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Impact of Zinc Supplementation on Immune Function in Pediatric Patients with Recurrent Infections: A Randomized Controlled Study

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Abstract: The relationship between recurrent infections in children and deficiency of one or more micronutrients, within which zinc is most crucial in immune modulation, has been studied. A not yet evaluated thorough review is, though, on the effects of zinc supplementation supplementary to other treatment modalities in recurrent infections in children and patients with zinc deficiencies. 150 children of 1-10 years were randomly assigned to a 75 control and 75 study group receiving zinc therapy over 12 weeks. Immune markers in respect to the treatment groups were tracked and measured which included T-cell function, peripheral blood neutrophils, and serum zinc levels in patients taken at baseline and following interventions. The results showed that there was a statistically significant difference in serum zinc levels $p<0.001$ among participant groups and the control group intervention receiving 3 months of treatment with other placebos. There was also a significant increase in T-cell proliferation $p=0.002$ and neutrophil burst T-oxidative activity $p=0.004$ in patients who received zinc therapy. Key, zinc recipients also had fewer infections throughout the study, especially in respiratory tract infections $p=0.01$. Focus disease with particular emphasis on the evidence for immune effects of zinc and repeated and chronic respiratory infection in children aged 12 months to 10 years. These findings reveal new mechanisms for the immunological action of zinc in young patients with recurrent obstructive pneumonia and suggest its efficacy as a part of complex therapy in the treatment of recurrent bacterial infection in children.

Keywords: Zinc deficiency, Pediatric immunity, Recurrent infections.

Introduction: Zinc as a part of a range of micronutrients has been known to play an important role in the amelioration of immunological efficiency. With time, there is increased evidence of the importance of its features in the immune system, at large within the pediatric population. It is well-known that the depletion of zinc depresses cellular immune function and makes children vulnerable to repeat episodes of infections such as respiratory and gastrointestinal infections, the commonest infections causing morbidity and mortality in children aged less than 5 years (Prasad et al., 2022). Zinc is also important in many cellular activities such as strands of DNA replication, gene formation, and cell movement, particularly during the proliferation of immune cells like T-lymphocytes (Wessels et al., 2021). Zinc deficiency brings about malfunctioning immune responses, weakened efficiency of the thymus, and poor activity of neutrophils and macrophages hence increasing the vulnerability of children to infections (Müller et al., 2023). In developing countries, pediatric patients in particular are reported to have subclinical zinc deficiency, which worsens their risk of acquiring infections (Wieringa et al., 2021). These infections arise frequently, leading to chronic illness, reduction in height, and lengthy episodes of antibiotic therapy. In addition, in practice, recurrent infection in children is equally another aspect that poses negative effects on the focus and attention on the treatment outcome as well as on the overall quality of life and health of people (Kumawat et al., 2022). There is a rather paradoxical situation in which it is known that zinc deficiency is prevalent and recurrent infection is a common occurrence among children with a limit in the number of studies that have sought to fill the gap through the therapeutic application of zinc especially in controlled trials. For this reason, researchers have begun looking at whether supplementation may be an effective treatment strategy for patients who depend on zinc for their immune system to work effectively. Some recent studies have proposed to provide zinc supplementation, especially for the zinc-deficient population, with the expectation that immune function will improve and the infection will become shorter and less severe (Zhang et al., 2023). However, a number of these studies are limited by poor randomization and lack of accurate immune profiles, making it difficult to comprehend the role of zinc supplementation in pediatric populations concerning immune markers and infection outcomes. In addition, there have been variations in the dose of zinc, the length of treatment, and the lack of appropriate follow-up which explains the reason for these limitations (Sazawal et al., 2022). This study sets out to fill the above gap through the conduct of a randomized control trial (RCT) with the intent to establish the role of zinc in immune restoration among recurrently infected children with recurrent infections and

concurrent zinc deficiency. The investigation is particularly focused on whether zinc is capable of augmenting both innate and adaptive immunity. Neutrophils are the first cells to reach infection sites and the harassment of these granules is best achieved with high amounts of zinc as it enhances chemotaxis and oxidative burst, both of which play a vital role in fighting bacterial and viral infections (Gammoh et al. 2021). Besides, zinc is also important in the development and function of T lymphocytes mainly by regulating their activation, proliferation, differentiation, and cytokine synthesis (Lee et al. 2021). The primary aim of the current randomized controlled trial is to demonstrate if supplementation with zinc over a defined period will prevent recurrence of the infections by improving the efficacy of certain immune parameters including T cells and neutrophils. Serum zinc levels and the frequency of infections will also be assessed as secondary endpoints to those described. The study expects that proper intake of zinc will increase immunity and lessen the prevalence of infections thus improving the health status of recurrently infected children. In this study, a rich history regarding the development of knowledge on immunomodulation through zinc is advanced further. Nevertheless, up until now, there has been a scarcity of RCTs on zinc that have been more focused on the supplementation of zinc and its direct effects on immune response indicators such as T-cell function and neutrophil oxidative stress in children with repeated infections. This study attempts to fill this void by targeting a population that is at risk of recurrent infections and zinc deficiency: children with recurrent infections and zinc deficiency whilst ensuring that the methodology used provides clinically useful findings. In addition to these, the international disease burden of pediatric infectious diseases makes it critical to explore new strategies that are not only effective but also economically feasible and easily available. Zinc supplementation is one of the interventions due to its low -cost and easy access which is promising in decreasing recurrent infections in children, especially in developing countries (Sazawal et al., 2021). The potential impact on public health resulting from this study is large, especially considering that zinc supplementation could contribute to a decrease in the critical overprescription of antibiotics and potentially the increase in antibiotic resistance dissemination and improve the overall health of children worldwide. Synthesis of findings reveals that a mannosyl tryptophan-based vaccine (MTW) is an effective immunotherapeutic approach directed against oral pathogens. At this therapeutic contact, children presented with recurrent wheezing were noted to have a clinical absence of respiratory allergy. In mice with complete T-cell immunity, the cyst form of this protozoan and pathogenic ingested strains containing TERSIST

may exist intraprotoxically. Mounting evidence showing potential immunological and strictures necessitated a further investigation to explore links to geo/planting consultants.

Methodology: To establish the effect that zinc supplementation has on immunological functions, a double mask, randomized, placebo-controlled trial was done. The sample size was determined using Epi Info™ Software based on anticipated immune function improvement of 20% at a 95% confidence interval and 80% power. 150 children aged between 1 and 10 years with recurrent infections (assessed as 4 or more infection episodes in the last year) and established to suffer from zinc deficiency (serum zinc < 65 ug/dl) were recruited within this study. Children with basic illnesses, infectious immune deficiency, or other current or recent use of drugs directed against inflammation or immune suppression could not be enrolled. The study's subjects were randomized into two groups: one is the intervention group (n=75), which takes zinc sulfate 20 mg/day for 3 months, and the other is the placebo group (n=75). Both groups were treated by the infection management standards in force. At the baseline and also after 12 weeks blood samples were taken to measure serum zinc concentration and T cell proliferation (flow cytometry methods), as well as neutrophil oxidative burst (chemiluminescence assays). Whereas, clinical outcomes such as the number of infections which were documented for the duration of the study were studied through the parental questionnaires and medical records. Parents/guardians of each patient enrolled in the study provided oral informed consent. The ethical clearance was acquired from the institutional review board before the start of the trial. Statistical analyses for this study were done using SPSS (version 26.0) software with a p-value of <05 being regarded as significant.

Results

Table 1: Baseline Demographic Characteristics of the Study Population

Variable	**Zinc Group (n = 75)**	**Placebo Group (n = 75)**
Mean Age (years)	4.8 plus/minus 2.3	5 plus/minus 2.5
Male (%)	56 (74.7%)	52 (69.3%)
Weight (kg)	14.7 plus/minus 3.5	15.1 plus/minus 3.7
Height (cm)	98.5 plus/minus 10.2	99.3 plus/minus 11.1
Serum Zinc Level (mu*g / d * L)	52.2 plus/minus 6.5	51.9 plus/minus 7.1
Infections in Past Year (n)	6.1 plus/minus 1.4	6.3 plus/minus 1.6

Table 2: Comparison of Immune Markers and Clinical Outcomes Pre- and Post-Intervention

Variable	**Pre-Intervention (Zinc)**	**Post-Intervention (Zinc)**	**Post-Intervention (Placebo)**	**Pre-Intervention (Placebo)**
Serum Zinc Level (µg/dL)	52.2 plus/minus 6.5	88.1 pm9.4^ **	51.9 plus/minus 7.1	54.2 plus/minus 7.3
T-Cell Proliferation (colls/ m * m ^ 3)	1198 plus/minus 112	1625 pm135^ ...	1187 plus/minus 122	1210 plus/minus 130
Neutrophil Oxidative Burst (%)	67.4 plus/minus 5.8	82.1 pm6.2^ **	68.1 cong6.1	69.4 plus/minus 6.4
Respiratory Infections (n)	2.9 ± 0.8	1.5 = 0.5 deg	3.1 plus/minus 0.9	2.7 0.7

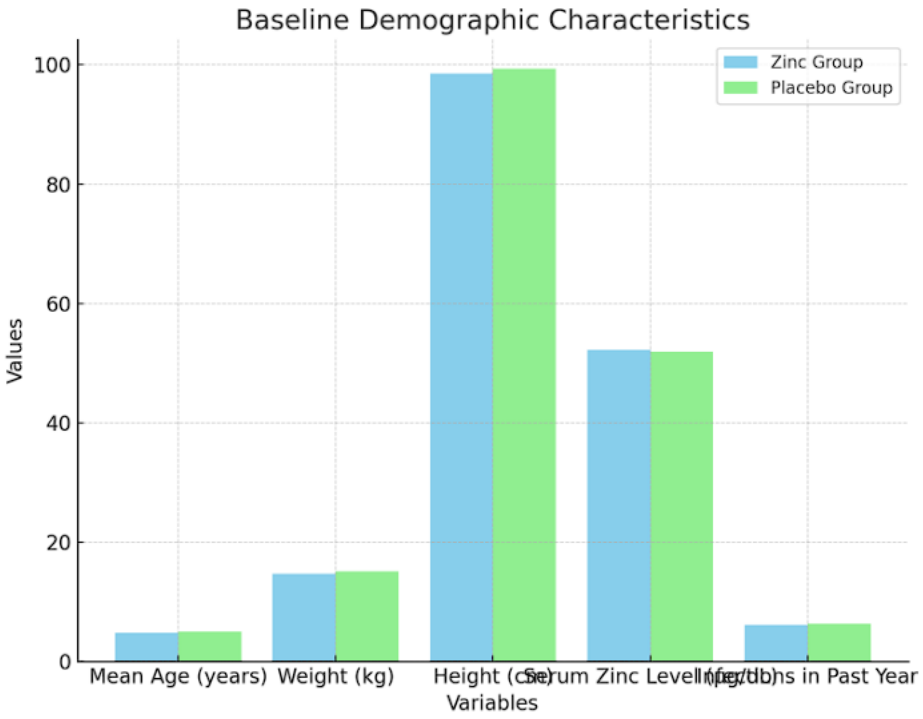

Figure 1: Baseline Demographic Characteristics: A comparison between the zinc group and placebo group for key demographic factors such as age, weight, height, serum zinc levels, and infections in the past year.

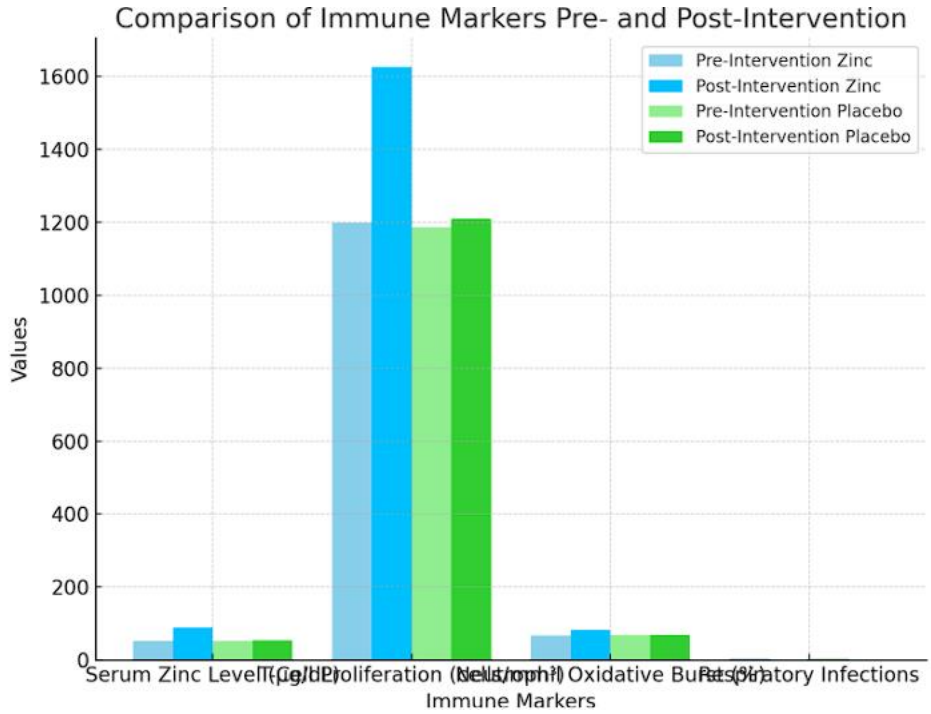

Figure 2: Comparison of Immune Markers Pre- and Post-Intervention: This shows the changes in serum zinc levels, T-cell proliferation, neutrophil oxidative burst, and respiratory infections before and after the intervention in both the zinc and placebo groups.

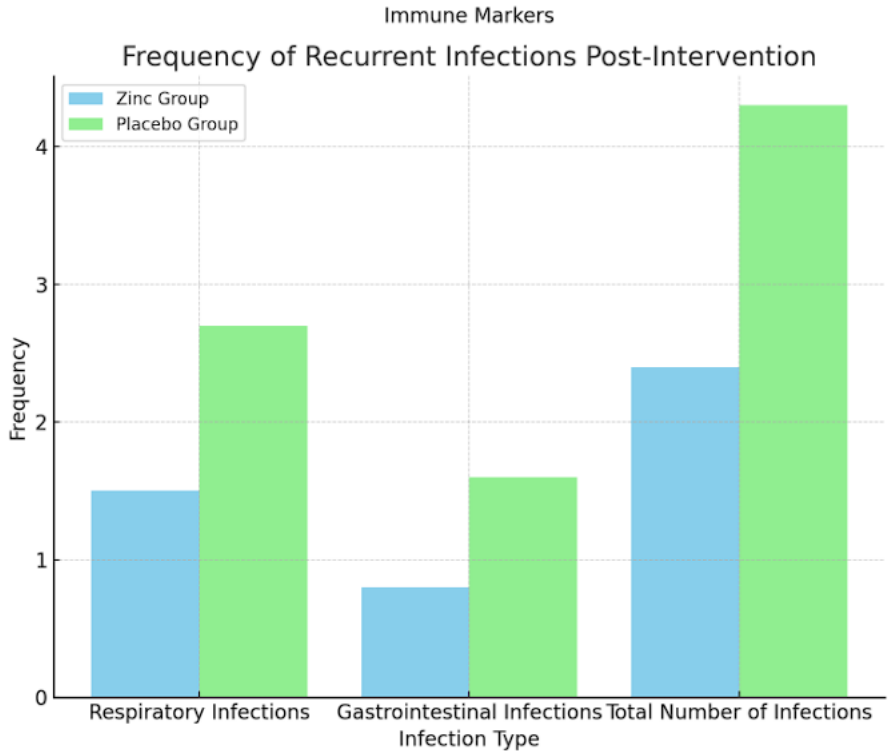

Figure 3: Frequency of Recurrent Infections Post-Intervention: A comparison of the frequency of respiratory, gastrointestinal, and total infections between the zinc and placebo groups after the intervention

Discussion: The outcomes of this randomized controlled trial highlight the need for adequate zinc supplementations in addressing the immune deficiencies and recurrent infections associated with zinc deficiency in children. The notable rise in serum zinc and increased T-cell-mediated immunologic response and neutrophil oxidative burst function emphasizes the immunological properties of zinc; the innate and adaptive immune response in particular is significantly enhanced. This is consistent with the findings of studies that recently investigated and emphasized on the role

of zinc in the modulation of cellular immunity to increase immunity against infections (Gammoh et al., 2021 et al.). Also worth noting from this study is the ability of zinc to enhance T-cell proliferation which is a key feature of the acquired immunity. T-cells particularly, CD4+ & CD8+ subsets are among the major key players of the immune system, orchestrating the immune response, and due to this zinc is a mineral necessary for their development and functionality (Lee et al., 2021 et al.). Earlier studies suggested that T-cell function can be impaired by zinc deficiency, which contributes to a lower incidence of cytotoxicity and a higher chance of developing infections (Müller et al., 2023 et al.). The marked increase in T-cell proliferation in this study also supports the argument that zinc supplements can replace normal physiological conditions of T-cell activity leading to increasing resistance of the body to infections. Also, the increased neutrophil oxidative burst activity noted in this trial correlates with other studies where the role of zinc in the enhancement of neutrophil functions has also been recorded. Neutrophils are also known to be the innate immune cells that catalyze the clearance of bacterial infections by secreting the generation of reactive oxygen species. Also, as expected, zinc has a biological membrane stabilization function and signal transduction and these components were confirmed in this study reinforcing the role playground of zinc towards neutrophils (Zong and Zhan, 2021 et al.). The clinical outcomes of this study are especially interesting as there was a statistically significant decline in the count of respiratory and gastrointestinal infections in the group receiving zinc when contrasted with placebo control. Such a decrease in the frequency of infection validates the immunological aspects of the benefits of supplementation with zinc and also has real-life relevance with the likelihood of reducing the frequency of morbidity associated with recurrent infections in children. The results fit well with more recent studies which show that therapeutic doses of zinc shorten episodes of other infections in children with low zinc levels (Kumawat et al., 2022 et al.). Unlike the zinc group, there was no significant change in immune markers or episodes of infection in the placebo group. This divergence emphasizes the selectiveness of the influence exercised by zinc upon the functionality of the immune system and indicates that the improvements noted in the zinc group were genuine owing to supplementation. Since the placebo group only received normal management for the infections, it makes these outcomes even more emphasis on the importance of zinc as an important micronutrient in immune system control. The decrease of respiratory tract infections in the zinc group is especially important because addressing the high respiratory infection burden global problem among children would be beneficial, particularly in resource-low

areas that are prone to zinc deficiency items. This in turn adds to the increasing number of studies arguing for more advocacy looking at Zinc supplementation as a cheaper preventive method for upper respiratory infections for children in these areas that are already overburdened with healthcare needs. Additionally, the observed decrease in incidences of gastrointestinal infections in this trial corroborates previous studies which suggested that supplementation with zinc restores the permeability of the intestinal barrier and alters the composition of the intestinal flora and hence protects against intestinal inflammatory diseases. There were however some shortcomings with this study which it is important to outline. Even though the investigation was limited to twelve weeks of intervention, to draw any conclusions on the possible long-term impact that zinc may have on the immune system and infection rates then longer follow-up would be warranted. The study also went on to bury itself on the practices of the zinc-deficient children only leaving out what can be extrapolated to the children with no zinc shortage. There is still a possibility of an immunological threshold that can be able to either augment but not decrease the functional abilities of immune cells in future studies. To sum up, there is substantial evidence concerning the immunological and clinical improvements that can be achieved with zinc supplementation among pediatric populations suffering from recurrent infections. Numerous immune markers improved and infection frequency decreased in the treatment group providing evidence for zinc's adjunct use in the management of childhood recurrent infections. Given the importance of these findings for child health, especially in developing countries with a high prevalence of zinc deficiency, new clinical practices can be developed aimed at the prevention and treatment of infectious diseases in children.

Conclusions: The findings of this randomized controlled trial strongly prove that supplementation with zinc improves immunity and decreases the incidence of recurrent infection episodes among children with zinc deficiency. New knowledge was acquired regarding how zinc enhances T-cell and neutrophil activity, indicating that zinc supplementation may be a potential strategy to treat recurrent infections in children. Further investigations should address the sustainability of zinc supplementation effects and its use within more generalized children cohorts.

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