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**Current understanding of the metabolism of micronutrients in chronic alcoholic liver disease**

Wu J *et al*. Micronutrients in chronic alcoholic liver disease

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**Abstract**

Alcoholic liver disease (ALD) remains an important health problem worldwide. Perturbation of micronutrients has been broadly reported to be a common characteristic of patients with ALD, given the fact that micronutrients often act as composition or coenzymes of many biochemical enzymes responsible for the inflammatory response, oxidative stress, and cell proliferation. Mapping the metabolic pattern and the function of these micronutrients is a prerequisite before targeted intervention can be delivered in clinical practice. Recent years have registered a significant improvement in our understanding of the role of micronutrients on the pathogenesis and progression of ALD. However, how and to what extent these micronutrients involved in the pathophysiology of ALD remains largely unknown. In the current study, we provide a review of recent studies that investigated the micronutrients imbalance in patients with ALD with a focus on zinc, iron, copper, magnesium, selenium, vitamin D and vitamin E, as well as dissect how disturbance in micronutrients relates to the pathophysiology of ALD. Overall, zinc, selenium, vitamin D, and vitamin E uniformly exhibited a deficiency, and iron demonstrated an elevated trend. While for copper, both an elevation and deficiency were observed from existing literature. More importantly, we also highlight several challenges in terms of low sample size, study design discrepancies, sample heterogeneity across studies, and use of machine learning approaches.

**Key words:** Alcoholic liver disease; Metabolism; Trace elements; Vitamins; Malnutrition; Oxidative stress

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**Core tip:** Perturbation of micronutrients has been broadly reported to be a common characteristic of patients with Alcoholic liver disease (ALD). In the current study, we provide a review of recent studies that investigated the micronutrients imbalance in patients with ALD with a focus on zinc, iron, copper, magnesium, selenium, vitamin D and vitamin E, as well as dissect how disturbance in micronutrients relates to the pathophysiology of ALD. More importantly, we also highlight several challenges in terms of low sample size, study design discrepancies, sample heterogeneity across studies, and use of machine learning approaches.

**INTRODUCTION**

The hepatitis B virus infection remains hitherto a major cause of chronic liver disease because of its high prevalence and high susceptibility to progress to cirrhosis. With the intensive implementation of hepatitis B vaccination and the treatment programs, the epidemiology of the liver disease is undergoing major changes in the Asia–Pacific region. Converging evidence has suggested the dramatic benefits of moderate alcohol consumption to cardio-protection, which is the so-called “J” shaped curve in the relationship between alcohol consumption and overall mortality[1]. However, the threshold of consumption is of great difficulty to define. Heavy alcohol consumption may eventually end up with a broad spectrum of liver damage ranging from liver steatosis, alcoholic hepatitis, liver cirrhosis, and finally to hepatocellular carcinoma[2]. The incidence of alcoholic liver disease (ALD) is increasing, which entails paying more attention[3]. Globally, excessive alcohol consumption accounts for nearly half of the burden of liver disease[4]. Notably, the estimated number of deaths from diseases caused by alcoholism was about 3.3 million in 2012 globally, accounting for 7.6% of all deaths among males and 4.0% among females[5]. From the year 2005 to 2015, alcoholism was responsible for 9.8% and 22.1% of the global incidence of liver cirrhosis and liver cancer respectively[6].

For patients with severe liver damage, there are frequent complications including malnutrition, ascites, spontaneous bacterial peritonitis, encephalopathy, and esophageal varices. Specifically, protein-energy malnutrition, which is associated with poor prognosis, is uniformly recognized in almost all patients with alcoholic hepatitis and ALD, which further increases the liver vulnerability to alcohol toxicity[7]. For these patients, nutritional support is indispensable to prevent further progression. Current guidelines from European Society for Clinical Nutrition and Metabolism and the American Association for the Study of Liver Disease recommend a daily energy intake of 35-40 kcal/kg and protein intake of 1.2-1.5 g/kg through night time snacks and morning feeding for patients with ALD[5]. However, it is really difficult to achieve this objective in practice, since alcohol ingestion usually constitutes half of the daily energy intake in these patients, resulting in a deficiency of energy converted from daily food.

Apart from protein-energy deficiency, metabolic disturbances of micronutrients including vitamins and mineral elements malnutrition are quite common in patients with ALD, as liver dysfunction may affect the metabolism of these elements. ALD patients usually exhibit a clinical spectrum of manifestations including poor-quality diet, polyuria, diarrhea, and vomiting, which to some extent carry an elevated risk of nutrient loss. In addition, portal hypertension in patients with cirrhosis exerts adverse effects on nutrition absorption, another synergistic contributor resulting in the fluctuations in the concentration of micronutrients. Accordingly, screening for micronutrient-deficiency and giving adequate supplementation are also recommended by American Association for the Study of Liver Disease guidelines[8]. However, a definite amount of daily micronutrient intake is not given. Thus, in contrast to protein-energy malnutrition, perturbation of micronutrients in ALD patients has attracted less attention. Oxidative stress is one of the most important contributors facilitating pathogenesis and progression of ALD[9]. Trace elements are cofactors or structural constituent of key antioxidant enzymes and other crucial metabolic enzymes for the maintenance of homeostasis. Consequently, a deficiency of these trace elements would lead to disturbance of antioxidant systems, which has long been recognized in the ALD[10]. In addition, the abnormal accumulation of elements like iron in the liver and/or other organs can also trigger the malfunction of the corresponding organ.

Recent years have witnessed a significant improvement in our understanding of the role of micronutrients on the pathogenesis and progression of ALD. However, the highly complex nature of ALD poses an immense challenge for understanding the precise biological mechanisms. The goal of this review is to summarize findings of the micronutrients imbalance in patients with ALD with a focus on zinc, iron, copper, magnesium, selenium, vitamin D, and vitamin E, as well as discuss their potential mechanisms (Table 1). Moreover, we also highlight some challenges emerging from existing studies that aim to dissect how disturbance in micronutrients relates to the pathophysiology of ALD, as well as present some promising future directions.

**MINERAL MALNUTRITION IN ALD**

***Zinc deficiency***

Investigation of mineral malnutrition in ALD has been most active in Zinc (Zn). As an indispensable metallic element, Zn plays a pivotal role in multiple biological processes including the regulation of neurotransmitter functions, intracellular signaling transduction, inflammatory response, reactive oxygen species (ROS) production, immunoregulation, wound healing, as well as gene expression[11-15]. Independent lines of research suggest that approximately 10% of the human proteome, which includes a total of 2800 proteins, may bind with Zn and cellular zinc fluctuations may dramatically disturb the biological functions of these Zn-binding proteins[16]. Convergent findings suggested that there was a significant zinc deficiency in patients with ALD[17]. Dietary zinc supplementation could provide protection from metabolic dysfunction and alcoholic liver injury[18-21]. Apart from the common factors (*e.g.*, poor-quality diet, polyuria, diarrhea), that can result in zinc deficiency, the zinc deficiency-induced anorexia or acrodermatitis enteropathica might, in turn, exacerbate the deficiency[22,23]. Zn may protect against ethanol-induced liver injury through participating in multiple pathways. A study in a mice model suggested that Zn could decrease the tight-junction proteins and further increase the risk of intestinal barrier dysfunction, thereby resulting in endotoxemia and liver injury[15]. Another study observed that the reduction of the Zn level was linked with mitochondrial dysfunction and oxidative liver injury through the ROS generation and depletion of glutathione. Glutathione is the most important member of antioxidants in cellular antioxidant defense[10]. Consequently, the hepatoprotective effect of zinc on alcoholic liver injury may be ascribed to its inhibition of oxidative stress[10]. Moreover, some studies found that Zn may get involved in hepatocyte apoptosis. Zinc depletion contributed to the overexpression of Fas ligand and elevation of cytosolic cytochrome, which may further activate the caspase-3, a hallmark of cell apoptosis[24]. In terms of immunomodulatory, Zn could interfere with the NF-kB pathway, which can influence the production of LPS-induced hepatic TNF-α and disturb dendritic cells’ ability to respond to LPS. Growing *in vivo* experiments suggest that oral zinc supplementation has therapeutic potential in the prevention and/or treatment of ALD[10,25].

***Iron overload***

Iron is critical in many fundamental biological processes as it participates in the hemoglobin and myoglobin formation, which control the transportation of oxygen, as well as deoxyribonucleic acid biosynthesis and ATP synthesis[26]. In addition, iron is a cofactor of multiple enzymes that regulate the tricarboxylic acid cycle and the electron transport chain[27,28]. The iron metabolic disorder may induce irreversible damage to cellular homeostasis. There is a growing consensus that patients with ALD are frequently characterized by serum iron elevation and hepatic iron overload and it was estimated that significant pathological iron deposition could be detected in approximately 50% of ALD patients[29]. Excessive alcohol exposure promotes iron absorption and subsequent increase of ferritin. Actually, ethanol by itself can directly induce ferritin synthesis and suppress IL-6-mediated hepcidin production[30,31]. The increased iron content and ferritin expression subsequently contribute to disease progression[32,33]. Specifically, it has been widely reported that ferritin could interfere with hepatic stellate cells (HSC) and disturb the balance between extracellular matrix deposition and degradation, which can significantly increase the risk of liver fibrosis[34,35]. On the other hand, there are also studies implying that iron itself could activate HSC and promote the gene expression of the type I collagen, which is a clinical indicator of liver fibrosis, ﻿providing solid evidence that iron overload could promote the development of liver fibrosis[36].

Additionally, studies have demonstrated that iron overload could result in ferroptosis *via* ROS production and lipid peroxidation. The ferroptosis is a form of iron-dependent oxidative cell death that is morphologically, biochemically, and genetically different from autophagy and apoptosis. In addition, excessive iron-induced ROS burst could lead to mitochondrial dysfunction, which is a typical characteristic of ferroptosis[37]. Inhibition of ferroptosis could relieve ethanol-induced liver injury[38-40]. Therefore, preventing the abnormal accumulation of iron and even ferroptosis would be a potential candidate for the design of novel therapeutic strategies for patients with ALD.

Accumulating research has unfolded the association between iron and immune function. Excessive iron is associated with a more likelihood of activating the transcription factor NF-kB and upregulating the expression of proinflammatory cytokines. Besides, considering the close relationship between iron and bacterial multiplication as well as virulence, iron overload could behave as a deleterious factor of infections[41,42]. Apart from the above mentation mechanisms, iron-induced oxidative stress is another extensively investigated biological process. During oxidative stress, iron could produce oxygen free radicals *via* Fenton reaction. Then, oxygen free radical could receive electrons transferred from the lipids, resulting in the decomposition of cytoplasm membrane, and damage of intracellular organelles, a process known as lipid peroxidation. Moreover, as demonstrated in some investigations, oxidative stress could also trigger collagen expression in HSC, and further contribute to the development of liver fibrosis[43].

Some recent studies have also established the relationship between iron overload and cognitive or behavioral deficits in patients with ALD. Generally, these patients demonstrated greatly overlapped behavioral, cognitive, physiological, and social problems[44]. Putatively, studies suggested that iron brought these phenotypic dysfunctions through exerting influences on the brain systems. Specifically, iron can influence myelination as well as the synthesis and metabolism of neurotransmitters[45]. Moreover, chronic excessive alcohol induced-abnormal iron deposition in brain areas including basal ganglia and dentate nucleus may act as a contributor to this phenomenon[46].

***Copper imbalance***

Copper is an extracellular element responsible for the precise function of bone marrow and central nervous system, and it also functions as a cofactor of many antioxidases[47]. Consequently, copper metabolic disorder may induce dysfunction in the corresponding organ. Compared with the two trace elements (*i.e.*, Iron and Zn) mentioned above, investigations focusing on revealing the relationship between copper metabolism and the potential pathophysiology of ALD are relatively limited. And findings derived from these studies were far from conclusive and sometimes even inconsistent. For example, results from the study of Shibazaki *et al*[48] observed that people with excessive alcohol consumption tended to exhibit a significant copper deficiency, which concurs with prior evidence showing copper metabolism perturbation in patients with ALD[48]. In contrast, another study found that copper levels in patients with ALD were elevated or unchanged as compared with healthy controls[49]. Unfortunately, most of these available studies only reported the differences of copper levels between patients and healthy controls from the perspective of statistical analysis, with the mechanistic insights into the involvement of copper imbalance in the pathogenesis of ALD being significantly unexplored. This may be partially ascribed to the fact that the copper has a complex interaction with other trace elements, especially iron and Zn. Specifically, hyperzincemia could suppress copper absorption, and copper deficiency usually has a synergistic effect with zinc reduction in impairing normal functioning of the central nervous system in patients addicted to alcohol[50]. In addition, the copper deficiency could dampen iron transport *via* suppressing the activity of hephaestin, a copper-containing ferroxidase necessary for iron efflux from enterocytes[51]. All these three metals function as cofactors of antioxidase that are responsible for antioxidant defense, which is critical in preventing the oxidative damage for patients with ALD. Taken together, it deserves further investigation to elucidate the specific metabolic pattern of copper in patients with ALD.

***Serum selenium deficiency***

Selenium is an important component of antioxidant-glutathione peroxidase and thus it has been broadly used in clinical for its antioxidant property. Abnormal metabolism of selenium has been reported in a growing body of research, which suggested that low selenium level is a common feature of patients with ALD[52]. Selenium metabolic disorder may lead to liver dysfunction[52,53]. However, the involvement of selenium depletion in the pathogenesis of ALD has not been fully defined. Substantial efforts have hitherto been devoted to revealing the potential mechanisms. For example, a study suggested that selenium was capable of alleviating liver histopathological features including hepatocyte injury, abnormal accumulation of liver fat and liver neutrophils infiltration, and can reduce elevated ALT levels after selenium supplementation *in vivo* experiments[54]. Putatively, the protective effects of selenium predominantly may lie in that selenium could increase the level or the enzyme activity of glutathione peroxidase and thus affords marked protection against oxidative injury. Other studies implied that the participation of selenium in autophagy, caspase-involved apoptosis, and NF-kB-implicated inflammation regulation may be another protective mechanism[55-57]. In spite of the above findings, some investigations derived inconsistent results suggesting that chronic excessive alcohol intake might have no significant effect on the serum selenium levels[58], even though it may be not that common. Therefore, further investigation is still urgent in unfolding the metabolism of selenium in patients with ALD.

***Hypomagnesemia***

Magnesium is the second most abundant intracellular cation after potassium, and mitochondria, endoplasmic reticulum, and cytosol constitute the top three cellular pools that are rich in Mg2+[59]. Consequently, serum magnesium levels could not reflect the real storage. Magnesium participates in diverse biological processes, including enzymatic reactions, neurotransmission, glycolysis, and mitochondrial function[60,61]. Growing evidence suggests that magnesium metabolic disorder is common in patients with severe malnutrition, diabetes, hypertension, and ALD[62,63]. Importantly, hypomagnesemia is also a significant electrolyte abnormality in critically ill patients, and these patients have higher mortality than the normomagnesemia patients[64]. With regard to excessive alcohol exposure populations, convergent findings suggest that magnesium deficiency is a common feature[65]. It was reported that alcohol could decrease whole tissue magnesium by approximately 14%, among which liver magnesium accounted for 5%-10%. In addition, hepatocytes from EtOH-treated rats exhibited a 25% reduction in cellular magnesium compared with the control group[66]. Alcohol may induce magnesium disturbance *via* perturbing the extrusion of cellular magnesium through Na+-dependent and Na+-independent manner. Meanwhile, there was also a distinct decline in ATP content. All these pieces of evidence indicated that chronic alcohol consumption could considerably impair Mg2+ homeostasis and transport of liver cells after prolonged exposure to alcohol. The inability of liver cells to reserve Mg2+ might, at least in part, explain the reduction in tissue Mg2+ content after prolonged exposure to alcohol. Particularly, alcohol administration-cells became insensitivity to the catecholamine-induced magnesium accumulation, which to some extent prevented hepatocytes from restoring cellular magnesium[66,67].

**VITAMIN METABOLISM IN ALD**

***Vitamin D deficiency***

Existing work in liver diseases concerning vitamin metabolism has mostly focused on vitamin D. In the past years, vitamin D has been well documented for its classical effects on bones and calcium metabolic homeostasis. Results from recent functional and mechanical studies support that vitamin D could also behave as a regulatory factor modulating many other biological functions like cell proliferation, apoptosis, cell cycle, differentiation, and immunomodulatory. Additionally, the effects of vitamin D in anti-fibrosis, anti-tumor, and anti-inflammation have also been systematically investigated.

It was estimated that approximately one billion people worldwide were insufficient in vitamin D[68]. Accumulating research has indicated that people with a lower concentration of vitamin D are always companied with a higher body mass index and are predisposed to be diagnosed hypertension and many cancer types[69,70]. The decrease in vitamin D concentration is one of the most consistent observations in patients with chronic disease, especially those with severe liver disease. An enormous number of studies have implied that vitamin D could modulate the biological function of HSC, which can effectively attenuate liver fibrosis. Specifically, Potter *et al*[71] observed that VDR could combine with a proximal Sp1.1 site and a newly identified distal site on the collagen promoter, through which vitamin D could suppress TGFβ1-induced type I collagen formation in HSC[71].

It was estimated that 96% of alcoholic patients have repressed levels of serum vitamin D, and 86.1% were deficient and 60.4% were severely deficient. In addition, among alcoholic patients, a severe deficiency in vitamin D was quite common in those with alcoholic steatohepatitis[72]. This concurs with prior evidence that decreased serum vitamin D was associated with increased susceptibility to ethanol-induced liver damage, which was manifested with abnormal serum AST, steatosis, and liver cirrhosis. Typically, Trépo *et al*[73] reported that severe deficiency in vitamin D was significantly associated with a poor prognosis like complications of portal hypertension[73]. This study also added another piece of information that vitamin D treatment or supplementation could suppress the expression of pro-inflammatory cytokines TNFα, which further confirmed the role of vitamin D in immunomodulatory. Moreover, results of a prospective study among patients with alcoholic liver cirrhosis found that oral vitamin D supplementation did decrease the Child-Pugh score and ameliorate liver damage[74]. Collectively, these pieces of information highlight the possibility that vitamin D may serve as a diagnostic biomarker and a potent agent in the management of ALD. However, the specific role of vitamin D on the pathogenesis, disease progression, and other complications in the course of ALD is not yet fully understood. Therefore, there is a pressing need for further studies to elucidate the precise mechanisms underlying vitamin D and alcohol-induced hepatotoxicity, which can facilitate clinical applications and promisingly improve diagnosis, prevention, and treatment of ALD.

***Vitamin E inadequacy***

As a nonenzymatic antioxidant, vitamin E has been intensively investigated for its antioxidative properties. Dietary sources of vitamin E predominately include vegetables, nuts, olive oil, and lean meats. The endogenous metabolites of vitamin E consist of multiple isomers, among which α-tocopherol is the most important biological active form[75]. Through suppression of oxidative and inflammatory reactions, vitamin E could alleviate the progression of atherosclerosis in low-density lipoprotein receptor-deficient mice fed with a high-fat diet[76]. Moreover, vitamin E has beneficial effects on the prevention of cancers and diabetes due to its antioxidative effects[77]. Chronic vitamin E deficiency could increase the risk of damage in response to oxidative stress. A recent study observed that a moderate intake of vitamin E could change the composition of gut microbiota and altered intestinal microbiota always involved in the pathogenesis of ALD[78]. In a clinical trial on patients with nonalcoholic steatohepatitis and advanced fibrosis, Vilar-Gomez *et al*[79] found that vitamin E supplementation improved patients’ clinical outcomes including reducing the risk of death or liver transplant and the probability of hepatic decompensation[79]. Moreover, for other chronic liver diseases such as steatocholestasis and drug-induced liver injury, vitamin E also protected against hepatocyte necrosis and maintained mitochondrial integrity[80,81]. Notably, apart from the effects of anti-inflammation and antioxidative properties, some studies have also highlighted that vitamin E is involved in signal transduction and gene expression. Specifically, it is postulated that vitamin E achieves its anti-inflammation, anti-tumor, and anti-apoptosis effects partly through regulating the expression of related genes (*e.g.*, P53, NF-kB, cyclin D1)[82].

It has gained widespread acceptance that vitamin E deficiency is common in patients with ALD[83]. The malnutrition, along with impaired transport by the lipoproteins may be the primary reason that causes vitamin E deficiency[84]. Clinical administration of vitamin E increased the plasma α-tocopherol but did not improve the parameters of liver function and clinical outcomes such as motility and one-year survival. However, vitamin E decreased the expression of hyaluronic acid, an indicator correlated with hepatic fibrosis[85,86]. Studies in the animal model showed that vitamin E could diminish alcohol-induced oxidative damage through removing ROS, reducing lipid peroxidation, and improving antioxidant defense[87], which is in harmony with findings from the study of Yao *et al*[88]. Treatment with vitamin E, especially together with tannic acid, relieved the histology damage, reduced collagen, and glycogen deposition in addition to the hepatoprotection role in decreasing the levels of serum hepatic damage markers (*e.g.*, ALT, AST). The hepatoprotection effects may result from vitamin E’s antioxidative property and its suppression of inflammatory response as well as cell apoptosis through regulating the EGFR-AKT and EGFR-STAT3 pathways[89].

**CHALLENGES AND FUTURE DIRECTIONS**

The studies surveyed above open interesting cues to systematically explore the benefits of micronutrients-based therapeutic interventions in the cure of alcohol-induced liver injury. However, some important issues should be discussed. Here, we elaborate on some representative challenges that have emerged from the reviewed studies, and present some promising future directions as follows.

***Sample size***

Most of the studies discussed in this review included a limited number of subjects. Although small studies have multiple practical advantages, such as being timesaving in the enrollment of subjects, and high flexibility in data analyses[90], results from these small samples are usually attached to low statistical power[78], and have a more likelihood of generating false-positive results. In this regard, these biomedical findings may only demonstrate statistically significant effects but have no clinical utility. ﻿Consequently, future investigators should perform their analyses by leveraging larger studies involving more subjects.

***Study design***

There is a pyramid of evidence, which represents a general hierarchy of multiple clinical study designs. The top of the pyramid is the double-blind, randomized, controlled studies, and such types of investigations without the use of surrogate endpoints are always most rigorous and reliable to evaluate the effects of a specific intervention[91]. However, many of the clinical studies discussed in the current review enrolled patients with liver diseases from a single clinic and were carried out in a non-randomized manner. In contrast to the randomized controlled trials, the non-randomized controlled investigations cannot invariably eliminate bias occurred in the studies efficiently, which may silently affect the results and fool the investigators[92]. As such, the results may be confusing and misleading. Additionally, some of the important studies were conducted in mice that are innately different from human beings. Animal research is at the base of the pyramid with the lowest forms of evidence, thereby limiting its wider application in clinical settings. For example, although various independent animal studies reported that vitamin E administration alleviated liver damage, supplementation of vitamin E to ALD patients had no significant influence on clinical status[86]. Therefore, we encourage future studies assessing the impact of micronutrients on ALD to be designed as randomized controlled trials.

***Sample heterogeneity across studies***

To minimize the imbalance of sample properties between two groups being compared, it is really necessary to ensure that the two populations are propensity matched on the irrelevant variables (*e.g.*, age, gender, body mass index) except the one of interest. However, we can’t guard against the possibility that there exist some unrecognized confounders that may contribute to the imbalance between groups, and further affect the results[79]. This may also be one of the reasons that inconsistent results were sometimes derived from existing studies, especially when group comparison was conducted in small samples.

On the other hand, there is also heterogeneity in the variable of interest per se between studies. To explore the effect of a specific micronutrient, varied treatment doses and periods were administrated across reported studies, since there is no definite “golden standard” for them, especially for exploratory studies that at an early-stage. Despite the fact that the confounding variables have been balanced largely, the findings might also be inconsistent across different trials. A case in point was that whether vitamin E replacement benefits ALD patients. A clinical study by de la Maza *et al*[86] observed that supplementation with 500 IU vitamin E for one year had no significant effect on the hepatic laboratory parameters and mortality[86]. However, Mezey *et al*[85] fund that vitamin E could decrease the serum hyaluronic acid, a biomarker represented liver fibrosis, when ALD patients were given 1000 IU vitamin E for three months[85]. These findings, to some extent, might fail to help investigators to reach a firm decision in clinical practice. Of note, excessive drug (which was intended to serve as a therapy) exposure has a detrimental effect, which might also mislead the researchers. For example, a meta-analysis by Miller *et al*[93] discovered that high-dosage vitamin E (≥ 400 IU/d) showed an increased risk for all-cause mortality[93]. Therefore, many efforts are required to control extensively for potential confounders.

***Machine learning methods***

Among reviewed studies, univariate analytical techniques are the most widely applied methods in the investigation of micronutrient imbalance in alcoholic-induced liver diseases. Such types of investigations maintain a focus on group-level comparison to examine whether significant group difference exists in a specific micronutrient between patients with liver disease and healthy controls. Although these studies have advanced our understanding of the mechanisms underlying ALD, the biggest disadvantage of them is that they don’t have the ability of providing individualized guidelines at the individual level. In recent years, machine learning-based methods have attracted substantial attention from multiple research fields, which can build a multivariate predictive model by employing cross-validation strategies to ensure generalization[94]. However, the application of machine learning models in the investigation of micronutrients in ALD is relatively limited. Futures studies can capitalize on the strengths of machine learning to better reveal the role of micronutrients in the pathology of ALD.

**CONCLUSION**

In this review, we summarized studies investigating micronutrients imbalance in patients with ALD, with a focus on zinc, iron, copper, selenium, magnesium, vitamin D and vitamin E. Overall, zinc, selenium, vitamin D and vitamin E uniformly exhibited a deficiency, and iron demonstrated an elevated trend. While, for copper, both an elevation and deficiency were observed from existing studies, which entails further investigation. In conclusion, this review study helps delineate the imbalance of micronutrients in ALD, thus shedding light on the underlying mechanism, and promisingly offering possibilities for clinical intervention.

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**Table 1 Micronutrients imbalance in patients with alcoholic liver disease**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Micronutrient** | **Metabolic status** | **Effects** | **Potential mechanisms** | **Ref.** |
| Zinc | Deficiency | Intracellular signaling transduction, inflammatory response, ROS production, immunoregulation | Decrease the tight-junction proteins, increase the risk of intestinal barrier dysfunction; Inhibition of oxidative stress; Disturb dendritic cells’ ability to respond to LPS; Activate apoptosis | [15,17,24] |
| Iron | Overload | Control the transportation of oxygen; DNA biosynthesis; ATP synthesis | Activate HSC, promoting liver fibrosis; Induce ferroptosis and mitochondrial dysfunction; Provoke oxidative damage through Fenton reaction; influence myelination and neurotransmitters | [34-37,43,45] |
| Copper | Deficiency/ overload | The precise function of bone marrow and central nervous system; A cofactor of many antioxidases | Interacts with other trace elements, and function as a cofactor of antioxidase that is responsible for antioxidant defense | [48-51] |
| Selenium | Deficiency | Antioxidant property | Increase the enzyme activity of glutathione peroxidase and protect against oxidative injury; participant in autophagy, caspase-involved apoptosis, and NF-kB-implicated inflammation regulation | [52,55-58] |
| Magnesium | Deficiency | Participate in enzymatic reactions, neurotransmission, glycolysis, and mitochondrial function | Perturb the extrusion of cellular magnesium through Na+-dependent and Na+-independent manner | [66-68] |
| Vitamin D | Deficiency | Anti-fibrosis, anti-tumor, and anti-inflammation; Immunomodulatory | Not yet fully understood | [73,74] |
| Vitamin E | Deficiency | Antioxidative properties;  protected against hepatocyte necrosis and maintained mitochondrial integrity | Diminish alcohol-induced oxidative damage, and improve antioxidant defense; Regulate the EGFR-AKT and EGFR-STAT3 pathways. | [84,88-90] |

ALD: Alcoholic liver disease; ROS: Reactive oxygen species; DNA: Deoxyribonucleic acid; HSC: Hepatic stellate cells.