Zinc and Selenium: Key Players for Healthy Immunity

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Adequate nutrition is essential for the normal functioning of the immune system, although some nutrients are more important than others when it comes to defending the body from infection.[1] Among the essential minerals, deficiencies in either zinc or selenium can greatly increase one's susceptibility to infection and may worsen the course of any infection when it does occur. In fact, a study of patients admitted to a hospital's infectious disease ward revealed that zinc and selenium were among the most prevalent micronutrient deficiencies, finding that two thirds of the patients were deficient in zinc, and nearly half were deficient in selenium.[2]

Widespread evidence from laboratory, epidemiological, and clinical investigations further suggest that infections and other disease conditions can further *deplete* the body's supply of these minerals and worsen the prognosis.[3],[4],[5],[6]

Herein, we take a look at the mechanisms by which zinc and selenium affect immune function, epidemiological data, outcomes of clinical interventions, and populations at greatest risk for deficiency.

Zinc

Zinc promotes immunity through direct, indirect, and antioxidant mechanisms,[7],[8],[9],[10]and a deficiency state is well documented to increase one's susceptibility to opportunistic infections.2,[11],[12],[13],[14] In vitro studies have also shown that zinc and its complexes have antiviral effects, and can inhibit the replication of many different respiratory viruses, including influenza, rhinovirus, and respiratory syncytial virus.[15],[16],[17],[18],[19]

Zinc is essential for the structure and activity of thymulin, a hormone that regulates the production and maturation of T-lymphocytes.[20],[21],[22],[23] Prolonged zinc deficiency leads to thymic atrophy, a reduction in T-cell numbers, and impaired immunity.[24],[25]As discussed below, zinc supplementation may help prevent and/or reverse these changes.

Zinc deficiency is thought to contribute to the incidence and severity of respiratory tract infections in children. Randomized controlled trials (RCT), for example, have shown that supplemental zinc can reduce the risk of acute lower respiratory tract infections (ALRTI).[26],[27] In an RCT of infants and preschool children, supplemental zinc (10 mg zinc gluconate daily for 120 days) reduced the risk of acute lower respiratory tract infections (ALRTI) by 45%.[26] The children who received zinc supplements also recovered more quickly from infections. In another RCT, looking at children under the age of five, zinc supplementation (10 mg zinc gluconate daily for 60 days) reduced the incidence of ALRTI by more than 50% after six months.[27] The number of episodes of ALRTI and severe ALRTI were significantly lower in the zinc group compared to the placebo group (20.8% vs. 45.8%, and 21.7% vs. 58.3%, respectively).

Zinc deficiency not only compromises immunity, but it shifts the immune system toward an inflammatory state that can predispose the body for damage to the lungs and other organs.[28],[29]Zinc supplementation has been shown to ameliorate lung damage in animal models of respiratory infections.[7],[30]

Zinc deficiency is also associated with poor outcomes in patients with sepsis.[31],[32],[33]In one study, 20 out of 22 septic patients had below-normal plasma zinc concentrations, and there was a correlation between lower plasma zinc concentrations and greater disease severity.30 In another study, *both* zinc and selenium were significantly lower in patients with sepsis than in controls, and the low levels of these nutrients were associated with elevated levels of inflammatory markers.[34]

Zinc deficiency has been observed in 30% or more of individuals over the age of 60. It contributes to the age-related decline in immune system function known as immunosenescence, which in turn increases the risk and severity of infections in the elderly.[35],[36],[37],[38],[39],[40]Animal and human studies suggest that various measures of immunosenescence, including thymulin activity and peripheral immune function, can be corrected by simply supplementing with zinc.[41],[42],[43],[44],[45],[46]

Similarly, although white blood cells (WBCs) collected from elderly individuals produce less interferon (IFN) than those from young adults, the IFN-producing capacity may not be permanently lost. When WBCs from the elderly were incubated with physiologic concentrations of zinc, they produced IFN in amounts comparable to those from the younger subjects.[47]

Clinically, we also see the impact of zinc on immune function, particularly in the elderly. In one randomized, double-blind, placebo-controlled trial, study participants were given a daily multivitamin and mineral supplement, including zinc, for one year.[48] Individuals who

developed normal zinc levels had a lower incidence and duration of pneumonia, and a reduced need for antibiotics, compared to subjects with low serum zinc concentrations. Another study showed that zinc supplementation reduced the risk of pneumonia by 64% in critical care (trauma) patients on ventilators.[49]

In addition to the well-documented effects of zinc on infections, population studies have shown that the maintenance of adequate serum zinc concentrations is associated with a reduced risk of mortality from all causes.[50],[51],[52]

Who is at risk for zinc deficiency?

Zinc is found in many different foods but it is particularly concentrated in meat, poultry, and shellfish.[53] As a result, vegetarians, and especially vegans who consume no animal products, have an increased risk of zinc deficiency, particularly if they also avoid nuts and seeds which contain relatively high levels of zinc.[54],[55],[56] The zinc present in plant-based foods is also less bioavailable due to the presence of phytates, which strongly bind zinc and prevent its absorption.[57],[58],[59]

Obese and diabetic patients typically have lower levels of zinc than healthy individuals,[60],[61],[62],[63]along with an increased risk for respiratory tract infections.[64],[65],[66]In one study of young, obese females, at baseline, multiple inflammatory markers were significantly higher in the obese than the non-obese women.[67] However, levels of both high sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6 were significantly decreased by zinc supplementation (in the obese women), suggesting that zinc may have a favorable effect on obesity-related inflammation. Zinc also has positive effects on glucose metabolism and insulin resistance in diabetic and prediabetic patients.[68],[69],[70],[71],[72]

Zinc levels decline with age as a result of physiopathological changes of various kinds.[73] Intestinal malabsorption,[74],[75] inflammatory bowel disease,[76] autoimmune disease,[77] kidney or liver disease,[78],[79],[80] cancer or cancer treatments,[81] and the use of medications (including antibiotics, statins, and blood pressure medications)[82],[83]can all contribute to zinc deficiency. Individuals with celiac disease, including those consuming gluten-free (GF) diets, may also be at risk for a deficiency of zinc and several other nutrients.[84] One study reported that 67% of newly diagnosed adult patients with celiac disease had suboptimal serum zinc levels,[85] while another study observed that 40% of individuals consuming long-term GF diets still were deficient in zinc.[86]

Selenium

Adequate selenium is also essential for a normal, healthy immune response.[87],[88],[89],[90],[91] Among the enzymes most impacted by selenium status is glutathione peroxidase 1 (GPX1), a selenium-containing protein with known antiviral properties. GPX1 decreases oxidative stress by utilizing glutathione to reduce hydrogen peroxide to water, thereby decreasing the damaging effects of this reactive oxygen species (ROS) on immune cells.[92],[93],[94],[95]The reduction of ROS also may have the effect of reducing viral virulence, as increased ROS can lead to further viral mutations.[96] In states of selenium deficiency, the amount of GPX1 can drop to a mere 10% of normal levels.[97] This impairs the immune response and allows viruses to replicate freely.[98],[99],[100],[101]

Selenium deficiency has been extensively studied in China, which has populations ranging from the lowest to the highest selenium levels in the world.[102] One of the selenium-deficient regions in China is Keshan county, which is the locus of a serious cardiomyopathy that has been dubbed Keshan disease.[103],[104] A study of the etiology of the disease showed that selenium deficiency produces extreme oxidative stress within cells.[105],[106]This state enables otherwise benign strains of Coxsackie virus to mutate to highly pathogenic forms, which infect the heart muscle, causing the disease.[107] As noted by the author of one of these studies: "What the results seemed to say was that one could be immersed in a sea of benign Coxsackie virus without any apparent ill effects until one suffered a decline in selenium to the point that the virus would exhibit its cardiovirulent properties."[99] Selenium supplementation not only boosted antiviral immunity, but prevented the virus from mutating to a pathogenic form.[99],[100]

Selenium deficiency has been shown to increase one's susceptibility to influenza, as well as to hepatitis B, hepatitis C, West Nile virus, and hantavirus infections.[108],[109],[110],[111],[112] In a mouse model of influenza, the mortality of the selenium-deficient mice was 75%, whereas the mortality of selenium-supplemented mice was reduced to 25%.[113] Selenium deficiency also was shown to produce more severe lung pathology in animals with influenza infections.[114],[115],[116]

Low selenium levels not only increase the risk of infections, but also contribute to the emergence of new and more virulent flu strains.[117] In fact, children with the highly infectious H1N1 subtype of influenza were found to have low blood levels of selenium.[118] There was a 45% decrease in GPX1 activity and a 245% increase in CRP levels in H1N1-infected children compared to a control group,[118] suggesting that virus-induced oxidative stress plays a key role in the pathology of the disease.[119] Adding to these findings, a population study found that persons living in regions with low selenium levels in China had a four- to fivefold higher death rate from COVID-19 than those in areas with high selenium levels.[120]

Elderly individuals are particularly susceptible to nutrient deficiencies, including selenium, which can contribute to the risk for respiratory infections. The effect of selenium and zinc on immunity was examined in a RCT of 725 institutionalized elderly patients from 25 geriatric centers in France.91 The study participants received an oral daily capsule containing one of the four following preparations: (1) zinc sulfate and selenium sulfide (providing 20 mg of zinc and 100 μg of selenium)—the trace element (T) group; (2) ascorbic acid (120 mg), beta carotene (6 mg=1000 retinol equivalents), and α-tocopherol (15 mg)—the vitamin (V) group; (3) trace element and vitamin supplements—the vitamin and trace element (VT) group; or (4) placebo.

After 6 months of supplementation, there was a significant increase in serum nutrient values in the supplemented groups. The percentage of selenium-deficient patients decreased from 79% to 5% and from 81% to 9% in the T and VT groups, respectively. The proportion of patients who remained free from respiratory tract infections was greater in groups that received selenium and zinc (T or VT groups) than in those who did not. Also, the antibody response to influenza vaccine was better in the T and VT groups than in the V or placebo groups. The results suggest that zinc and selenium supplementation improves the humoral response to influenza vaccination in elderly people.

Another RCT assessed whether selenium supplementation would improve vaccine efficacy in otherwise healthy UK adults who were given a live attenuated polio vaccine.[90] Sixty-six subjects with the lowest plasma selenium concentrations (<1.2 μmol/L, about 60% of the total population screened) were sequentially allocated to one of three groups, to receive one capsule containing either 50 or 100 μg selenium per day (as sodium selenite) or a placebo for 15 weeks. All subjects received an oral live attenuated poliomyelitis vaccine after the first six weeks. Blood was collected and used to measure T-cell proliferation and the production of cytokines in vitro. The supplemented groups had a significantly greater production of IFN, an earlier peak T-cell proliferation, and an increase in T helper cell numbers, suggesting a stronger immune response to the virus. Analysis of poliovirus RNA in fecal samples revealed that placebo-treated subjects had mutations of the attenuated poliovirus, but these were not apparent in the supplemented groups. This result suggests that selenium insufficiency increased the probability of generating poliovirus variants with new pathogenic potential.

Selenium deficiency is also implicated in the prevalence and severity of HIV.[121],[122] A multinational study of 270 treatment-naïve, HIV-positive adults showed that 53% were deficient in selenium, making it the most common micronutrient deficiency in this cohort.[123] Moreover, several studies have shown that low serum selenium concentrations are associated with a more severe HIV disease course and a higher mortality rate.[124],[125],[126]

An RCT was done to assess the effects of supplementation with 200 μg/day of high-selenium yeast in HIV-positive men and women.[127] Of the 450 participants who underwent screening, 262 initiated treatment and 174 completed a 9-month follow-up assessment. The serum selenium concentration increased significantly in the selenium-treated group. Greater selenium levels were associated with significantly decreased viral loads, which in turn correlated with increased CD4-positive cell counts in the supplemented group. These results suggest that selenium may be a valuable supportive nutrient for individuals with HIV.

Who is at risk for selenium deficiency?

The main dietary sources of selenium are Brazil nuts, seafood, meat, poultry, fish, eggs, and whole-grain bread.[128] Vegan, gluten-free, and low-protein diets provide suboptimal amounts of selenium.[129],[130],[131],[132],[133] Individuals with malabsorption or inflammatory bowel disease may also be deficient in this mineral.[134]

One’s selenium status also depends in part on the region in which one lives. Selenium deficiency is generally thought to be uncommon in the U.S.,[36],[135]but a study of Caucasian and African-

American women living in Southern U.S. states found that the diets of more than 60% of the population were deficient in selenium.[136] Suboptimal intakes of zinc, copper, and vitamins C and E were also noted. The scientists concluded, “All women in this population reported dietary intakes of antioxidant vitamins and minerals below recommended values, conditions that could contribute to subsequent health risks unless nutrient-dense food choices and antioxidant supplementation are considered in their overall nutritional support.”

As mentioned previously, a study of patients admitted to a hospital’s infectious disease ward revealed that nearly half of the patients were deficient in selenium.[2] A recent review concluded that the typical diet is often not sufficient to meet the increased demands for micronutrients in infectious diseases, and that supplements containing selenium up to 200 μg per day may be indicated for individuals with viral infections, including HIV and influenza.[87]Further studies suggest that total selenium intakes (from diet and supplementation) greater than 300 μg per day should be avoided.[137]

Conclusion

Zinc and selenium deficiency can be added to the factors predisposing individuals to opportunistic infections, and may increase their severity or the risk of adverse outcomes if infections do occur. Zinc and selenium supplementation may be beneficial for many individuals, especially those with insufficient dietary intakes or with conditions that predispose to infections. This category includes individuals with diabetes, obesity, malabsorption, infections, or other comorbidities; and the elderly. Because deficiencies in multiple immune system nutrients have been reported throughout the population, multi-nutrient supplementation may be particularly helpful.

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