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Original Article

# Zinc and selenium in critically ill children: where do they stand?

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## Abstract

The purpose of the present article is to highlight the important role zinc and selenium play in various critical illnesses in children. There is also need to study various benefits and rationale for supplementation with these trace elements as a potential pharmacotherapeutic strategy in critically ill children and stimulating further research in this field. Normal homeostasis of zinc and selenium is required for proper functioning of immune system, adequate antioxidant activity, glucose homeostasis, and wound healing. In addition, zinc acts as a cofactor for many enzymes, transcription factors, and replication factors. In critically ill children, zinc and selenium levels are found to be low and few studies suggested that supplementation with zinc may be associated with clinical improvement in this group of patients. However, the evidence to recommend the routine use of zinc and selenium supplementation in the critically ill children is inadequate. Further studies are needed to uncover the exact mechanisms for low levels of zinc and selenium; therapeutic role of zinc and selenium supplementation; and optimal dose that has a maximal beneficial clinical effect on underlying inflammatory, immunologic, and various metabolic processes in critically ill children.

**Keywords:** Zinc, selenium, trace elements, critical care, children

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## Introduction

Over the last few years, there has been increase in our understanding of pathophysiology of various critical illnesses in children. The fact that oxidative stress is central to the pathophysiology of critical illness is now well established. In critically ill, low endogenous stores of antioxidants are associated with an increase in free radical generation, augmentation of the systemic inflammatory response, cell injury, and increased morbidity as well as mortality [1]. Therefore, augmentation of endogenous antioxidant defense system can improve the outcome. One of the important emerging treatment strategies under evaluation is antioxidant

supplementation in critically ill children. Trace elements especially zinc and selenium is cornerstone of the antioxidant defense in acute systemic inflammation response syndrome [SIRS]. SIRS is known to be associated with redistribution of zinc and selenium to tissues involved in protein synthesis and immune cell proliferation [2] and this leads to decrease in their serum levels.

Acquired critical illness stress-induced immune suppression [CRISIS] plays an important role in the development of nosocomial infection and sepsis [3]. CRISIS has been shown to be associated with deficiencies in zinc, selenium [4, 5], amino acids [6] and hypoprolactinemia [7]. Immune dysfunction induced by CRISIS increases the likelihood of acquiring nosocomial infections. Several studies have therefore, explored the role of supplementation of trace elements in critically ill as a strategy to prevent acquired immune suppression and nosocomial infections.

However, the exact role of zinc and selenium in critically ill children, mechanisms leading to decrease in serum concentration during critical illnesses, beneficial or harmful effects of these, and effects of supplementation of zinc and selenium in critically ill children are yet to be elucidated. In the following sections, we review the current knowledge regarding epidemiology of zinc and selenium deficiency and its clinical implications, potential role of these elements, and discuss the role of zinc and selenium supplementation in critically ill children. The data was collected from publications in English language till October 2013 using keywords zinc, selenium, and critically ill children. The full articles of the selected abstracts were reviewed by the reviewers.

**Zinc in critically ill children:**

It was estimated that approximately 10% of the U.S. population has a diet that results in some degree of zinc deficiency, whereas zinc deficiency has been responsible for up to 4.4% of deaths attributable to infection in developing countries [8]. Various studies from India demonstrated that prevalence of zinc deficiency in apparently healthy children and adolescents ranged from 44%-72% [9-11].

Zinc homeostasis is tightly controlled through regulation of intestinal absorption and excretion as well as through regulation of renal excretion [12]. In the cellular level, zinc influx and efflux are regulated by 2 families of ubiquitous transporter genes, the ZincT and the Zip proteins [13].

Zinc is an essential trace element, which plays an important role in many important biological functions. These include mucosal barrier function, innate and adaptive immunity, oxidative stress responses, neuro-cognitive function, glucose homeostasis, wound healing, and as cofactor for various enzymes [4, 12, 14-17]. In the brain, zinc is involved in control of apoptosis and also acts as an important neuromodulator [18]. Intracellular zinc is used for variety of function: in liver for synthesis of acute phase proteins [19] and in the pancreas for insulin metabolism [20]. [Figure 1].

Zinc deficiency causes a loss of T- and B-cell maturation, which leads to lymphopenia and impaired natural killer [NK] cell and function of phagocytes [4, 16, 21]. Zinc deficiency also results in altered secretion of a number of cytokines including interferon-γ, tumor necrosis factor-α, and interleukin-2 [22].

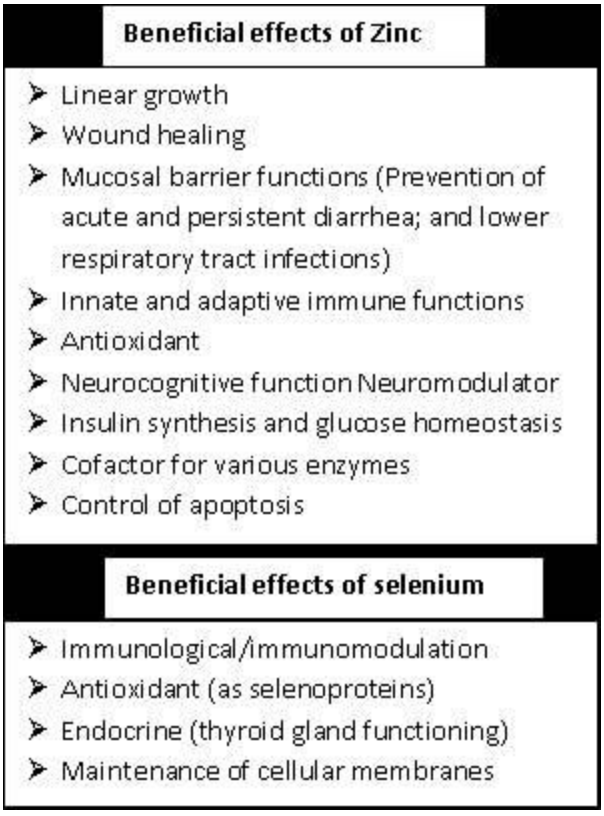

Figure 1: Showing beneficial effects of zinc and selenium in the human body.

The lymphopenia described in zinc deficiency is thought to be a result of markedly increased apoptosis of pre-B-cells and pre-T-cells as these cells are more susceptible to programmed cell death because they express low levels of the antiapoptotic proto-oncogene Bcl-2, in contrast to mature B- and T-cells [23]. The exact mechanism by which zinc deficiency stimulates lymphocyte apoptosis is unclear. Zinc deficiency may directly induce apoptosis via DNA fragmentation, caspase activation, and cleavage of the cell-cycle regulator p21 [24]. Zinc deficiency also known to cause activation of the hypothalamic–adrenal–pituitary axis and increased production of glucocorticoids, which in turn stimulates apoptosis of lymphocytes [4]. The resultant marked reduction in number of pre–B and pre–T-cells leads to the immunoparalysis that has been recognized as a feature of sepsis and an indicator of poor prognosis in critically ill patients [16]. In nutshell, zinc is required for proper functioning of immune system and its deficiency affects several immunologic cells and soluble mediators of immunity, leading to susceptibility to infections.

Infections and Inflammation are known to be associated with reduced plasma levels of zinc. A study demonstrated that when healthy volunteers were subjected to endotoxin [lipopolysaccharide], there was increase in interleukin-6 and tumor necrosis factor-α levels and a concomitant decrease in plasma zinc levels [25]. In children with acute *falciparum* malaria, baseline plasma zinc levels were very low and correlated inversely with serum C-reactive protein and degree of parasitemia [26]. Patients with burns and children undergoing bone marrow transplantation have been shown to have significantly depressed plasma zinc levels [27, 28]. Linko *et al* [29] detected low serum zinc in 95.8% critically ill adult patients with acute respiratory failure. Cvijanovich *et al* [30] estimated plasma zinc and copper levels, metallothionein [MT] isoform expression, and cytokine levels on day 1 and day 3 of illness in 20 critically ill children. All patients had low zinc levels on day 1 of PICU admission, and remained low on day 3. Bhatnagar *et al* [31] found that serum zinc concentration was low in 44% of infants with probable serious bacterial infection. In pediatric CRISIS prevention trial, zinc deficiency was present in 84% [235/280] patients at baseline [32, 33].

The exact mechanisms by which plasma zinc decreases in acute illness and inflammation as well as whether low zinc levels are beneficial or detrimental are not

yet clear. In acute illness, zinc is redistributed from the serum to other tissues, particularly the liver, where zinc is required for synthesis of acute phase proteins [19]. Liuzzi *et al* [19] demonstrated that induction of interleukin-6 as a result of the release of interleukin-1 may be responsible for hypozincemia in the acute-phase response. They also found that after turpentine and lipopolysaccharide administration, Zip14, a zinc transporter found in the liver, was significantly up-regulated and this led to increase in cytoplasmic zinc concentrations. Therefore, low plasma levels of zinc may reflect zinc redistribution during inflammation rather than a true nutrition deficiency [19]. In addition, losses though biological fluids, renal replacement therapy, hemodilution, and underlying malnutrition may also contribute to zinc deficiency in critically ill patients [34].

The low serum zinc in critically ill patients and its supplementation is surrounded by controversies similar to replacement of iron in critically ill patients. Weinberg [35] proposed that reduction of plasma zinc levels in inflammation could be a protective function in a manner similar to infection-induced hypoferremia and this phenomenon has been termed as 'nutritional immunity'. Most microorganisms require zinc for maintenance of their cell function. It has been proposed that the decrease in plasma zinc levels induced by the acute phase response could be protective by limiting zinc availability to bacteria and limiting the cytokine response during inflammation [19]. High concentrations of zinc *in vitro* shown to inhibit macrophage activation, mobility, phagocytosis, and oxygen consumption [36]. Another *In vitro* study has shown that zinc can bind to bacterial pili and augment bacterial adherence [37]. It has been suggested that the internal redistribution of zinc from plasma to liver, bone marrow, and thymus serves as an adaptive response to protect against the invading pathogens [38]. Calprotectin [a zinc binding protein produced by neutrophil] works in synergy with decreased extracellular zinc levels to augment antimicrobial activity [39]. All these effects are beneficial to the host and detrimental to the inflammatory cascade triggered by infection and inflammation. So, the cautions need to be applied when hypothesizing about the benefits of providing additional zinc to correct low plasma zinc concentrations in these patients.

In contrast to above findings, few studies have shown that low serum zinc level is associated with poor outcome. Linko *et al* [29] shown an association between low baseline serum zinc and admission organ failure score [SOFA at 24 h] and total organ failures during the intensive care stay in critically ill adult patients with acute respiratory failure. Cvijanovich *et al* [30] concluded that plasma zinc concentrations were low in critically ill children and it was correlated with measures of inflammation [C-reactive protein and interleukin-6] and degree of organ failure on day 3. In a study involving 20 critically ill children presenting with a wide range of diagnoses, low plasma zinc levels were correlated with degree of organ failure [30]. Wong *et al* [40] studied 42 pediatric septic shock patients and shown that low serum zinc levels were associated with organ failures and worse outcome. In a recent study of genomic responses of children with systemic inflammatory response syndrome/sepsis, decreased plasma zinc levels were

associated with non-survival in the setting of septic shock [40].

Since low zinc levels are shown to be associated with poor outcome in critically ill, few studies have examined the effects of zinc supplementation in this group of patients. In critically ill adult patients, a randomized trial found that zinc supplementation was associated with a nonsignificant reduction in mortality and length of stay in intensive care [16]. In clinical trials involving children with acute gastroenteritis in developing countries, both duration and severity of diarrhea were significantly decreased by oral zinc supplementation [41]. Other studies have also demonstrated that oral zinc supplementation during an episode of childhood diarrhea reduces the duration and severity of illness [42-44]. Bhatnagar *et al* [31] concluded that zinc supplementation as adjunctive treatment in infant aged 7-120 days with serious bacterial infection reduced the risk of treatment failure by 40%. Brooks *et al* [45] shown that weekly zinc supplementation significantly reduced the episodes of pneumonia and diarrhea, as well as significantly lowered the risk of mortality in children lower than 2 years in a developing nation. It has been shown that zinc supplementation in children with severe pneumonia hastened their recovery [46]. In a randomized double blind placebo-controlled trial, Srinivasan *et al* [47] found that zinc supplementation in children with severe pneumonia significantly decreased case fatality rate, though no significant effect on time to normalization of the respiratory rate, temperature and oxygen saturation was noted. Basnet *et al* [48] in a randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children [2-35 months] concluded that there was only marginal reduction in time to cessation of severe pneumonia and the risk of treatment failure in hospitalized children. The pediatric CRISIS prevention trial [32] was designed to determine if daily enteral supplementation with zinc, selenium, glutamine, and parenteral metoclopramide prolongs the time until onset of nosocomial infection or sepsis in critically ill children; it was found that these agents didn't confer any advantage in immune-competent population. Some of these studies support the hypothesis that low plasma zinc that is associated with critical illness may be detrimental to the patient and the restoration of adequate zinc may have beneficial effects, though conclusive evidence is lacking.

Reference values for adequate serum zinc concentration have been developed based on the distribution of serum zinc values in presumably healthy, zinc-replete individuals in the USA and it is showed that they differs by age group, fasting status, time of day, and presence of illness [49]. The suggested lower cut-offs for serum zinc concentrations in young children are 9.9 μmol/l [65 μg/dl], if studied in the morning while non-fasting, and 8.7 μmol/l [57 μg/dl], if studied in the afternoon. The mean plasma zinc concentration in adult humans is approximately 100 μg/dL and constitutes <0.2% of total body zinc content [50]. Zinc is distributed throughout the body; in plasma it is primarily protein bound, but the primary functions of zinc are carried out at the intracellular level [30]. Hence, plasma zinc may not be a sensitive predictor of zinc status. Indeed, plasma zinc concentration as a clinical parameter to estimate total body zinc status has been widely criticized [51].

To summarize, caution should be exercised in interpreting the results of low

plasma zinc in critically ill patients, because it may be a metabolic response to sepsis. Few studies offer provocative data suggesting that zinc supplementation may play an important role in correcting the pathophysiological derangements observed in severe sepsis. Low zinc levels are consistently documented in both adult and critically ill children, but the evidence as to whether supplementation with zinc should become a key therapeutic strategy in the critically ill children is not consistently supported. Further studies evaluating the role of zinc in treatment of critically ill children are warranted.

**Selenium in critically ill children:**

Selenium is a trace element involved in many immunologic, endocrine and antioxidant pathways. Selenium is important for maintenance of cellular membrane integrity [17, 52]. [Figure 1] In healthy individuals, 40–70% of the total plasma selenium occurs as selenoprotein P, 20-40% as Glutathione peroxidase, 6–10% as albumin-bound and free selenium less than 1% [53]. Selenium deficiency has been identified in China, Tibet, New Zealand and the Russia [17], whereas, from India there are only few studies in this field [54, 55]. So, the exact prevalence of selenium deficiency may be difficult to estimate from Indian subcontinent.

Several studies have demonstrated reduced plasma selenium concentrations in critically ill adult patients and its inverse correlation with mortality [56-58]. In 134 consecutive ICU patients, Forceville *et al* [56] observed low plasma selenium concentrations in ICU patients at admission, especially those with septic shock and low levels persisted for more than 2 weeks despite selenium supplementation and correlated inversely with illness severity. In addition, the frequency of ventilator-associated pneumonia, rate of organ system failure, and mortality rate were 3 times higher in patients with low plasma selenium concentration than in patients with higher selenium concentrations. More recently, Sakr *et al* [57] reported that 92% of 60 consecutive surgical ICU patients had low plasma selenium concentrations and minimum plasma selenium concentration was inversely correlated to admission APACHE II and SAPS II scores, parameters of inflammation, and the maximal degree of organ dysfunction/failure during the ICU stay. In addition, minimum selenium level was an independent predictive factor for mortality. Dylewski *et al* [59] assessed the longitudinal selenium status in 20 pediatric patients with burns exceeding 10% of their total body surface and these were followed for first 8 weeks of admission or until 95% wound closure was achieved. Plasma selenium was low throughout the study period despite adequate dietary selenium intake and plasma selenium was inversely related to incidence of total infection [59]. Manzanares *et al* [60] concluded that selenium and glutathione peroxidase levels significantly decreased early in SIRS and MODS and they had a predictive value for SIRS. In addition, selenium has good predictive value for ICU mortality whereas glutathione peroxidase doesnot. In pediatric CRISIS prevention trial [32, 33], it was found that selenium deficiency was seen in 56% [156/278] patients.

In a meta-analysis involving critically ill adult patients, it was found that trials using more than 500 µg per day of selenium showed a trend towards a lower mortality whereas trials using doses lower than 500 µg had no effect on mortality [61]. Forceville *et al* [62] concluded that continuous infusion of selenium as sodium selenite [4,000 µgm

on the 1st day followed by 1,000 µgm/day for next 9 days] did not improve the clinical outcome in septic shock patients. In a randomized trial in critically ill adults, supplementation with glutamine, selenium, or both in parenteral nutrition showed no difference in the occurrence of new infections and mortality, except for those who had received ≥5 days of supplementation [63]. Six month mortality, length of stay, days of antibiotic use, and modified SOFA score were not significantly affected by selenium or glutamine supplementation. A meta-analysis included ten randomized trials involving 1172 critically ill adult patients concluded that there was limited evidence to recommend selenium supplementation of critically ill patients [64].

In summary, various studies have consistently demonstrated decreased plasma selenium concentration in critically ill patients, especially those with septic shock, and have suggested that persistent low concentrations may be associated with worse outcomes. These findings have encouraged several selenium supplementation trials, which however, didn't consistently or convincingly demonstrated improved outcomes.

**Conclusion:**

Though the serum concentrations of zinc and selenium are demonstrated to be low in critically ill children early after PICU admission, the basic pathophysiological mechanisms associated with critical illness that cause these changes and effect of these deficiencies need to be further studied. Given the important role that zinc plays in immunity, oxidative stress, glucose homeostasis, wound healing, functioning of many enzymes, transcription factors, and replication factors; the importance of zinc supplementation in critically ill patients has been recognized. Unfortunately, the evidences from randomized trials are too sparse to make conclusive recommendations about the role of zinc supplementation in critically ill children, and same is also true for selenium. Future research should confirm or refute the finding of positive effects in critically ill children by treating them with zinc and selenium.

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