Branched Amino Acids and Zinc in the Nutrition of Liver Cirrhosis

To the Editor,

I read the excellent publication on the pathogenesis and treatment of malnutrition and sarcopenia in liver cirrhosis by Anand¹ in the Journal of Clinical and Experimental Hepatology with great interest. This truly highly complex subject involves and impairs many metabolic processes. Due to its biochemical structure (e.g. enzyme equipment), the skeletal muscle plays an important role in handling the diverse metabolic processes (amino acids, ammonia, glucose, etc.) in addition to the liver, serving as a kind “liver”.

Here, I would like to discuss the effects of the supplementation of Branched Chain Amino Acids (BCAAs) in combination with zinc. Liver cirrhosis as most advanced stage of chronic liver diseases is associated with energy malnutrition, with numerous metabolic disorders, such as hyperammonemia, hypoalbuminemia, with imbalance between BCAAs (valine, leucine, isoleucine) and Aromatic Amino Acids (AAAs; phenylalanine, tyrosine, tryptophan) and with reduced serum/plasma zinc concentrations.²

Zinc is an essential trace element that strongly influences human health and nutrition its involvement in several biological processes. Zinc function as structural and functional components of many transcription factors and enzymes that regulate cell growth, gene expression, and immune response, and its deficiency can lead to retard growth, impaired immune function, and several chronic diseases, such as diabetes mellitus, chronic inflammatory intestinal disorders, chronic renal and chronic liver diseases (Figure 1).³

As the main organ involved in zinc metabolism, the liver plays a important role in maintaining zinc homeostasis. Subsequently, liver diseases can alter zinc levels and, in turn may be influenced by zinc deficiency.²

Zinc deficiency consequently initiates a variety of metabolic abnormalities, including insulin resistance, hepatic steatosis, iron overload and Hepatic Encephalopathy (HE) in patients with chronic liver disease.⁴ Plasma levels of ammonia tend to be high in liver dysfunction and portal hypertension, and as skeletal muscle have a significant role in ammonia detoxification. Despite the well recognized neurotoxic effects of ammonia on neurons and astrocytes, skeletal muscle effects have only been reported.⁵ Hyperammonemia cause reduced protein synthesis and sarcopenia. Davuluri et al.⁵ describes that ammonia plays a key role in causing muscle loss in patients with cirrhosis. The authors⁵ demonstrates for the first time that skeletal muscle hyperammonemia induces a cellular response that resembles some features of amino acid starvation without an adaptive integrated stress response.

Other potential mediators of sarcopenia besides ammonia have been proposed decreased testosterone and reduced IGF-1 (Insulin-like Growth Factor 1), alterations in gut microbiome, and endotoxemia due to impaired gut barrier function, which may also lead to an increased protein breakdown and reduced synthesis.¹

Two major organs are involved in the metabolism of ammonia: the liver in which ammonia converted to urea via ornithine transcarbamylase and to glutamine via glutamine synthetase, and the skeletal muscle, where ammonia is metabolized to glutamine via glutamine synthetase.⁶⁻⁸ Complications (e.g. ascites, HE, infections) in liver cirrhosis patients are associated with high prevalence of zinc deficiency.^{2,7} Poor zinc status resulted in the impairment of nitrogen metabolism by reducing the activity of these both zinc depending enzymes.^{7,8} Zinc deficiency is, therefore associated with hyperammonemia, both in experimental model of cirrhosis in the rat and in patients with advanced liver disease.^{2,4} Zinc supplementation has shown to reduce ammonia levels in experimental animals and humans through stimulation of hepatic urea synthesis in the liver and glutamine synthesis in the liver and in the muscle.^{2,4}

Several authors reported that the supplementation of BCAAs alone or in combination with zinc may contribute to an improvement of hypoalbuminemia and ascites through an increased supply of substrate for proteins and the stimulation of protein synthesis.² Albumin has been shown to be a multifunctional protein with antioxidant, immunomodulatory and detoxification functions.⁹ It plays a fundamental role in the distribution of many metabolites and other substrates. Albumin is the major carrier of zinc in the plasma.¹⁰ BCAAs are involved in various biological processes such as stimulation of albumin and glycogen synthesis, improvement of insulin resistance, inhibition of ROS production, hepatocyte apoptosis, and liver regeneration.¹¹ Several current studies have demonstrated a positive effect on ascites reduction secondary to oral administration of BCAAs, either alone or in combination with zinc.²

The efficacy of BCAAs rich supplements ameliorating hypoalbuminemia is based on two mechanisms. First, administration of BCAAs provides an increased supply for protein (albumin) synthesis. Second, by stimulating intracellular signal transducers, BCAAs increase mRNA expression, promoting albumin synthesis.^{12,13} Furthermore, Kuwahata et al.¹⁴ reported that continuous supplementation with BCAAs induced phosphorylation of ribosomal protein S6 in livers of rats with chronic liver disease. Zinc supplementation might result in a decrease of muscular BCAAs consumption and consequently the administered BCAAs be used for albumin synthesis, which

Zinc's functions in the human body

Figure 1 Zinc's functions in the human body.

leads to an increase in serum albumin levels and a decrease in the amount of ascites.²

Zinc supplementation also significantly improved other nutrition parameters, such as serum prealbumin, retinol-binding protein, and IGF-1.¹⁵

In conclusions, the serum levels of zinc in the blood or plasma of patients with decompensated liver cirrhosis should be analyzed at all times. If a zinc deficit is evident, controlled substitution until normalization (8–24 weeks) of the zinc values is indicated. This alone or in combination with BCAA will improve various metabolic processes and, as a result, hepatic and muscle functions.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Anand AC. Nutrition and muscle in cirrhosis. *J Clin Exper Hepatol*. 2017;7:340–357.
2. Grüngreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. *Ann Hepatol*. 2016;15:7–16.
3. Maret W. Zinc and human disease. *Met Ions Life Sci*. 2013;13:389–414.
4. Himoto T, Masaki T. Association between zinc deficiency and metabolic abnormalities in patients with chronic liver disease. *Nutrients*. 2018;10:88.
5. Davuluri G, Krokowski D, Guan B-J, et al. Metabolic adaptation of skeletal muscle to hyperammonemia drives the beneficial effects of L-leucine in cirrhosis. *J Hepatol*. 2016;65:929–937.
6. Rabbani P, Prasad AS. Plasma ammonia and liver ornithine transcarbamoylase activity in zinc-deficient rats. *Am J Physiol*. 1978;235:E203–E206.
7. Yoshida Y, Higashi T, Nouse K, et al. Effects of zinc deficiency/supplementation on ammonia metabolism in patients with decompensated liver cirrhosis. *Acta Med Okayama*. 2001;55:349–355.
8. Riggio O, Merli M, Capocaccia L, et al. Zinc supplementation reduces ammonia and increases liver ornithine transcarbamoylase activity in experimental cirrhosis. *Hepatology*. 1992;16:785–789.
9. Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology*. 2013;58:1836–1846.

10. Lu J, Stewart AJ, Sadler PJ, Pinheiro TJ, Blindauer C. Albumin as a zinc carrier: properties of its high-affinity zinc-binding site. *Biochem Soc Trans.* 2008;36:1317–1321.
11. Holecek M. Branched-chain amino acids and ammonia metabolism liver diseases: therapeutic implications. *Nutrition.* 2013;29:1186–1191.
12. Itou M, Kawaguchi T, Taniguchi E, et al. Branched-chain amino acid supplements reduced ascites and increased the quality of life in a patient with liver cirrhosis: a case report. *Mol Med Pep.* 2009;977–981.
13. Hara K, Yonezawa K, Weng QP, Kozlowski MT, Belham C, Avruch J. Amino acid sufficiency and mTOR regulate p70 S6 kinase and eIF-4E BP1 a common mechanism. *J Biol Chem.* 1998;273:14484–14494.
14. Kuwahata M, Kubota H, Katsukawa M, et al. Effect of branched-chain amino acid supplementation on the oxidized/reduced state of plasma albumin in rats with chronic liver disease. *J Clin Biochem.* 2012;50:67–71.
15. Mohammad MK, Zhou C, Cave M, Barve A, McClain CJ. Nutrition in clinical practice. *Nutr Clin Pract.* 2012;27:8–20.

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Zinc and Branch Chain Amino Acids (BCAAs), Both are Important

Dear Editor

I am grateful to Dr. Kurt Gruengreiff for the interest he has shown in the review paper about relationship between nutrition and muscle in the patients of cirrhosis.¹ We have no conflict with many of the points raised by Dr. Gruengreiff, about the role of zinc and branch chain amino acids in nutrition among cirrhotic patients.² In fact the review clearly mentions that *Malnutrition in cirrhosis includes deficiency of several micronutrients including zinc*. In fact, zinc deficiency is common in patients with cirrhosis.³ Zinc levels have been reported to be low among patients with cirrhosis and they seem to affect taste.⁴ It can not only alter appetite and taste, but also impairs wound healing, immune reaction, and protein metabolism.⁵ Zinc supplements have been shown to improve clinical outcomes in cirrhosis.⁶ And the review paper recommends that *whenever zinc deficiency is detected it should be corrected*. The role of Branched Chain Amino Acids (BCAAs) has been covered more extensively in several paragraphs and figures.¹

There is minor difference in our perception about certain aspects of the impact of zinc supplementation. There is earlier evidence to show that decrease in albumin synthesis as well as relative increase in alpha-2 macroglobulin in cirrhosis possibly lead to zinc deficiency and are not really the consequences of zinc deficiency.^{7,8} Similarly changes in the gut seen in cirrhosis and portal hypertension may also contribute to zinc deficiency.^{9,10} Zinc deficiency in cirrhosis is further aggravated by oxidative stress and may lead to enhanced lipid peroxidation, iron overload and decrease in free IGF-1 levels adding to the insulin

resistance.^{11,12} There is no denying however, as has been suggested by Dr. Gruengreiff, that decrease in ornithine transcarbamylase activity related to zinc deficiency can aggravate hyperammonemia and hepatic encephalopathy.¹³ Zinc deficiency in cirrhosis also interferes with function of glutamine synthetase thus hampering the metabolism of ammonia in muscles with resultant rise in blood ammonia levels. The review has amply stressed on the relationship of hyperammonemia and reduced protein synthesis leading to sarcopenia. The role of other factors contributing to protein breakdown and sarcopenia, such as decreased testosterone and reduced insulin-like factor-1 along with alterations in gut microbiome and endotoxemia related to impaired gut barrier function, have also been alluded to in the review paper.¹

Dr. Gruengreiff has stated that supplementation of BCAAs alone or in combination with zinc significantly contributes to improvement of hypoalbuminemia and ascites through an increased supply of substrate for proteins and the stimulation of protein synthesis. I would like to mention that clinical evidence in favor of the role of zinc alone toward correction of hyperalbuminemia is not very robust. It is accepted by all that BCAAs are involved in various biological processes such as stimulation of albumin and glycogen synthesis, improvement of insulin resistance, inhibition of ROS production, hepatocyte apoptosis, and liver regeneration.¹⁴ There are some studies to show a reduction in ascites after oral administration of BCAAs, either alone or in combination with zinc. BCAAs not only provide an increased supply for protein synthesis in muscle, but also increase mRNA expression, promoting

albumin synthesis.¹⁵ The impact of zinc supplementation on improving barrier function and reducing inflammatory activity is widely accepted, but its impact on protein synthesis and albumin levels needs more research.^{16,17} In conclusion, I thank Dr. Gruengreiff, who has done legendary work on zinc metabolism, for his insightful comments on the review paper. He has rightfully underlined the importance of zinc and BCAAs in chronic liver disease.

REFERENCES

1. Anand AC. Nutrition and muscle in cirrhosis. *J Clin Exper Hepatol*. 2017;7:340–357.
2. Gruengreiff K. Letter to Editor Under Discussion. Reference to be Corrected by Editor.
3. Bavdekar A, Bhawe S, Pandit A. Nutrition management in chronic liver disease. *Indian J Pediatr*. 2002;69(5):427–431.
4. Stamoulis I, Kouraklis G, Theocharis S. Zinc and the liver: an active interaction. *Dig Dis Sci*. 2007;52(7):1595–1612.
5. Madden AM, Bradbury W, Morgan MY. Taste perception in cirrhosis: its relationship to circulating micronutrients and food preferences. *Hepatology*. 1997;26:40–48.
6. Matsuoka S, Matsumura H, Nakamura H, et al. Zinc supplementation improves the outcome of chronic hepatitis C and liver cirrhosis. *J Clin Biochem Nutr*. 2009;45(3):292–303.
7. Schechter PJ, Giroux EL, Schlienger JL, Hoenig V, Sjoerdsma A. Distribution of serum zinc between albumin and 2-macroglobulin in patients with decompensated hepatic cirrhosis. *Eur J Clin Invest*. 1976;31:147–150.
8. Kiilerich S, Christiansen C. Distribution of serum zinc between albumin and 2-macroglobulin in patients with different zinc metabolic disorders. *Clin Chim Acta*. 1986;154:1–6.
9. Karayalcin S, Arcasoy A, Uzunalimoglu O. Zinc plasma levels after zinc tolerance test in nonalcoholic cirrhosis. *Dig Dis Sci*. 1988;33:1096–1102.
10. Himoto T, Masaki T. Association between zinc deficiency and metabolic abnormalities in patients with chronic liver disease. *Nutrients*. 2018;10:88.
11. Rabbani P, Prasad AS. Plasma ammonia and liver ornithine carbamyltransferase activity in deficient rats. *Am J Physiol*. 1978;235:E203–E206.
12. McClain CJ, Antonow DR, Cohen DA, Shedlofsky SI. Zinc metabolism in alcoholic liver disease. *Alcohol Clin Exp Res*. 1986;10:582–589.
13. Grüngreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. *Ann Hepatol*. 2016;15:7–16.
14. Holecsek M. Branched-chain amino acids and ammonia metabolism liver diseases: therapeutic implications. *Nutrition*. 2013;29:1186–1191.
15. Kimball SR, Jefferson LS. *Curr Opin Clin Nutr Metab Care*. 2001;4(1):39–43.
16. Mohammad MK, Zhou C, Cave M, Barve A, McClain CJ. Nutrition in clinical practice. *Nutr Clin Pract*. 2012;27:8–20.
17. Takuma Y, Nouso K, Makino Y, Hayashi M, Takahashi H. Clinical trial: oral zinc in hepatic encephalopathy. *Aliment Pharmacol Ther*. 2010;32(9):1080–1090.

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