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EDITORIAL

Zinc Deficiency in Cirrhosis: Micronutrient for Thought?

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Involved in several physiological processes related to human health, zinc (Zn) is the second most abundant essential "trace" element. The actions of Zn, mostly related to its catalytic or structural properties, also include serving as an enzymatic cofactor in the regulation of carbohydrate, fat, and protein metabolism. Though Zn is part of the important metalloenzyme copper–Zn superoxide dismutase, Zn can also alter oxidative stress [1, 2] and is also associated with innate and adaptive immune processes [3]. Zn also exhibits anti-apoptotic and anti-inflammatory effects: chronic ethanol exposure in an animal model induced Zn deficiency in the hepatic endoplasmic reticulum (ER) and in the mitochondria, which stressed these organelles in vitro, activating intrinsic cell death signaling pathways, and Zn supplementation protected against apoptosis [4]. In fact, ER and mitochondrial stress are present in advanced liver disease [5, 6]. Zn is therefore of potential therapeutic value in this condition.

Zinc homeostasis following dietary intake is highly regulated, with body stores and tissue concentrations affected by intestinal absorption, gastrointestinal and urinary losses, and cellular retention. Dietary Zn is absorbed through enterocytes predominantly in the proximal small intestine. After enteric absorption, Zn enters a rapidly turning-over but small (0.1 %) plasma pool. It is then redistributed to tissues, which comprises the major Zn pool in the body. About 90 % of body Zn is stored in skeletal muscle and bones, whereas ~5 % is stored in the liver. Net intestinal Zn absorption is essential for the homeostatic regulation of overall Zn status; dietary Zn intake activates adaptive mechanisms that maintain normal Zn status. Dietary factors can influence Zn bioavailability: in healthy individuals, feeding low-zinc diets increased zinc absorption via homeostatic mechanisms that upregulated zinc absorption and retention [7], confirming an earlier stable isotope based study [8].

The prevalence of Zn deficiency depends on underlying conditions. Diseases such as cirrhosis reportedly have a high prevalence of Zn deficiency [9]. Overt manifestations of Zn deficiency such as skin lesions, alopecia, hypogonadism, immune system dysfunction, and neurological disorders are often not present, are not easily recognized, or can be confounded by the presence of complications associated with underlying cirrhosis. Furthermore, alcoholics, including those that have developed cirrhosis, are a population at high risk of the development of Zn deficiency. Further, lower dietary zinc intake has been reported in alcoholics [9]. Interestingly in an animal model, alcohol use accompanying a Zn-deficient diet was reported to synergistically increase hepatic lipid accumulation, inflammatory cell infiltration, oxidative stress, and expression of cell death receptors, accompanied by increased gut permeability and plasma endotoxin concentrations [10]. Human and animal studies have collectively established that Zn deficiency is associated with alcohol use and with cirrhosis [9].

In this issue of *Digestive Diseases and Sciences*, Sengupta et al. [11] highlight the importance of assessing zinc deficiency in a high-risk population. In this retrospective study, two thirds of the subjects had cirrhosis complicating hepatitis C infection and excessive alcohol intake.

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Moreover, Zn deficiency (serum Zn concentration <0.66 μg/mL) was more frequent in subjects with hepatitis C-related, cholestatic, or alcoholic liver disease when compared with other etiologies of cirrhosis, consistent with earlier observations cited by the authors. They also measured Zn deficiency in 83 % of the subjects, more predominantly in decompensated cirrhotics; 91 % of subjects classified as Child–Pugh class B, 94 % classified as Child–Pugh class C, and 95 % of patients with Model for end-stage liver disease (MELD scores) >15 had Zn deficiency. These findings support previous reports that Zn deficiency is remarkably prevalent in advanced liver disease.

In this study, Sengupta et al. further correlated Zn deficiency to complications of cirrhosis and to clinical outcomes. Using univariate and multivariate regression analysis, they reported that serum zinc concentrations inversely correlated with the presence of infection and ascites. While diuretic and lactulose use were significantly associated with decreased median Zn concentrations on univariate regression analysis; these findings, however, do not directly implicate low Zn concentrations in the occurrence of increased complications and should thus be interpreted cautiously. Infection can decrease serum zinc concentrations, making it appear spuriously low. The proposed mechanism of decreased serum zinc concentrations in infection is through Zn redistribution to tissues, mainly liver, which is mediated by transcriptional regulation of metallothionein [12–15]. This Zn redistribution is probably a cytoprotective host response mediated through Zn-mediated regulation of intracellular redox balance [16]. Further, in an animal model of sepsis, Zn redistribution attenuated nuclear factor κ light chain enhancer of activated B cells (NF-κB) activation and inflammation [17]. It is therefore possible that the decreased serum Zn concentrations observed by Sengupta et al. may actually be an adaptive phenomenon.

The authors also correlated low serum Zn concentrations to low albumin concentrations and to ascites. In plasma, 80 % of zinc is bound to the albumin. Also, serum albumin concentration is used in the calculation of the Child–Pugh score. In the present study, the authors reported mean and median albumin concentrations of 3.3 g/dL. Subjects with Child–Pugh classes B and C would thus have lower circulating albumin concentrations that would certainly confound measured serum Zn concentrations. Moreover, no formula is available to adjust Zn plasma concentrations for low serum albumin concentrations similar to those used to "correct" measured plasma calcium. Therefore, decreased serum Zn concentrations, as observed by Sengupta et al., should be carefully interpreted in the presence of hypoalbuminemia. Moreover, the presence of ascites indicates increased total body volume which could dilute serum Zn concentrations, since hemodilution (as in pregnancy) can influence serum Zn concentrations [18]. No convincing data, however, exist to support this hypothesis in cirrhosis. Furthermore, lactulose-induced diarrhea and diuretics can increase gastrointestinal and urinary Zn losses, further worsening Zn deficiency. These issues merit attention while interpreting the observations made by Sengupta et al.

In this study, the authors also reported that Zn deficiency correlated with shorter transplant-free survival. The authors observed that Zn-deficient subjects had a 77 % transplant-free survival rate at 1 year versus 96 % for non-deficient subjects and 51 % at 3 years versus 74 % for non-deficient subjects. These survival differences should again be viewed cautiously in light of the higher MELD score and Child–Pugh class observed in the Zn-deficient subjects. As noted earlier, Zn deficiency was exceedingly prevalent in subjects with MELD scores >15 and those with Child–Pugh classes B and C, suggesting that transplant-free survival rates were directly influenced by disease severity itself.

The authors then addressed the response to Zn supplementation with initial daily doses of either Zn sulfate 220 mg or Zn gluconate 50 μg/day. They reported an improvement in median serum zinc concentrations from 0.49 to 0.60 μg/mL ($p < 0.001$) in 31 % of subjects with Zn supplementation. These results should be carefully interpreted for the following reasons: (a) only a third of study subjects had paired serum Zn measurements; (b) although median serum Zn values improved with supplementation, it was well below Zn deficiency levels (<0.66 μg/mL); (c) different Zn preparations and an as-needed dosing strategy limit adequate interpretation of the response to Zn supplementation; and (d) improved median Zn concentrations following supplementation had no significant correlation with changes in the MELD score. These observations pose more questions than providing answers. Which zinc preparation should be used, for how long, and how frequently to monitor the changes? What outcomes should be evaluated and what serum Zn concentration should be used as a response and for which outcomes?

Sengupta et al. further recommended that a select subset of cirrhosis patients (Child–Pugh classes B and C, MELD scores >15) should be screened for Zn deficiency based on its high prevalence, and its correlation with disease severity, infection, and shorter transplant-free survival. The authors also suggested that Zn can be used as a marker for predicting disease severity in cirrhosis. While it is reasonable to screen a subset of cirrhotics for Zn deficiency, there remain several caveats, some of which have already been stated above.

In cirrhosis, serum Zn measurement is less sensitive and specific marker for the diagnosis of Zn deficiency than in health. Also, the plasma Zn pool is only 0.1 % of the total body pool, representing the rapid Zn homeostasis pool

given rapid fluctuations in plasma concentrations including diurnal and dietary influences. Several confounding factors highlighted above including inflammation, the acute-phase reaction, and hypoalbuminemia may lower serum Zn concentrations. In some situations, tissue redistribution of Zn may actually represent an adaptive physiological response and not necessarily indicate Zn deficiency. Additionally, increased gut permeability, decreased intestinal Zn absorption, increased gastrointestinal and urinary losses, malnutrition, portosystemic shunts, and diminished hepatic Zn extraction also affect Zn status in cirrhotics, confounding interpretation of serum measurements. What further remains to be defined is whether current standard replacement dosing is adequate for patients with advanced cirrhosis. The route of administration also needs to be considered in cirrhosis where intestinal absorption and altered bioavailability due to changes in first-pass metabolism may be compromised. Future studies could include a comparison of the efficacy of enteral versus parenteral replacement therapy and of different Zn compounds, as well as different doses for replacement in this patient population. The impact of Zn repletion on complications of cirrhosis such as hepatic encephalopathy, and increased susceptibility to infections, and clinical outcomes such as transplant-free survival deserves attention.

In conclusion, Zn is integrally linked to macronutrient metabolism, immune function and protein structure in the body. Accurate identification of Zn deficiency assumes importance in this high-risk population of cirrhosis. There is a need to further investigate novel sensitive biomarkers of Zn deficiency, such as measurement of Zn-activated gene transcription and signal transduction. Based on current evidence, Zn replacement is not expected to alter major outcomes of patients with cirrhosis. Nevertheless, correction of Zn deficiency can potentially influence the quality of life with improved symptoms including anorexia, diarrhea, rash, and muscle cramps. A potential for decreased infection risk and hepatic encephalopathy merits rigorous investigation.

In broader terms, our current understanding of the mechanisms responsible for managing Zn metabolism in the liver and other tissues, such as in the pancreas, prostate, and mammary gland, remains immature. Nonetheless, Zn-based intervention strategies may complement currently available therapeutic approaches. Key avenues to explore in the future involve understanding the contribution of genetic alterations of Zn management proteins in the liver and other organs. Improving the understanding of how specific tissues regulate Zn transport and metabolism and elucidating the effects of nutrition, environmental factors, and aging on Zn homeostasis are key to improving human health and disease.

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