it is not recommended [30].

Vitamin D

The levels of serum concentration of vitamin D are 28% lower in alcoholics than in non-alcoholics, due to malabsorption caused by cholestasis or pancreatic insufficiency, poor dietary intake, lack of sunlight exposure, impaired renal synthesis, increased 1,25-dihydroxyvitamin D($1,25OH_2D$) degradation, and direct bowel mucosal lesions [31]. There is evidence that not only alcoholic cirrhosis is correlated with lower levels of serum vitamin D, but also that adequate vitamin D supplementation seems to improve the prognosis, as determined in the Child-Pugh score [32]. Despite the standard dose supplementation, in a large proportion of cirrhotic patients serum concentrations of vitamin D remain low, which may suggest a need to use a higher-dose supplementation [33]. There is also some evidence that a single megadose of vitamin D (300,000 international units in the form of cholecalciferol, orally) is also effective in the treatment of vitamin D deficiency [34]. Despite promising results, the overall availability of high-quality evidence is still low, and more studies need to be conducted.

Zinc

The liver is the most important organ responsible for the metabolism and storage of zinc [35]. In ALD the zinc content in the body is decreased due to reduced hepatic secretion (including albumin), redistribution of fluids (zinc moves from the intracellular to extravascular space), and loss in urine due to increased muscle catabolism and the use of diuretics, disorders of absorption in the intestine due to portal hypertension, and reduced food consumption [36].

Additionally, there is a negative correlation between the degree of liver fibrosis and the body's zinc content, and zinc deficiency is positively associated with an increase in the inflammatory response and apoptosis of hepatocytes [37]. There is evidence that liver function improves in ethanol-induced liver disease patients after receiving zinc supplementation [36]. Miwa *et al.* described a promising effect of zinc supplementation in the prevention of hepatic encephalopathy and improved prognosis in patients with hepatic encephalopathy in cirrhosis [38]. The supplementation of zinc probably also reduces the risk of neoplastic transformation into HCC in liver cirrhosis [39]. The latest proposition of a dosing regimen of zinc in ALD deficiency was presented by Bloom *et al.*, who recommended a dose of 75 or 50 µg of elemental zinc for a period of 3–6 months depending on the degree of deficiency found in laboratory tests. It is recommended that the serum zinc concentration is tested once every 3 months during supplementation [40]. Due to the promising impact of zinc supplementation on ALD patients, further clinical trials are needed to determine the optimal doses and duration of zinc supplementation.

Selenium

Selenium deficiency is often seen in ALD [41]. It has been shown that the level of selenium is lower in the group of patients with alcoholic liver cirrhosis compared to healthy ones, and it decreases proportionally with the degree of liver fibrosis [42]. The lowest concentration of serum selenium among liver diseases is found in HCC [18].

Selenium loss is mostly caused by the use of diuretics [43]. In the analysis conducted by Adali *et al.* on rats, it was found that selenium supplementation leads to a decrease in histological damage to the liver [44], which is the theoretical basis for the possible beneficial effect of selenium supplementation in ethanol-induced liver disease patients [44]. However, there are no prospective studies in humans.

Summary

Ethanol-induced liver disease is the third most common cause of preventable diseases worldwide after smoking and hypertension. It is a great burden for healthcare systems worldwide. There is no specific treatment, but cessation of alcohol consumption may stop further liver damage. Proper supplementation of vitamins and micronutrients may prevent malnutrition and therefore help in liver cell regeneration and improved metabolism.

Conflict of interest

The authors declare no conflict of interest.

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