

ORIGINAL COMMUNICATION

Zinc and immune function

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It is well recognized that zinc is an essential trace element, influencing growth and affecting the development and integrity of the immune system. Research has begun to clarify the molecular mechanisms underlying the action of zinc on the immune function. It is clear that this trace element has a broad impact on key immunity mediators, such as enzymes, thymic peptides and cytokines, explaining the paramount importance of zinc's status on the regulation of lymphoid cell activation, proliferation and apoptosis. Ongoing and future studies regarding the immunological status of zinc deficiency 'at risk' groups could lead to public health interventions with nutritional doses of zinc supplements to prevent alteration of the immune system and improve resistance to infections.

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Introduction

How nutritional factors influence the immune system's functions is now better known. The abnormal incidence of various infections and the existence of lymphopenia and lymphoid organ atrophy in malnourished children have been repeatedly demonstrated, and evidence points to zinc insufficiency as a link to this type of immunodeficiency. It is now widely recognized that zinc is one of the essential trace elements, and a member of one of the major micronutrient subgroups in human nutrition and health. Zinc is active in a variety of cellular functions, including signal transduction, transcription and replication (Vallee & Falchuk, 1993) and strongly influences the immune system affecting both non-specific and acquired immunity (Fraker *et al*, 2000). Progress has been recently made to better understand this ion's molecular principles of action and to provide new insights into the role of such a nutritional deficiency on the composition of the peripheral immune system and on haematopoiesis regulation.

Zinc deficiency

Experimental zinc deprivation

During the past decade, considerable knowledge has been accumulated concerning the role of Zn on cellular immunity (Bach, 1981; Shankar & Prasad, 1998). To better understand

the impact of a single nutritional deficiency on the immune system, and to identify the role of zinc on immune function and apoptosis, the impact of moderate and severe dietary deficiencies in zinc have been studied using the young adult mouse as the paradigm. In experimental animals, zinc deficiency results in atrophy of the lymphoid tissue. Studies in young adult Zn-deficient mice have shown greatly depressed responses to both T-lymphocyte-dependent and T-lymphocyte-independent antigens. Both primary and secondary antibody responses have been reported to decrease in Zn-deficient mice. A decline in *in vivo*-generated cytotoxic T-killer activity to allogenic tumour cells in Zn-deficient mice has been observed. Decreased NK cell activity and responses to cutaneous sensitization have been reported in Zn-deficient mice (Fernandes *et al*, 1979). All these effects of Zn deficiency on immune functions in mice can be reversed with Zn supplementation. Mice maintained on a Zn-deficient diet for as little as 2 weeks develop severe impairment of their ability to generate a cytotoxic response when challenged with tumour cells. Moreover, challenging zinc-deficient mice with sub-acute levels of infectious agents such as *Trypanosoma cruzi* or nematodes results in death due to an impaired defence system (Fraker *et al*, 1982). Therefore, these studies have been helpful to clarify how essential zinc is to the integrity of the immune system.

Zinc deficiency in humans

In humans, several abnormalities of cellular immunity have been observed. Acrodermatitis, a genetic disorder of Zn

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malabsorption, is characterized by mucocutaneous lesions, diarrhoea, failure to thrive, and frequent severe infections with fungi, viruses and bacteria. Affected subjects have thymic atrophy, anergy, a reduced lymphocyte proliferative response to mitogens, a selective decrease in T4⁺ helper cells, and deficient thymic hormone activity. All of these symptoms may be corrected with Zn supplementation.

Less severe cellular immune defects have been reported in patients who become Zn-deficient while receiving total parenteral nutrition. These abnormalities include lymphopenia, decreased ratio of helper and suppressor T lymphocytes, and decreased NK cell activity, whereas a defective natural killer (NK) function, and anergic delayed type hypersensitivity (DTH) responses have been observed in patients with sickle cell anaemia, presenting only a modest depletion of serum zinc (Kaplan *et al*, 1988).

Similar immunological abnormalities have also been observed in human experimental model subjects in whom mild Zn deficiency has been induced by dietary means. A mild zinc deficiency results in decreases in serum thymulin activity (corrected by *in vitro* and *in vivo* zinc supplementation), T naive cell recruitment, T cytolytic cell percentage and NK cell lytic activity (Prasad, 2000). In addition, in this experimental human model, the production of IL-2 and IFN- γ is decreased, whereas the production of IL-4, IL-6 and IL-10 is not affected. These studies show that even mild zinc deficiency in humans may be accompanied by an imbalance in Th1 cell and Th2 cell functions, resulting in an unregulated resistance to infection. In most studies regarding elderly subjects, plasma zinc has reported to be normal or slightly decreased (Kaplan *et al*, 1988). However, some authors point out deficient zinc levels in lymphocytes and granulocytes as compared to younger control subjects. Nevertheless, decreased IL-2 production, lymphopenia and reduced response to skin-test antigens have been observed in individuals with marginal zinc status.

Effect of foetal zinc deficiency

Gestational zinc deficiency in mice has short- and long-term deleterious effects on their offspring (Beach *et al*, 1982). Significant reductions are seen in lymphoid organ size and immunoglobulin concentrations in offspring from marginally zinc-deficient mice. Other murine studies have shown that several immunodeficiencies seen at birth persist into adulthood even when groups are fed a diet containing normal amounts of zinc after weaning. For instance, at 6 weeks of age, serum IgM concentrations are only 1% of normal values, whereas IgG2 and IgA concentrations are 40–60% of normal values. In addition, the PFC response to T-dependent and T-independent antigens may be significantly reduced.

In humans, intra-uterine growth retardation linked to maternal zinc deficiency, induces persistent cellular immune deficiency (Meadows *et al*, 1981). Altogether, these observations suggest that a moderate zinc deficiency occur-

ring during gestation may induce long-term deleterious consequences for the immune system, which is an important public health issue.

Effect of excessive zinc intake

Controversial results have been obtained regarding the effects of elevated zinc intake on the immune system. In experimental models, high-zinc diets have been shown to reinforce immune functions above basal levels such as: increased mitogenic responses, increased macrophages or T-lymphocyte functions; this outcome has been described in rats or mice. However, other studies on neonates have demonstrated the adverse effects of zinc excess (Shankar & Prasad, 1998). In humans, Chandra (1984) has reported a substantial impairment of lymphocyte proliferative responses and a reduction in chemotaxis and phagocytosis of circulating polymorphonuclear leukocytes in healthy adults who received a 10–20-fold excess of the daily recommended zinc requirement. Other studies suggest that very high intakes by children and adults can induce anaemia, growth retardation, copper deficiency and immunosuppression. Thus, excessive zinc supplementation in healthy people could have deleterious effects on the immune system, and caution must be exercised when taking large zinc supplements for prolonged periods of time.

Possible modes of action of zinc on the immune function

As briefly summarized above, zinc has a number of effects on the immune system's cells, both *in vivo* and *in vitro*. However, mechanisms underlying the relationship between zinc and immunity are still open to speculation. Several hypotheses can be made:

(1) Zinc is an essential factor for the activity of many enzymes—it is known to form part of more than 300 metalloenzymes which cannot function in its absence. Thus, zinc is essential to the function of DNA polymerase, thymidine kinase and DNA dependent RNA polymerase, whose involvement in nucleic acid synthesis could explain the effects of zinc on lymphoid-cell proliferation. Zinc also influences the activity of the transcriptional regulator family, known as zinc finger DNA binding proteins. In addition, zinc forms the active enzymatic sites of many metalloproteases (Frieke, 2000).

(2) Zinc is necessary for the activity of some immunity mediators. This has been clearly shown for thymulin, a nonapeptidic hormone (Glu-Ala-Lys-Ser-Gln-Gly-Gly-Ser-Asn) secreted by thymic epithelial cells, and requiring the presence of zinc for its biological activity. This peptide promotes T lymphocyte maturation, cytotoxicity, and IL-2 production. Zinc is bound to thymulin in a 1:1 stoichiometry via the side chains of asparagine and the hydroxyl groups of the two serines. Thymulin activity, *in vitro* and *in vivo*, in both animals and humans, is dependent on plasma zinc

concentrations so that marginal changes in zinc intake or availability affect thymulin activity (Dardenne *et al*, 1982). Thymulin is detectable in the serum of zinc-deficient patients, but is not active. The binding of zinc to the peptide results in a conformational change that produces the active form of thymulin. The use of thymulin as an indicator of zinc deficiency has been suggested and the assay of serum thymulin activity with or without zinc addition *in vitro* may be used as a sensitive criterion for diagnosing mild zinc deficiency in humans. Zinc could also be critical for some cytokine activity. For instance, it has been demonstrated that the production or the biological activity of IL-1, IL-2, IL-3, IL-4, IL-6, IFN- γ and TNF- α are affected by zinc deficiency. In addition, and as mentioned above, zinc deficiency in humans affects the cytokine production of TH1 cells leading to an imbalance between TH1 and TH2 cells (Prasad, 2000).

(3) Zinc could contribute to membrane stabilization, acting at the cytoskeletal level. An effect on membranes could explain the depression of phagocytosis, oxygen consumption and bactericidal activity induced by zinc in phagocytic cells and the modification of Con A surface receptor availability on lymphoid cells.

(4) Zinc is a major intracellular regulator of lymphocyte apoptosis *in vitro* and *in vivo*. Thus, it is becoming evident that the thymic atrophy and lymphopenia which accompany zinc deficiency are mainly due to an alteration in the production of lymphocytes, and the loss of precursor cells via an apoptotic mechanism (Fraker *et al*, 1993). In this regard, the increased production of glucocorticoids induced by suboptimal zinc status could play a significant role.

Impact of zinc and other trace element supplementation in the elderly

It is well known that aging is often associated with a decreased immune function, particularly the cell mediated response and substantial vulnerability to respiratory tract infections, associated with greater morbidity and mortality (Lesourd, 1997). Changes associated with aging may be in part the result of zinc deficiency, which induces comparable impairment of immune response (Table 1).

In this population, supplementation with different trace elements has been shown to improve the immune status, such as delayed type hypersensitivity, skin response, thymic function, proliferative responses to mitogens and antibody

Table 1 Common alterations of the immune system induced by zinc deficiency and aging

	Zinc deficiency	Elderly
Anergy	+	+
Thymic atrophy	+	+
Decreased thymic hormone levels	+	+
Depressed cell-mediated cytotoxicity	+	+
Decreased helper T cell activity	+	+
Diminished NK cell activity	+	+

response to vaccine, although in a few studies immunological responses have been found to be impaired with large quantities of nutrients. Studies using low-dose supplementation of zinc alone (Boukaiba *et al*, 1993) or zinc associated with selenium (Girodon *et al*, 1999) in elderly patients, provide a significant improvement in thymic function and antibody response, respectively, after vaccination. These results suggest that these nutrients play a beneficial role, and, more particularly, that zinc improves an elderly person's resistance to infections, thereby increasing his or her immunity.

Marginal zinc deficiency and suboptimal zinc status have been observed in several 'at risk' population groups, such as the elderly, in both developing and industrialized countries. Adequate zinc supplementation administered to vulnerable individuals could prevent the impairment of the immune system and substantially improve the host's resistance to infections in these populations.

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