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A REVIEW ON SERUM ZINC LEVELS IN HEPATIC ENCEPHALOPATHY

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ABSTRACT

Zinc is necessary for various metabolic processes of the body. Since serum zinc levels are lowered in liver diseases, it has been postulated to be a precipitating factor for hepatic encephalopathy. Even in patients who are not zinc deficient, zinc administration has the potential to improve hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle. The subsequent increase in urea genesis results in the loss of ammonia ions. Researchers prospectively studied serum zinc levels in consecutive patients with fulminant hepatic failure, subacute hepatic failure and chronic liver disease with encephalopathy. Serum zinc levels were correlated with various clinical and biochemical parameters and final outcome of patients. The amount of serum zinc levels were estimated by atomic absorption spectrometry at admission and also 24 hours after recovery in all the survivors. During the study it was observed that patients with hepatic encephalopathy had significantly lower serum zinc levels. High serum bilirubin levels and prothrombin time showed inverse relationship with serum zinc levels. There was no relationship of serum zinc levels with age, sex, grade and duration of encephalopathy, liver size or splenomegaly. Hepatic encephalopathy is associated with low serum zinc levels. Antioxidant and zinc supplementation can improve minimal hepatic encephalopathy in patients with liver cirrhosis. Additional studies are needed to establish the role of correcting hypozincemia to prevent worsening of cirrhosis and development of encephalopathy.

KEYWORDS

Hepatic Encephalopathy, Serum Zinc Levels and Cirrhosis.

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INTRODUCTION

Hepatic Encephalopathy is a disease may be unresponsive to protein restriction, lactulose, and neomycin. Zinc supplements have been reported to improve psychometric performance in liver cirrhosis, but the importance of zinc deficiency in overt hepatic encephalopathy has not yet been clearly

understood. A patient with severe recurrent hepatic encephalopathy was studied to determine the relation between there signs of encephalopathy and zinc deficiency. In a study the researchers included a period in which zinc deficiency was artificially induced by oral histidine. An episode of overt encephalopathy occurred that was identical to earlier episodes and responded to oral zinc. The study showed an association between encephalopathy and zinc deficiency by successive zinc depletion and supplementation regimens. Long term zinc supplementation improved severe recurrent hepatic encephalopathy and intern the quality of life also increased. Encephalopathy is a complication of acute and chronic liver failure. Its pathogenesis is still unresolved but the accumulation of gut-derived nitrogenous substances due to impaired hepatic clearance is generally thought to be a major mechanism involved in understanding the progression of the diseases[1].

Hepatic encephalopathy is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers. In addition, cognitive impairment associated with cirrhosis results in utilization of more health care resources in adults than other manifestations of liver disease. Progress in the area has been hindered by the complex pathogenesis that is not yet fully elucidated. Apart from such biological factors, there remains the larger obstacle that there are no universally accepted standards for the definition, diagnosis, classification, or treatment of hepatic encephalopathy, mostly as a result of insufficient clinical studies and standardized definitions. Clinical management tends to be dependent on local standards and personal views. This is an unfavorable situation for patients and contrasts with the severity of the condition and the high level of standardization in other complications of cirrhosis. The lack of consistency in the nomenclature and general standards renders comparisons among studies and patient populations difficult, introduces bias, and hinders progress in clinical research for hepatic encephalopathy (Table No.1). The latest attempts to standardize the nomenclature were published in 2012 and suggestions for the design of hepatic encephalopathy trials in 2017. Because there is an unmet need for recommendations on the clinical management of hepatic encephalopathy, the EASL (European Association for the Study of the Liver) and the AASLD (American Association for the Study of Liver Diseases) jointly agreed to create these practice guidelines. It is beyond the scope of these guidelines to elaborate on the theories of pathogenesis of hepatic encephalopathy, as well as the management of encephalopathy resulting from acute liver failure (ALF), which has been published as guidelines recently. Rather, its aim is to present standardized terminology and recommendations to all health care workers who have patients with hepatic encephalopathy, regardless of their medical discipline, and focus on adult patients with chronic liver disease (CLD), which is, by far, the most frequent scenario and need of the hour. While the liver is the primary organ for metabolism of nutrients, liver cirrhosis causes protein and energy metabolic disorders, which contribute to poor prognosis or the development of various complications including hepatic encephalopathy[2-7].

Several studies have shown that nutritional interventions are effective for patients with liver cirrhosis who exhibit nutritional and metabolic disorders[8-10]. It has been demonstrated that treatment of liver cirrhosis with branched-chain amino acids (BCAAs) relieves nutritional and metabolic dysfunction, prevents the development of complications and liver cancer, and improves prognosis.

Furthermore, among many trace elements existing in the body, zinc has recently been shown to be deeply associated with the pathology of liver cirrhosis[11-14]. Protein restriction, lactulose, and neomycin, given to reduce the production of nitrogenous toxins, are effective in some but not all patients. In patients without liver disease, zinc deficiency may induce neurological and psychiatric symptoms including ataxia, lethargy, depression, and hallucinations[15]. In liver disease, the concentrations of zinc in serum[16], leukocytes[17] and liver[18] are decreased.

The importance of zinc deficiency in hepatic encephalopathy has not yet been clearly established,

although zinc supplements have been reported to improve mild chronic hepatic encephalopathy, as measured by psychometric testing[18], as well as some episodes of hepatic encephalopathy following gastrointestinal bleeding[19]. We have studied a patient with incapacitating recurrent hepatic encephalopathy to determine the relation between there signs of encephalopathy and markers of zinc deficiency.

Zinc is an essential trace element with various biological effects[20]. As more than 300 proteins contain domains with zinc and these domains are important for regulating cellular functions, zinc plays an important role in cell growth, differentiation, apoptosis and metabolism[12]. Zinc homeostasis is primarily preserved by a balance between the zinc-binding protein metallothionein and the expression of two zinc transporters[21]. There were some reports that zinc deficiency resulted in numerous problems, including growth disorder, cognitive disorder, and compromised immune function[22].

Zinc deficiency occurs as a result of nutritional factors, but also in various disease states (malabsorption, Crohn's disease, alcoholism, liver cirrhosis, chronic renal disease, and other chronically debilitating diseases). Factors that are potentially responsible for zinc deficiency in liver cirrhosis include disturbed zinc absorption by the digestive tract and increased zinc excretion in the urine. The effects of cytokines, mainly interleukin-6 and endotoxins also contributed zinc deficiency[23]. Furthermore, diuretics aggravate zinc deficiencies in patients with liver cirrhosis by increasing zinc excretion in the urine[24.]

Several studies showed a statistically significant inverse relationship between the serum levels of zinc and ammonia. Zinc deficiency is related to the pathogenesis of hepatic encephalopathy[25]. On the basis of these findings, there were some reports which examined the effects of zinc supplementation in liver cirrhosis with hyperammonemia[26]. Marchesini *et al*, showed that 3-month supplementation of zinc in patients with hepatic encephalopathy reduced serum ammonia levels, but this was not a randomized-controlled trial[14]. Two randomized-controlled trials of rather short period (8 and 10 days) have been performed to examine these effects, and the results were controversial[27]. Recently, researchers performed a longer period randomized, placebo-controlled double-blind trial, and indicated that zinc supplementation for 3 months seems effective and safe for treating hyperammonemia in liver cirrhosis[28].

The main effect of zinc supplementation on reducing serum levels of ammonia proposed thus far is increased activity of ornithine transcarbamylase, a key enzyme of the urea cycle in the liver. Riggio O *et al*, showed that liver ornithine transcarbamylase activity decreased and plasma ammonia level increased in zinc-deficient rats, while the activity of the enzyme significantly increased in zinc-supplemented cirrhotic rats[29]. Because zinc has been revealed to play an important role in the synthesis, storage, and secretion of insulin, zinc deficiency affects not only insulin secretion but also insulin resistance[30]. In diabetes mellitus, zinc deficiency has been found to be associated with glucose tolerance and the development of complications of diabetes mellitus, whereas there are some reports that zinc supplementation improves glucose tolerance and reduces the incidence of complications[31]. Although glucose intolerance is also prevalent in liver cirrhosis, the association between glucose intolerance and zinc in liver cirrhosis has been little studied.

These previous studies have increasingly shown that zinc deficiency is associated with nitrogen metabolic disorders, mainly affecting ammonia in liver cirrhosis, and that zinc supplementation is effective for patients with these conditions. However, not all patients with liver cirrhosis exhibit zinc deficiency. In addition to nitrogen metabolic disorders, other metabolic disorders, such as glucose intolerance, often coexist with liver cirrhosis. A large-scale study on the prevalence of zinc deficiency in liver cirrhosis and the associations between zinc deficiency and various pathological conditions of liver cirrhosis may provide answers to the questions of which cirrhosis patients should be suspected of having zinc deficiency and for which cirrhosis patients should zinc supplementation be considered. Previous study conducted by a prospective study enrolling 299 cirrhosis patients to assess the effects of BCAA

therapy. Using data obtained in this previous study, the prevalence of zinc deficiency in liver cirrhosis and the association between zinc deficiency and clinical symptoms is the need of the hour for the management of hepatic encephalopathy (Figure No.1).

HEPATIC ENCEPHALOPATHY PATHOGENESIS[35,36]

Since long time, discussion about the pathology is there about the creation of the dangerous substances which is causative for the modified cerebral state. There has been always consideration about the role of ammonia, GABA, synergic toxins or endogenous benzodiazepines in the development of hepatic encephalopathy. There are peripheral multi-systemic dysfunctions, and changes in the intercellular transmission in brain, produced by changes in astrocytes. Key role in pathogenesis in hepatic encephalopathy are neurotoxin produced by gut, dysfunction of astrocytes, brain water homeostasis, unsettling influence of synapses, oxidative pressure and aggravation in mind and contamination.

ZINC ROLE IN TREATMENT OF HEPATIC ENCEPHALOPATHY[37]

Zinc is an essential trace element which plays an important role in the regulation of protein and nitrogen via urea cycle As a co-factor of many enzymes use in urea cycle, Zinc deficiency has been implicated in the pathogenesis of hepatic encephalopathy as decreased serum zinc levels and low zinc level associated with in inverse correlation with blood ammonia levels in those patients. Zinc short term therapy improved ammonia clearance via urea cycle that decreased serum ammonia level in cirrhosis patient and improve his /her neurophychiatric manifestation. A double blind randomized placebo controlled study of zinc acetate 600 mg/d for 7 days demonstrated improved mental status that was associated with increase in serum zinc levels[38].

In another study after 3 months of supplementation with 600 mg zinc sulfate daily there was normalization of serum zinc levels and improvement in neuropsychiatric testing in hepatic encephalopathy. The Recommended Dietary Allowance (RDA) is 8 mg/day for women and 11 mg/day for men. Red meats, especially beef, lamb and liver have some of the highest concentrations of zinc in food.

DISCUSSION

The liver plays an important role in Zn homeostasis and different Zn compartments have been recognized to explain Zn kinetics in humans; the liver represents a fast-exchangeable Zn pool with an important role in the metabolism of Zn and other trace elements[39].

The low serum zinc level is common in patient with liver cirrhosis due to decreased intake, decrease absorption, decreased bioavailability, and increased losses (because of malabsorption). There is also reduced liver protein synthesis in patients with liver cirrhosis, the metallothionein (MT) is an important zinc-binding protein (formed by liver) and is involved in zinc metabolism, homeostasis and its release in number of oxidants, the released zinc will inhibit the activity of the enzymes involved in fibro genesis (fibrosis) in the liver, all these are yet known pathophysiological mechanisms[40,41].

Zinc is also essential for some of the neutrophil functions and it appears that zinc has a role in the maintenance of human immunity. Recent evidence suggests that thymic-dependent lymphocytes (T cells are zinc dependent. T-helper and suppressor cells, T-effector cells and T-natural killer cells appear to be zinc dependent[42]. In a study of Stamoulis et al published by Digestive Diseases and Sciences in 2007 the prevalence of low serum zinc level in cirrhotic patients was 65.3%[43]. In a previous study the serum zinc level was low in patient with liver cirrhosis, however such observation resembled with two different studies conducted by Go *et al*[44], Where as Kalkan *et al*, also identified zinc deficiency in patients with liver disease in his study published in 2002[45].

It has long been speculated that Zn has a protective effect against liver fibrosis and Zn intake in cirrhosis are based mostly on observations of reduced Zn levels in cirrhotic patients and on the beneficial effects of Zn supplementation on liver metabolism[46]. The study had 94% subjects with viral hepatitis C

induced liver cirrhosis, the viral infection induced cirrhosis causes oxidative stress and secondary cellular damage, Low plasma Zn concentrations contribute to oxidative stress and its replenishment by high doses has been considered mandatory[47]. It has also been thought that Zn could directly affect Hepatitis C viral (HCV) replication, thus supporting structural and functional stability of certain HCV proteins like NS5A and NS3. In one more study we noticed that the three patients had alcohol induced liver cirrhosis and we identified and observed that their serum zinc level was low, where as a study on "Hepatic zinc content in patients with various stages of alcoholic liver disease and in patients with chronic active and chronic persistent hepatitis" shown similar finding[48].

Animal model studies have shown that Zn supplementation prevented ethanol-induced liver injury under both acute and chronic exposure conditions. Zn supplementations decreases ethanol-induced hepatic Zn depletion, suppressed the elevated cytochrome P450 2E1 activity, and enhances the activity of enzyme alcohol dehydrogenase which will responsible for the suppression of ethanol-induced oxidative stress. Zn administration also enhanced hepatic glutathione (GSH) and Zn related antioxidant capacity[49].

It has been suggested that some of the clinical features of liver cirrhosis, such as testicular atrophy, loss of body hair, night blindness, poor wound healing, poor appetite, decreased taste and smell acuity, susceptibility to infections, enhanced sensitivity to drugs, and decreased neurocognitive performances, may be related to conditioned Zn deficiency. In some cases Zn supplementation was beneficial to this patients[50]. The zinc supplementation also reduces the inflammation and contributes to faster inflammation resolution, therefore further advance, modified and related studies are needed to update the data, knowledge and information regarding medical workup of patients with liver cirrhosis. Zinc is important co-factor for many enzymes. Zn has key role in physiological detoxification of ammonia via urea cycle in liver and as a co factor in ornithine Transcarbamylase (OTC) so low zinc level associated with decreased OTC activity and higher plasma concentration of ammonia. Low plasma Zn impairs nitrogen cycle in muscle and increase glutamine in blood. As result in advanced grade in Hepatic encephalopathy significantly more drop in plasma Zinc. Short term oral Zinc supplement is very useful as an adjunct treatment in DCLD patient with hepatic encephalopathy[51].

Researchers revealed that the serum zinc concentration aids in assessing the body zinc status. Zinc status has been measured in a number of tissues such as serum or plasma, different blood cell types, hair, and nails[52]. However serum zinc concentration is viewed as the most appropriate indicator for evaluating individual's zinc status, as compared to other assessment[53], although the sensitivity and specificity of the serum zinc level might be limited by responsiveness to confounding factors such as acute stress, infection, or altered steroidal hormone levels[54]. Furthermore serum zinc concentration is the only biomarker to show a dose-response relationship to dietary zinc manipulations[55], so mean serum zinc level in a population may reflect the status of dietary zinc intakes or zinc supplementation, and could be used as an indicator of zinc deficiency at the population level.

Table No.1: Clinical Grading of Hepatic Encephalopathy[32-34]

grade HE	consciousness	intellectual function	personality/ behavior	neuromuscular abnormalities
0	normal	normal	normal	normal
1	inverse sleep pattern hypersomnia insomnia	impaired calculation short attention span mild confusion	depression or euphoria anxiety slowness	tremor impaired handwriting incoordination
2	lethargy	disorientation in time amnesia for past events	decreased inhibition inappropriate behavior	flapping tremor ataxia slurred speech grimacing
3	stupor, pre-coma arousable	disorientation in place/person	bizarre behavior incontinence	hyperactive reflexes Babinskis muscle rigidity
4	coma			coordinated response, flexion or extension to painful stimuli

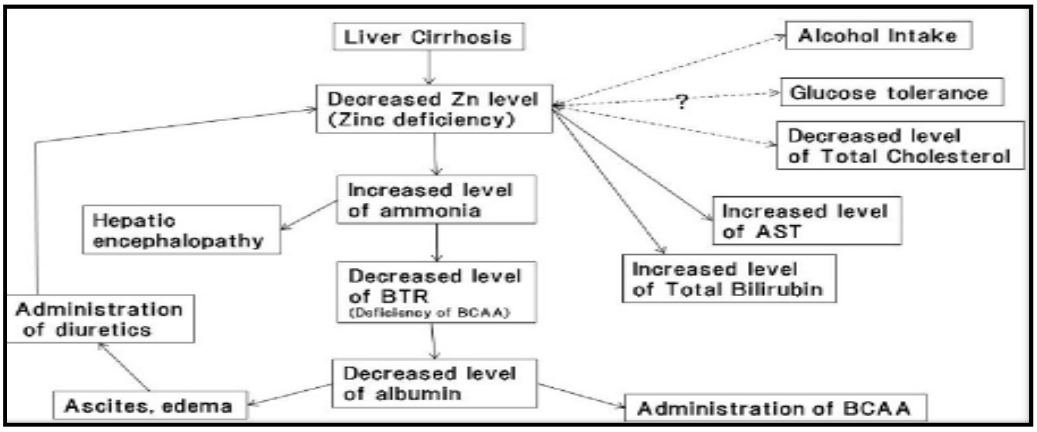

Figure No.1: Theories of causal connections between zinc lack and obsessive states of liver cirrhosis. The strong bolt demonstrates the nearness of a causal relationship; dashed bolts show the causal relationship is obscure

CONCLUSION

The medical management of hepatic encephalopathy predominates due to various medical or social problems e.g. low economic profile, co morbidities associated with advancing age, etc. We have identified the lower level of serum zinc level in patients with liver cirrhosis. Therefore a routine biochemical assessment of zinc status in patients with liver cirrhosis is an important step in the management protocol and to reduce progression of the disease.

Zinc supplementation will definitely improve the mental status of patients with hepatic encephalopathy from chronic liver disease as shown by a significantly greater improvement in the liver cirrhosis patients given oral zinc as an add-on to standard therapy compared to those on standard therapy alone. Other studies revealed that the zinc supplementation also helps significantly in the improvement of ammonia metabolism by increasing BUN levels and decreasing serum ammonia levels. It is observed in de compensated chronic liver disease patients with a complication of Hepatic encephalopathy identified with low serum Zinc concentration as it is associated with higher grade of hepatic encephalopathy. More decrease in serum Zn is correlated with worse grade of hepatic encephalopathy. A low level of serum zinc is an indirect precipitating factor in the management of Hepatic encephalopathy. Short term Zn supplement may be useful in prevention treatment and management of hepatic encephalopathy patients.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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