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REVIEW ARTICLE

Zinc supplementation in pediatric practice

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Abstract:
Scientific Knowledge about the essentiality of zinc in human health and diseases is emerging. Children are more prone to infectious diseases like diarrhoea, pneumonia, common cold and sepsis that lead to enormous deaths in the developing world. Zinc is mainly required for the maturation of B and T cells and its deficiency adversely affects the growth and functions of immune cells leading to impaired immune functions and increased susceptibility to infection. This review makes a summary of the effects of zinc supplementation in diarrhoea, common cold focusing more on the future perspective of zinc in sepsis.

Keywords: *Zinc supplementation, Immunity, Sepsis, Diarrhoea, Common cold*

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Introduction

Health education programmes should implement proper planning/guidelines focusing on the awareness of zinc, its rich dietary sources and its role in controlling morbidity in children with diarrhoeal and respiratory diseases [1]. There is much supportive evidence to incorporate zinc, the trace element in tablet or liquid form [2]. Next to iron, zinc is present in every cell of the body and it occurs in all enzyme classes, hence it is mainly involved in the biological functions of the immune system and response to infection [3]. Studies have reported that 10% of the human proteome contain zinc binding proteins [4].

It is an integral component of many metalloenzymes in the body involved in the synthesis and stabilization of proteins, DNA and RNA, gene expression, signal transduction and apoptosis. It is also involved in oxygen transport and protection against free-radical damage. The biological role of zinc is ubiquitous in the body. High concentration of zinc is present in the brain, muscles, bones, kidney, liver, prostrate and parts of the eye [5]. Reports on zinc supplementation studies are vast and is associated with contradictory results stating the various zinc levels in individuals [6]. Previous studies have reported the importance of zinc in all age groups in various diseases. The present review highlights mainly on the effects of zinc supplementation in diarrhoea, respiratory infections and sepsis in pediatric age groups.

Zinc supplementation

After 6 months of age, breast milk is insufficient to provide the necessary nutrients to the infants [7]. There is increased requirement of zinc in developing fetus and there is a high loss of zinc through breast milk from the mother after birth [8]. Zinc requirement increases in the body during periods of rapid growth like pregnancy, infancy, childhood and adolescence. Since immune system is immature in children, zinc deficiency manifestations are more common in children hence this necessitates zinc supplements to boost the immune functions [9]. The Estimated Average Requirement (EAR) was finalized by factorial analysis. The Recommended Dietary Allowance (RDA) is 8 mg/day for women and 11 mg/day for men. In the United States, the median intake from food was very recently calculated to be approximately 9 mg/day for women and 14 mg/day for men [10].

Zinc supplements are considered to be beneficial where people consume a lot of foods rich in phytates and cereals that impair the absorption of zinc leading to low plasma zinc levels and deficiency diseases [12].

Zinc and immunity

Zinc deficiency adversely affects the growth and functions of immune cells [14]. Thymus gland is mainly required for the maturation of B and T cells. This gland contains thymulin, a specific hormone with the amino acid sequence (glu-Ala-Lys-Ser-Gln-Gly-Gly-Ser) requires zinc as its cofactor. Zinc binds to thymulin in a 1:1 stoichiometry through side chains of asparagine and the hydroxyl groups of the 2 serines. In animals and humans, thymulin activity is dependent on plasma zinc concentrations both in vitro and in-vivo. The active form of thymulin is formed by the conformational change brought about by the binding of zinc to the peptide. Zinc deficiency leads to increased apoptosis of pre-B and pre -T cells resulting in lymphopenia and decreased B cell production [15-17].

Table1: Average daily recommended intake of zinc (mg) in different groups [11]

Life Stage	Recommended intake (mg)
Birth to 6 months	2 mg
Infants 7–12 months	3 mg
Children	
1–3 years	3 mg
4–8 years	5 mg
9–13 years	8 mg
Teens	
14–18 years (boys)	11 mg
14–18 years (girls)	9 mg
Adults	
Men	11 mg
Women	8 mg
Special groups	
Pregnant teens	12 mg
Pregnant women	11 mg
Breastfeeding women	12 mg

Table 2: Food rich in zinc [13]

Dietary sources	Zinc content(mg/100gm)
Oysters	25
Meat (especially red meat)	5.2
Nuts	3
Poultry	1.5
Eggs	1.3
Milk products	1.2
Cereals	1
Bread	1
Fish	0.8
Sugars & preserves	0.6
Canned vegetables	0.4
Green vegetables	0.4
Potatoes	0.3
Fresh fruits	0.09

In zinc deficient individuals, there is a decrease in Th1 function leading to decreased IL-2 and IFN-g. This results in impairment in the function of natural killer cells and cytolytic activity of T cells. In contrast IL-12 is produced by macrophages and monocytes. These processes altogether are involved in phagocytosis of the invading microbes. IL-10 in contradiction is increased in zinc deficiency. This adversely affects the Th2 cell function. Hence the balance between the Th1 and Th2 cells is disturbed. This results in increased production of IL-1B, IL-8 and TNF-α. Studies have reported that these mechanisms are regained with zinc supplementation [18-20]. Therefore overall the programming of the immune system is impaired, decreasing the NK cell activity in zinc deficiency [21]. In HUT 78 cells, the binding of NFkB to DNA and gene expression of IL-2 and its receptors are affected. Phosphorylation and ubiquitation of IκB and Iκκ are also found to be zinc dependent [22].

Zinc in various diseases

Zinc deficiency in milder forms is not that easily recognizable, thus can lead to impaired immune functions and higher susceptibility to infection. Zinc deficiency is correctable either by increased dietary zinc or zinc supplements. Its dramatic manifestation is acrodermatitis enteropathica (AE), which if left untreated results in an overall 18-20% mortality rate. Its symptoms vary with age, but common manifestations include dermatitis, intermittent diarrhoea, recurrent infections and growth retardation [23, 24]. Several attempts have been made in testing zinc supplements in many diseases like diarrhoea, common cold, malaria, leishmaniasis, diabetes, eye diseases etc. But zinc supplementation proved to be effective only in limited number of diseases. In a malaria endemic region of Papua New Guinea, zinc supplementation reported to lower incidence of Plasmodium falciparum-mediated febrile episodes in preschool children [25].

Zinc supplementation also showed beneficial effect in children from Gambia [26]. There are contradictory reports regarding zinc supplementation in treating childhood malaria [1]. Zinc supplements have resulted in improved immunologic indexes in sickle cell anemia patients [27]. In South African population, children affected with HIV have high prevalence of malnutrition and limited access to medication. A recent study reported zinc supplementation given at moderate dosage of 10 mg elemental zinc per day has no adverse effects in HIV patients [28, 29].

Diarrhoeal diseases

Diarrhoea being one among the major life threatening diseases particularly in under five in children as they are more prone to risk factors due to under development of immune function. Incidence of diarrhoea is more common in low income groups below poverty line, poor sanitation, unhygienic eating habits and intake of foods deficient in nutrition. A randomized trial was conducted in a community of Bangladeshi children with diarrhoea. One group was treated with 20mg/day zinc for 14 days. Other groups were treated with oral rehydration therapy. Outcome measures like duration of diarrhoeal episodes, incidence of diarrhoea, acute lower respiratory infection and child mortality were assessed. A shorter duration (hazard ratio 0.76, 95% confidence interval 0.65 to 0.90) and lower incidence of diarrhoea and acute respiratory tract infection, admission to the hospital with diarrhoea and acute lower respiratory tract infection were observed to be reduced in intervention group than the comparison group in children. Results proved that zinc can be supplemented as an innovative and affordable intervention which can be incorporated in

existing efforts to control child mortality and morbidity rates [30].

Meta-analysis and systematic reviews found valuable effect of zinc on the two of the five diarrhoea related outcomes. The results thus indicate the need for continued efforts for better understanding the effect of zinc in diarrhoea [31]. In zinc deficient population, zinc was shown to act as an adjunct therapy in diarrhoea and to reduce mortality and morbidity. Daily zinc supplementation was shown to reduce the duration of diarrhoeal episodes by 12 hrs and persistent diarrhoea by 17 hrs. Zinc supplementation have also been reported that diarrhoeal mortality in children aged 12-59 months is reduced by 23%. Daily zinc supplementation for all children > 12 months of age shows reduction in incidence of diarrhoea by 11-23% [32].

Annually it is reported that diarrhoea causes 2 million child deaths. In children aged 1-3 years, 3 mg/day of zinc syrup was administered by enrolling 6165 participants in eighteen trials. Oral rehydration therapy is the most important treatment to save the lives of children over years to prevent dehydration during diarrhoea. Reviews have identified 18 trials involving 6165 children of all ages. Reports have shown that zinc has no impact on children aged < 6 months compared to children aged 6 months or more with diarrhoeal disease [33]. Moreover persistent diarrhoea and dysentery which account for 65% of all diarrhoea associated deaths in India and especially among low socio economic class is said to reduce in incidence with zinc supplementation [34]. In a community based double- blind, randomized controlled trial conducted in children of 6-35 mon of age, zinc supplementation reduced the incidence and prevalence of diarrhoea with increased plasma zinc concentrations [35].

Diarrhoea and pneumonia being the two leading causes of deaths especially in children in developing countries and they are reduced substantially by zinc supplementation [9]. Likewise in a pooled analysis of randomized controlled trials, oral zinc supplementation reduced the duration and severity of acute and persistent diarrhoea in children [36]. Zinc as an adjunct therapy in diarrhoea shortens the duration of illness. Zinc deficiency should be addressed in context of other health and nutrition programs to ensure that all children meet their essential nutritional needs to reduce the morbidity and mortality [37]. Zinc supplementation is an effective therapy for diarrhoea when introduced and scaled up in low income countries by decreasing diarrhoea morbidity and mortality [38].

Respiratory infections

As the name suggests, common cold affects mostly children causing day to day inconvenience, unable to concentrate and absence from school and work. Common cold is the most frequently occurring infection in all age groups in the United States. Common cold which is usually caused by rhinovirus is the most wide spread illness and a leading cause of doctoral visits and absence from school and work. Since there is no proven treatment, even a partially effective solution for treating and preventing common cold can markedly reduce the health problems and economic losses associated with it.

Reports have been exclusively searched, discussed and tabulated from the year 1980-2003, for common cold by Hulisz [39]. No further investigation is needed on the issue focusing on the beneficial role of zinc in reducing the duration and severity of common cold. In a double blind randomized, placebo-controlled clinical trial, the efficacy of zinc supplementation in children with severe

pneumonia was evaluated either by elemental zinc (from day 2, 10 mg of their assigned treatment by mouth twice a day for 7 days along with antimicrobial therapy) or placebo by mouth. Results proved that there was no statistically significant reduction in duration of disease thus concluding that zinc treatment during acute episode does not help in short term clinical recovery from severe pneumonia [40].

Table 3: Effect of zinc supplementation in diarrhoeal diseases:

Condition	Country	Age Group	Drug & dosage (Zinc/day)	Duration of treatment	Effects of zinc	Follow –up	Author
Diaarhoea and ALRI	Bangladesh	3-59mon	20mg	14 days	Zinc showed substantial lower rates in child morbidity and mortality	Two yr period	Baqui AH et al [30]
Diarrhoea	Ethiopia	12- 59 mon	10mg	14 days	Zinc was well tolerated in children under I yr of age,but large scale set up is needed.	15 days	Shimelis D et al [32]
Persistent diarrhoea & dysentery	India	6-35 mon	10mg	6 mon	zinc supplements showed beneficial reduction in children > 1 y old and on DD in boys.	180 days	Sazawal S et al [34]
Acute diarrhoea	USA	6-35 mon	10mg	6 mon	significant effect was observed on acute diarrhoeal morbidity in children > 1 1 mo old and in children with low plasma zinc concentrations.	180 days	Sazawal S et al [35]

In a randomized, double-masked, placebo controlled clinical study, the effectiveness of zinc supplementation was tested in children aged 6-30 months. In infants 10mg elemental zinc and 20 mg or placebo was administered to older children on a daily basis for four months. Lower incidence of pneumonia was observed in zinc supplemented infants [41]. A double-blind, randomized controlled trial was conducted among children aged 9 mo–15 y who had pneumonia associated with severe measles. Zinc dosage of 20 mg was given daily for 6 mon in addition to vitamin A. But there was no additional benefit reported in children severely affected with measles accompanied by pneumonia [42]. In children aged 6- 35 months with acute lower respiratory tract infection, 10 mg elemental zinc was given daily for 6 months. Findings showed that zinc supplementation resulted in a significant reduction in respiratory morbidity among preschool children [43].

In a pooled analysis of randomized controlled trials, the prevention of diarrhoea and pneumonia by zinc was evaluated in children in developing countries by providing oral supplements containing atleast one half of US recommended daily Allowance (RDA) of zinc in less than 5 year old i.e, continuous trials providing 1 to 2 RDA of elemental zinc 5 to 7 times per week and 3 short course trials providing 2 to 4 RDA daily for 2 weeks followed by 2 to 3 months of morbidity surveillance. The prevention of serious infectious morbidity through household visits was also evaluated and results showed substantial reductions in diarrhoea and pneumonia rates, the two leading causes of deaths in these settings [36].

Table 4: Effect of zinc supplements in respiratory diseases

Condition	Country	Age Group	Participants	Drug & dosage (Zinc)	Duration of treatment	Effects of zinc	Author
Severe pneumonia	Nepal	2 mon-5 yr	64/53	10mg	7 days	No significant reduction in duration of severe pneumonia and duration of hospital stay.	Sheh et al [40)
ALRI and pneumonia	India	6-30mon	1241/1241	10mg	4 mon	Lowers the incidence of pneumonia	Bhandari et al [41)
Measels accompanied by pneumonia	India	9mon-15 yrs	42/43	20mg	6 days	No beneficial effect	Mahalanabis et al [42)
ALRI	India	6-35 mon	298/311	10mg	120 days	Significant reduction in respiratory morbidity in preschool children.	Sazawal et al [43)

Zinc in sepsis

In a double-blind, placebo –controlled clinical trial, the reduction in duration of common cold was tested using zinc gluconate lozenges. After an initial dose, one 23 mg zinc lozenges or matched placebo was dissolved in mouth every 2 wakeful hour and this was done for 10 days. Results showed that after 7 days, 86% of 37 zinc treated subjects had no symptoms compared to only 46% of 28 placebo treated subjects. However, the choice of subjects raised concern about superimposed allergies or bacterial infections and about the disproportionate number of dropouts from zinc group [44].

Zinc which inhibits viral replication has been tested in trials for treating common cold. This review identified 18 randomized controlled

trials, enrolling 1781 participants from all age groups, comparing zinc with placebo. Results found that zinc lozenges or syrup, when taken within 24 hours of symptom set, reduced the average duration of common cold and symptoms less likely persisted beyond 7 days. Prophylactic zinc supplementation for atleast 5 months reduces incidence, school absence and prescription of antibiotic for children with common cold. Zinc lozenges being widely studied shows that a dose of ≥ 75mg/d significantly reduces duration of cold and is best when used throughout the cold. However side effects include bad taste and nausea when zinc lozenges are not used as syrup or tablet. No firm recommendation can be made with prophylactic zinc supplementation due to insufficient data [45].

Table 5: Effect of zinc in sepsis

Condition	Country	Age Group	participants	Drug & dosage (Zinc/day)	Effects of zinc	Author
Serious bacterial infections	India	7-120 days	Zinc-332 Control-323	10mg	Zinc has proved as an adjunct treatment to reduce the risk of treatment failure by 40 % infants less than 120 days with serious bacterial infection.	Bhatnagar et al [58]
Neonatal sepsis	Nepal	>32 weeks	Drug-307 Placebo-307	1mg/kg/day	Zinc supplements did not show significant reduction in mortality rate, duration of hospital stay and requirement of higher lines of antibiotics.	Mehta et al [59]

The data available from various hospitals and community based studies suggest that the most common causes of neonatal deaths are infections, including septicemia, meningitis, respiratory infections, diarrhoea and neonatal tetanus(32%) followed by birth asphyxia, injuries (29%)and prematurity (24%/) [46]. Sepsis is a heterogeneous, dynamic syndrome caused by imbalances in the inflammatory network [47].

In the first instance, it is to detect, diagnose and treat sepsis which are equally important in both low and high income settings. Deliveries conducted at home, unclean prelacteal feeding practices are the commonest predisposing factors for acquiring sepsis [48]. Very few studies have distinguished between early onset and late onset sepsis [49, 50]. Neonatal mortality and morbidity are the most common aspects in sepsis contributing to 30- 50 % of deaths in developing world [51]. According to Brown et al, an estimated 23 % of world's population is zinc deficient [52]. Sepsis contributes to be the main cause of mortality and morbidity in critically ill patients with few treatment options beyond antibiotics like intensive care unit- based organ transplant and vaccines [53, 54, 55]. It was also reported that Gram- negative bacteria were the most commonly isolated organisms. They were found to be highly resistant to third generation

cephalosporins due to extended spectrum β-lactamase production [56].

In the developed countries resistant to several groups of antibiotics is the problem whereas in the countries where population is below the poverty line, choice or the availability of alternative antibiotics is scarce. Hence, as much quick as possible, promising measures need to be initiated to provide simple and affordable interventions to reduce the severity of sepsis [57]. In AIIMS study conducted in 2012, it has been reported that in infants aged 7- 120 days with probable serious bacterial illness, zinc supplementation given at 10mg dosage was shown to reduce the treatment failure by 40% and improve the survival rate [58].

In a double- blinded, randomized, placebo controlled trial conducted in Nepal, the intervention group received 1mg/kg/day zinc dissolved in expressed breastmilk whereas the other group received placebo in addition to antibiotics. But reports did not show any significant reduction in duration of hospital stay, mortality rates and need of higher lines of antibiotic therapy in neonates with sepsis [59]. However, the dose of zinc used was much less compared to AIIMS study. By identifying zinc deficiency and replenishing the zinc stores in patients with sepsis, zinc supplementation may be a beneficial adjunct that influence the outcomes of sepsis [60].

In humans, gene expression profiling was done in pediatric septic shock using microarray analysis. Researchers have found that there is a difference in the gene regulation between children with septic shock and those without septic shock. Those children who had genes differentially regulated, two isoforms of mettalothionein (MT) showed increased expression and they had lowered levels of zinc. These findings indicate that zinc homeostasis is related to genome - level alteration which is mostly prevalent in pediatric septic shock thus warranting a therapeutic supplementation [61].

In a murine model of sepsis, prophylactic zinc supplementation have shown to decrease the bacterial load and increase the rate of survival, but till date the mechanism by which zinc plays a role in this condition is unclear [62].

The main difference between zinc and iron supplementation is that zinc leads to reduced mortality rates (Zanzibar trial), whereas iron supplementation increases the mortality rate in a murine model of polymicrobial sepsis [63, 64]. Reducing newborn sepsis and its related mortality is in high progress in industrialized countries. Providing access to skilled and hygienic deliveries, risk based intrapartum antibiotic prophylaxis and high quality intensive cares of newborns along with most cost-effective and feasible intrapartum approaches are more important in developing countries.

But practicability of implementating these new advances must be considered as in developing countries, the whole scale adoption of these strategies is precluded due to resource constraints.

Further implementation of diagnostic technologies and home based antibiotic treatment face more obstacles in large scale implementation in neonatal sepsis. Hence the risks and benefits of modern technologies and interventions must be carefully assessed. Many experienced practitioners administer parenteral antibiotics rather than waiting for diagnostic tests since neonatal sepsis is the most rapidly fulminating and deadly disease. The individual patients health is more important thus in all research and evaluation programs, front line health workers and families must be partners. Therefore resource allocation across and within countries must be equitable and modeling

techniques should evaluate public health impact on neonatal sepsis intervention that must be widely used and developed [65].

Over the years technically challenging transcriptomic and bioinformatic approaches have been made by applying microarray technology to understand the complexity of these heterogenous clinical syndromes i.e, sepsis and septic shock at multiple levels. Hopefully moving towards novel findings of stratification biomarkers, stratifying the patients into clinically relevant and expression-based subclasses will help in improving the outcome [66].

The variable bioavailability of zinc when given enterally makes the intravenous route a more preferred and reliable method of zinc delivery [67], but the dose and duration of therapy still remains unknown. A controlled, double-blind study was conducted among infants (n=19) administered with zinc-fortified formula and the other group (n=20) with unfortified formula. Phagocytic and fungicidal capacity, zinc, copper, iron and growth were assessed in both groups on admission and after 60 and 105 days of nutritional rehabilitation. Infants with decreased fungicidal activity showed significant increase in zinc fortified group than controls after 105 days. The duration of impetigo episodes were also found higher in infants receiving zinc fortified formula [68]. Zinc supplementation improved other measures of immune function (delayed hypersensitive skin reactions of lymphoproliferative response to phytohemagglutinin and salivary IgA concentrations) as well as improved linear growth in children with marasmus [69]. In another study of a small animal model with polymicrobial sepsis, short term zinc supplementation has shown to reduce the inflammatory responses by reducing NF-KB [70].

Beyond supportive care and antibiotic therapy, neonatal sepsis continues to increase at a rapid rate. There is proven evidence that zinc supplementation reduces the rate of infection in several diseases like diarrhoeal and respiratory infections. Another area of concern is that zinc therapy in higher doses is harmful as it suppresses the immune functions.

Conclusion

It is clearly understood that zinc supplementation proves to be beneficial in reducing the severity and duration of diarrhoeal diseases and common cold. It is also found to be effective in improving the survival rate in low birth weight infants, children and neonates with sepsis. The important aspect to be noted is that it is very difficult to maintain zinc supplements routinely in children and neonates. The other point is that zinc supplements respond differently in each individual depending on the unique zinc status in each person. If the assessment of zinc status is made readily available, standard supplementation protocols can be prepared accordingly as early as possible to bring out this trace elements beneficial role in various alarming diseases. Hence it is necessary to determine the optimal dose and dosing schedule to prevent common morbidities. Zinc rich plants and those that does not inhibit the zinc absorption should be cultivated for future benefits.

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