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Zinc and Its Paradoxes Involving some Human Health Issues on Supplementation

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

This paper aims at echoing the health implications of zinc in humans to the scientific world in order to designing a proper means to streamlining its research. The paper looks at some important functions of zinc, some health risks of zinc deficiency and, the boons and ambiguities associated with zinc supplementation trials. Zinc supplementations have, among others, such important health benefits as; improving immune system functions, reducing the duration and severity of diarrhea in children, and of common cold, reducing the incidence of pneumonia and of HIV/AIDS infections, may reducing the incidence of clinical attacks of malaria in children. However, the optimum zinc doses and dosages for these health conditions have not been ascertained for supplementation due to lack of its sensitive nutritional status biomarker and or improper zinc study design. Zinc bioavailability is relatively high in meat, eggs and seafood because of the relative absence of compounds that inhibit its absorption and the presence of sulfur-containing amino acids like cysteine and methionine that improve its absorption. The future of zinc research is promising as it would help addressing such health challenges as malaria, tuberculosis, diabetes, blindness, sexual dysfunction, diarrhea, cancer and others when at the cutting edge. It is therefore suggested, inter alia, that a sensitive and specific biomarker should be holistically designed for zinc to help detecting marginal zinc deficiency in humans as this will streamline its associated health studies;

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more and well-designed randomized controlled trials of zinc supplementation should be conducted to determining optimum dosage, formulation and duration of treatment for a specific health condition.

Keywords: Zinc; sources; functions; deficiencies; human health.

1. INTRODUCTION

Zinc ranks about 23th in abundance among the elements in Earth's crust [1]. After iron, zinc is the second most abundant trace metal in the human body, constituting 2.3 g in an average 70 kg adult human [2] and essential for all forms of life, including microorganisms, plants and animals [3]. Zinc deficiency in humans was first reported in the 1960s in Egypt and Iran, where children and adolescent boys with stunted growth and undeveloped genitalia responded to treatment with zinc [4] and hence predicated zinc insufficiency as an important public health issue especially in developing countries by a number of experts [5]. Some such clinical syndromes as growth retardation, male hypogonadism, skin changes, mental lethargy, hepatosplenomegaly, iron deficiency anemia, and geophagia are known to be associated with zinc deficiency [6]. The global prevalence of zinc deficiency was estimated to be 31% with a high prevalence of 37%-62% found in southern and central Africa regions [7] while in Nigeria, the prevalence was 20% [6]. Moderate zinc supplementation had demonstrated that marginal zinc deficiency contributed to impaired physical and neuropsychological development and increased susceptibility to life-threatening infections in young children [8] which resulted in more than 450,000 deaths annually in children under five (5) years old, comprising 4.4% of global childhood deaths [9]. Severe zinc deficiency is a rare, genetic or acquired condition but marginal is quite common in the developing world, affecting an estimated 2 billion people [10]. The central of these clinical features is increased susceptibility to infectious diseases [11] leading to a speculation that zinc must be important for host immunity [12]. Numerous aspects of cellular metabolism are zinc-dependent so much so that zinc plays important roles in growth and development, immune response, neurological function, and reproduction [13].

Despite the phenomenal roles of zinc for life, its research is still in a relatively early stage of evolution [14] considering the reported cases of contradictions involving its research findings on such health-related issues as the effect of zinc supplementation on the common cold [15,16,17] ,malaria [18], pregnancy complication [19], delayed neurological and behavioural development in young children [20] etc., perhaps due to the lack of a sensitive and specific index of marginal zinc deficiency [21] and perhaps due to poor experimental design. The most commonly used indices, plasma or serum zinc levels, for evaluating dietary zinc deficiency do not necessarily reflect cellular zinc status due to tight homeostatic control mechanisms [22]. It is on this the article is orchestrated to echoing the health implications of zinc to the scientific world in order to developing the wherewithal to streamlining its research.

1.1 Distribution of Zinc in the Body

Zinc is present in human body exclusively as Zn^{2+} bound to such cellular proteins as zn-transferrin, albumin, α_2-macroglobulin and metallothionein [12]. There are no specific storage sites known for zinc and thus a regular supply in the diet is required. It is found in all parts of human body as a component of various proteins and nucleic acids [22]; 60% in the muscle, 30% in bone and about 5% in the skin. Particularly high concentrations are in the prostate gland and semen [23].

1.2 Recommended Zinc Intake

Table 1 shows the current Recommended Dietary Allowances (RDA) for zinc. For infants aged 0 to 6 months, an Adequate Intake (AI) for zinc that is equivalent to the mean intake of zinc in healthy, breastfed infants was established by the Food and Nutrition Board [22]. RDA is the average daily level of intake sufficient to meet the nutrient requirement of nearly all (97%-98%) healthy individual. Adequate Intake (AI) is established when evidence is insufficient to develop a RDA and is set at a level assumed to ensure nutritional adequacy [22]. The requirement for zinc by men is more than that of women because male semen contains 100 times more zinc than is found in the blood [23].

Table 2 shows the Tolerable Upper Intake level (UL) for zinc. UL is the maximum daily intake

unlikely to cause adverse health effects. However, the UL may not be applied to individuals receiving zinc for medical treatment.

1.3 Sources of Zinc

Zinc is an essential mineral that is naturally present in some food, available as a dietary supplement and others found in cold remedies [22].

1.3.1 Dietary source

A wide variety of foods particularly those associated with protein foods contain zinc [23]. Shellfish, beef, and other red meats are rich sources of zinc, legumes and nuts are relatively good plant sources of zinc [24], and snails [25] are also good sources of zinc. Zinc bioavailability is relatively high in meat, eggs and seafood because of the relative absence of compounds that inhibit its absorption and the presence of such sulfur-containing amino acids as cysteine and methionine that improve its absorption. The zinc in whole-grain products and plant proteins is less bioavailable due to their relative high content of phytic acid. However, leavened whole-grain breads have more bioavailable zinc than that of unleavened whole-grain because enzymatic action of yeast reduces its level of phytic acid [24]. In Table 3 below, as adopted from [24], are selected food sources and their zinc content in milligrams (mg).

1.3.2 Dietary supplements

Zinc supplements are commercially available in forms of zinc gluconate, zinc acetate, zinc sulfate and zinc picolinate [24] with variable percentage of elemental zinc [22].

1.3.3 Other sources

Zinc is present in some zinc-containing cold lozenges, present in some products used for homeopathic medication that are sold over the counter for the treatment and prevention of cold, is also present in some denture adhesive creams [22].

1.4 Functions of Zinc

Zinc is a nutritionally essential mineral involved in numerous aspect of cellular metabolism: It is required for the catalytic activity of over 300 enzymes [24] including alcohol dehydrogenase, carbonic anhydrase, carboxyl peptidase A etc. It plays a central role in immune function, protein synthesis, wound healing, DNA synthesis and cell division. Zinc support normal growth and development during pregnancy, childhood and adolescence. It is required for proper sense of taste and smell [22]. The zinc presents in the pancreas may aid in the storage of insulin [25]. Zinc supports reproductive system of men and women and helps with infertility [26]. Zinc plays

Table 1. Recommended dietary allowances (RDA) for zinc

Age	Male	Female	Pregnancy	Lactation
0–6 months	2 mg*	2 mg*		
7–12 months	3 mg	3 mg		
1–3 years	3 mg	3 mg		
4–8 years	5 mg	5 mg		
9–13 years	8 mg	8 mg		
14–18 years	11 mg	9 mg	12 mg	13 mg
19+ years	11 mg	8 mg	11 mg	12 mg

*Abbreviation: * Adequate Intake (AI)*
Source: [22]

Table 2. Tolerable upper intake levels for zinc

Age	Male	Female	Pregnant	Lactating
0–6 months	4 mg	4 mg		
7–12 months	5 mg	5 mg		
1–3 years	7 mg	7 mg		
4–8 years	12 mg	12 mg		
9–13 years	23 mg	23 mg		
14–18 years	34 mg	34 mg	34 mg	34 mg
19+ years	40 mg	40 mg	40 mg	40 mg

Source: [22]

Table 3. Selected food sources of zinc

Food	Serving	Zinc (mg)
Oysters	6 medium (cooked)	27-50
Beef	3 ounces (cooked)	3.7-5.8
Crab, Dungeness	3 ounces (cooked)	4.7
Pork	3 ounces (cooked)	1.9-3.5
Turkey (dark meat)	3 ounces (cooked)	3.0
Beans, baked	1/2 cup	0.9-2.9
Chicken (dark meat)	3 ounces (cooked)	1.6-2.7
Yogurt, fruit, nonfat	1 cup (8 fl. oz.)	1.8
Cashews	1 ounce	1.6
Chickpeas (garbanzo beans)	1/2 cup	0.5-1.3
Milk	1 cup (8 fl. oz.)	1.0
Almonds	1 ounce	0.9
Peanuts	1 ounce	0.9
Cheese, cheddar	1 ounce	0.9

an important role in the structure of proteins and cell membranes. A finger-like structure, known as a zinc finger motif, stabilizes the structure of a number of proteins. For example, copper provides the catalytic activity for the antioxidant enzyme copper-zinc superoxide dismutase (CuZnSOD), while zinc plays a critical structural role. The structure and function of cell membranes are also affected by zinc. Loss of zinc from biological membranes increases their susceptibility to oxidative damage and impairs their function [24].

1.5 Zinc Deficiency

Zinc deficiency may be caused by; a) An increased loss of zinc from the body via the faeces, urine, hair, skin, sweat, semen and menstruation [23], b) An inadequate zinc intake, c) Mal-absorption of zinc, d) An increased requirements for zinc [24], and e) The practice of clay eating which interferes with the absorption of zinc, iron and other minerals [4].

1.5.1 Severe zinc deficiency

Severe zinc deficiency, which could be genetic or acquired condition, is rare. What is known about it was derived from the study of individuals born with acrodermatitis enteropathica, a genetic disorder resulting from the impaired uptake and transport of zinc. The condition is characterized by slowing or cessation of growth and development, delayed sexual maturation, characteristic skin rashes, chronic and severe diarrhea, night blindness, swelling and clouding of the corneas and behavioral disturbances [24]. Zinc mal-absorption or conditions of increased zinc loss, such as severe burns or prolonged diarrhea may result in severe zinc deficiency. People on total parenteral nutrition without zinc, on certain medications like penicillamine and those who abuse alcohol have been reported to incur severe zinc deficiency [24].

1.5.2 Marginal zinc deficiency

Milder zinc deficiency contributes to a number of health problems especially common in children who live in developing countries [24]. Its clinical signs consist of depressed immunity, impaired taste and smell, onset of night blindness, impairment of memory and decreased spermatogenesis in male [11].

1.6 Excessive Zinc Intake

Intake of excessive zinc is toxic. Too much zinc will interfere with the metabolism of other minerals in the body, particularly iron and copper [23]. Consumption of excessive zinc, 50mg/day or more, over a period of weeks can interfere with copper bioavailability. High intake of zinc induces the intestinal synthesis of metallothionein, a copper-binding protein. Metallothionein traps copper within intestinal cell and prevents its systemic absorption [24]. Intakes of 150-450 mg of zinc per day was found to be associated with such chronic effects as low copper status, altered iron function, reduced immune function and reduced levels of high-density lipoproteins. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headaches [22]. Chronic

zinc toxicity was found to be associated with a significant increase in hospitalizations for genitourinary causes when 80 mg per day of zinc in the form of zinc oxide for 6.3 years, on average, was used in age-related eye disease study (AREDS) [27].

1.7. Zinc and Human Health

The lack of sensitive indicators for zinc nutritional status in human makes it difficult to determine the level of zinc intake most likely to promote optimum health. Nevertheless, the potency of zinc in the prevention of diseases or conditions related to zinc deficiency is promising considering the near success of some of the trials conducted to testing its efficacy. Some of these health-related conditions or diseases are described below.

1.7.1 Impaired immune system function

Adequate zinc intake is essential in maintaining the integrity of the immune system [28] specifically for normal development and function of cells that mediate both innate (neutrophils, macrophages, and natural killer cells) and adaptive (B-cells and T-cells) immune responses [29,30]. Moreover, zinc plays a structural role in the antioxidant enzyme, CuZnSOD. Zinc deficiency adversely affects a number of immune functions, resulting in decreased production of certain cytokines; Reduced activation of zinc-dependent enzymes and transcription factors; and decreased activity of thymulin, a zinc-dependent thymic hormone important for T-cell function [31]. Consequently, zinc-deficient individuals are known to experience increased susceptibility to a variety of infectious agents [12]. [32] proposed some modes of action of zinc on the immune function base on such hypotheses as: Zinc is an essential factor for the activity of more than 300 metallo-enzymes, including DNA polymerase, thymidine kinase etc., that cannot function in its absence; Zinc is necessary for the activity of some immune mediators including thymulin, cytokine etc.; Zinc could contribute to membrane stabilization, acting at the cytoskeletal level; Zinc act as a major intracellular regulator of lymphocyte apoptosis in vitro and in vivo.

1.7.2 Wound healing

Zinc helps maintaining the integrity of skin and mucosal membranes [33]. Patients with chronic leg ulcers have abnormal zinc metabolism and low serum zinc levels, and clinicians frequently treat skin ulcers with zinc supplements [34].

1.7.3 Diarrhoea

It is estimated that diarrheal diseases result in the deaths of over 1.8 million children less than five years of age in developing countries annually [35]. The adverse effects of zinc deficiency on immune system function are likely to increase the susceptibility of children to infectious diarrhoea, and persistent diarrhoea contributes to zinc deficiency and malnutrition. Research indicates that zinc deficiency may also potentiate the effects of toxins produced by diarrhoea-causing bacteria like *E. coli* [36]. Zinc supplementation in combination with oral rehydration therapy has been shown to significantly reduce the duration and severity of acute and persistent childhood diarrhoea and to increase survival in a number of randomized controlled trials [37,38]. The World Health Organization and the United Nations Children's Fund currently recommended the use of Zinc/Oral rehydration salt (ORS) for the treatment of diarrheal diseases in young children in Africa including Nigeria [39], an implication of the effectiveness of zinc in this regard. The exact mechanism by which zinc is an effective therapy for diarrhoea and also prevents subsequent morbidity is not clearly known. One plausible mechanism is via the important role zinc plays in maintaining proper immune function and specifically enhancing cellular immunity [40]

1.7.4 Pneumonia

It was analysed by [41] that zinc supplementation may also reduce the incidence of lower respiratory infections, such as pneumonia, on considering a pooled analysis of a number of studies in developing countries that demonstrated a substantial reduction in the prevalence of pneumonia in children supplemented with zinc. This was supported by two meta-analyses that found that zinc supplementation reduces the incidence of pneumonia or respiratory tract illnesses in children less than five years of age [42,43]. In the study of [44], as shown in Table 4, zinc was shown to be efficacious in reducing the time to recovery in children with very severe pneumonia [HR(hazard ratio): 1.52;95% CI: 1.03, 2.23].

1.7.5 Growth retardation

Significant delays in linear growth and weight gain, known as growth retardation or failure to thrive, are common features of mild zinc deficiency in children. In the 1970s and 1980s,

Table 4. Effect of oral zinc on clinical outcomes in children with very severe pneumonia

Outcomes	Zinc	Placebo	Values
Time to recovery (h)[1]	80 (63, 114)[2]	106 (66, 117)[2]	1.52 (1.03, 2.23)[3]
Recovered by 2 d [n(%)]	4 (6.8)	5 (8.2)	----------
Recovered by 5 d [n(%)]	43(72.9)	31 (50.8)	----------
Treatment failure [n(%)][4]:			
Any failure	5 (8.8)	8 (14.0)	0.63 (0.2, 1.8)[5]
Death	1 (1.8)	2 (3.5)	0.50 (0.05, 5.4)[5]
Need for intensive care	0 (0)	1 (1.8)	----------
Not recovered by 14 d	0 (0)	0 (0)	----------
Change of antibiotics	4 (7.0)	5 (8.8)	0.80 (0.2, 2.8)[5]

[1]Number of patients in whom primary outcome could be assessed was 59 in the zinc group and 61 in the placebo group.[2]Median; IQR (Inter-quarter range) in parentheses. [3]HR; 95% CI in parentheses. Time-to-event analyses by using a Cox proportional hazards regression model. [4]Number of patients in whom treatment failure could be assessed was 57 in the zinc group and 57 in the placebo group. [5]RR (Risk ratio); 95% CI in parentheses.

several randomized placebo-controlled studies of zinc supplementation in young children with significant growth delays were conducted in Denver, Colorado. For example [45] found that modest zinc supplementation (5.7 mg/day) resulted in increased growth rates compared to placebo. More recently, a number of larger studies in developing countries observed similar results with modest zinc supplementation. Meta-analyses of growth data from zinc intervention trials have also confirmed the widespread occurrence of growth-limiting zinc deficiency in young children, especially in developing countries [46,47].

1.7.6 Diabetes mellitus

Both marginal and moderate zinc deficiencies may be relatively common in individuals with diabetes mellitus due to their frequent urination [20,48]. Supplementation with zinc has reportedly improves immune function in diabetics. For example, supplementation of type 2 diabetics with 30 mg/day of zinc for six months reduced a non-specific measure of oxidative stress (plasma TBARS) without significantly affecting blood glucose control [49].

1.7.7 The common cold

Researchers have hypothesized that zinc could reduce the severity and duration of cold symptoms by directly inhibiting rhinovirus binding and replication in the nasal mucosa and suppressing inflammation [50,51]. The use of zinc lozenges within 24 hours of the onset of cold symptoms, and continued every two to three hours while awake until symptoms resolve, has been advocated for reducing the duration of the common cold. For example, in a randomized double-blind placebo-controlled clinical trial, 50 subjects (within 24 hours of developing the common cold) took a zinc acetate lozenge (13.3 mg zinc) or placebo every 2-3 wakeful hours. Compared with placebo, the zinc lozenges significantly reduced the duration of cold symptoms [52]. In another clinical trial involving 273 participants with experimentally induced colds, zinc gluconate lozenges (providing 13.3 mg zinc) significantly reduced the duration of illness compared with placebo but had no effect on symptom severity [17]. More recently, [53] in a Cochrane review concluded that zinc lozenges is beneficial in reducing the duration and severity of the common cold in healthy people, when taken within 24 hours of onset of symptoms. The mechanism by which zinc acts against the common cold is still not completely understood. It has been found that zinc inhibits the rhinovirus 3C protease, and hereby viral replication, but this effect was only observed in vitro and not in vivo. Also discussed is an interference of zinc with the binding of the rhinovirus to its cellular receptor, the adhesion molecule ICAM-1, or an interaction of zinc with host immune function [54].

1.7.8 Age-related Macular Degeneration (AMD)

A leading cause of blindness in people over the age of 65 years in the United State (U.S.) is a degenerative disease of the macula, known as age-related macular degeneration. The macula is the portion of the retina in the back of the eye involved with central vision. Zinc is hypothesized to play a role in the development of AMD for several reasons, namely; Zinc is found at high concentrations in the part of the retina affected by AMD; Retinal zinc content has been shown to decline with age, and the activities of some

zinc-dependent retinal enzymes have been shown to decline with age. Although scientific evidence that zinc intake is associated with the development or progression of AMD is limited, a randomized controlled trial found that supplementation with 200 mg/day of zinc sulphate, containing 81 mg/day of elemental zinc, over two years reduced the loss of vision in patients with AMD [55] and recently, a randomized double-blind placebo-controlled trial in 74 AMD patients reported that supplementation with 50 mg/day of zinc mono-cysteine for six months improved measures of macular function, including visual acuity, contrast sensitivity, and photo-recovery [56]. The Age-related Eye Disease Study (AREDS) formulation containing anti-oxidants zinc and copper is currently the standard of care for AMD patients [57], a breakthrough for zinc as a component of formulation for health care.

1.7.9 Delayed neurological and behavioural development in young children

Low maternal zinc nutritional status has been associated with diminished attention in new-born infants and poorer motor function at six months of age. The finding of [19] had revealed that maternal zinc supplementation was associated with improved motor development in very low-birth-weight infants, more vigorous activity in Indian infants and toddlers, and more functional activity in Guatemalan infants and toddlers, and additionally, zinc supplementation in children was associated with better neuropsychological functioning (e.g., attention) in Chinese first grade students, but this was observed only when zinc was provided with other micronutrients [58].

1.7.10 Malaria

In the finding of [59], some studies have showed that zinc supplementation may reduce the incidence of clinical attacks of malaria in children. A good example of this is a placebo-controlled trial in preschool-aged children in Papua New Guinea that found zinc supplementation to have reduced the frequency of health centre attendance due to *Plasmodium falciparum* malaria by 38% [60] and more so the number of malaria incidences accompanied by high blood levels of this malaria-causing parasite was reduced by 68%, suggesting that zinc supplementation may be of benefit in preventing more severe episodes of malaria. Also, a lower but not statistically significance incidence of malaria in zinc supplemented children from Gambia was reported [54].

1.7.11 Immune response in the elderly

Age-related declines in immune function are similar to those associated with zinc deficiency, and the elderly are vulnerable to mild zinc deficiency [61]. In the review of [62], zinc supplementation in the elderly has been found to improve certain aspects of immune function. For examples, a randomized placebo-controlled study in men and women over 65 years of age found that a zinc supplement of 25 mg/day for three months increased levels of some circulating immune cells (i.e., CD4 T-cells and cytotoxic T-lymphocytes) compared to placebo [34] and according to [63], a randomized double-blind placebo-controlled trial in 49 older adults, aged 55-87 years, 35% of which were considered zinc deficient, found that zinc supplementation of 45 mg/day for 12 months reduced the incidence of infection and *ex vivo* markers of inflammation (TNF-α) and oxidative stress (MDA + HAE, 8-OHdG).

1.7.12 Pregnancy complications

It has been estimated that 82% of pregnant women worldwide are likely to have inadequate zinc intakes, due to the foetus additional burden [19]. Poor maternal zinc nutritional status has been associated with a number of adverse outcomes of pregnancy, including low birth weight, premature delivery, labor and delivery complications, and congenital anomalies [64]. Some studies had found maternal zinc supplementation increased birth weight and decreased the likelihood of premature delivery. For example, a recent systematic review of 20 randomized controlled trials [65] found that zinc supplementation during pregnancy was associated with a 14% reduction in premature deliveries especially in low-income women.

1.7.13 HIV/AIDS

Sufficient zinc is essential in maintaining immune system function, and HIV-infected individuals are particularly susceptible to zinc deficiency. In HIV-infected patients, low serum levels of zinc have been associated with a more advanced stage of the disease and also with increased mortality [66, 67]. In one of the few zinc supplementation studies conducted on AIDS patients, 45 mg/day of zinc for one month resulted in a decreased incidence in opportunistic infections compared to placebo [68]. A placebo-controlled trial in 231 HIV-positive adults with low plasma levels of zinc (<0.75 mg/l) found that zinc supplementation,

15 mg/day for men and 12 mg/day for women, for 18 months reduced the incidence of immunological failure, as defined by a CD4+ count <200 cells/mm^3, by 76% and the rate of diarrhoea by 60% [69]. Moreover, a recent systematic review of six randomized controlled trials, including 1,009 participants, concluded that zinc supplementation was safe and efficacious in reducing opportunistic infections in adults [70]. Zinc supplementation may prevent immunological failure through its action on thymic functions, expression of interleukin 2, T cell proliferation, and potential reduction of mitochondrial toxicity and oxidative stress [71]. Thymulin, a thymic peptide important for the maturation and differentiation of immature thymocytes [72], in particular for $CD4^+$ cell growth and function [73], is active only when bound to zinc, and its activity is reduced in immune-suppressed and zinc-deficient conditions [74]. Hence increasing the levels of the active zinc-bound thymulin on supplementation could offer an additional mechanism for slowing HIV disease progression.

2. CONTRADICTIONS OF ZINC SUPPLEMENTATION ON HUMAN HEALTH

Despite the numerous health benefits of zinc in human, its therapeutic supplementations in some cases of human health are contradictory. Ambiguities in zinc supplementation trials are common in the following conditions.

2.1 Diarrhoea

Prophylactic zinc seems to be effective in decreasing the incidence of diarrhoea, in decreasing respiratory infections and in improving growth in children with impaired nutritional status. There is less conclusive evidence that prophylactic zinc reduces diarrhoea duration or diarrhoea severity. While some studies indicated that prophylactic zinc may have an impact on mortality due to diarrhoea and pneumonia, an impact on overall mortality has not been demonstrated. Zinc used in treatment of diarrhoea in children seems to reduce diarrhoea duration, stool frequency and respiratory infection in zinc deficient children, but stool output is reduced only in children with cholera. There is less conclusive evidence that therapeutic zinc reduces mortality due to diarrhoea and respiratory infections [40].

2.2 Pneumonia

In the zinc supplementation trial conducted by [44], as shown in the Table 5, the time to recovery from severe or very severe pneumonia was similar in both groups (HR: 0.98; 95% CI: 0.82, 1.17).Showing that there was no overall benefit of zinc supplementation in reducing the time to recovery in children with pneumonia. To date, a clear benefit of zinc in the treatment of pneumonia has been seen in 2 of 8 studies that examined the impact of zinc on pneumonia outcomes. Furthermore, studies in India and Nepal found no benefits of zinc supplementation in children with pneumonia [75].

2.3 Malaria

In a 6 months zinc supplementation trial conducted in more than 700 West African children as reported by [76], there was no difference in the frequency or severity of malaria episodes caused by *P. falciparum* in children

Table 5. Effect of oral zinc on clinical outcomes in children with severe or very severe pneumonia

Outcomes	Zinc	Placebo	Values
Time to recovery (h)[1]	78.5 (59, 122)[2]	77.0 (58,117)[2]	0.98 (0.82, 1.17)[3]
Recovered by 2 d [n(%)]	33 (12.0)	37 (13.4)	----------
Recovered by 5 d [n(%)]	194 (70.8)	195 (70.7)	----------
Treatment failure [n(%)] [4]:			
Any failure[5]	37 (14.1)	28 (10.6)	1.3 (0.8, 2.1)[6]
Death	4 (1.5)	4 (1.5)	1.0 (0.3, 4.0)[6]
Need for intensive care	0 (0)	1 (0.4)	----------
Not recovered by 14 d	2 (0.8)	1 (0.4)	2.0 (0.2, 22.0)[6]
Change of antibiotics	31 (11.8)	22 (8.4)	1.4 (0.8, 2.4)[6]

[1]Number of patients in whom primary outcome could be assessed was 274 in the zinc group and 276 in the placebo group. [2]Median; IQR in parentheses. [3]HR; 95% CI in parentheses. Time-to-event analyses by using a Cox proportional hazards regression model. [4]Number of patients in whom treatment failure could be assessed was 262 in the zinc group and 263 in the placebo group. [5]Absolute risk reduction was 3.5% (95%CI: -22%, 9.1%) [6]RR; 95% CI in parentheses.

supplemented with zinc compare with those given placebo. Additionally, a randomized controlled trial reported that zinc supplementation did not benefit preschool-aged children with acute, uncomplicated *P. falciparum* malaria [77]. Further, a randomized controlled trial in over 42,000 children aged one to 48 months found that zinc supplementation did not significantly reduce mortality associated with malaria and other infections [78].

2.4 Common Cold

In a trial in which zinc acetate lozenges was examined on cold symptoms, it was discovered that zinc acetate lozenges had no different effect from placebo on reducing the duration or severity of cold symptoms [17]. Three intranasal zinc gluconate placebo-controlled studies found intranasal zinc to be of no benefit to the reduction of the duration of cold symptoms [79,80]. In the most rigorously controlled of these studies, intranasal zinc gluconate did not affect the severity or duration of cold symptoms in volunteers inoculated with rhinovirus, a common cause of cold [79].

2.5 Pregnancy Complication

It was found in Peruvian and Bangladeshi women in a two-placebo controlled studies that zinc supplementation did not affect the incidence of low birth weight or premature delivery [81, 82]. There was also a contradiction in supplementation studies designed to examine the effect of zinc supplementation on labor and delivery complications, though few have been conducted in zinc-deficient populations [19].

2.6 Age-related Macular Degeneration

A randomized-controlled trial found that supplementation with 200 mg/day of zinc sulfate (81 mg/day of elemental zinc) over two years had no beneficial effect in patients with a more advanced form of AMD in one eye [83]. Also a five-year trial of Age-related eye degeneration study (AREDS) recently found that lowering the dose of zinc (25 mg vs. 80 mg) in the formulation containing antioxidants (500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta carotene) and high-dose zinc (80 mg of zinc and 2 mg of copper), had no effect on AMD progression [84]. Data from smaller trials have generally not observed a protective effect of vitamin and mineral supplementation on AMD [53,85].

2.7 Delayed Neurological and Behavioral Development in Young Children

A 2012 Cochrane review of 13 clinical trials of zinc supplementation in infants and children found no evidence that zinc supplementation improves mental or motor development [20]. Two other studies failed to find an association between zinc supplementation and measures of attention in children diagnosed with growth retardation [59].

3. CONCLUSION

Zinc plays important roles in human health. Researchers have shown that Zinc supplementations have, among others, such important health benefits as; improving immune system functions, reducing the duration and severity of diarrhea in children, and of common cold, reducing the incidence of pneumonia and of HIV/AIDS infections and may reducing the incidence of clinical attacks of malaria in children and improving the outcomes of pregnancy. But the lack of a sensitive and specific indicator of marginal zinc deficiency has made its studies relating to human health confounding. By and large, with evolving zinc research, there is no gainsaying that humans would achieve robust long life expectancy via reducing child and maternal morbidity and mortality attributable to under-nutrition, and at large to infectious diseases in human population.

4. RECOMMENDATION

The importance of zinc to human health is numerous and for these to be properly harnessed, the following are highly recommended;

1. A sensitive and specific biomarker should be holistically designed for zinc to help detecting marginal zinc deficiency in humans as this will streamline its health-related issues.
2. More and well-designed randomized controlled trials of zinc supplementation should be conducted to determining optimum dosage, formulation and duration of treatment for a health specific condition.
3. Zinc should come primarily and daily from good and absorbable sources of food that will help to preventing zinc deficiency.
4. Zinc supplement should not be taken alongside phytate-containing foods to avoid

zinc mal-absorption. For example whole-grain products and plant proteins that are relatively high in phytate.

5. Zinc supplement should be taken under medical advice to avoid interactions with some medications and to avoid taking much beyond the daily recommended amount that can result in copper deficiency.

CONCENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

COMPETING INTERESTS

Author has declared that no competing interests exist.

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