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ZINC: A Micronutrient with Pleiotropic Actions

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Abstract

Zinc is a micronutrient with multiple functions in the human body, including physical growth, immune competence, reproductive functions, as well as neuro-behavioural development and metabolic activities. Zinc is a component of more than 300 enzymes. It is the most important essential trace element in human nutrition. One of the leading causes of zinc deficiency is inadequate intake of dietary zinc rather than poor absorption of the mineral. Although zinc does not supply energy, this micronutrient is essential to the breakdown and absorption of other micronutrients. The present review comprehensively describes the well known functions of zinc besides highlighting the newly discovered ones. Further, the clinical implications in relation to the biological functions and molecular mechanisms of action of zinc are also emphasised.

Keywords: Zinc, micronutrient, function, deficiency, disease

Introduction

Micronutrients are nature's wonder drugs, playing a central role in metabolism and in the maintenance of various homeostatic functions. By definition, those nutrients whose daily requirements is <100 mg are called micronutrients, e.g. iron, zinc, copper, manganese, and fluoride. There is a highly integrated system to control the flux of micronutrients in illness, and this demonstrates just how important the body perceives the micronutrients to be. An adequate intake therefore is necessary to sustain metabolism and tissue function, but provision of excess supplements to individuals who do not need them may be harmful. Clinical benefit is most likely in those individuals who are severely depleted and at risk of complications, and is unlikely if this is not the case [1]. A plethora of information has accumulated on zinc, whose normal metabolism is depicted in Fig.1.

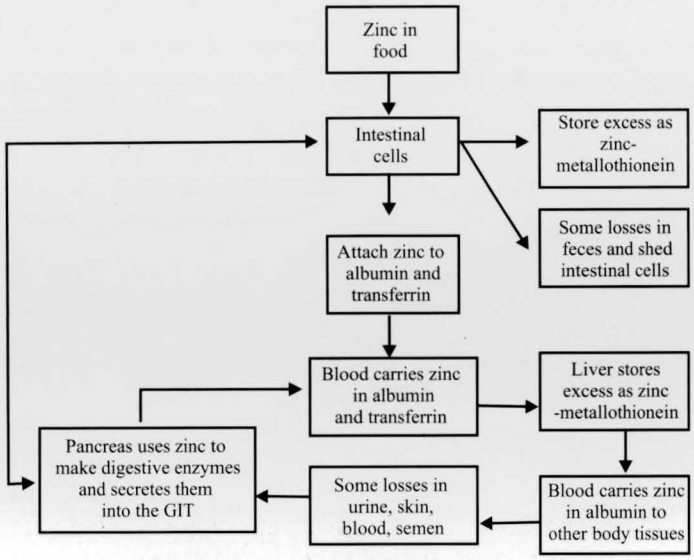

Figure 1. Zinc metabolism.

While zinc is present in all cells/tissues, the muscle and bone contain the highest amount (90%). In the serum, zinc is present predominantly in combination with albumin. Liver is the main storage site of zinc (interestingly, zinc supplementation improves liver pathology and reduces the incidence of hepatocellular carcinoma in patients with chronic hepatitis C) [2]. Oysters, lobster, red meat (especially beef), lamb and liver have some of the highest concentrations of zinc in food. The concentration of zinc in plants varies based on levels of the element in soil. When there is adequate zinc in the soil, the food plants rich in zinc are wheat (germ and bran) and various seeds (poppy, sesame, alfalfa, celery, mustard). Zinc is also found in beans, nuts, almonds, whole grains, pumpkin seeds, sunflower seeds and blackcurrant [3].The present

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review attempts to highlight the functions of zinc especially in the light of recent developments and to emphasize the clinical perspectives wherever possible.

Metabolism of carbohydrates

The effect of zinc ions on carbohydrate metabolism and intracellular Zn^{2+} was studied in hepatocytes from fed rats. The addition of $ZnCl_2$ to the medium led to an almost 3-fold increase in lactate production and an increase in net glucose production of about 50%. Half-maximal rates occurred at about 40 μM $ZnCl_2$. These effects were not seen with Mn^{2+}, Co^{2+}, or Ni^{2+} up to 80 μM, whereas Cu^{2+} at 80 μM and Cd^{2+} or Pb^{2+} at 8 μM exhibited similar effects as 80 μM $ZnCl_2$. Changes in intracellular Zn^{2+} were followed by single cell epifluorescence using zinquin as a specific probe. Intracellular free Zn^{2+} in isolated hepatocytes was 1.26 ± 0.27 μM, and the addition of $ZnCl_2$ led to a concentration-dependent increase in epifluorescence. $CdCl_2$ or $PbCl_2$ at 8 μM was as potent as $ZnCl_2$ at 20-80 μM, whereas $NiCl_2$ at 80 μM was without effect. $ZnCl_2$ completely abolished the inhibition of glycolysis by glucagon (cAMP). Glucagon led to a pronounced drop in cytosolic Zn^{2+}. Both glucagon and zinc stimulated glycogenolysis by increasing the phosphorylation of glycogen phosphorylase but acted oppositely on glycolysis. Zinc overcame the inactivation of pyruvate kinase by glucagon without changing the hormone-induced protein phosphorylation. The antagonistic action of zinc and cAMP on glycolysis together with the rapid and marked decrease in free zinc concentration induced by glucagon (cAMP) may indicate an as yet unknown role of zinc as an important mediator of regulation of carbohydrate metabolism [4,5].

The effect of Zn^{2+} on glycolysis is strongly dependent on the concentration of Zn^{2+}. Phosphofructokinase (one of the key enzymes of glycolysis) is activated by low concentration of Zn^{2+} (an effect which is more pronounced compared to Mg^{2+}) but is inhibited at higher concentration approaching 0.23 mM. Thus, glucose flux through glycolysis and amount of lactate produced depend on phosphofructokinase activity which in turn is subjected to regulation by Zn^{2+} concentration [6].

The role of zinc deficiency, which could, at least potentially, exacerbate the cytokine-induced damage in the autoimmune attack which destroys the islet cell in type 1 diabetes, is unclear. Since Zn plays a clear role in the synthesis, storage and secretion of insulin as well as conformational integrity of insulin in the hexameric form, the decreased Zn, which affects the ability of the islet cell to produce and secrete insulin, might then compound the problem, particularly in type 2 diabetes. Zinc homeostasis is regulated by the ZnT (*SLC30A* gene family) and Zip (*SLC39A* gene family) zinc transporters. The ZnTs transport zinc ion from the cytoplasm to extracellular spaces or lumen of organelles, while the Zips transport zinc ion from extracellular spaces or lumen of organelles to the cytoplasm. A nonsynonymous single nucleotide polymorphism (SNP) in *SLC30A8* (rs13266634 C>T) which changes from arginine (R) to tryptophan (W) at position 325 is associated with type 2 diabetes. Furthermore, major epitope(s) for ZnT8A lie within the cytoplasmic domain of the molecule (aa268-369) and R325W is a key determinant of humoral autoreactivity to this protein [7]. Several of the complications of diabetes may be related to increased intracellular oxidants and free radicals associated with decreases in intracellular Zn and in Zn dependent antioxidant enzymes. In a study by Marreiro et al, it was found that zinc supplementation enhanced insulin sensitivity in obese women who were not zinc-deficient [8, 9].

Lipid metabolism

Zinc seems necessary for at least two stages in essential fatty acid (EFA) metabolism, the conversion of linoleic acid to γ-linolenic acid, and the mobilisation of dihomo-γ-linolenic acid (DGLA) for the synthesis of 1 series prostaglandins. Zinc may also be important in the conversion of DGLA to arachidonic acid and in arachidonic acid mobilisation for 2 series prostaglandins (PG) formation. These interactions shed considerable light on a number of clinical syndromes, including acrodermatitis enteropathica, diabetes mellitus, the glucagonoma syndrome and sickle cell anaemia. It also underscores the zinc based acne therapy in pregnancy [10].

Leptin, the product of the *ob* gene, plays a key role in a feedback loop that maintains energy balance by signaling the state of energy stores to the brain and by influencing the regulation of appetite and energy metabolism. Zinc also plays an important role in appetite regulation. Zinc restriction decreases leptin levels while zinc supplementation of zinc-depleted subjects increases circulating leptin levels. In addition, zinc supplementation increases interleukin-2 (IL-2) and tumour necrosis factor-α (TNF-α) production that could be responsible for the observed increase in leptin concentrations. Zinc may influence serum leptin levels, possibly by increasing the production of IL-2 and TNF-α [11].

Metabolism of nucleic acids (DNA and RNA) and proteins

Zinc is an essential element in the nutrition of human beings, animals, and plants. Zinc is required in the genetic make-up of every cell and is an absolute requirement for all biologic reproduction. Zinc is needed in all DNA and RNA synthesis and is required at every step of the cell cycle. DNA is about 5000 times less susceptible to damage by Zn^{2+} ion than is RNA, suggesting its role in the predominant evolutionary selection of DNA, rather than RNA, as the bearer of the primary genetic information. Zinc remains an essential component of all DNA and RNA polymerases examined today. With a poly C template, Zn^{2+} alone can catalyze the assembly of an activated GMP derivative (guanosine 5'-phosphoimidazolide) into poly G chains 30 to 40 residues in the natural 3'-5' linkage. Although other metals are catalytic, zinc produces greater fidelity [12]. Zinc is also involved in protein synthesis, a vital function, where it is required for several key enzymes in RNA and DNA synthesis [13]. The interaction of several DNA binding proteins is mediated through unique structural motifs including zinc finger motifs [14].

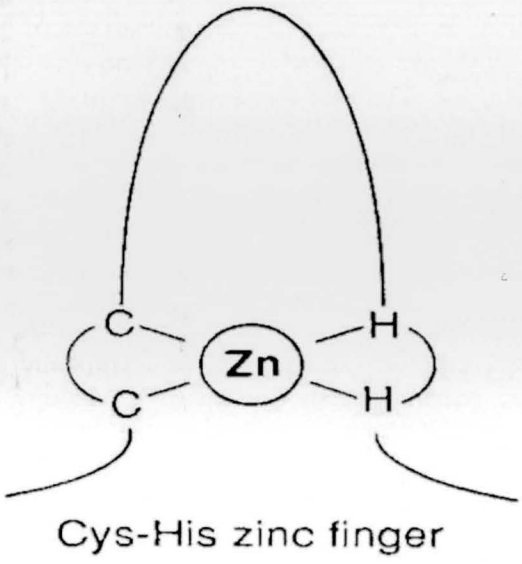

Figure 2. Zinc finger motif. C, cysteine; H, histidine.

Zinc fingers (Fig. 2) are finger-like protrusions extending from transcription factors or gene-regulating proteins and fastening to the wide, major groove of a DNA molecule. Over 200 proteins, many of which are transcription factors, incorporate zinc fingers. The finger-like projections are suited for DNA recognition by means of their three-dimensional shape. From an evolutionary perspective, it is proposed that ancestral genes specifying a small peptide would easily pick up zinc from the environment and would fold without assistance into a stable conformation where they would have the ability to bind to DNA and RNA [15-21]. Zinc finger motifs are subjected to redox signalling mediated by reversible thiol co-ordination of Zn^{2+}. It has been documented that the fidelity of intron cleavage is controlled by redox-responsive Zn^{2+} cycling. Zn^{2+} is best suited for this purpose compared to any other metal. This is especially important under oxidative stress [22].

Zinc is required for the activity of >300 enzymes, covering all six classes of enzymes. Zinc binding sites in proteins are often distorted tetrahedral or trigonal bipyramidal geometry, made up of the sulfur of cysteine, the nitrogen of histidine or the oxygen of aspartate and glutamate, or a combination. Zinc in proteins can either participate directly in chemical catalysis or be important for maintaining protein structure and stability. In all catalytic sites, the zinc ion functions as a Lewis acid [23].

Epithelial integrity

Zinc improves the absorption of water and electrolytes, improves regeneration of the intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens. Another report has recently provided evidence that zinc inhibits toxin-induced cholera, in cultured Caco-2 cells. Thus, Zinc plays an important role in modulating the host resistance to infectious agents and reduces the risk, severity, and duration of diarrheal diseases. There is a close association between diarrhea and zinc deficiency particularly with co-existing malnutrition (Fig. 3) [24].

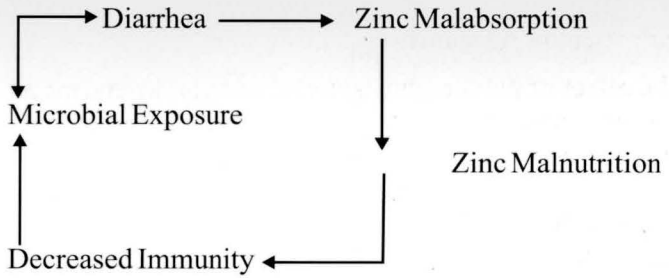

Figure 3. A plausible link between malnutrition, diarrhea and zinc deficiency

Vitamin A metabolism

Zinc status influences several aspects of vitamin A metabolism, including its absorption, transport, and utilization. Two common mechanisms postulated to explain this dependence relate to-

(i) The regulatory role of zinc in vitamin A transport mediated through protein synthesis. Zinc deficiency can depress the synthesis of retinol-binding protein (RBP) in

the liver and lead to lower concentrations of RBP in the plasma. Thus, reductions in plasma holo-RBP in animals fed zinc-deficient diets compared with their pair-fed, zinc-supplemented control counterparts may be due to impaired hepatic synthesis of the transport protein although partial food intake and growth restriction may confound this relation;

(ii) The oxidative conversion of retinol to retinal that requires the action of a zinc-dependent retinol dehydrogenase enzyme in the visual cycle in the retina of the eye [25, 26].

Heme synthesis

Zinc protoporphyrin (ZnPP) is a normal metabolite that is formed in trace amounts during heme biosynthesis (Fig. 4). The final reaction in the biosynthetic pathway of heme is the chelation of iron with protoporphyrin. During periods of iron insufficiency or impaired iron utilization, zinc becomes an alternative metal substrate for ferrochelatase, leading to increased ZnPP formation. Evidence suggests that this metal substitution is one of the first biochemical responses to iron depletion, causing increased ZnPP to appear in circulating erythrocytes. Because this zinc-for-iron substitution occurs predominantly within the bone marrow, the ZnPP/heme ratio in erythrocytes reflects iron status in the bone marrow. In addition, ZnPP may regulate heme catabolism through competitive inhibition of heme oxygenase, the rate-limiting enzyme in the heme degradation pathway that produces bilirubin and carbon monoxide. Physiological roles, especially relating to carbon monoxide and possibly nitric oxide production, have been suggested for ZnPP [27, 28].

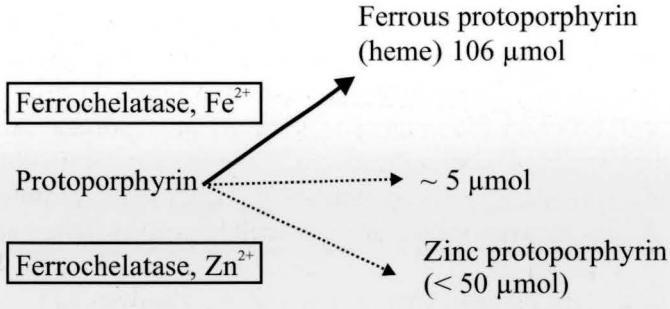

Figure 4. Iron versus zinc protoporphyrin.

Clinically, ZnPP quantification is valuable as a sensitive and specific tool for evaluating iron nutrition and metabolism. Diagnostic determinations are applicable in a variety of clinical settings, including paediatrics, obstetrics, and blood banking. In addition to diagnostic tests and metabolic studies, ZnPP has a potential therapeutic application in controlling bilirubin formation in neonates as a preventive measure for hyperbilirubinemia [27, 28].

Metabolism of alcohol

Alterations in zinc metabolism or zinc deficiency frequently occur in patients with alcoholic liver disease. Potential manifestations of zinc deficiency include skin lesions, hypogonadism, impaired night vision, impaired immune function, anorexia, altered protein metabolism, diarrhea, and depressed mental function. Because of the variety of ways in which zinc deficiency may present in alcoholic liver disease, clinicians must maintain a high index of suspicion for this nutrient deficiency when caring for these patients. Recent data from alcoholic hepatitis patients demonstrate increased serum levels of the monokine IL-1, which is known to cause hypozincemia and an internal redistribution of zinc. This monokine has a host of metabolic functions other than its effect on mineral metabolism that have relevance for alcoholic liver disease such as fever, neutrophilia, and muscle catabolism [29].

Wound healing

Zinc confers resistance to epithelial apoptosis through cytoprotection against reactive oxygen species and bacterial toxins possibly through antioxidant activity of the cysteine-rich metallothioneins. Zinc deficiency of hereditary or dietary cause can lead to pathological changes and delayed wound healing. Oral zinc supplementation may be beneficial in treating zinc-deficient leg ulcer patients, but its therapeutic place in surgical patients needs further clarification. Topical administration of zinc appears to be superior to oral therapy due to its action in reducing superinfections and necrotic material via enhanced local defence systems and collagenolytic activity, and the sustained release of zinc ions that stimulates epithelialization of wounds in normozincemic individuals. Zinc oxide in paste bandages (Unna boot) protects and soothes inflammed peri-ulcer skin. Zinc is transported through the skin from these formulations, although the systemic effects seem insignificant. [30].

Immunity

Zinc has a number of effects on the immune system. Possible modes of action of zinc on the immune function are:

(i) Zinc is an essential factor for the activity of many enzymes- it is known to form part of more than 300

metalloenzymes. Thus, zinc is essential to the function of DNA polymerase, thymidine kinase and DNA dependent RNA polymerase, whose involvement in nucleic acid synthesis could explain the effects of zinc on lymphoid-cell proliferation. Zinc also influences the activity of the transcriptional regulator family, known as zinc finger DNA binding proteins. In addition, zinc forms the active sites of many metallo-proteases [31].

(ii) Zinc is necessary for the activity of some immunity mediators. This has been clearly shown for thymulin, a nonapeptidic hormone (Glu-Ala-Lys-Ser-Gln-Gly-Gly-SerAsn) secreted by thymic epithelial cells, and requiring the presence of zinc for its biological activity. This peptide promotes T lymphocyte maturation, cytotoxicity, and IL-2 production. Zinc is bound to thymulin in a 1:1 stoichiometry via the side chains of asparagine and the hydroxyl groups of the two serines. Thymulin is detectable in the serum of zinc-deficient patients, but is inactive. The binding of zinc to the peptide results in a conformational change that produces the active form of thymulin. The use of thymulin as an indicator of zinc deficiency has been suggested and the assay of serum thymulin activity with or without zinc addition in vitro may be used as a sensitive criterion for diagnosing mild zinc deficiency in humans. Zinc could also be critical for cytokine activity. For instance, it has been demonstrated that the production or the biological activity of interleukins (IL-1, IL-2, IL-3, IL-4, IL-6), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α) are affected by zinc deficiency. In addition, and as mentioned above, zinc deficiency in humans affects the cytokine production of T_H1 cells leading to an imbalance between T_H1 and T_H2 cells [31].

(iii) Zinc could contribute to membrane stabilization, acting at the cytoskeletal level. An effect on membranes could explain the depression of phagocytosis, oxygen consumption and bactericidal activity induced by zinc in phagocytic cells and the modification of Con A surface receptor availability on lymphoid cells [31].

(iv) Zinc is a major intracellular regulator of lymphocyte apoptosis. Thus, it is becoming evident that the thymic atrophy and lymphopenia which accompany zinc deficiency are mainly due to an alteration in the production of lymphocytes, and the loss of precursor cells via an apoptotic mechanism. In this regard, the increased production of glucocorticoids induced by suboptimal zinc status could play a significant role [31].

Antioxidant

Zinc is a component of several antioxidants such as the cytosolic enzyme copper-zinc superoxide dismutase (Cu-Zn SOD). This enzyme is responsible for the detoxification of superoxide anion free radicals O_2^- produced under physiological as well as several pathological conditions. Zinc also attenuates oxidative damage via stabilization of sulfhydryl (-SH) protein and inhibition of xanthine oxidase [32].

Reproductive system and foetal growth

Inadequate levels of zinc can result in low levels of the male hormone testosterone, limit sperm formation and decrease sperm mobility [33]. Since zinc plays a critical role in normal growth and development, cellular integrity and many biological functions, including protein synthesis and nucleic acid metabolism, and all these are involved in cell division and growth, zinc is believed to be important for foetal growth and development. Low levels of zinc are associated with preeclampsia in the mother, premature birth, retarded growth and low birth weight in the baby. This is possibly due to the fact that zinc is needed for proper cell division. Slow growth of the infant, in the first few months of life, has been associated with low levels of zinc in the mother's breast milk [34].

Taste

Gustin is the major zinc protein in human parotid saliva and is important for taste perception. Zinc supplements have been used to improve taste perception in people taking medications which reduce taste sensation, and in cancer patients undergoing radiation therapy. This can be valuable in helping to maintain normal weight and nutrient intake during treatment [35].

Hair Growth

Though hair contain many micronutrients such as calcium, copper, iron, magnesium, phosphorous and zinc, the latter is especially important for the proper functioning of hair follicles in several ways- (i) proper synthesis and functioning of keratin, an important hair protein; (ii) general utilization of proteins to maintain skin integrity; and (iii) maintaining epidermal immune function [36]. Although it is difficult to prove whether an isolated zinc deficiency may result in hair loss, lower hair zinc levels have been found in several disorders such as acrodermatitis enteropathica [37], type 2 diabetes mellitus [38], autism [39] etc. Zinc supplementation promotes hair growth in alopecia [40]. Hair zinc is a reliable biomarker of zinc status [41].

Conclusion

The above discussion clearly proves that zinc is a micronutrient with pleiotropic actions. Further research is

needed to identify the as yet undiscovered functions of zinc and to extrapolate the knowledge into clinical applications.

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