Zinc: Mechanisms of Host Defense[1–3]

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Abstract

Zinc deficiency in humans decreases the activity of serum thymulin (a thymic hormone), which is required for maturation of T-helper cells. T-helper 1 (Th_1) cytokines are decreased but T-helper 2 (Th_2) cytokines are not affected by zinc deficiency in humans. This shift of Th_1 to Th_2 function results in cell-mediated immune dysfunction. Because IL-2 production (Th_1 cytokine) is decreased, this leads to decreased activities of natural-killer cell and T cytolytic cells, which are involved in killing viruses, bacteria, and tumor cells. In humans, zinc deficiency may decrease the generation of new CD4+ T cells from the thymus. In cell culture studies (HUT-78, a Th_0 human malignant lymphoblastoid cell line), as a result of zinc deficiency, nuclear factor-κB (NF-κB) activation, phosphorylation of IκB, and binding of NF-κB to DNA are decreased and this results in decreased Th_1 cytokine production. In another study, zinc supplementation to humans decreased the gene expression and production of pro-inflammatory cytokines and decreased oxidative stress markers. In HL-60 cells (a human pro-myelocytic leukemia cell line), zinc deficiency increased the levels of TNF-α, IL-1β, and IL-8 cytokines and mRNA. In these cells, zinc induced A20, a zinc finger protein that inhibited NF-κB activation via tumor necrosis factor receptor associated factor pathway, and this decreased gene expression of pro-inflammatory cytokines and oxidative stress markers. We conclude that zinc has an important role in cell-mediated immune functions and also functions as antiinflammatory and antioxidant agent. J. Nutr. 137: 1345–1349, 2007.

It has been known for many years that zinc deficiency in experimental animals results in atrophy of thymic and lymphoid tissue (1). Later studies in young adult zinc-deficient mice showed thymic atrophy, reductions in the absolute number of splenocytes, and depressed responses to both T-cell-dependent and T-cell-independent antigens (2–5). In response to sheep red blood cells, a T-cell-dependent antigen, the zinc-deficient mice produced only 40% as many IgM and IgG plaque-forming cells per spleen as did the zinc-adequate mice. Although the ratio of T and B cells was not changed, the deficient mice had nearly double the proportion of B cells bearing surface IgM in comparison to the control mice. It was suggested that immature B cells were accumulating in the spleens of zinc-deficient mice (3). Nash et al. (6) observed earlier that greater numbers of immature T cells were also present in zinc-deficient mice.

Both primary and secondary antibody responses have been reported to be depressed in zinc-deficient mice. An investigation into the influence of suboptimal zinc nutrition on the memory cells in mice also showed an impairment that was only partially corrected by zinc repletion (7). A decrease in in vivo-generated cytotoxic T-killer activity to allogeneic tumor cells in zinc-deficient mice was observed by Fernandes et al. (2) and Good and Fernandes (8). Frost et al. (9) reported impairment in cell-mediated response to non-H_2 allogeneic tumor cells in zinc-deficient mice. Animals maintained on a zinc-deficient diet for as little as 2 wk developed a severe impairment in their ability to generate a cytotoxic response to the tumor challenge. This phenomenon was reversed by zinc supplementation.

In this review, the effect of zinc deficiency on cell-mediated immunity in humans is presented and possible mechanisms of zinc action on T cell functions are discussed. The effect of zinc deficiency on production of cytokines in a suitable cell culture model is presented briefly. The role of zinc as an antiinflammatory agent and antioxidant is also reviewed.

Studies of immune functions in experimental human models

Although zinc deficiency in animals has been known to occur for many decades (10), zinc deficiency in humans was described only in the early 1960s (11,12). During our studies in the Middle East, we observed that most of the zinc-deficient dwarfs did not

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live beyond the age of 25 y. The cause of death appeared to be infections, although the exact nature of infective organisms was not known. Parasitic infections were common; however, viral and bacterial infections remained undocumented. The possibility that zinc deficiency may have played a role in immune dysfunctions in the zinc-deficient dwarfs was considered, but lack of proper facilities prevented us from gathering meaningful data on immune functions in the patients from the Middle East.

We developed an experimental human model that allowed us to study specific effects of mild zinc deficiency on immune functions (13–15). A semipurified diet based on texturized soy protein was prepared for consumption by human volunteers (males aged 20–45y). The subjects consumed a hospital diet containing animal protein daily for 4 wk. This diet averaged 12 mg zinc/d, consistent with the RDA. Subjects then received a semipurified soy-protein-based experimental diet that supplied 3.0–5.0 mg zinc/d. This regime was continued for 28 wk, after which the subjects received 27 mg zinc/d supplement for 12 wk while still consuming the experimental diet.

Throughout the study, the amounts of all nutrients, including protein, amino acids, vitamins, and minerals (both macro- and microelements), were kept constant, meeting the RDA, except for zinc, which was varied as outlined above. By this technique, we were able to induce a specific zinc deficiency in human volunteers.

We assayed serum thymulin activity in mildly zinc-deficient human subjects (14) evaluated by a rosette assay, described earlier (16). Thymulin is a thymus-specific hormone, which requires the presence of zinc for its biological activity to be expressed (16,17). Thymulin binds to high-affinity receptors on T cells, induces several T-cell markers, and promotes T-cell function, including allogenic cytotoxicity, suppressor functions, and IL-2 production (16,17).

As a result of mild deficiency of zinc, the activity of thymulin in serum decreased significantly and was corrected by both in vivo and in vitro zinc supplementation. The in vitro supplementation studies indicated that the inactive thymulin peptide was present in the serum in zinc-deficient subjects and was activated by addition of zinc (14). The assay of serum thymulin activity, with or without zinc, in vitro thus may be used as a sensitive criterion for the diagnosis of mild zinc deficiency in humans.

An increase in T_{101}-, slg- cells, a decrease in the ratio of T4+ to T8+, and decreased IL-2 activity were observed during the zinc-depletion phase, all of which were corrected after repletion with zinc (14). We previously reported that natural-killer (NK)[4] cell activity was also sensitive to zinc restriction (18); thus, it appears that zinc may play a very important and critical role in the functions of human T cells.

In our studies, we showed that a mild deficiency of zinc leads to an imbalance of T-helper 1 (Th_1) and T-helper 2 (Th_2) functions, decreases the recruitment of T naive cells (CD4+ CD45RA+), and decreases the percentage of CD73+ cells in the CD8+ subset that are precursors to cytotoxic T lymphocytes (15,19). Our studies also showed that the production of IFN-γ was decreased, whereas the production of IL-4, IL-6, and IL-10 was not affected due to zinc deficiency (15). Earlier, we showed a significant effect of zinc deficiency on IL-2 activity and production in experimental human subjects and in patients with sickle cell disease and head and neck cancer patients (20). Taken together, our studies suggest that zinc affects mainly the functions of Th_1 cells.

IFN-γ is known to downregulate the Th_2 clone and IL-10 may downregulate the Th_1 clone (21,22). An imbalance between Th_1 and Th_2 responses in patients with HIV infection has been implicated in the immune dysregulation in these patients and researchers proposed that resistance to infection and/or progression to acquired immunodeficiency syndrome is dependent on a $Th_1 > Th_2$ dominance (23). Our data in the experimental human model suggest that cell-mediated immune dysfunctions in human zinc deficiency may be due to an imbalance between Th_1 and Th_2 cell functions.

Th_1 cells are known to promote macrophage activation and production of complement fixing and opsonizing antibodies (21,22). IFN-γ is the major component of Th_1 response panel and it upregulates major histocompatibility complex class I antigen expression.

T cell subpopulation studies revealed that the CD4+ to CD8+ ratio was significantly related to zinc status (15). A decrease in this ratio was observed during zinc deficiency and was corrected by zinc supplementation. A borderline significant effect of zinc status on the ratio of CD4+ CD45RA+ to CD4+ CD45R0+ cells was observed in the human volunteers. The newly produced CD4+ T lymphocytes express CD45 isoforms, which are designated CD45RA+, and once these cells encounter a specific antigen, they become "memory" T lymphocytes, expressing a small isoform of cleaved CD45 designated CD45 R0+ cells (23,24). It appears that zinc is required for the regeneration of new CD4+ T cells. In as much as zinc is essential for the activity of thymulin, zinc may possibly be intrinsically involved in the development of hematopoietic stem cells in the thymic microenvironment (16,17).

Even a mild deficiency of zinc in humans may be accompanied by an imbalance of Th_1 and Th_2 cells, decreased serum thymulin activity, decreased recruitment of T naive cells, decreased percentage of T cytolytic cells, and decreased NK cell lytic activity (see **Table 1**). **Figure 1** shows the role of zinc on thymulin activity and Th_1 cells.

Zinc activates nuclear factor-κB in HUT-78 cells

Nearly 2000 transcription factors require zinc for their structural integrity; however, it is not known if cellular zinc deficiency results in any change in activation of any of the transcription factors. A short segment of DNA, 275 bp in the promoter area of the IL-2 gene, integrates numerous signaling pathways leading to IL-2 synthesis and the activation and proliferation of T lymphocytes (25). Both the murine and human IL-2 promoters contain 1 binding site for genuine Rel/nuclear factor-κB (NF-κB)

TABLE 1 Effect of zinc deficiency on immune functions in experimental human models

Variables
1. Thymulin activity Decreased; corrected by both in vivo and in vitro zinc supplementation
2. T cell subpopulation studies
CD4+ to CD8+ Ratio decreased
CD4+ CD45RA+ to CD4+ CD45R0+ Borderline significant decrease
3. Th_1 cytokines Both cytokines decreased
IL-2
IFN-γ
4. Th_2 cytokines No change
IL-4, IL-6, IL-10
5. NK cell lytic activity Decreased
Precursors of cytotoxic T Lymphocytes
CD8+ CD73+ Decreased

[4] Abbreviations used: NF-κB, nuclear factor-κB; PHA, phytohemagglutinin-p; PMA, phorbol-12 myristate 13 acetate; PMNC, peripheral blood mononuclear cells; Th_1, T-helper 1; Th_2, T-helper 2.

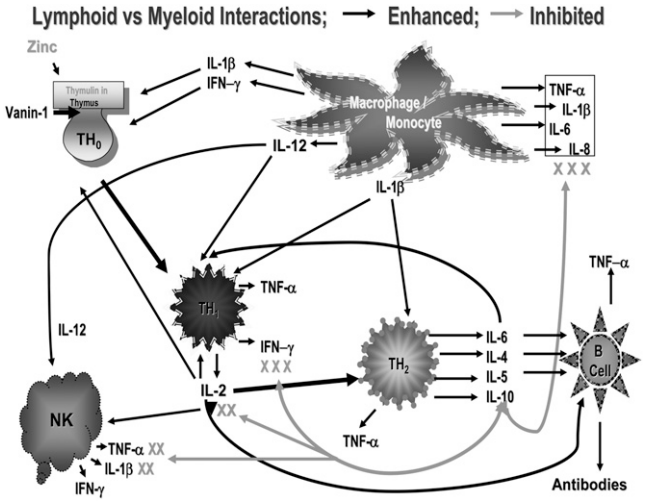

FIGURE 1 Effect of zinc on lymphoid and myeloid cells. Thymulin, a thymic hormone, requires zinc for its activity. In zinc deficiency, Th_1 cytokines decrease, but Th_2 cytokines are not affected. Thus, Th_1 shifts to Th_2 function. Zinc decreases the gene expression and generation of TNF-α, IL-1β, and IL-8 cytokines. Solid lines represent pathways enhanced by zinc; dotted lines represent pathways inhibited by zinc.

factors. The sequence of this site, GGGATTTCAC, is identical for both promoters. NF-κB factors are rapidly induced by a variety of stimuli-activating T cells. Almost every stimulus leading to T cell activation also activates NF-κB (26–28). Because NF-κB binds to the promoter enhancer area of IL-2 and IL-2Rα genes, we investigated the effect of zinc deficiency on activation of NF-κB and its binding to DNA in HUT-78. In zinc-deficient HUT-78 cells, phosphorylated IκB, IKK, and ubiquitinated IκB and binding of NF-κB to DNA were all significantly decreased compared with zinc-sufficient cells (29). Zinc increased the translocation of NF-κB from cytosol to nucleus. We also demonstrated that the binding of recombinant NF-κB $(p50)_2$ to DNA in HUT-78 cells was zinc specific (29). Thus, we concluded that zinc plays an important role in activation of NF-κB in HUT-78 cells.

Zinc enhances the expression of IL-2 in HUT-78 cells

The fact that IL-2 plays a central role in: *1*) expansion and maintenance of thymocyte and peripheral T cell populations; *2*) generation of antiviral- and antitumor-specific cytotoxic T cells; *3*) delayed type hypersensitivity responses; and *4*) upregulation of NK lytic activity implies that even a mild deficiency of zinc could lead to enhanced susceptibility to infections and malignancies by impairing production of this cytokine.

Our previous studies showed that even in mild human zinc deficiency, IL-2 production by PMNC is decreased (1,15). Tanaka et al. (30) reported that zinc may be essential for IL-2-mediated T-cell activation. These investigators demonstrated that optimal zinc concentration induced the expression of high affinity receptors for IL-2 (CD25+) in lymphocytes.

The production of IL-2 is a key and early event in the activation of T lymphocytes. IL-2 triggers peripheral T lymphocytes to enter the S phase of the cell cycle and to divide. This is probably due to the suppressive effect of IL-2 on cell cycle inhibitors, which interfere with the activity of cyclin-dependent kinases at checkpoints of the cell cycle (25). IL-2 also takes part in the differentiation of thymocytes and proliferation of peripheral T and B lymphocytes and other cells of hematopoietic origin (25).

We utilized HUT-78 to study the effect of zinc on IL-2 production in PHA-/PMA-activated T-cells. In zinc-deficient cells, the gene expression of IL-2 decreased by 50% compared with the zinc-sufficient cells (31). The effect of zinc was specific and at the transcriptional level. Zinc also affected the gene expression of IL-2 receptors α and β. Binding of NF-κB (a zinc-dependent transcription factor) to DNA decreased in zinc-deficient cells. By utilizing transfection of expression vectors of anti-sense NF-κB p105 (precursor of NF-κB p50) in cells, we showed that a decrease in gene expression of IL-2 and IL-2Rα may be partly due to decreased activation of NF-κB in zinc-deficient cells. These studies showed the role of zinc on gene expression of IL-2 and its receptors (31) and documented that the binding of NF-κB to DNA was adversely affected, thereby decreasing the gene expression of IL-2 and IL-2 Rα in zinc-deficient HUT-78 cells (31). **Figure 2** shows the role of zinc on NF-κB activation in HUT-78 cells.

Zinc modulates mRNA levels of cytokines

We examined the effect of zinc deficiency on IL-2, IFN-γ, IL-4, and IL-10 in HUT-78 (Th_0) and D1.1 (Th_1) cell lines, and TNF-α, IL-1β, and IL-8 in HL-60 (a human pro-myelocytic leukemia) cell line (32). The results demonstrated that zinc deficiency decreased the levels of IL-2 and IFN-γ cytokines and mRNAs in HUT-78 cells after 6 h of PMA/PHA stimulation compared with zinc-sufficient cells. Zinc deficiency also decreased the levels of IL-2 and IFN-γ cytokines and mRNAs in D1.1 cells compared with zinc-sufficient cells. However, it increased the levels of TNF-α, IL-1β, and IL-8 cytokines and mRNAs in HL60 cells after 6 h of PMA stimulation compared with zinc-sufficient cells (32). Actinomycin D studies suggested that the changes in the levels of these cytokine mRNAs were not due to the stability affected by zinc but were due to the altered expression of the cytokine genes (see **Table 2**).

Antioxidant effect of zinc in humans

Oxidative stress is known to be an important contributing factor in many chronic diseases. We tested the hypothesis that in healthy normal subjects, zinc acts as an effective antiinflammatory and antioxidant agent (33). Ten healthy volunteers were administered daily oral zinc supplementation (45 mg zinc as

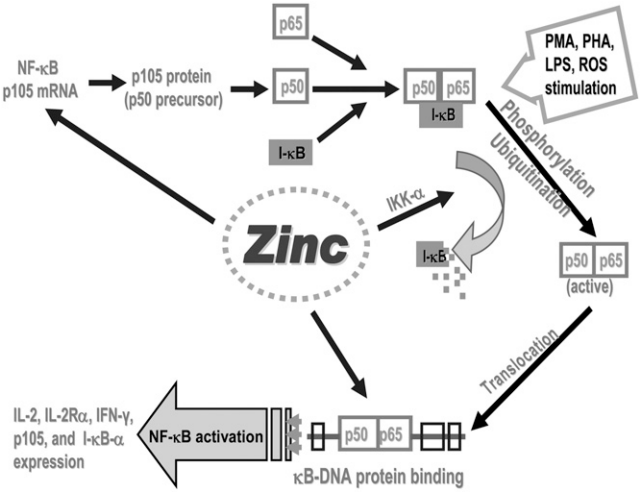

FIGURE 2 Effect of zinc on NF-κB activation in HUT-78 cells. Zinc is required for the expression of NF-κB p105 mRNA, for IκB phosphorylation, and for κB-DNA protein binding.

TABLE 2 Effect of zinc deficiency in cell culture models

1. HUT-78
   a. IL-2 production and IL-2 mRNA decreased
   b. The effect of zinc on IL-2 production was specific and was at the transcriptional level
   c. IL-2 Rα and IL-2 Rβ production and mRNAs decreased
   d. Binding of NF-κB to DNA and its translocation from cytosol to nucleus were decreased
   e. IκB phosphorylation was decreased accounting for decreased activation of NF-κB
2. HL-60
   a. Increased the levels of TNF-α, IL-1β, and L-8 cytokines and mRNA
   b. Increased lipid peroxidation by-products (malondialdhyde plus 4-hydroxyalkenals) (HA) and nitric oxide
   c. Decreased production and mRNA of A-20
   d. Increased NF-κB-DNA binding in LPS-stimulated cells

acetate) and 10 volunteers received placebo for 8 wk. Plasma zinc, malondialdhyde, HA, and 8-hydroxy deoxyguanine. levels, LPS-induced TNF-α and IL-1β mRNA and ex vivo TNF-α-induced NF-κB activity in PMNC were determined before and after supplementation. In subjects receiving zinc, plasma levels of lipid peroxidation products and DNA adducts decreased, whereas no change was observed in the placebo group. LPS-stimulated PMNC isolated from zinc-supplemented subjects showed reduced mRNA for TNF-α and IL-1β compared with placebo. Ex vivo, TNF-α-induced NF-κB activity showed a decrease following zinc supplementation. In parallel studies using the HL-60 cell line, we observed that zinc enhanced the upregulation of mRNA and DNA-specific binding for A20, a transactivating factor that inhibits the activation of NF-κB (33). These results suggest that zinc supplementation may lead to downregulation of the inflammatory cytokines through upregulation of the negative feedback loop A20 to inhibit induced NF-κB activation and show that zinc has both antiinflammatory and antioxidant effect in vivo. **Figure 3** shows the mechanism of zinc action on NF-κB activation in HL-60 cells.

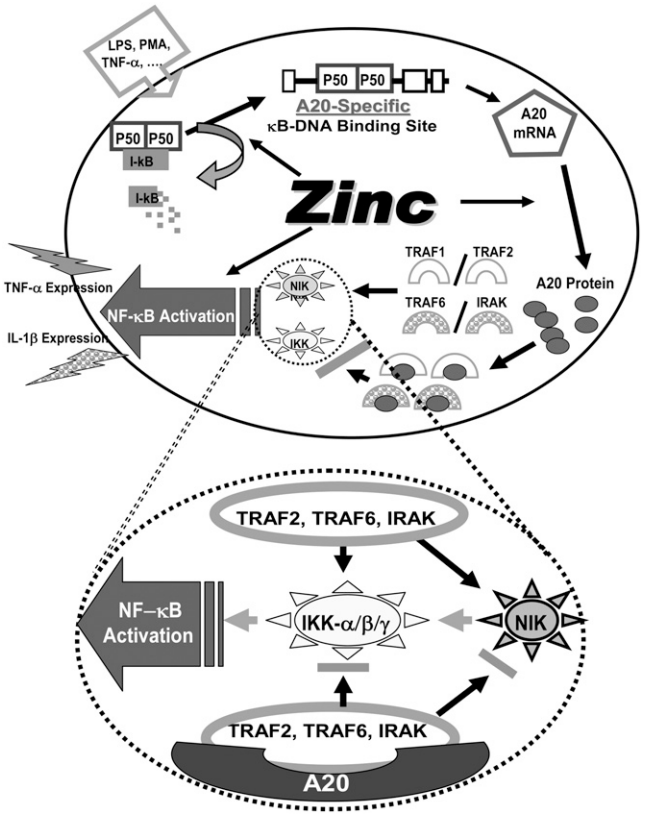

FIGURE 3 Inhibition of NF-κB-induced TNF-α and IL-1β by zinc-activated A20 pathway in HL-60 cells. Zinc induces A20 in HL-60 cells. A20 protein binds to TRAF-1, 2, and 6, which inhibits IKK-$\alpha/\beta/\gamma$ and results in decreased IκB phosphorylation and NF-κB activation (33).

Studies in elderly subjects

We recently completed a 12-mo, placebo-controlled zinc supplementation trial in elderly subjects (age 55–87 y) who were free of any significant chronic diseases and who were ambulatory and active. Fifty men and women (ages 55–87 y) were recruited from St. Patrick's Senior Citizen Center (Detroit, MI) for the trial. We had complete data on 49 participants (zinc group, $n = 24$; placebo group, $n = 25$).

For 12 mo, the zinc-supplemented group received 1 capsule of zinc gluconate (15 mg elemental zinc) per day orally 1 h before breakfast and 2 h before going to bed. Participants were observed for 12 mo to document the incidence of infections (primary end point). This plan eliminated the effect of seasonal variations on the incidence of infections. A nurse practitioner evaluated subjects who appeared to have infections. The secondary end points were laboratory variables, such as generation of cytokines and oxidative stress markers. Methods for these have been established in our laboratory and published previously.

A comparison of baseline data between younger adults (ages 18–54 y) and elderly subjects showed that in the elderly, plasma zinc decreased and the percentage of cells producing IL-1β and TNF-α and the generated levels of these cytokines increased. The intercellular adhesion molecule-1, vascular endothelial cells adhesion molecule-1, and E-selectin in the plasma also increased, as did IL-10 generated by Th_2 cells (known to produce a negative effect on IL-2 generation) (34). The oxidative stress markers also increased in the elderly compared with the younger adults (34).

The mean incidence of infections in 12 mo decreased in the zinc-supplemented group compared with the placebo group (0.29 ± 0.46 vs. 1.4 ± 0.95, respectively, $P < 0.001$) (34). Decreases in the incidences of common cold, cold sores, and the flu were observed in the zinc-supplemented group compared with the placebo group. Plasma zinc significantly increased in the zinc-supplemented group. Ex vivo generation of TNF-α and plasma oxidative stress markers were lower in the zinc-supplemented group compared with the placebo group (34). Plasma zinc and PHA-induced IL-2 mRNA in isolated mononuclear cells for zinc-deficient elderly subjects were higher in zinc-supplemented subjects compared with the placebo group (34).

Therapeutic effects of zinc supplementation

The beneficial effects of zinc in the management of infantile diarrhea and acute respiratory infections in children in the developing world, as evidenced by decreased mortality, morbidity, and incidence of infections in patients with sickle cell disease and in the elderly subjects, are due to the important roles of zinc in the cell-mediated immune functions. Zinc has been used as an antioxidant for the treatment of age-related macular degeneration for the past 10 y in a study organized by the National Eye Institute, NIH (35). Zinc is very effective in decreasing the progression of age-related macular degeneration and has prevented blindness in many patients (35). Another report found that mortality significantly decreased in zinc-treated subjects (36).

In conclusion, we reviewed the effects of zinc deficiency on cell-mediated immune functions and in cell culture models. The possible mechanisms of a shift for Th_1 to Th_2 on cell-mediated immunity have been discussed. Besides the effect of zinc on cell-mediated immunity, zinc is also an antiinflammatory and antioxidant agent. Because many chronic diseases, such as atherosclerosis, cancer, neurodegenerative disorders, rheumatoid arthritis, and even aging, may be due to chronically increased pro-inflammatory cytokines and oxidative stress, zinc may prove to be a useful chemopreventive agent for many chronic disorders.

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