Zinc: role in immunity, oxidative stress and chronic inflammation

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Purpose of review

Zinc is essential for multiple cellular functions including immunity. Many investigators have used zinc supplementation in an attempt to affect the outcome of various diseases. These efforts were aimed at either supporting immunity by zinc administration or correcting the zinc dependent immune functions in zinc deficient individuals.

Recent findings

In this review, recent findings of zinc supplementation in various diseases have been presented. Beneficial therapeutic response of zinc supplementation has been observed in the diarrhea of children, chronic hepatitis C, shigellosis, leprosy, tuberculosis, pneumonia, acute lower respiratory tract infection, common cold, and leishmaniasis. Zinc supplementation was effective in decreasing incidences of infections in the elderly, in patients with sickle cell disease (SCD) and decreasing incidences of respiratory tract infections in children. Zinc supplementation has prevented blindness in 25% of the elderly individuals with dry type of AMD. Zinc supplementation was effective in decreasing oxidative stress and generation of inflammatory cytokines such as TNF-α and IL-1β in elderly individuals and patients with SCD.

Summary

Zinc supplementation has been successfully used as a therapeutic and preventive agent for many conditions. Zinc functions as an intracellular signal molecule for immune cells.

Keywords

anti-inflammatory agent, antioxidant, immune function, zinc

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Introduction

Role of zinc in biology was fist recognized by Raulin in 1869 [1]. He observed that zinc was required for the growth of *Aspergillus niger*. In 1934 the essentiality of zinc for rats was shown [2]. Until 1961 it was considered improbable that zinc deficiency in humans could occur and lead to any significant clinical problems. In 1961 we published a description of the clinical syndrome of iron deficiency anemia, hepatosplenomegaly, hypogonadism, dwarfism and geophagia, affecting Iranian males and speculated that zinc deficiency may have caused growth retardation and hypogonadism in these individuals [3]. Our studies later showed that zinc was essential for humans and that zinc deficiency was prevalent in the Middle East [4].

The villagers from Iran and Egypt ate only bread and beans. The phytate content of their diet was very high and this decreased the availability of iron and zinc, leading to deficiency of both iron and zinc. Several studies have now confirmed that zinc deficiency in the developing countries is fairly prevalent, affecting nearly two billion individuals and that growth retardation commonly observed in these countries may indeed be due to zinc deficiency [5].

The possibility that zinc deficiency may have played a role in immune dysfunction and intercurrent infections in the dwarfs responsible for their early death was considered but due to lack of facilities, immunological studies could not be carried out.

In this paper, the role of zinc in cell-mediated immunity and its role as an antioxidant and an anti-inflammatory agent will be reviewed.

Zinc and immunity

Zinc affects multiple aspects of the immune system [6•,7•,8]. Zinc is essential for normal development and function of cell-mediating innate immunity, neutrophils, and natural killer cells. Macrophages are also affected by zinc deficiency. Phagocytosis, intracellular killing and cytokines production are all affected by zinc deficiency. The growth and function of T and B cells are also affected adversely due to zinc deficiency. Zinc is needed for DNA synthesis and RNA transcription, cell division

and cell activation. Apoptosis (programmed cell death) is potentiated by zinc deficiency. Zinc deficiency adversely affects the secretion and functions of cytokines, the basic messengers of the immune system. Zinc functions as an antioxidant and stabilizes membranes.

Zinc deficiency leads to atrophy of the thymus and lymphoid tissue in experimental animals [8,9]. In young adults, zinc deficient mice, thymic atrophy, decrease in absolute number of splenocytes, and decreased responses to both T-cell-dependent and T-cell-independent antigens have been observed [9,10]. Animals maintained on a zinc-deficient diet for as little as 2 weeks developed a severe impairment in their ability to generate a cytotoxic T killer response to the tumor challenge [11].

Immune functions in experimental model of human zinc deficiency

We induced in humans a mild deficiency of zinc by restricting dietary daily zinc intake to 3–5 mg daily. As a result of mild deficiency of zinc, the serum thymulin activity (a zinc dependent thymic hormone) was decreased within 12 weeks of a zinc-restricted diet. A decrease in the ratio of T4+ to T8+, decreased IL-2 and decreased NK cell lytic activity were observed in mildly zinc deficient individuals [12]. All of these changes were promptly corrected after zinc supplementation. Our studies in the experimental human model of zinc deficiency also showed that the generation of INF-γ was decreased whereas the production of Th_2 cytokines IL-4, IL-6 and IL-10 were not affected due to zinc deficiency [13]. IFN-γ is known to downregulate Th_2 clone and IL-10 may downregulate Th_1 clone. IFN-γ is also a major component of Th_1 response panel, and it upregulates major histocompatibility complex class 1 antigen expression. Thus, our data in a human experimental model showed that the cell-mediated immune dysfunctions in human zinc deficiency might be due to an imbalance between Th_1 and Th_2 cell functions.

Therapeutic effects of zinc supplementation in humans

Several studies have now shown the benefits of zinc supplementation in humans.

Viral infections

We have recently published the results of our placebo-controlled trial of zinc lozenges for the treatment of the common cold [14•]. Compared with the placebo group, the zinc group had a shorter mean overall duration of cold (4.0 vs. 7.1 day, $P < 0.0001$) and shorter duration of cough (2.1 vs. 5.0 day, $P < 0.0001$) and nasal discharge (3.0 vs. 4.5 day, $P = 0.02$). Blinding of individuals was adequate. Symptoms severity scores were decreased significantly in the zinc group. Plasma sIL-1ra and ICAM-1 levels decreased significantly in the zinc group.

sIL-1ra is an anti-inflammatory cytokine which functions as a specific inhibitor of IL-1α and IL-1β inflammatory cytokines. Our results indicate that in the zinc supplemented group, sIL-1ra decreased, suggesting that overall inflammation was decreased in this group. Plasma ICAM-1 was also decreased in zinc treated individuals. Human rhinovirus type 14 'docks' with ICAM-1 on the surface of somatic cells. Thus, zinc may in effect act as an antiviral agent by reducing ICAM-1 levels. Another possibility is that zinc ions may form a complex with ICAM -1, preventing the binding of rhinovirus to cells.

The effect of zinc lozenges on the duration or severity of common cold symptoms has been examined in at least 14 different studies since 1984. Results of trials in which no effect of zinc was demonstrated were criticized for having inadequate sample sizes or for using inadequate doses of zinc or formulations that reduced the release of zinc ions from the lozenges. Zinc acetate and gluconate are suitable salts, inasmuch as zinc ions are released at physiological pH. Several zinc lozenges use glycine or citrate as ligands, which prevent release of, zinc ions and therefore, are not effective in curing common cold. In our experience, two other factors are important. One is that zinc lozenges must be started within 24 h of the onset of common cold and the other is that the daily total dose of elemental zinc should be at least 75 mg.

Infection with HIV results in AIDS, a disease where zinc supplementation was used as a supporting therapeutic intervention [15,16]. The initial study found an increase in HLA.DR positive cells, a stimulation of lymphocytic transformation by PHA and concavalin A, and augmented phagocytosis by polymorphonuclear neutrophils [16]. A report by Mocchegiani *et al.* [17] showed an increase in the number of Th cells and a reduced frequency of opportunistic infections with *Pneumocystis firoveci* and *Candida*.

So far the results of zinc supplementation in AIDS are not consistent [18,19]. The explanation for the contradictory reports may be that only zinc deficient patients would respond to zinc supplementation and zinc sufficient patients may not have any beneficial effects. Inasmuch as zinc is essential for immune functions, those patients of AIDS who are zinc deficient should receive zinc in order to correct their zinc status. Obviously, more studies are needed in this important area.

Several studies have investigated the effect of zinc supplementation on hepatitis C, which is induced by an infection with hepatitis C virus (HCV). After zinc

treatment, decreases in the incidence of gastrointestinal disturbances, body weight loss, and mild anemia were found in patients with chronic hepatitis C [20,21]. Zinc given in combination with IFN-α was more effective against chronic hepatitis C than therapy with IFN-α alone [21]. It's also possible that zinc has an antioxidant effect and this may have benefited a few cases of hepatitis. Zinc may also be able to inhibit herpes simplex virus [22] and rhinoviruses [23]. The in-vitro relevance of an inhibition of viral replication as a mechanism for antiviral actions of zinc in humans remains to be determined.

Bacterial infections

Zinc can reduce the duration, severity and incidence of diarrhea in children in the developing countries [24,25]. The combined results of seven trials of continuous zinc supplementation confirmed that zinc significantly reduced the incidence of prevalence of diarrhea. However, a recent report shows that this may not be the case for infants younger than 6 months of age [26].

Correction of zinc deficiency improves the absorption of water and electrolytes by the intestine, leads to a faster regeneration of the gut epithelium and increases the levels of enterocyte brush-border enzymes [25,27]. Finally, loss of zinc contributes to immune dysfunction, which is corrected by zinc supplementation.

Several reports have shown beneficial effects of zinc in treatment of shigellosis [28,29]. Most of these effects are mediated by a modulation of immune function.

Zinc supplementation to leprosy patients has shown beneficial effects [30,31]. One study found a reduction in the required dose of clofazimine, a withdrawal of primarily essential steroids, and an improved toleration of dapsone after zinc treatment. They also observed a reduced incidence and severity of erythema nodosum leprosum, a gradual decrease in the size of granuloma and a gradual increase in the number of lymphocytes [30–32].

Zinc supplementation to patients with *Mycobacterium tuberculosis*, showed an increase in plasma retinol concentration, earlier sputum conversion, and resolution of radiograph lesions [33]. Effective clearance of mycobacterial infections requires a Th_1 mediated activation of infected macrophages by IFN-γ. Zinc acts by inducing T cell activation or alteration of lymphokine production, which in turn may activate macrophages to promote bacterial clearance [34]. In humans, zinc deficiency is characterized by a reduction of IL-2 and IFN-γ and zinc induces the generation of both IL-2 and IFN-γ [13,34].

Zinc may be an effective adjunct therapy for the treatment and eradication of *Helicobacter pylori* infection. Treatment with polaprezinc (zinc-L-carnosine), which is used as an antiulcer drug in Japan, leads to an improved cure rate when administered together with antimicrobial triple therapy [35].

Parasitic infections

Patients with cutaneous, mucosal and visceral leischmaniasis have lower plasma zinc levels [7•]. Zinc supplementation results in a decrease in erythemas and size of induration and an increase in cure rate.

Autoimmune diseases

One study reported the beneficial affects of zinc supplementation with respect to joint swelling, morning stiffness and walking, in patients with rheumatoid arthritis (RA) [7•], however, this observation was not confirmed in two other studies. In patients with RA, low plasma zinc correlates negatively with levels of TNF-α and IL-1β as well as parameters for inflammation such as acute-phase proteins and erythrocyte sedimentation rate.

Patients with IDDM typically exhibit hyperzinccuria and a mild deficiency of zinc [6•,7•]. They have increased oxidative stress. In one study, zinc supplementation showed a beneficial effect in patients with IDDM with respect to oxidative stress as measured by an increase in selenium-glutathione peroxidase activity and a decrease in plasma indicators of lipid peroxidation [7•]. Two other studies, however, detected an increase in the glycosylated form of hemoglobin [7•]. In view of the important role of zinc as an antioxidant and anti-inflammatory agent, a carefully conducted trial of zinc supplementation in IDDM and RA is indicated.

In a study, which investigated whether micronutrients supplementation had any effect on the vibriocidal antibody response in children to a killed oral cholera vaccine, only zinc supplementation improved sero-conversion to vibriocidal antibody, and hence, has the potential to improve the efficacy of oral cholera vaccine in children [7•].

Preventive effects of zinc supplementation

Elderly individuals

A randomized double-blind, placebo-controlled trial of zinc supplementation was conducted in elderly individuals aged 55–87 years [36]. The zinc supplemented group received zinc gluconate (45 mg elemental zinc d/orally) for 12 months. The incidence of infections and ex-vivo generation of TNF-α and plasma oxidative stress markers were significantly lower in the zinc supplemented group than in the placebo group. Plasma zinc and PHA induced IL-2 mRNA in isolated mononuclear cells (MNC) were

significantly higher in the zinc supplemented group than in the placebo group. Thus, this study demonstrates the beneficial effect of zinc supplementation on cell-mediated immunity, oxidative stress markers and inflammatory cytokines in the elderly.

Sickle cell disease patients

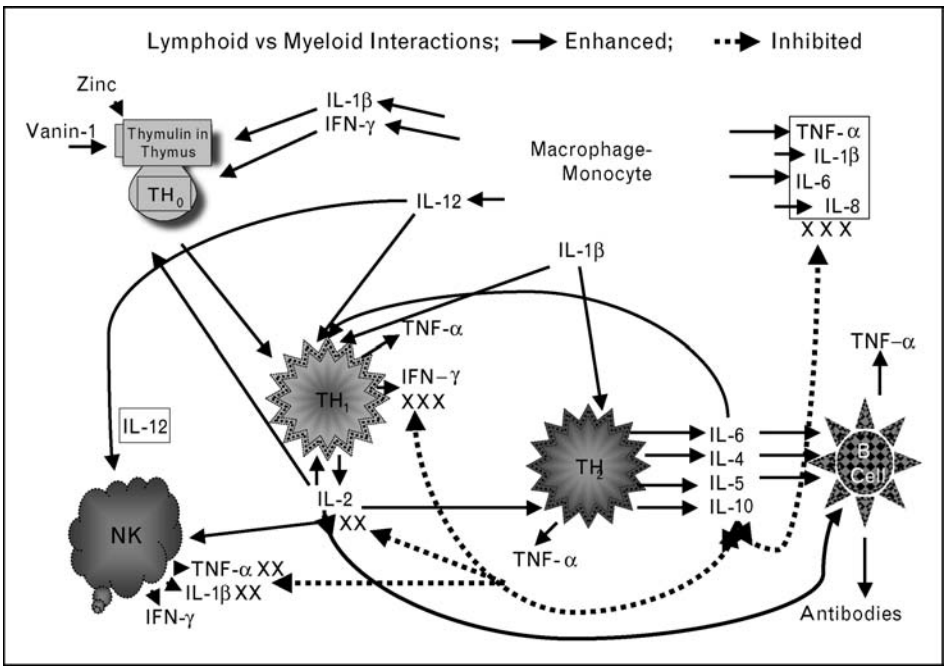
A randomized double-blind, placebo-controlled trial of zinc supplementation was carried out in patients with SCD [37•]. The zinc group received 25 mg elemental zinc (as acetate) three times a day for 3 months. The other group received placebo.

The zinc-supplemented group had decreased incidences of infection in comparison to the placebo group. After zinc supplementation, plasma zinc and antioxidant power increased; plasma nitrite and nitrate (NOx), lipid peroxidation products, DNA oxidation products, and soluble vascular cell adhesion molecule-1 (VCAM-1) decreased compared to the placebo group. Zinc-supplemented individuals exhibited significant decreases in LPS induced TNF-α and IL-1β mRNAs, and TNF-α induced NF-κB-DNA binding in MNC compared with the placebo group. Ex-vivo addition of zinc to MNC isolated from the placebo individuals decreased TNF-α and IL-1β mRNAs. Zinc supplementation also increased relative levels of IL-2 and IL-2Rα mRNAs in PHA stimulated MNC. These studies show the beneficial effect of zinc supplementation on prevention of infections in SCD individuals, improvement in generation of Th_1 cytokines, and decrease in oxidative stress and generation of inflammatory cytokines.

Age-related macular degeneration

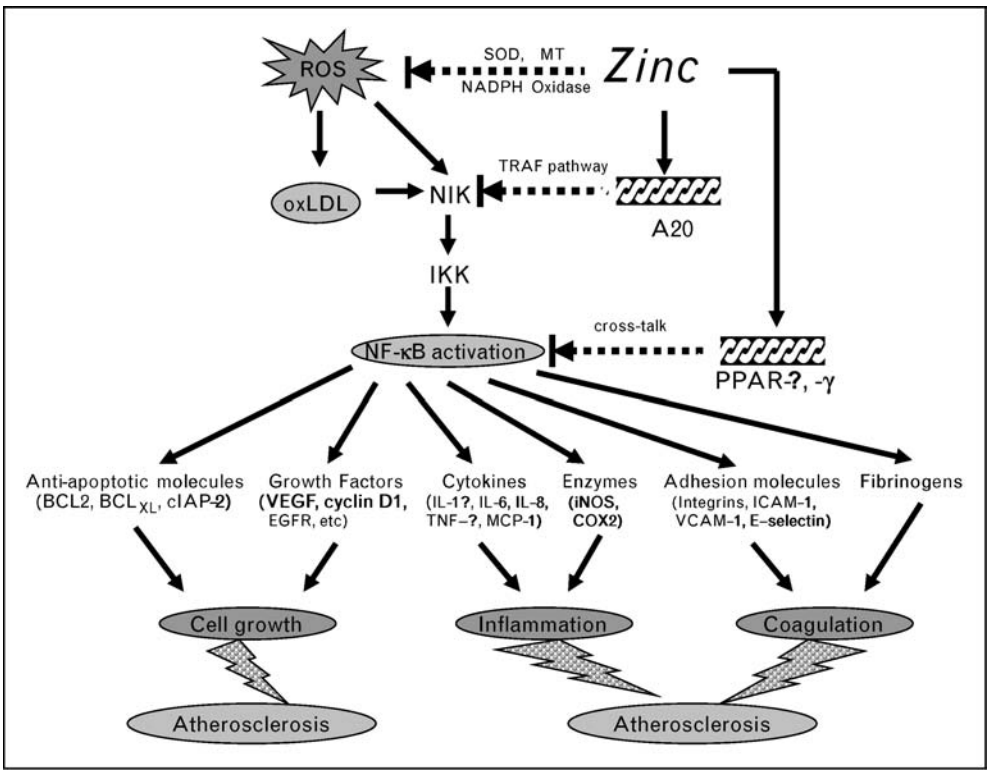
In a large study organized by the National Eye Institute, NIH, it was reported that zinc and antioxidants (vitamin C, Vitamin E and beta carotene) significantly reduced the odds of developing advanced age-related macular degeneration (AMD) and prevented blindness in the high-risk group of elderly individuals [38,39]. Zinc alone had almost a similar effect and prevented blindness in 25% of the elderly. These individuals received 80 mg zinc daily as oxide and in order to prevent copper deficiency due to high dosage of zinc, 2 mg of copper a day was also administered. Although the mechanism of zinc action was not defined, one may safely presume that zinc reduced

Figure 1 Landscape of zinc effect on immune cells



Zinc is an integral part of a thymic hormone molecule, thymulin. Thymulin is required for maturation of T-cells. Zinc deficiency-induced decrease in thymulin activity is associated with decreased maturation of T-cells and Th_1 production of IL-2 and INF-γ. Decreased IL-2 leads to decreased NK- and T cytolytic cell activities. Macrophages-monocytes produce IL-12 (a zinc-dependent cytokine), which along with INF-γ kills parasites, viruses and bacteria. Th_2 cytokines, in general are not affected by zinc deficiency except IL-10, which may be increased in zinc deficient elderly individuals. Increased IL-10 from Th_2 cells further affects Th_1 functions adversely. Thus, in zinc deficiency there is a shift from Th_1 to Th_2 functions and cell-mediated immune functions are impaired. Zinc deficiency also leads to stress and activation of macrophages-monocytes, resulting in increased generation of inflammatory cytokines, IL-1β, IL-6, IL-8 and TNF-α. Solid lines indicate pathways leading to generation of selected cytokines and dotted lines represent pathways, which lead to inhibition of cytokine generation. NK represent natural-killer cells; Th_1 represent activated Th_1 type T- cells and secreted cytokines (small triangles); Th_2 represents activated Th_2 type T-cells and secreted cytokines (small rounds); B-cell represents B-cell lineages and associated immunoglobulins (triangles). Reproduced with permission [40].

Figure 2 Zinc as an antioxidant and anti-inflammatory agent



Zinc decreases ROS (reactive oxygen species) by several mechanisms. Zinc is an inhibitor of NADPH oxidase, zinc is required for superoxide dismutase (SOD), and it induces MT (metallothionein), which is very effective in decreasing ·OH. ROS activates NF-κB that in turn activates growth factors and antiapoptotic molecules resulting in cancer cell proliferation. NF-κB, which, in turn activates growth factors and antiapoptotic molecules resulting in cancer cell proliferation. NF-κB activation also induces the generation of inflammatory cytokines and adhesion molecules. One mechanism by which zinc reduces inflammatory cytokine production involves the zinc-induced upregulation of a zinc-finger protein, A20, which inhibits NF-κB activation via TRAF pathway. Zinc, thus not only functions as an antioxidant but is also an anti-inflammatory agent. Arrows represent directional flow for events presented in this figure. Solid arrows represent events leading to selected events and dotted lines represent inhibition of selected events. Reproduced with permission [6•].

the oxidative stress and was thus beneficial in AMD. Another interesting observation was that only the zinc supplemented group showed increased longevity [39]. The risk of mortality was reduced by 27% in participants of the Age-Related Eye disease Study (AREDS) (aged 55–81 years) who received a high dose of zinc (80 mg/day as oxide during median follow-up of 6.5 years [39]).

A 7-month randomized double blind, placebo-controlled trial involving 40 cadets to evaluate the effectiveness of zinc (15 mg zinc as gluconate orally daily) in reducing the risk of upper respiratory tract infections was recently conducted [41•]. Self-reported symptoms as recorded by a weekly website survey revealed that a supplemented group experienced significantly more symptom-free intervals than those in the placebo group ($P = 0.01$). No significant differences were found between the two groups who consulted physicians for their cold symptoms. Although the study suggested that zinc may have prevented upper respiratory tract infections in the cadets, it was not conclusive and perhaps a trial with higher levels of zinc supplementation may have been more appropriate. We have used 45 mg zinc (as acetate) supplementation in the elderly for one year with an excellent outcome [36] and no copper deficiency was observed. We recommend daily intake of 2 mg copper, which is RDA for copper for prevention of copper deficiency in individuals who are taking zinc supplementation above 50 mg daily.

A recent observational study showed, that 29% of nursing home residents have low serum zinc levels (<70 μg/dl) despite supplementation with 7 mg/day of zinc (as sulfate) over a period of 1 year [42]. All-cause mortality was 39% lower in those with normal (≥70 μg/dl) versus low (≤70 μg/dl) preintervention or baseline serum zinc concentrations ($P = 0.049$). These findings suggest that zinc may play a crucial role in influencing all-cause mortality in the elderly.

In the observational study, individuals with normal post-intervention or final serum zinc concentrations had lower

incidence of pneumonia, reduced total antiobiotic use (by almost 50%), and shorter duration of pneumonia and antibiotic use (all P values ≤ 0.004) relative to those with low serum zinc concentrations.

Mechanism of zinc effects

Figs. 1 and 2 summarize the effects of zinc on cell-mediated immunity, and define its role as an antioxidant and anti-inflammatory agent [6•].

Figure 1 shows the landscape of zinc action on immune cells. Zinc is an essential component of thymulin, a thymic hormone involved in maturation and differentiation of T-cells. The gene expression of IL-2 and IFN-γ, (Th_1 cytokines) are zinc dependent. IL-2 is involved in the activation of NK and T cytolytic cells. IL-12 is generated by stimulated macrophages-monocytes and is zinc dependent. IFN-γ and IL-12 together play a major role in the killing of parasites, viruses, and bacteria by macrophages-monocytes.

Th2 cytokines are not affected by zinc deficiency except for IL-10 production, which is increased in the zinc-deficient elderly individuals. This is correctable by zinc supplementation. Increased IL-10 affects adversely Th_1 and macrophage functions.

Figure 2 summarizes our concept regarding the role of zinc as an antioxidant and anti-inflammatory agent. ROS is known to activate NF-κB. Zinc decreases ROS generation. NADPH oxidase is inhibited by zinc and SOD is both a zinc and copper containing enzyme. SOD is known to decrease oxidative stress. Metallothionein (MT) is induced by zinc and MT, which contains 26 moles of cysteine per mole of protein, decreases $^{\bullet}OH$ burden. Zinc via A20 inhibits NF-κB activation and this results in a decrease in generation of inflammatory cytokines and adhesion molecules. This figure also shows that zinc may have a preventive role in some cancers such as colon and prostate and in atherosclerosis inasmuch as chronic inflammation has been implicated in the development of these disorders.

Conclusion

Zinc is an intracellular signaling molecule and it plays an important role in cell-mediated immune functions and oxidative stress. Zinc is also an anti-inflammatory agent. These unique properties of zinc may have significant therapeutic benefits in several diseases in humans. In many diseases concurrent zinc deficiency may complicate the clinical features, affect adversely immunological status, increase oxidative stress and increase the generation of inflammatory cytokines. It is currently believed that oxidative stress and chronic inflammation may play important causative roles in many chronic diseases, including atherosclerosis, several malignancies, neurological disorders, and autoimmune diseases. It is therefore, important that the status of zinc is assessed and zinc deficiency corrected in these chronic diseases. A controlled clinical trial of zinc supplementation in these disorders in order to document the preventive and therapeutic effects of zinc is warranted.

Acknowledgements

I have confirmed that there is no conflict of interest and that no competing financial interests exist. I acknowledge Sally Bates for her secretarial help.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 678).

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