Mini-Review

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Should Zinc be taken with Food?

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Abstract

A recent clinical study reported greater effects of a zinc supplement on indices of essential fatty acid desaturation when the zinc was taken with food, in contrast to a greater plasma zinc response when taken in the fasted state. These results indicate that zinc with food may be more effectively directed toward metabolic functions. This mini review summarizes current knowledge of zinc absorption and metabolism, and the effects of food intake, that may explain these observations.

Keywords:

Supplemental zinc; Plasma zinc; Essential fatty acid metabolism

Introduction

Massih and colleagues recently reported that a zinc supplement, supplying 25 mg of zinc daily as zinc gluconate for two weeks, increased indices of essential fatty acid desaturation when taken with breakfast vs. when taken in the fasted state 30 minutes before breakfast [1]. The dependence of essential fatty acid metabolism on zinc has been previously reported. Early studies associated deficiencies of omega-6 polyunsaturated fatty acids with severe zinc deficiency [2,3]. More recently, a zinc supplement increased indices of erythrocyte membrane fatty acid desaturation and leukocyte fatty acid denaturise 1 mRNA among patients with type 2 diabetes [4]. However, it appears that Massih and colleagues were the first to study the metabolic effects of zinc when taken in the fasted state vs. with food. Given current knowledge on how food intake may moderate zinc metabolism, these findings suggest that zinc with food may be more effectively directed toward zinc-dependent metabolic function, and emphasize the need for further mechanistic study on the dynamics of zinc metabolism.

Zinc Nutrition

Zinc contributes to the structure or function of approximately one tenth of human proteins, in other words, one tenth the molecular machinery behind metabolic and physiological functions [5]. These structural and functional roles provide essential support for numerous metabolic and physiological functions. Essential fatty acid metabolism, vascular and immune functions, and DNA repair, all respond to changes in dietary zinc intake [4,6,9].

In the clinical setting, zinc status is primarily determined by changes in plasma zinc concentration (PZC) [10]. However, due to its tight regulation within the body, PZC varies more within an individual over the course of a day than it does between individuals [11-13]. Except for the diagnosis of severe zinc deficiency, PZC is only recommended as an indicator of population zinc status [10,14].

Part of the need for tight homeostatic control of zinc metabolism is dictated by its lack of a labile storage site in the body. In contrast to micronutrients that may be stored in the body, (e.g., iron, vitamin A, or vitamin D), there are no zinc stores that can be mobilized to maintain zinc nutritional status over periods of low zinc intake [10]. A level of zinc deficiency that leads to impaired functions may thus occur over a relatively short period of low zinc intake.

For example, when healthy men were fed a low zinc diet (4 mg zinc per day, with phytic acid to further inhibit zinc absorption) for two weeks, PZC was conserved. However, increases in double stranded breaks and oxidative damage to DNA were observed, as well as decreases in indices of essential fatty acid desaturation [8,15]. After restoration of dietary zinc by providing 10 mg zinc per day for four weeks, DNA damage and fatty acid metabolic indices were returned to baseline levels. These data demonstrate the potential effects of marginal decreases in dietary zinc on genomic stability and essential fatty acid metabolism over a relatively short period of time. They also highlight the ability of the body to maintain PZC, while zinc-dependent functions decline.

Absorption of dietary zinc

Dietary zinc, solubilized to ionic zinc in the acidic gastric environment, is primarily absorbed in the upper small intestine: the duodenum and proximal jejunum. Zinc absorption is mediated by Zip4, a zinc transport protein localized to the apical membrane of small intestine enterocytes [16,17]. Its absorption is saturable; as the concentration of zinc in the digestate increases, the fraction of zinc absorbed decreases, until a plateau, or transport maximum, is reached [18].

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Zinc, in the form of supplements taken in the post absorptive state after an overnight fast, is rapidly absorbed and increases PZC [19]. In contrast, when zinc is taken with food, the appearance of zinc in plasma is delayed [20]. Some components of food can inhibit zinc absorption. Notably, dietary phytic acid, the storage form of phosphorus in plants, inhibits zinc absorption by forming an insoluble complex with zinc. Calcium joins this complex of phytate and zinc, further reducing zinc absorption [21,22]. The global prevalence of zinc deficiency is associated with the intake of foods high in phytic acid, such as legumes, tubers, whole grains, and seeds [23,24]. However, as protein is added to a meal, a predictable increase in the fractional absorption of dietary zinc is observed, and the capacity of phytic acid to inhibit zinc absorption is reduced [21].

Enterohepatic recirculation

During food intake, a substantial amount of zinc is secreted into the gastrointestinal tract as a component of digestive juices, and it is reabsorbed distally [16,25]. The efficient conservation of this secreted zinc is crucial to survival. Kinetic studies support enterohepatic recirculation of zinc, similar to the recirculation needed for conservation of digestive enzymes [26,27]. The mechanism of enterohepatic zinc recirculation has not been determined in humans. In the ileum, the distal portion of the small intestine where much of the reabsorption of digestive enzymes occurs, the amount of Zip4 ionic zinc transport proteins is not sufficient to account for the reabsorption of digestive zinc. Likewise, passive diffusion, which is observed in animal models at high concentrations of zinc, has not been observed in studies of human zinc absorption [28,29]. Reabsorption of this secreted zinc is therefore most likely mediated by co-transport with another molecule.

Co-absorption of zinc via amino acid transporters could explain the reabsorption of endogenously secreted zinc. Amino acid transporters are localized over the entire length of the small intestine, and cell models support the co-transport of zinc with amino acids [30]. Moreover, several amino acids and related molecules have high affinities for zinc binding [31,32] and their complexes with zinc have the greatest absorption in the ileum compared with other portions of the small intestine [33,34]. The co-absorption of zinc via amino acid transporters may explain the enhancing effect of dietary protein on zinc absorption. Thus, there may be opportunity for zinc from the diet, or a zinc supplement taken with food, to be caught up in enterohepatic recirculation and absorbed distally.

In the absence of food and all the secretions that are stimulated by food (i.e., in the fasted state), the chance of oral zinc getting caught up in this recirculation would be substantially reduced. Essential fatty acid desaturation occurs in most tissues, though primarily in the liver [35,36]. A tendency for supplemental zinc to get caught up in enterohepatic recirculation when taken with food, would naturally direct that zinc to the liver where these cellular metabolic processes take place. Future studies are needed to determine whether zinc co-transport with amino acids, or another mechanism, mediates the enteric recirculation of the zinc contained in digestive secretions.

Effects of food intake on plasma zinc

Interestingly, PZC decreases rapidly after food intake [11,37]. Tracer studies indicate that zinc is directed postprandially into tissues, most likely to the liver [38,39]. However, according to the results of Massih et al., zinc taken in the fasted state, while effective in elevating PZC, does not appear to be directed as efficiently toward essential fatty acid desaturation compared with zinc taken with food [1]. This may be due to the nature of how zinc is utilized: i.e.., as a structural component and cofactor for proteins. The absorption of zinc with amino acids, the building blocks of proteins, may thus be important for the optimal metabolic effects of zinc.

In this case, increases in PZC do not necessarily indicate increased zinc utilization. There is a growing number of examples of demonstrable effects of zinc intake on health outcomes, without detectable changes in PZC [8,40-42]. Further, the lack of correlation between dietary zinc and PZC is a growing theme in zinc clinical research [43]. It is possible that changes in PZC better represent a magnified stress on zinc homeostasis, whether due to severe zinc deficiency, or the absorption of abnormally high amounts of zinc due to the concentration present in the digestive tract. Functional indicators of intracellular zinc, where most zinc-dependent processes occur, therefore, may provide a stronger basis for the development of future clinical indicators of zinc status [10,44,45].

Conclusion

Despite gaps in knowledge of zinc metabolism, a body of scientific evidence is consistent with the concept that zinc may be more effectively directed toward zinc-dependent processes when it is consumed with food. This may be due to co-absorption of some dietary zinc with amino acids, or otherwise entering the pathway for recirculation of endogenously secreted zinc. Furthermore, the kind of food is likely to be important. While foods high in phytic acid inhibit zinc absorption, the addition of protein to a meal can enhance zinc absorption. The functional dependence of zinc on co-absorption with food, how diets may be structured to optimize zinc utilization, and the mechanism of reabsorption of endogenous zinc, represent important areas of future research.

Conflicts of Interest

None

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