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Review Article

Zing thing about zinc: A mini review

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ABSTRACT

Zinc is a micromineral present in the body tissues and fluids. Zinc is absorbed from the duodenum and stored in the form of metallothionine in the liver and excreted through sweat. Zinc plays a vital role in protein biosynthesis, gene expression; it also acts as an antioxidant and is used in the growth of the fungus. Due to the deficiency of zinc, a patient will be suffering from poor wound healing, lesions of skin, impaired spermatogenesis, hyperkeratosis, dermatitis and alopecia.

An unprecedented COVID-19 pandemic caused by a novel corona virus called SARS-CoV-2, produces severe acute respiratory distress syndrome (ARDS). Zinc is used to treat COVID 19 because it improves the immunity. As the COVID patients are susceptible to zinc deficiency, they are prescribed with zinc supplements. Intake of zinc more than1000mg/day causes Zinc toxicity. Fungus utilises zinc for its growth. Mucormycosis caused by fungus Rhizopus species seen in most of the post COVID patients. Since, Zinc has assumed importance in this COVID 19 pandemic, this review article unfathoms the explicit roles of Zinc in humans.

1. Introduction

Zinc is a microelement essential for the foremost effective function of a ramification of biochemical and physiological processes. Its role in healthy aging is incredibly presiding because it fends off neoplastic cell growth complexed in the mitotic process, DNA and RNA repair. Although zinc is widely accessible in diet, the regular supplementation in each individual could even be not up to the requirement.

Zinc is essential for activity of diverse enzymes, functional proteins, and living tissue cells.[1] Deficiency of zinc causes various disease with various clinical symptoms, like dysgeusia (i.e. distortion of taste), abnormal bone metabolism, skin lesions, gonadal dysfunction, decreased appetite, immune dysfunction,[2] and retarded wound healing.[3] Studies show that zinc additive is effective in ameliorating these conditions, highlighting zinc's homeostatic importance.[4] Lack of zinc in diet causes diseases, widespread in developing countries; it is habitual and aggravated by intercurrent acute and chronic infections.[5] Previous studies have shown that regular intake of zinc through diet is essential for maintaining the health of children that can remarkably bring down the morbidity and mortality[6] and reduces the convalescence from a common infectious disease. Zinc is found in cells, tissues and body fluids. Next to iron, it is the second most abundant element within the body and conciliates a large kind of physiological function. It is a required component of diverse metalloproteins, including DNA replication and organic process, and is crucial for maintaining the immunological integrity, predominantly cellular immunity,[7] together with antioxidant activity. Due to its role in maintaining cell integrity and immunity, it is considered to play a key role in cells that have a rapid turnover and a critical role, the control and

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prevention of infections. Because of these functions, the body doesn't store zinc. This is abundant in nature and simply soaks up from white meat and animal proteins, seafood, dairy products, cereals and nuts. Most vegetables don't serve as good sources of zinc due to the presence of Phytate, a component of plants that chelates zinc and prevents its soak up.[8] Diets that are less in animal protein and rich in phytate thus contribute to the high prevalence of deficiency disease in developing countries.

Metallic zinc was first produced in India during 1400s by heating the mineral calamine (ZnCO3) with wool. Zinc was rediscovered by Andreas Sigismund Marggraf in 1746 by heating calamine with charcoal.Raulin (1869) was earliest to indicate that zinc as a necessity for the growth and development of Aspergillus niger, which was validated fourty years later by Bertrand and Javillier(1911). Tucker and Salmon(1955) reported that zinc could cure and stop the disease called parakeratosis in Swine. By feeding dogs with low in zinc and high in calcium, causes the deficiency of zinc whose clinical characteristics included retardation of growth, emaciation, emesis, conjunctivitis, keratitis, general debility, and skin lesions on the abdomen and extremities. In 1954, P Vallee and Neurath reported that bovine pancreatic carboxypeptidase- A contained one metric weight unit of zinc per mole critical for function.[9]

2. Distribution of Zinc in Human Body

Minerals are inorganic elements, required for a variety of functions. The microminerals or trace elements are required in amounts less than 100 mg/day. Zinc is one among the microminerals, distributed in all organs, tissues, fluids and secretions of the body.

Prostate, liver, kidneys, muscles, heart, skin, bones, teeth, etc. are particularly rich in zinc. In the plasma, about 18% of the zinc (normal range 700–1200 g/L) is tightly bound to α2 -macroglobulin, 80% is loosely bound to albumin, 2% is bound to transferrin, ceruloplasmin, or the amino acids, and a small fraction is present as free zinc.

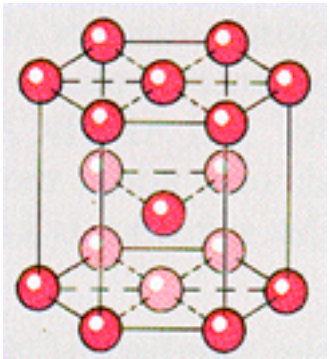

Fig. 1: Structure of zinc

Sources

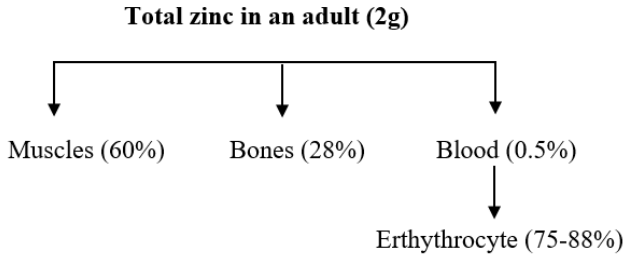

Fig. 2:

1. Richest source: Oysters
2. Rich source: Colostrum.
3. Good sources: Red meat, liver, seafood, eggs, pork, milk including breast milk.

Table 1: Recommended dietary allowance

Age Group	Quantity
Infants	5 mg
Children and adolescents	10 mg
Adults (males)	15 mg
Adults (females)	12 mg

3. Metabolism of Zinc and Absorption

According to Menard and Cousins (1983), zinc uptake by high-molecular-weight proteins within the intestinal mucosa is a lively process requiring ATP. Zinc uptake by low-molecular-weight proteins (such as metallothionein) is passive. Uptake of zinc by the intestinal cells is bifacial, maximum amount is taken from the intestinal lumen and from the blood supply. Metabolism of Zinc starts absorption from the duodenum. Its absorption is hampered by the presence of certain interfering substances (e.g. fibers and phytates) present in the food, which form insoluble complexes with zinc to impair its absorption. Copper, iron, cadmium and calcium also interfere with zinc absorption. Within the plasma, there is no specific binding protein, and zinc is transported mainly in association with albumin. It is stored many in tissues as metallothionein, which also binds copper and few other heavy metals. Metallothionein protects the cells from the toxic effects of the free unbound metal ions.[10]

Factors affecting Zinc absorption:

1. Zinc absorption is increased during zinc deficiency.
2. The transport process of zinc appears to be under metabolic control.
3. Endogenous zinc secretion: Significant amount of zinc is produced into the intestinal lumen via the epithelial cells, bile, and pancreatic secretion.

4. Zinc leap to one or more ligands, impede and others enhance absorption.

Most of the data with regard to zinc absorption is restricted to experimental animal model examination. During digestion, zinc is set free from its dietary ligands (mostly proteins) and bounds to intestinal low molecular-weight ligands which make zinc available to the intestinal microvilli. A number of these ligands like histidine and other amino acids are of dietary origin but others like metallothionein is also of endogenous origin. [11]

Zinc is present in pancreatic secretions, and stools are the most important route for its excretion. Urine, sweat and body fluids are the excretory routes of minor importance. Acute deficiency disease in humans, especially in growing children, manifests as skin lesions, testicular atrophy, poor growth, delayed sexual development, increased susceptibility to infections, neuropsychiatric impairments and decline taste acuity.

4. Functions of Zinc

1. Activation of enzymes such as Carboxypeptidase A, DNA and RNA polymerase, alcohol dehydrogenase.
2. Secretion and storage of insulin.
3. Maintain the taste: Gusten, a protein containing zinc, helps in gustatory perception.
4. Encompasses a role in apoptosis, hair growth, sperm maturation and wound healing.
5. Along with other trace metals (copper and manganese), zinc acts as a co-factor to Superoxide dismutase, which scavenges the free radical thereby acting as a powerful anti-oxidant.
6. Additionally required for immunological functions.
7. Zinc brings out the synthesis of metallothionein, a tiny low protein of 61 amino acids (MW 7000). Both zinc and copper are reserved in tissues which are leaped to the protein. The protein binds copper more firmly than zinc forming complex within the alimentary canal thereby decreasing the copper absorption. Hence, dietary zinc supplementation is thought to significantly lower the absorption of copper and should elicit copper deficiency symptoms. (Zinc fingers, defined as domains of zinc-binding proteins that also bind to DNA, are involved within the organic phenomenon of metallothionein).

5. Zinc as an Activator or Cofactor

The enzyme that is in need of inorganic metal ions as their cofactors are termed as metalloenzymes. In most of the cases, the binding of metal ion is necessarily required for the enzymatic activity (e.g. zinc for carbonic anhydrase). [12]

6. Zinc in Iron Deficiency

Patients with iron deficiency can use zinc, alternative to the iron, ferro-chelatase used as a substrate. Red cell lysates in such instances contain more quantities of zinc-hemoglobin. Additionally, red cells from iron deficient, patients are contained with increased amounts of protoporphyrin IX. Both Zinc-hemoglobin and protoporphyrin IX determinations are therefore employed in the diagnosis of iron deficiency anemia. Co-proporphyrinuria: a small (less than twofold) increase in urinary co-proporphyrin is most ordinarily caused problems, unrelated to heme synthesis, like disease, acute illness or exposure to toxic chemicals. [13]

7. Zinc in Thyroid Metabolism

Thyroid hormones play a vital role in carbohydrate and lipid metabolism, regulating metabolic adaptations, responding to commute in energy consumption, and managing thermo-genesis. Proper metabolism and action of those hormones need the involvement of several nutrients. Among them, zinc interacts with thyroid hormones and tunes both the synthesis and mechanism of action of those hormones. Scientific evidence shows that zinc plays a key role in the metabolism of thyroid hormones by regulating de-iodinase, thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) synthesis, by modulating the transcription factors involved in the synthesis of thyroid hormones. Serum concentrations of zinc also influence the amount of serum T3, T4 and TSH. Additionally, studies have shown that Zinc transporters (ZnTs) are present within the hypothalamus, pituitary and thyroid, but their functions remain unrevealed. Therefore, it is essential to further investigate the roles of zinc in regulation of thyroid hormones metabolism, and their importance in the treatment of the diseases related to ductless gland dysfunction. [14]

8. Zinc on Reproductive Hormones

Zinc is an effectual element in the reproductive system. The serum concentrations of zinc may be reduced in patients with polycystic ovarian syndrome (PCOS), with impaired glucose tolerance compared with patients with normal glucose tolerance; however, the differences were not significant. It shows that zinc deficiency might play a major role in the pathogenesis of PCOS, which may be associated with its long-term metabolic consequences. [15]

9. Zinc Finger Motif

The zinc finger was the second DNA binding motif whose atomic structure was illuminated. The protein Transcription Factor IIIA (TFIIIA), a positive regulator of 5S RNA gene transcription, requires zinc for its activity. Structural and

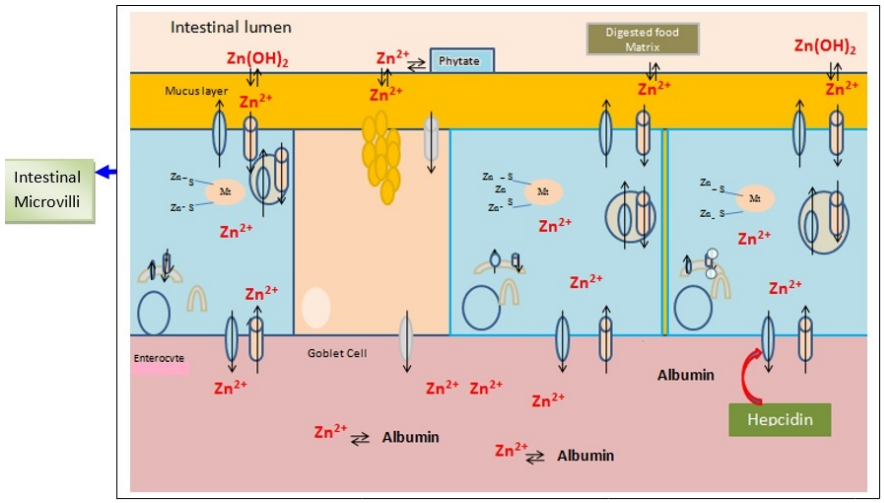

Fig. 3: Absorption of zinc in intestinal mucosa

biophysical analysis of DNA revealed that every TFIIIA molecule contains zinc ions in an repeating coordination were complex formed closely. Engineered nucleases and proteins that are capable of manufacturing double stranded cuts at specific DNA sequences. They include zinc-finger nucleases (ZFNs) and transcription activator–like effectors nucleases (TALENs).[16]

10. Zinc in Gene Expression

Zinc plays a vital role in gene expression. A role of zinc in growth and development and the teratological abnormalities of zinc deficiency in fetal development have been known for several years. However, its role in cell differentiation and organic phenomenon has been appreciated. Cells synchronized in G1 phase, and placed in zinc-deficient media, that has been not progressed into S phase. Studies show that zinc is crucial for the biochemical events of the pre-mitotic state which involves initiation of DNA synthesis, and progression from G2 phase to mitosis.[17]

11. Zinc and Cells

11.1. Lymphocytes

Zinc ions as an integral a part of tissues and biologic fluids plays a significant role in omeostatic mechanisms. As DNA-synthesizing enzymes are zinc dependent, enhanced mitosis of lymphocytes may be the result of increased activity of enzymes involved in cell mitosis. The essential role of zinc in DNA replication in PHA-stimulated human lymphocytes was demonstrated by adding a chelator with high affinity for zinc to the culture medium, which inhibited the incorporation of thymidine by lymphocytes.[18]

11.2. Mast cells

The shielding effect of zinc on histamine was unchained by the mast cells apparently only after some days of zinc administration to animals. Unsaturated zinc: 8- HQ (1: 1) complex was more powerful potent inhibitor of histamine as observed, but not noted from remote mast cells other than zinc, it absolutely proposed that zinc acts on the cell membrane. Maximum amount of zinc has prevented the histamine release from mast cells only if it had been included simultaneously with compound 48/80 to the medium, it appeared that zinc competed with compound 48/80 for similar receptor binding sites.[19]

11.3. Platelets

Zinc influences thrombocyte aggregation and coagulation.[20] Zinc was shown significantly it inhibits collagen-induced aggregation of dog platelets and release serotonin from the platelets. The concentration of zinc required for these functions was 10 to 15 mM. The presence of plasma within the incubating medium was essential for the inhibitory effect of zinc; only fibrinogen, not albumin or globulin, substituted for plasma. The uptake of calcium by platelets was also inhibited by zinc.[18]

12. Fungal Growth

Fungal cells must obtain zinc for its growth during their life cycle; zinc is utilized during the infection processor in the saprophytes phase, this hamper the pathogen growth. Mammalian hosts typically decrease the degree of free zinc and other metals. The concentration of zinc in human tissues varies dramatically, starting from 10μg/g (lungs) to 83.2μg/g (liver). In body fluids, the zinc concentration ranges from 0.2 to 8.7μg/mL. Thus, pathogenic fungi have developed efficient strategies to uptake zinc to beat the bounds imposed by host.[19]

13. Deficiency of Zinc

As noted in sources, pork being prime source of bioavailable zinc, vegetarians is at much greater risk for deficiency of zinc. Deficiency diseases are Acrodermatitis-enteropathica, poor wound healing, lesions of skin, impaired spermatogenesis, hyperkeratosis, dermatitis and alopecia.[21]

13.1. Acrodermatitis enteropathica

Acrodermatitis enteropathica is a rare autosomal recessive disease resulting from impaired uptake and transfer of zinc; patient presenting with perioral, genital, anal dermatitis, hair loss, growth retardation, diarrhea and decreased cell-mediated immunity. The disease has been mapped to 8q24 and also the defective gene identified as SLC39A4, which encodes the zinc transporter Zip4. The diagnosis is by clinical presentation along with histopathology and laboratory tests.[22]

14. Covid-19 and other Diseases

Now we are all experiencing an unprecedented COVID-19 pandemic caused by a completely unique RNA corona virus called SARS-CoV-2, which produces a severe acute respiratory distress syndrome (ARDS).[23] It had been first detected in Wuhan province most of people infected with the COVID-19 virus has experienced mild to moderate respiratory illness and they had recovered without requiring any special treatment. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. Deficiency disease could also be present in up to 17% of the inhabitants worldwide. Patients with morbidities like low immune system, diabetes mellitus, etc are especially at higher risk of zinc deficiency and its adverse effects. Impairment of zinc homeostasis has also been explained in metabolic diseases including diabetes, obesity indicating that the precise control of zinc homeostasis is crucial for maintaining health and preventing various diseases, including lifestyle-associated diseases.[24]

Many anti-hypertensive tablets like ACE inhibitors, angiotensin2 receptor antagonists, and thiazide diuretics are zinc chelators. The copper: zinc ratio is a marker for the prognosis of deficiency disorder. Sulphate supplementation at 20 mg/day for 5 months decreases acute tract contamination morbidity.[25] Zinc is essential in both the adaptive and innate immune systems. For example, the functionality of natural killer (NK) cells, which are essential for maintaining the immune response against viruses and tumors, is affected by low levels of zinc.[26] Further, more zinc supplementation significantly increases NK cell numbers in whole blood cultures and NK cell activity in vivo. Zinc deficiency may increase ACE-2 receptor activity on type 2 pneumocytes. Normal circulating zinc increases the concentration of ion and improves NK lytic activity. In excessive, zinc homeostasis directly influences the formation of lymphocytes and the secretion of cytokines and indirectly alters their stimulation by the innate immune system. In Coronaviruses, Zinc inhibits both the proteolytic processing of replicase polyproteins and the RNA-dependent RNA polymerase (RdRp) activity. Adding high concentrations of zinc to cells impairs viral polyprotein processing integral to virus replication.[27]

15. Toxicity of Zinc

Most of the cases reported acute toxicity of that have been in response to food poisoning incidents. Several cases, described by Brown et al, resulted from storage of food or drink in galvanized containers. Typically, the food or drink was somewhat acidic in nature and the storage period was fairly long; presumably, sufficient zinc was leaked from the galvanized coating to cause the toxic manifestations. Acute toxicity manifests as fever and leucocytosis. Chronic toxicity produces peptic ulcer, pancreatitis, anemia, nausea, vomiting and pulmonary fibrosis. In poisonous conditions, chemotaxis, phagocytosis and platelet aggregation are defective. Ingestion of extra quantities of zinc reasons averts poisonous manifestations. The employment of zinc dietary supplements is visible to intervene with the usage of different nutrients, especially copper; to impair immune function; and to adversely have an effect on lipoprotein profiles.[28]

16. Mucormycosis

Mucormycosis commonly known as Black fungus, is an uncommon, unprecedented threat.[29] As the disease afflicts immune-compromised suppression with co-morbidities i.e organ failure, uncontrolled diabetes or ketoacidosis and different forms of acidosis are most effective vulnerable to disease. Also, any other affected person is uncovered to mucormycosis with covid-19 i.e Severe Acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Patients might also additionally come across with

mucormycosis due to concentrators of oxygen is failed to filled with mineralized water. This may be due to the health center had not gone through for the water pH checkup.[30] Doctors suspect the usage of extra quantities of zinc and iron dietary supplements can be one the various elements at the back of the black fungus instances in India, besides the regarded motives of steroid use and diabetes. The usage of zinc in treating Covid-19 patients fears that its miles going to be a notably contributing to the huge outbreak of Black Fungus, scientifically known as mucormycosis, throughout the country.

17. Conclusion

Zinc is a micromineral which performs various functions in human being such as the synthesis of RNA, also acts as an enzyme activator. Uses of Zinc is not only restricted to human beings in additionally it act as a good media for the growth of fungus. Zinc consumption need to be taken as per the RDA. In any other case zinc deficiency will lead to disease i.e Acrodermatitis enteropathica. It is an unprecedented autosomal recessive disorder, as a result of impaired uptake of zinc. The outbreak of SARS virus in the year 2019 brought about the disorder named COVID 19, the remedy for this outbreak was managed by the zinc supplementation. The deadly outbreak of mucormycosis has emerged as an existence threatening fungal contamination in India in 2021 that is seen in COVID 19 and post COVID 19 patients. Many reasons for the unexpected outbreak of mucormycosis have been analyzed; one of the reasons has been inadvertent use of zinc in COVID 19. Since, zinc has favored the fungal growth.

18. Source or Funding

None.

19. Conflict of Interest

The authors declare no conflict of interest.

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