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Tool-Box

Zinc

Efficient Zinc Supplementation and its Role in Health and Disease

Introduction

Zinc is an essential trace element, indispensable not only for human well-being but also for the growth and health of animals, plants, and microorganisms. In animals, and in particular humans, it is vital for both prenatal and postnatal development and later organism function. Given this universal significance, it's hardly surprising that zinc serves as a critical mineral vital to numerous biological functions. It acts as an indispensable element in numerous enzymes, facilitating a wide array of biochemical transformations and contributing to their structural integrity. These zinc interacting enzymes such as alcohol dehydrogenase, carbonic anhydrase, matrix metalloproteinase and superoxide dismutase represent some of the major players in human health and disease[1]. Moreover, zinc can influence gene expression acting as a ligand, where its presence at a specific site on a transcription factor is essential for enhancing the rate of transcription[2].

Zinc Transport and Protein Association

Human body zinc homeostasis is predominantly regulated by its intestinal absorption[3,4]. Only a small portion of the total zinc is present in serum in the human body, where it is primarily associated with (bound to) proteins such as albumin and 2-macroglobulin, leaving only a trace amounts present as free ions[5,6]. Thus, in healthy people, the concentration of zinc in plasma or serum ranges between 12 and 16 μM, accounting for a mere fraction of the body's 1% of total zinc content[7]. The majority of the zinc is placed within cells. In terms of cellular distribution, zinc is most abundant in the cytoplasm, followed by the nucleus and the cell

membrane. It exists within the cell in specialized locations such as organelles and vesicles or is linked to metalloproteins, metalloenzymes, and metallothioneins[8].

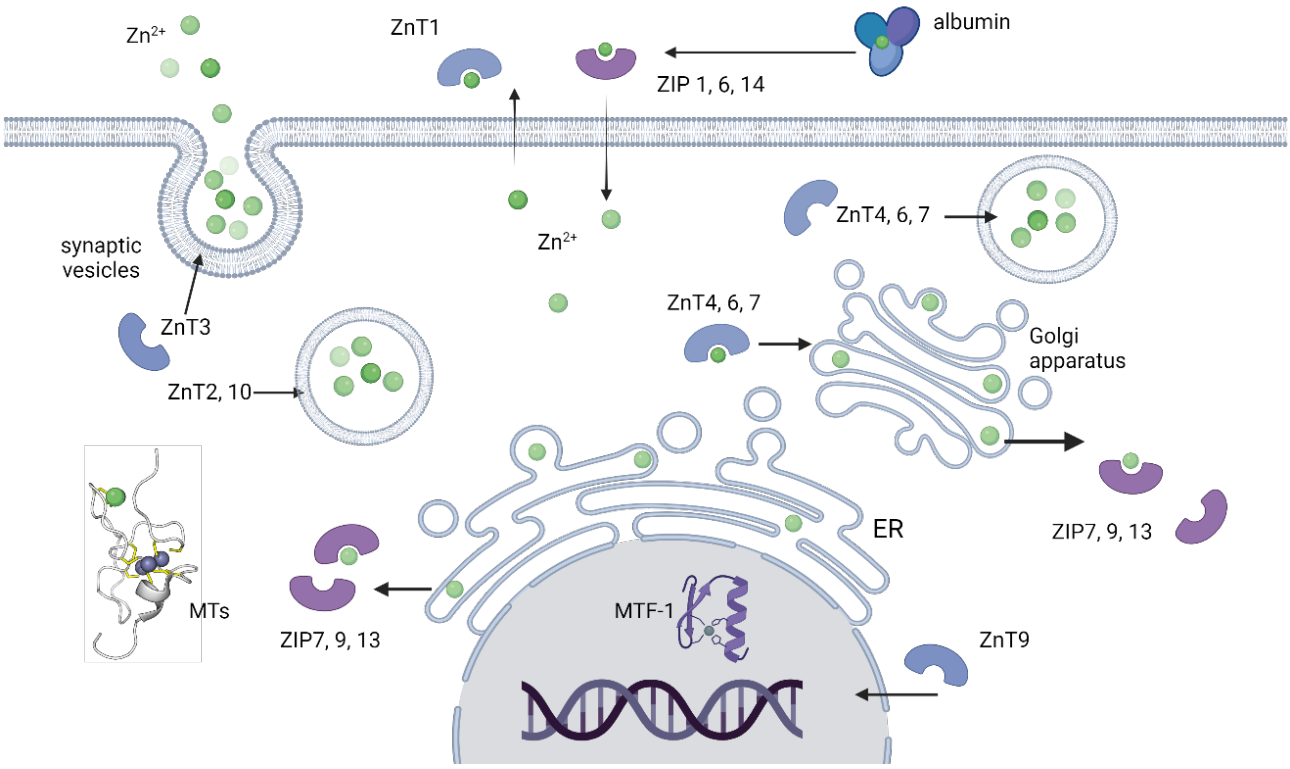

Figure 1. Zinc localization and transport in cell. Zinc transporters are abbreviated with Zrt-, Irt-like proteins (ZIP,), Zn transporters (ZnT,), metallothioneins (MTs), and metal response element-binding transcription factor-1 (MTF-1)

To enable zinc's multifaceted biological functions, specialized mechanisms for moving zinc through biological membranes are essential. Consequently, proteins responsible for zinc transport, such as Zn Transporters (ZnT) and Zrt-, Irt-related proteins (ZIP), are crucial for managing zinc's physiological roles. They play a vital role in a range of physiological and cellular processes, ranging from immune and endocrine systems to reproductive, skeletal, and neural functions, by meticulously regulating zinc balance within the body[6].

Zinc Biochemistry

The biochemical roles of zinc in zinc-based enzymes encompass the activation of substrates, water molecules, or other ligands that are bound to zinc, enabling catalytic reactions to occur[9]. Zinc's structural role is significant not only in shaping the overall form of proteins but also more specifically in organizing the structure of individual protein domains[10]. These

domains that bind to zinc serve as functional units that facilitate interactions between proteins and other key biological molecules, like DNA/RNA, other proteins, or lipids. The most notable class of these zinc-binding domains appears in proteins known as zinc fingers[11]. This term originated to describe the way these specialized domains latch onto DNA, similar to how fingers grasp an object. Zinc finger classification have evolved into over two dozen unique structural categories and are recognized as functional units that engage with an array of proteins, lipids, and nucleic acids[12–15]. In cell, zinc is stably bound to zinc finger type proteins usually surrounded by tetrahedral position oriented amino acid side chains[16]. This coordination complex is mostly represented by histidine, followed by cysteine side chains commonly called Zn–Cys_xHis_y sites[17].

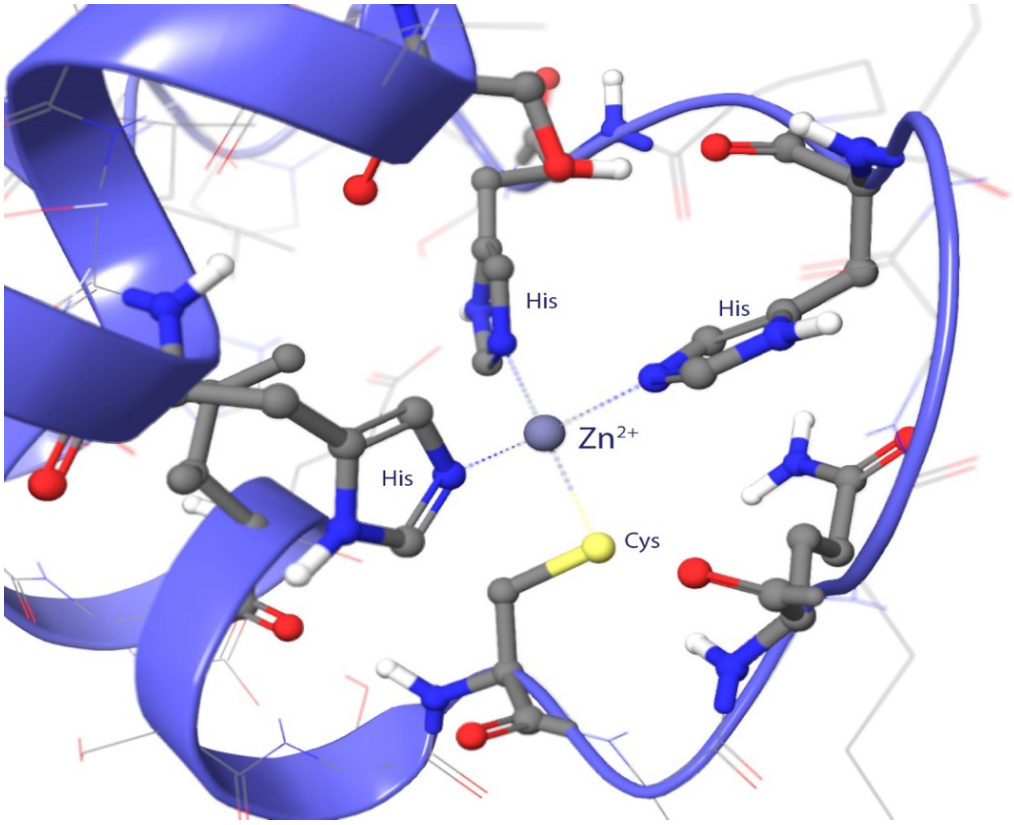

Figure 2: Zn–Cys_xHis_y site - The Crystal Structure of the Catalytic Domain of AMSH (PDB:3RZU). Zinc is coordinated with three histidine side-chains and one cysteine sidechain.

Importance of Zinc Supplementation

Given its myriad roles in biological functions, it's hardly surprising that a wide array of symptoms has been attributed to zinc deficiency. These include ongoing bouts of diarrhea, hair loss, taste abnormalities, weakened immunity, cognitive issues, delayed wound recovery, reduced appetite, sustained inflammation, heart failure, atherosclerosis, liver ailments, and psychological shifts like mood swings, irritability, and depressive states[18–25]. Despite the knowledge of its importance, zinc deficiency continues to be a significant issue affecting public health worldwide. In developing nations, it's estimated that such deficiency accounts for 4% of the overall illness and death rates among young children.

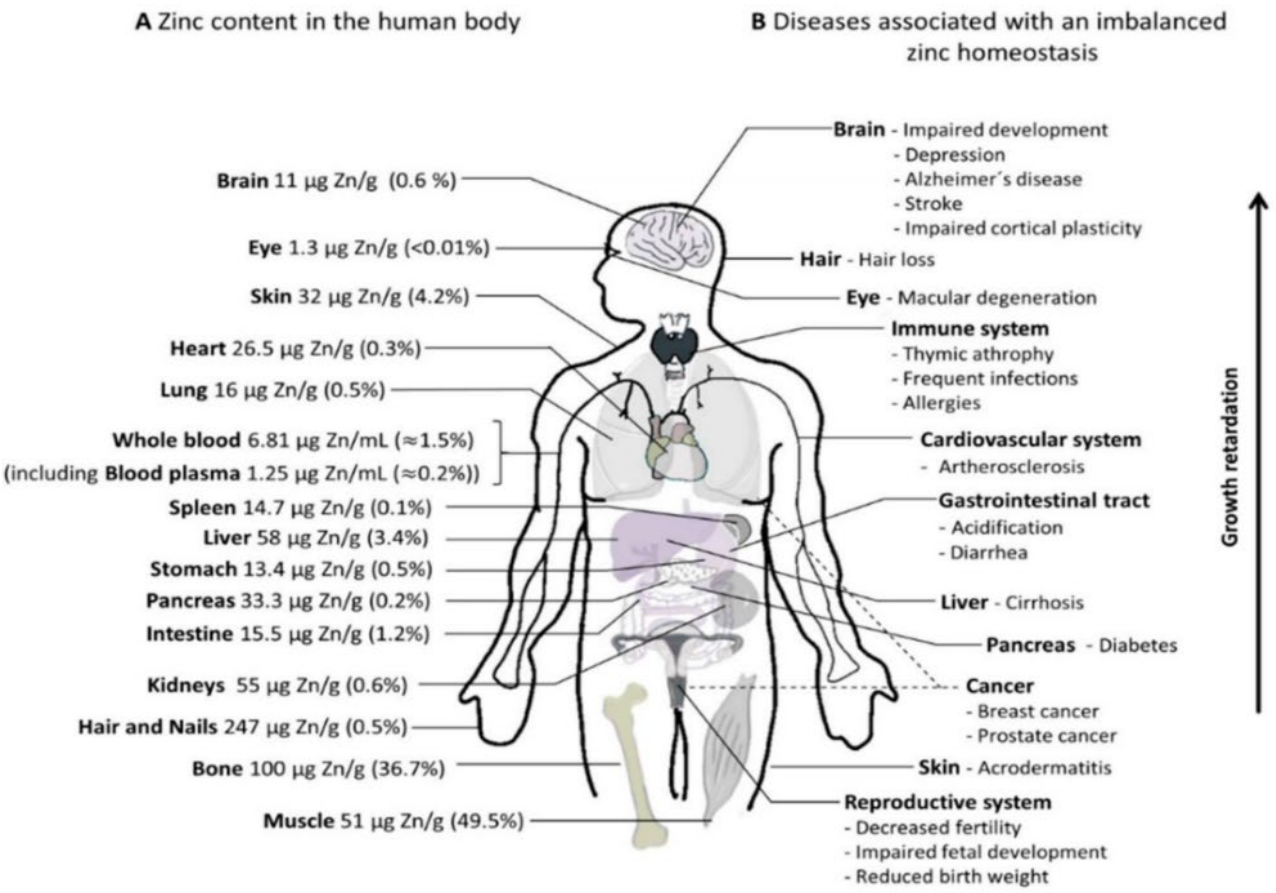

Figure 3: Overview of zinc distribution and disease association in the human body. (A) Approximate zinc content (µg per g wet weight) of the respective tissues and the resulting proportion of total body zinc. (B) Diseases of the respective organ systems associated with imbalanced zinc homeostasis. Authors and copyright: Maria Maares and Hajo Haase[26]

While it's clear that zinc deficiencies manifest in distinct symptoms and are linked to various health disorders, there is also compelling evidence to suggest that supplemental zinc can positively impact overall well-being. For example, supplementation of zinc can affect inflammatory and immune related factors as shown in various clinical trials[27], more specifically via decrease of CRP, hs-CRP and TNF-α, IL-6 expression and neutrophil count levels while increasing CD3 and CD4 t cell receptor presence. This correlates to modulation of immune system toward less pronounced inflammatory signaling while simultaneously improving "immunosurveillance" to fight microbial invasion[28] or reducing cancer occurrence more effectively[29]. The antimicrobial fighting mechanism of zinc is in consistency to efficacy in reducing symptoms of common cold[30,31] and respiratory tract infections in general[32]. In adults, higher dietary zinc intake compared to lower intake has been associated with a decreased likelihood of developing various digestive cancers[33], including colorectal[33,34] esophageal[35], and pancreatic cancers[36]. In regards to inflammation related conditions, zinc was successful in treatment of inflammatory acne[37–39], prevention of otitis media in children[40], and reduction of CRP levels in COVID-19 patients[41,42] a marker strongly associated systemic inflammation and adverse disease outcome[43].

In the meta-analysis, 24 studies were reviewed, encompassing 33 distinct zinc interventions, and involving a combined total of 14,515 participants in either the zinc-supplemented or control groups. The data revealed that zinc supplementation positively influenced plasma lipid profiles, leading to significant reductions in total cholesterol, LDL cholesterol, and triglycerides. Given these effects, zinc supplementation holds promise in potentially lowering the risks associated with atherosclerosis-related health issues and fatalities[44].

Several studies consistently demonstrated that zinc supplementation enhances the overall mood and efficacy of various antidepressant therapies in reducing depressive symptoms. For example, adding 25mg of zinc to SSRI therapy led to a reduction in symptoms as measured by the HDRS scale[45]. Another study found that 30mg of elemental zinc improved depressive symptoms in obese individuals, as assessed by the BDI II rating scale, while also increasing serum BDNF concentrations[46]. Supplementary research corroborated the previous results, demonstrating that adding 25mg of zinc to Imipramine therapy effectively alleviated symptoms in treatment-resistant individuals, as assessed by the BDI scale[47]. Notably, the last-mentioned study did not measure participants for zinc deficiencies, indicating that zinc supplementation regardless of status in blood can benefit mental health.

Improved Zinc Absorption (Role of Histidine)

For zinc to carry out its biological roles effectively, it needs to be available in the correct quantities, mainly via dietary absorption and cellular uptake. Nonetheless, several well-understood variables can negatively impact this bioavailability. Even though specific medical conditions can reduce the amount of available zinc by causing a decrease in the expression

of zinc transporters, the principal determinant of zinc bioavailability is generally considered to be the absorption of dietary zinc. Using small intestine perfusion techniques on healthy subjects, it's been determined that the primary sites for zinc absorption in the human digestive system are the duodenum[48] and jejunum[26]. Zinc is primarily absorbed at the surface of the intestinal lining, specifically in the brush border membrane. From there, it's transported into the absorptive cells known as enterocytes. Once inside these cells, zinc is then expelled on the other side, releasing it into the portal bloodstream. Here, it primarily binds to albumin, which further distributes the mineral throughout the tissues[3,49].

The efficiency of zinc absorption can be negatively influenced by certain components found in food. One of the main obstacles is myo-inositol hexakisphosphate, commonly known as phytate. This compound tends to form insoluble complexes with zinc, making the mineral less accessible for absorption by the intestines[50]. The human digestive system's lack of enzyme phytase, which breaks down phytate, further complicates the release of zinc from these complexes[51]. Additionally, the presence of phytate can contribute to zinc deficiency. Eating foods rich in iron, calcium, and copper can also hinder zinc absorption, as these elements compete with zinc for the same transport mechanisms and carrier proteins[52].

Conversely, protein intake increases zinc absorption[53]. This is of no surprise as proteins are cut into peptides and amino acids that can serve as direct binding ligands to zinc, reducing its salt precipitate formation and enhancing transport. At the same time the presence of intact excess proteins in digestive fluids can significantly reduce zinc absorption in the ileum. As a result, consuming high-protein foods, especially for those with immature digestive systems or specific protein requirements (sports), could lead to poorer zinc absorption which is why care is needed in timing of zinc intake[54]. Regardless, amino acids were indeed proposed to have a role in improved absorption of zinc[55], having a clear advantage over respective salts. There are two proposed ways for this augmentation to occur:

a) Amino acids create stable complexes with metals being co-absorbed via amino acid transporters and;
b) Ligands (amino acids and peptides) in the chyme that have a specific affinity for binding with zinc can enhance its absorption. They achieve this by establishing a gradient of affinity, effectively directing zinc toward the active sites of its transporters, thereby optimizing its uptake.

L-histidine showed to form stable complexes with bivalent ions more effectively than any other amino acid[56]. This was further supported by the fact that 2:1 to 3:1 ratio of histidine with zinc had superior absorption surpassing that of citrate, glucoronate and picolinate counterparts by the rat ileum[57]. Another study explored the impact of zinc levels in the brain, noting that both deficiency and excess can have detrimental effects, including impaired learning, memory, and increased dysfunction in aging brains. The research specifically

focused on the efficacy of zinc-histidine complex (Zn(His)(2)) in protecting cortical neurons from oxidative damage induced by hydrogen peroxide. Findings indicate that pre-treating neurons with subtoxic levels of zinc-histidine improved cell viability and minimized hydrogen peroxide-induced damage. More important, zinc-histidine was more effective than zinc in anti-apoptotic properties, inhibiting caspase-3 activation and c-jun-N-terminal kinase phosphorylation[58]. Histidine co-administration also improved zinc bioavailability from zinc oxide in rat study[59]. Finally, the study in human patients with liver cirrhosis corroborated usefulness of zinc histidine complex[60] showing superior results in terms of its bioavailability.

Conclusion

Kingnature® Zink Vida employs a potent zinc-histidine complex formula, designed to optimize absorption rates to a superior level, thereby significantly amplifying the health benefits associated with zinc. Kingnature® Zink Vida is not only effective but also exceptionally safe, as its high-affinity binding with histidine significantly minimizes the risk of zinc toxicity.

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