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Opinions

Why a pinch of zinc in liver disease matters

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Regarding the epidemic increase of non-alcoholic fatty liver disease in the Western World and its sequels and with reference to two recent authoritative reviews on liver cirrhosis [1,2], we deem it appropriate to draw attention to the importance of zinc for the liver. The article in the Lancet mentions zinc only once in the context of the recommendation that "zinc should be given as required" while the article in JAMA does not mention zinc at all. An extensive literature on the role of zinc in the liver and the role of the liver in zinc metabolism exists, dating back to seminal work of almost seventy years and demonstrating chronically decreased zinc in blood plasma and other tissues in liver cirrhosis [3]. There is a certain oversight in considering the importance of trace elements in the clinical literature, not only for liver disease but for many other chronic diseases as well. In part, this is due to the term "trace element" being somewhat outdated as it stems from a time when quantitative determination was a challenge, the juxtaposition of the terms trace elements and vitamins that receive more attention, and the lack of appreciation of the quantities involved. Thus, while magnesium is classified as a macromineral and zinc as a micromineral, the difference is only one order of magnitude, i.e., about 25 mg of magnesium vs. about 2.5 mg zinc in the human body, and only a factor of two in the case of their concentrations in the liver. Another comparison further illustrates the need for appreciating quantities in relation to functions. The importance of vitamin B12 is well established. The human body needs only about 2.4 μg per day, and it is involved in only two enzymatic reactions, methylmalonyl-CoA mutase and methionine synthase. As the chemical name cobalamin indicates, vitamin B12 carries a trace element in its organic structure, namely cobalt, which is critical for its function. In contrast, adult humans need 4000 times more zinc (11 mg for males, 8 mg for females), which is involved in hundreds of enzymatic reactions comprising all classes of enzymes. Overall, zinc is a cofactor in over 3000 proteins, meaning that every tenth human protein contains zinc. Seen with this perspective, it does no longer surprise that zinc is a type 2 nutrient of general importance whereas iron is a type 1 nutrient of specific importance [4] and zinc is a critically important chemical element of life and involved metabolically at every stage in liver disease [5]. If one were to name one important single function among the many, the effect of zinc on normalizing ammonia concentrations would be worth pointing out. Clearly, the role of zinc in liver disease calls for a need to screen for zinc deficiency at each stage as clinical or subclinical zinc deficiency has been confirmed in numerous investigations [5]. A major additional factor in liver health and disease is the interaction between the liver and the gut, the gut-liver axis. Zinc is necessary to maintain a healthy gut barrier, which protects the liver from invading microorganisms, their endotoxins, and from other toxins, all factors in the development of liver disease. In the gut as well as in the liver, an adequate zinc status mitigates oxidative stress which is a hallmark of inflammation [6].

Recent systematic reviews and meta-analyses of zinc supplementation in liver cirrhosis demonstrated a possible improvement in hepatic encephalopathy [7] but, while zinc deficiency was confirmed, 6-months mortality was not affected based on limited data from only four comparable investigations that qualified out of 712 [8]. This selection demonstrates that investigations on the impact of zinc on liver cirrhosis (genesis such as alcoholic vs. non-alcoholic, stages, ascites, hepatic encephalopathy, hepatic cellular carcinoma, bacterial and viral infections, comorbidities such as diabetes) are extremely heterogeneous in design, patient selection, complications of the disease, chemical formulation of zinc supplements, their dosage and treatment interval, timing of clinical tests and yet other factors. Therefore, it has thus far not been possible to provide strong and unanimously accepted support for recommending zinc supplementation, e.g., by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), though recommendations in Japan seem to call for supplementation, especially for hepatic encephalopathy, where "zinc deficiency predicts overt hepatic encephalopathy and mortality in liver cirrhosis patients with minimal hepatic encephalopathy" [9,10].

Zinc fulfills many characteristics as a disease-modifying agent in decompensated liver cirrhosis [11]. Similar to suggestions regarding the efficacy of albumin, simvastatin - a lipid lowering drug, rifampicin and other hard-to-resorb antibiotics, supplementation with zinc should be further evaluated in large-cohort, well-designed, high-quality randomized controlled trials or observational studies [5]. As there is a clear disjunct between the positive outcomes of basic

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research supporting critical roles of zinc in the liver and the poor evidence from clinical and epidemiological observations that often consider mortality as the only endpoint.

Evidence-based medicine, much as evidence-based nutrition, should capitalize on the knowledge in the biosciences, the reported zinc deficiencies, and the beneficial effects of zinc in liver diseases including the important recently discovered relationship between albumin, the main zinc-binding protein in blood plasma, zinc, and fatty acids [12]. We focused on zinc as an example without further discussions of other essential macro- and microminerals or the fact that they interact among each other and with yet other non-essential elements. Supplementation with single nutrients in the nutritional support of patients with liver disease clearly is not the answer. Rather, zinc is a very important adjuvant in treating liver disease, not only end-stage but throughout the trajectory of the disease [5,12,13]. Importantly, the zinc status of a patient needs to be monitored, and if supplemented at high doses of zinc, copper status needs to be determined as well [14,15]. Nutritional support is cost-effective, preventative and could be transformative. Zinc is not a life-style drug, but a specific medication that requires an adequately dosed prescription in specific indications of gut and liver disease.

Declaration of interests

None.

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