# ZINC DEFICIENCY IN CHILDREN

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## ABSTRACT

Zinc is the second most abundantly found trace element in the body after iron.It is an essential micronutrient important for growth and normal function of the immune system.Zinc deficiency is prevalent in many areas of the world, especially in developing countries and is a diagnostically challenging condition. It may occur due to inadequate dietary intake, increased requirements, malabsorption, increased losses and impaired utilization but inadequate dietary intake of absorbable zinc remains the primary cause of zinc deficiency in most situations. Zinc deficiency affects millions of children and is associated with increased risk for impaired linear growth (stunting), hypogonadism in males, lack of sexual development in females, rough skin, taste abnormalities, poor appetite, impaired immune function and increased risk for diarrhea and respiratory illness such as pneumonia. It contributes to significant diarrhea and pneumonia related morbidity and mortality among young children. Researchers suggest that zinc supplementation decreases the incidence and severity of diarrhea and pneumonia in children.

The objective of this paper is to provide a current overview of the significance of the zinc in children's health, zinc requirement, causes of zinc deficiency in children, evaluation of zinc status,clinical manifestations of zinc deficiency with an emphasis on malnutrition, diarrhea, pneumonia, stunting and impaired wound healing.

**Keywords**: Zinc; Zinc deficiency; Malnutrition; Diarrhea; Pneumonia, Children.

## INTRODUCTION

Zinc is the second most abundantly found trace element in the body after iron [1]. The importance of zinc for human health has been recognized since the early 1960s [2,3]. Zinc is an essential micronutrient required for the activity of more than 300 enzymes and 1,000 transcription factors and for the control of genetic expression. It also plays vital roles in nucleic acid or protein synthesis, cell replication, tissue growth and repair [2,3,4,5]. Zinc is required for normal growth and development from in utero to puberty. The common sources of zinc include variety of foods, such as beef, poultry, seafood, cheese, legumes and grains. Daily intake of zinc is required especially during

childhood, adolescence and pregnancy because the body has no specialized zinc storage system [6]. Growing children have an increased demand for all nutrients, zinc inclusive [7].

The clinical signs of zinc deficiency include suppressed immunity, diarrhea, poor wound healing, stunted growth and hypogonadism. Zinc status has been associated with reduced incidence,severity, and mortality due to diarrhea and respiratory infections.

Assessment of zinc concentration in plasma, urine and hair can be done in detecting the zinc deficient states but measurement of the serum zinc level has been recommended as an appropriate biomarker [8].The serum zinc concentration is affected by various factors such as age, dietary intake and infections [8]. Zinc deficiency is commonly prevalent in children in developing countries and plays a role in decreased immunity and increased risk of infection. Preventive zinc supplementation in healthy children can reduce mortality due to common causes like malnutrition, diarrhea and pneumonia.

## The role of Zinc in the body:

Zinc is the second most abundant trace metal found in the human body whichexhibits many functions. Zinc plays an important role in growth; it has a recognized action on more than 300 enzymes by participating in their structure or in their catalytic and regulatory actions [9].It is a structural ion of biological membranes and intimately related to protein synthesis [10]. The concept of zinc fingers explains the role of zinc in gene expression and endocrine function and mechanisms of action of zinc involve the effects of the metal on DNA synthesis, RNA synthesis and cell division [11]. Zinc also interacts with important hormones involved in bone growth such as somatomedin-c, osteocalcin, testosterone, thyroid hormones and insulin [9].Zinc is intimately linked to bone metabolism, thus, zinc acts positively on

growth and development.

Zinc is a metal with great nutritional importance and is particularly necessary in cellular replication and the development of the immune response.It affects multiple aspects of the immune system [41]. It is crucial for normal development and function of the cells mediating innate immunity, neutrophils and natural killer (NK) cells.The ability of zinc to function as an antioxidant and stabilize membranes suggests that it has a role in the prevention of free radical-induced injury during inflammatory processes.

Zinc is also essential for brain development and central nervous system function; and more than 200 enzymes are zinc metalloenzymes, requiring zinc for normal neuronal development [12].

## Zinc metabolism:

Zinc is an essential trace element in the body. Almost 90% of total body zinc is situated in bone and skeletal muscle. Zinc is absorbed in the small intestine by a carrier-mediated mechanism. Generally, 33% is accepted as the average zinc absorption in humans [13]. More recent studies have suggested different absorption rates for different population groups based on their type of diet and phytate: zinc molar ratio. Zinc absorption is concentration dependent and increases with increasing dietary zinc intake. Additionally, zinc status may influence zinc absorption. Zinc-deprived humans absorb this element with increased efficiency, whereas humans on a high-zinc diet show a reduced efficiency of absorption [14].During digestion, zinc is released from food in the form of free ions. These liberated free ions may then bind to endogenously secreted ligands before their transport into the enterocytes in the duodenum and jejunum. Specific transport proteins may facilitate the passage of zinc across the cell membrane into the portal circulation. Zinc is also absorbed through a passive paracellular route with the higher intake. The portal system carries absorbed zinc directly to the liver, and then released into systemic circulation for delivery to other tissues.About 70% of the zinc in circulation is bound to albumin, and any condition that alters serum albumin concentration can have a secondary effect on serum zinc levels. Although, serum zinc represents only 0.1% of the whole body zinc, the circulating zinc turns over rapidly to meet tissue demands [13].

Maintenance of a constant state of cellular zinc, or homeostasis, is essential for survival.Zinc homeostasis is primarily maintained via the gastrointestinal system by the processes of absorption of exogenous zinc and gastrointestinal secretion and excretion of endogenous zinc.Loss of zinc through gastrointestinal tract accounts for approximately half of all zinc eliminated from the body. Other routes of zinc excretion include urine and surface losses (desquamated skin, hair, sweat). Zinc bio-availability is determined by three factors: the individual's zinc status, the total zinc content of the diet, and the availability of soluble zinc from the diet's food components [15].

Zinc absorption is influenced by various dietary factors. Phytic acid (inositol hexa- and penta-phosphate) is the main dietary factor known to limit zinc bio-availability by strongly binding zinc in the gastrointestinal tract [16]. Phytic acid is the major phosphorus storage compound in plant seeds, especially, cereals and legumes, and can account for up to 80% of seed total phosphorus. The inhibitory effects of phytic acid (PA) on zinc can be predicted by the molar ratios of phytate: Zinc in the diet. Molar ratios in excess of 15: 1 according to World Health Organization (WHO), or 18:1 according to International Zinc Nutrition Consultative Group (IZiNCG) progressively inhibit zinc absorption and have been associated with suboptimal

zinc status in humans [13].

Proteins generally have positive influence on zinc absorption, because zinc absorption tends to increase with protein intake.Consumption of animal proteins (e.g. beef, eggs and cheese) improve the bioavailability of zinc from plant food sources possibly because amino acids released from the animal protein keep zinc in solution [15] or the protein binds the phytate.

## Zinc requirement:

According to WHO (1996), the estimated physiologic requirements for absorbed zinc during childhood by age group and sex and during pregnancy and lactation is shown in table 1[17].

| Age, sex, stage | Reference weight (kg) | Physiologic Requirement (mg/day) |
|---|---|---|
| 6-<12 months | 9 | 0.84 |
| 1-<3 years | 12 | 0.83 |
| 3-<6 years | 17 | 0.97 |
| 6-10 years | 25 | 1.12 |
| 10-12 years, M | 35 | 1.40 |
| 10-12 years, F | 37 | 1.26 |
| 12-15 years, M | 48 | 1.82 |
| 12-15 years, F | 48 | 1.55 |
| 15-18 years, M | 64 | 1.97 |
| 15-18 years, F | 55 | 1.54 |
| At pregnancy | - | 2.27 |
| During lactation | - | 2.89 |

**Table 1**

## Zinc deficiency:

Zincdeficiency is prevalent in many areas of the world, especially in developing countries and is a diagnostically challenging condition.Zinc deficiency is ranked 11th among global risk factors for mortality and 12th for burden of disease [18].

## Causes of zinc deficiency:

The general causes of zinc deficiency include inadequate intake, increased requirements, malabsorption, increased losses and impaired utilization [13].Inadequate dietary intake of absorbable zinc is

the primary cause of zinc deficiency in most situations [15]. This may result from low dietary intake or heavy reliance on foods with little or poorly absorbable zinc.High phytic acid content in diets, especially cereals and cereal-based diets, forms zinc-phytic acid complexes in the intestine and markedly inhibits intestinal absorption of zinc.

Malabsorption syndromes and inflammatory bowel diseases, resulting in poor absorption and loss of zinc, may lead to secondary zinc deficiency particularly if associated with marginal dietary intakes. Utilization of zinc is impaired in the presence of infection as decreased circulation of zinc reduces the availability of zinc to the tissues.Conditions of impaired intestinal integrity not only reduce absorption, but also result in increased endogenous losses of zinc.

The mechanisms that lead to zinc deficiency in infants may include unbalanced meals, lower absorption ability in the intestinal tract and low zinc concentration in maternal breast milk. In addition, maternal dieting and cigarette smoking have been reported to be associated with lower zinc and higher cadmium and lead concentrations in neonates [19].

Severe zinc deficiency in the rare inherited human disease acrodermatitis enteropathica has been reported to result from defective intestinal absorption of zinc due to mutations in the Zip4 transporter located in the intestinal tract [20, 21]. Furthermore, recent genetic studies have indicated that mutations in the ZnT2 transporter gene in mothers produce zinc-deficient milk and cause breast-fed infants to develop a severe zinc deficiency that can be reversed by zinc replacement therapy.

Compared with full-term infants, preterm infants are in negative zinc balance at birth because of the lower capacity for gut absorptionand thus the demand for zinc increases rapidly in thriving preterm infants [22]. Hence, the preterm infant has an increased risk of zinc deficiency and symptomatic zinc deficiency has been mostly found in breast-fed preterm infants [22].

## Evaluation of zinc status:

The zinc concentration in plasma, hair and urine can be assessed in detecting zinc deficient states but measuring the serum zinc level has been recommended as an appropriate biomarker[8]. Plasma (or serum) zinc concentration is the most widely used biomarker to determine zinc status. Plasma zinc concentrations normally respond to zinc supplementation, especially in subjects with a low or moderately low baseline[23]. Depriving subjects of zinc results, in general, in a reduction in plasma zinc concentrations. However, plasma zinc concentrations are affected by many other factors, including inflammation, fasting or eating, pregnancy and diurnal rhythm. Inflammation causes a depression of zinc concentrations, whereas fasting leads to higher zinc concentrations.Diurnal variation in zinc concentrations can be as large as 20%. Moreover, conditions that lead to hypoalbuminemia also reduce plasma zinc concentrations, as zinc is bound to albumin in the circulation. Current cut-offs for zinc deficiency are <9.9 μmol/L for children <10 years (morning, non-fasting) or <8.7 μmol/L (afternoon, non-fasting) [24].

## Clinical manifestations of zinc deficiency:

Zinc deficiency has been linked to growth retardation, weight loss, intercurrent infections, hypogonadism in males, lack of sexual development in females, rough skin, poor appetite, delayed wound healing, acne, poor immune system, diarrhea, pneumonia andtaste abnormalities [6]. Malnutrition, diarrhea and pneumonia are the principal causes of childhood morbidity and mortality globally.Undernutrition increases the risk and severity of diarrhea and pneumonia, and accounts for approximately 45% of all child deaths [25].A recent systematic review identified numerous effective interventions for reducing malnutrition and child deaths, including preventive zinc supplementation in populations at risk of zinc deficiency[26]. Zinc supplementation reduces the incidence and severity of diarrhea and acute lower respiratory infections in children.

## Zinc deficiency and the immune system:

The human immune system is quite sensitive to zinc deficiency.Briefly, sub-clinical zinc deficiency impairs cellular mediators of innate immunity such as phagocytosis by macrophages and neutrophils, natural killer cell activity, generation of the oxidative burst, and complement activity [27].These alterations contribute to increased susceptibility to infection [28].In-vitro studies and studies on zinc-deficient patients have demonstrated that zinc plays an essential role in both cell-mediated and humoral immunity [29]. Consistent findings in zinc deficiency are a decrease in lymphocyte numbers (lymphopenia), impaired lymphocyte development, reduced proliferation, increased apoptosis, and thymic atrophy [30].In experimentally induced zinc deficiency, patients had low serum thymulin activity, impaired T-cell and natural killer cell activities, and decreased IL-2 and interferon production [31].The defenses against infection are particularly sensitive to disturbances in zinc status. The barrier functions of the skin, as well as those of the pulmonary and gastrointestinal tracts, are damaged, and the development, function, or both of most immunologic cells suffer deleterious effects.

## Zinc deficiency and diarrheal disease:

Zinc plays an important role in modulating host resistance to infectious agents and reducing the risk, severity and duration of diarrheal diseases. According to World Health Organization (WHO), diarrhea is defined as the passage of loose or watery stool at least three times within 24 hours.Diarrhea is responsible for 15% of all deaths in children under five years of age and accounts for about 1.4 million annual infant deaths worldwide [32]. Diarrhea remains the second leading cause of death among children under 5 in the developing world [33]. A mild-to-moderate deficiency of zinc may result in profound effects on overall immune function, with increased susceptibility to diarrheal causing pathogens including bacteria, viruses and parasites. The adverse effects of zinc deficiency on the immune response are likely to increase the susceptibility of children to infectious diarrhea, and chronic or persistent diarrhea may further compromise

the zinc status because of increased fecal losses of zinc during diarrheal episodes [27]. Zinc supplementation provides therapeutic benefits in diarrhea. Therapeutic zinc supplementation during diarrheal episodes reduces the duration and severity of the illness [34]. Of the zinc compounds approved for human consumption, the preferred choices are zinc oxide or zinc sulphate, the two cheapest forms [35]. The mechanism of action of zinc for the treatment of diarrhea caused by different pathogens is not completely understood but studies conducted in this field reveal that zinc plays different roles in the intestine, such as regulation of intestinal fluid transport and mucosal integrity and modulation of expression of genes encoding important zinc-dependent enzymes like cytokines, which play important roles in the immune system and in modulation of oxidative stress [36, 37]. These different roles might explain the positive effect of zinc intake during acute diarrhea in children.Zinc supplementation seems even more necessary for malnourished children, as they already have a zinc deficiency, which predisposes them to diarrhea and worsens it [37]. World Health Organization recommends a daily dose of 10 to 20 mg of zinc (based on age) for 10 to 14 days for management of acute diarrhea [38]. The purpose of this treatment is to reduce the severity of acute diarrhea episodes and hasten recovery from severe pneumonia in developing countries. Zinc supplementation for diarrhea in children is a safe and effective measure to shorten the illness and to reduce other complications including death.

## Zinc deficiency and pneumonia:

Worldwide, pneumonia is a major cause of childhood mortality and morbidity [39].It is responsible for 18% of under-five mortality as a result of an estimated 151 million new episodes each year occurring mostly in themarginalized and malnourished children in the developing countries who are often zinc-deficient [40]. Malnutrition plays a significant role in the increased prevalence, severity, and prognosis of pneumonia, especially among children. Zinc plays a critical role in maintaining the integrity of immune system.Zinc deficiency decreases the ability of the body to respond to infection, and also adversely affects both cell-mediated and humoral immune responses [41]. The impaired immunocompetence due to low zinc states would not only enhance the establishment of a particular infection but is also associated with a reduction in the clearance of infectious agents [41]. Studies have shown that in children with pneumonia, the serum zinc level is significantly lower than healthy controls [42]. Prophylactic zinc supplementation can reduce the incidence of pneumonia. It has been reported that zinc supplementation can shorten the duration of pneumonia [42]. Studies showed that zinc supplementation for treatment of severe pneumonia led to not only decrease the time took to relieve severe pneumonia signs and symptoms but also decreased total hospital stay [39].

## Zinc deficiency and stunting:

Stunting is defined by the WHO as the gaining of insufficient height relative to age. The causes and etiology of stunting include the following: Nutrition (energy, macronutrients, micronutrients and toxic

factors); infection (injury to gastrointestinal mucosa, systemic effects and immunostimulation); and mother-infant interaction (maternal nutrition and stores at birth, and behavioral interactions) [43].Stunting is an indicator of chronic undernutrition, and is the result of extended periods of inadequate food intake, poor dietary quality, increased morbidity, or a combination of these factors [44].The processes that lead to stunting can occur both pre- and post-natally. The prevalence of stunting is generally highest during the second and third years of life, but it often persists into school-age years. Understanding stunting among this older age-group is important because, if still untreated, stunting results in a reduction in adult size. Of the growth-limiting micronutrients, zinc is likely to be most limiting in developing countries in which children consume plant-based diets with a low content of total or absorbable zinc [44]. Impaired linear growth is a prominent feature of zinc deficiency among children in both developed and developing countries. The WHO considers stunting to be a public health problem when the prevalence of stunting among children less than 5 years of age is more than 20% [45]. Decreased growth rate in children has been associated with increased morbidity, reduced scholastic achievement, and long-term negative effects on physical work capacity and reproduction performance [9].

Zinc deficiency has been associated with growth faltering and stunting, and indeed a meta-analysis of zinc studies showed that supplementation had a positive effect on length growth, especially in children under 2 years of age, and children stunted at baseline [24].

## Zinc deficiency and wound healing:

Zinc deficiency is associated with impaired wound healing [46].Nutrition is an important extrinsic factor influencing wound healing, and malnutrition has an adverse effect on a wound's ability to heal efficiently and effectively.Zinc is identified as a major trace element in the wound-healing process because of its involvement in many different cellular processes.Wound healing is a complex process involving the stages of inflammation, proliferation and maturation that occur on a continuum from injury to healing [47]. For optimum wound healing these stages must be progressed through smoothly and efficiently, and zinc has an identifiable role in all three stages. Zinc is involved in haemostasis through its interaction with platelets, and is essential for antibody production and immune cell function.It also inhibits bacterial growth. Zinc plays a central role in the proliferation of inflammatory cells and modulates cutaneous inflammation [48].Throughout the proliferation and maturation phases, zinc is required for collagen synthesis. The element is also necessary for the proliferation of fibroblasts and keratinocytes and quickens the process of re-epithelialisation, while strengthening the wound.

Zinc has been shown to play a significant part in the wound-healing process, but the evidence for routine zinc supplementation is poor and inconclusive.

## CONCLUSION

In conclusion, zinc deficiency is a common micronutrient deficiency in children which is prevalent in many areas of the world, especially in developing countries and is generally caused by inadequate dietary intake, increased requirement, malabsorption, increased losses and impaired utilization. Since zinc plays an important role in growth and immune system development, its deficiency leads to stunting and impaired immune function resulting in delayed wound healing and increased susceptibility to infections mostly diarrhea and pneumonia. Diarrhea and pneumonia remains the major cause for childhood morbidity and mortality worldwide and researches have suggested that zinc supplementation reduce both the incidence and severity of diarrhea and pneumonia in children.

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