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Opinion

Approaches to Research and Clinical Practice Relating to Zinc Deficiency

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Introduction

Zinc deficiency is common in developing countries and affects over 2 billion people worldwide. Wessells and Brown reported [1] that an estimated 17.3% of the global population is at risk of inadequate zinc intake, with the regional estimated prevalence of inadequate intake ranging from 7.5% in high-income regions to 30% in South Asia. Zinc deficiency often accompanies various conditions and diseases, and can affect the elderly, pregnant women, lactating women, patients with chronic diseases, such as diabetes mellitus, liver disease, kidney disease, and inflammatory bowel disease, and during the administration of chelators [2].

Zinc is essential for the function of more than 300 different enzymes and transcription factors. Manifestations of zinc deficiency include, for example, dermatitis, delayed wound healing, impaired taste, loss of appetite, hair loss, fertility issues, increased susceptibility to infection, and growth disturbances in children [2]. However, the exact link between zinc deficiency and its various manifestations are not entirely clear. Zinc deficiency is often difficult to detect since its manifestations are often non-specific.

This report discusses current challenges in research and clinical practice relating to zinc deficiency, as well as future directions.

Keywords: Zinc; Deficiency; Practice guideline; Biomarker

Practice guidelines for zinc deficiency

Although zinc deficiency is common, physicians generally lack awareness about the disorder because most symptoms are subtle and non-specific. Against this backdrop, the Japanese Society of Clinical Nutrition issued the Practical Guideline for Zinc Deficiency in 2018 [2]. To our knowledge, only one other report has been published on practice guidelines for zinc deficiency—the BMJ Best Practice: Zinc Deficiency [3].

Clinical practice guidelines are especially important in medical settings. When available, guidelines can increase physician awareness on the importance of zinc in health and provide guidance on means to prevent and treat zinc deficiency. Since dietary habits, physical characteristics, and other aspects differ across countries, practice guidelines tailored to each country and population are important. These practice guidelines can then be updated as evidence accumulates in medical practice and new data become available.

Biomarkers for zinc deficiency

The Japanese Practical Guideline lists low serum levels of zinc and alkaline phosphatase (ALP) as criteria for diagnosing zinc deficiency [2]. However, ALP levels can be inherently high in patients with liver disease, osteoporosis, chronic kidney disease, and diabetes mellitus. Moreover, normal serum ALP levels depend a great deal on age. Thus, serum ALP is not an ideal biomarker for zinc deficiency. The Japan Practical Guideline presents that a serum zinc level <60 μg/dL and 60–80 μg/dL indicates zinc deficiency and marginal zinc deficiency, respectively. However, The Guideline makes concurrently mentions that serum zinc levels may not accurately reflect zinc deficiency. The BMJ Best Practice of Zinc

Deficiency [3] suggests that a serum zinc level <60 μg/dL or <70 μg/dL is considered abnormal in nonpregnant adults. However, due to the relatively low sensitivity of serum zinc as a biomarker for marginal zinc deficiency, the BMJ Best Practice also recommends considering oral supplementation if symptoms are typical even if test results are normal. This suggests that low serum zinc levels may not always reflect a zinc deficient status.

More sensitive, accurate biomarkers which are easily measurable are needed to improve the diagnostic accuracy of the disorder. In this regard, Takeda et al. reported that zinc-dependent ectoenzymes such as ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) and CD73/ecto-5'-nucleotidase (NT5E) may become candidate biomarkers for zinc deficiency, as zinc deficiency severely impairs the activities of these enzymes [4].

Mechanisms underlying the impact and development of zinc deficiency

As mentioned above, zinc deficiency is common in many diseases. We previously reported that zinc deficiency enhances intestinal inflammation via macrophage activation in patients with inflammatory bowel diseases [2]. However, the detailed mechanisms underlying the impact of zinc deficiency on inflammatory responses remain unclear. The mechanism underlying the development of zinc deficiency in certain diseases is also a topic of great interest.

Since the prevalence of zinc deficiency appears to differ by study, further analyses involving comparisons by patient characteristics, such as disease condition, medication use, age, and sex, are warranted.

Therapies for zinc deficiency

Many studies have assessed the effects of zinc supplementation on diseases and conditions related to zinc deficiency. For example, since zinc deficiency can lead to nitrogen metabolic disorder in patients with liver cirrhosis, zinc supplementation improves not only ammonia metabolism, but also protein metabolism [2]. However, the effects of zinc deficiency on a particular disease appear to differ by study. A meta-analysis on the impact of zinc supplementation by disease would provide much needed clarity on this aspect.

Conflict of Interest

The author declares no conflict of interest.

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