

30 Zn  Zinc	31 Ga  Gallium
48 Cd  Cadmium	49 In  Indium

## Zinc

### Introduction

Zinc is a cofactor in over 300 metalloenzymes, and is able to directly affect gene expression, signal transduction, transcription, and cellular replication through nonenzymatic pathways.<sup>1</sup> Zinc plays a role in the synthesis of protein, fat, and cholesterol, as well serving as a cofactor for SOD, alcohol metabolism, and insulin function. Zinc is also important for its role in the immune system, cell growth and differentiation,

prostate health, and taste perception.

### Biochemistry and Mechanisms of Action

Zinc has anti-inflammatory action mediated through inhibition of nitric oxide formation.<sup>2</sup> There is a greater incidence of chronic diarrhea in zinc-deficient children,<sup>3</sup> and zinc supplementation has historically improved chronic diarrhea in malnourished children.<sup>4</sup>

Zinc acts as an antioxidant through mechanisms outside its role in the antioxidant enzyme superoxide dismutase. Zinc has been shown to protect vitamin E stores,<sup>5</sup> stabilize membrane structures,<sup>6</sup> prevent LDL and VLDL oxidation,<sup>7</sup> protect against carbon tetrachloride-induced hepatitis,<sup>8</sup> and maintain tissue levels of metallothionein, a potential free radical scavenger.<sup>9</sup>

Recent studies exploring the mechanisms of zinc deficiency and immune suppression have shown zinc deficiency (like protein-calorie malnutrition) elevates the production of glucocorticoids through up-regulation of the hypothalamic-pituitary-adrenocortical axis.<sup>10</sup> Emerging research in the mouse model has shown that zinc deficiency, through glucocorticoid release, actually causes a depletion of precursor T and B cells in the bone marrow and thymus, suppressing lymphocyte production.

Zinc has a regulatory role in apoptosis, as it both induces and blocks cellular apoptosis, depending on the cellular concentration.<sup>11</sup> At very high concentrations, zinc can induce apoptosis in immune cells, possibly the mechanism responsible for the immune suppression of high supplemental doses of zinc. Apoptosis plays a role in many disease states, including autoimmune diseases, Alzheimer's and Parkinson's disease, stroke, ischemia, cancer, and HIV infection.<sup>11</sup>

## Pharmacokinetics

Zinc absorption occurs throughout the length of the small intestine, but in greater amount in the jejunum, by active transport and diffusion. Active transport into the bloodstream is mediated by binding to albumin, alpha-2-macroglobulin, or transferrin.<sup>1</sup> Iron, copper, and phytates inhibit zinc absorption.

Zinc is stored in the spleen, muscle, liver, and bone marrow. Other tissues with high concentrations of zinc include the prostate, skin, spermatozoa, and retina. Red and white blood cells also have high concentrations of zinc. Elimination of zinc is primarily through the feces and urine, with smaller amounts eliminated through the skin.

## Deficiency States and Symptoms

Severe zinc deficiency is seen only in combination with protein-calorie malnutrition, long-term intravenous feeding, or in the inherited disorder acrodermatitis enteropathica.<sup>12</sup> Nutritional zinc deficiency, however, has been well documented in otherwise “well-nourished” infants and young children, children and adults with chronic diarrhea, infants and children with impaired physical growth,<sup>13</sup> children at risk for or with a history of pneumonia,<sup>14</sup> and in infants and children with impaired neuropsychological activity.<sup>15,16</sup> Zinc deficiency has also been documented in sickle cell anemia,<sup>17</sup> renal disease, alcoholism, teenage pregnancy,<sup>18</sup> anorexia nervosa, bulimia,<sup>19</sup> the elderly,<sup>20</sup> HIV infection,<sup>21</sup> burn patients, and those with chronic gastrointestinal disease.<sup>12</sup>

Because zinc is crucial in cellular growth and replication, rapidly replicating cells such as embryonic and fetal tissue, cells of the central nervous system, the gastrointestinal system, and the immune system are particularly vulnerable to zinc restriction. Infants, young children, and individuals with acute or chronic infections that necessitate mounting a continuous immune response, as well as people with injuries or illness that requires tissue repair, are most at risk for zinc deficiency.<sup>12</sup>

The immune system is particularly dependent on a steady supply of zinc. Studies in mice with 30 days of sub-optimal zinc intake have shown a 30-80 percent loss of immune function.<sup>22</sup> Alterations in the immune status of human subjects having only minimal zinc deficiencies include defective natural killer function, decreased interleukin-2 production, anergy,<sup>23</sup> and lymphopenia.<sup>22</sup>

Manifestations of severe zinc deficiency include diarrhea, dermatitis, alopecia, and poor wound healing. Signs of mild-to-moderate zinc deficiency include growth retardation (as related to protein metabolism) male hypogonadism, poor appetite, low immunity, rough skin, mental lethargy, and impaired taste acuity (hypogeusia). The symptoms of acrodermatitis enteropathica, an autosomal recessive disease with impaired zinc absorption, exhibit a classic manifestation of zinc deficiency: eczematoid skin lesions, alopecia, diarrhea, and concurrent bacterial and yeast infections.

## Clinical Indications

### *Anorexia Nervosa and Bulimia Nervosa*

Zinc deficiency symptoms, including anorexia, poor growth, weight loss, amenorrhea, and depression are common symptoms occurring in anorexia nervosa.<sup>24</sup> Altered gastrointestinal function that decreases zinc absorption, and high levels of exercise that increase zinc needs are factors that may predispose anorexics to zinc deficiency.<sup>25</sup> Zinc deficiency occurs in 50 percent of anorexia nervosa patients and 40 percent of bulimics.<sup>19,26</sup>

A controlled trial using zinc supplementation in anorexics found a significant increase in body mass index (BMI) in those on 14 mg elemental zinc from oral zinc gluconate.<sup>27</sup> Other trials have also found a significant increase in weight gain with zinc supplementation.<sup>28-31</sup>

### *Pediatric Diarrhea*

In diarrhea, decreased transit time, as well as secretory fluid released in the small intestine, prevents nutrient absorption. Zinc is necessary for regeneration of the absorptive mucosa of the intestine. In infants less than one year old, diarrhea lasting longer than 10 days typically results in low serum zinc levels.<sup>32</sup> This appears to precipitate a cycle of zinc malabsorption and intestinal inflammation that, if unabated, can create chronic intestinal pathology and further lowering of tissue zinc stores.<sup>32</sup> A meta-analysis of studies of zinc supplementation in childhood diarrhea concluded zinc supplementation has a consistent, positive effect on the duration and severity of episodes of diarrhea.<sup>33,34</sup> The doses used in the studies ranged from 20-40 mg elemental zinc per day.

### *Age-Related Macular Degeneration*

Clinical trials using zinc in age-related macular degeneration (AMD) have been based on the phenomenon of high zinc content in the retinal pigment epithelium, the tissue under the retina that nourishes the rods and cones. Using prior studies that provided evidence for pharmacological doses of zinc in prevention of vision loss in AMD,<sup>35</sup> the Age-Related Eye Disease Study (AREDS) assessed the effect of zinc in 3,640 patients with AMD. The study compared zinc alone, antioxidants alone, or zinc plus antioxidants against placebo.<sup>36</sup> The trial, lasting 6.3 years, assessed the effects of (1) antioxidants: vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg; (2) zinc: 80 mg as zinc oxide; and copper, 2 mg as cupric oxide; (3) antioxidants plus zinc; or (4) placebo. Comparison with placebo showed a statistically significant decrease in the risk of developing advanced AMD in the antioxidants-plus-zinc group, i.e., the odds were reduced by 27 percent. The use of zinc (and copper) alone resulted in a 25-percent reduction. When those who had only a small probability of progressing were excluded, the odds for the rest of the participants dropped even more, with 33 percent less likely to progress with both zinc and antioxidants and 30 percent less likely to progress with zinc alone. Those on both antioxidants and zinc were able to reduce their risk of losing vision by one-third.

Epidemiological studies assessing zinc intake in those with AMD found moderate levels of dietary and supplemental zinc – a median intake of 40 mg per day in men and 25 mg per day in women – were not effective in decreasing risk for AMD.<sup>37</sup>

## *Diabetes*

Diabetics have a significant risk for zinc deficiency. Low plasma and erythrocyte levels, abnormal taste acuity, and low levels of plasma thymulin activity have been found in significant proportions among type 1 and 2 diabetics.<sup>38-40</sup>

In murine models of diabetes, zinc supplementation has been shown to lower elevated serum glucose levels and to decrease risk for onset and severity of diabetes in diabetes-prone mice.<sup>41,42</sup> In zinc-deficient women with type 2 diabetes, 30 mg zinc glycinate was used to raise insufficient plasma zinc and 5' nucleotidase activities (a sensitive indicator of zinc status).<sup>40</sup> Zinc supplementation, at 30 mg per day, has also been shown to elevate selenium glutathione peroxidase levels in diabetics with retinopathy.<sup>43</sup> In another study with insulin-dependent diabetics, 660 mg of daily zinc salts were found to significantly improve peripheral neuropathy.<sup>44</sup>

## *HIV/AIDS*

Zinc deficiency has been documented in HIV infection in multiple studies.<sup>21,45</sup> The utility of supplemental zinc in HIV infection has been documented in both pediatric and adult HIV infection. Zinc supplementation has improved CD4 counts, reduced viral load, and reduced risk of recurrent opportunistic infections (specifically *Candidia esophagitis* and *Pneumocystis carinii* pneumonia) in CDC stage IV patients (CD4 cells under 50) on AZT.<sup>46</sup>

Caution has been expressed regarding supplemental zinc in HIV due to the fact that two HIV proteins in viral replication are zinc-dependent. Recent studies, however, have shown zinc finger proteins are also necessary for inactivation of the virus and evidence from feline HIV models implies low zinc levels contribute to the progression of the virus more than they offer protection against viral replication.<sup>46</sup>

## *Other Conditions*

Zinc has been shown to be effective in a number of other disease states. Supplementation has been shown to reduce infectious bronchitis in children<sup>15</sup> and in Downs Syndrome patients.<sup>47</sup> Zinc supplementation has also been shown to decrease risk for infection from leprosy, malaria, and congenital herpes;<sup>46</sup> to slow the progression of Alzheimer's Disease;<sup>48</sup> to decrease prostatic swelling in benign prostatic hypertrophy;<sup>49</sup> to improve mean sperm counts in oligospermia,<sup>50</sup> and to increase the healing rate of gastric and lower limb ulcers.<sup>51,52</sup> Zinc also enhances exercise performance<sup>53</sup> and immune function in the elderly.<sup>54</sup>

## Drug-Nutrient Interactions

Zinc reduces absorption of ciprofloxacin, penicillamine, and tetracyclines. Oral contraceptives and tetracyclines may reduce plasma zinc levels.<sup>55</sup> Zinc absorption is reduced with insufficient gastric acid production and with the use of H<sub>2</sub>-receptor antagonists.<sup>56</sup> It is suggested to take zinc supplements and acid-blocking drugs at separate times during the day.

## Nutrient-Nutrient Interactions

Large doses of zinc may reduce copper absorption. Long-term doses of zinc required to deplete copper are reported to vary from 150 to 5,000 mg per day.<sup>57</sup> Studies in patients with sickle cell anemia who were given 150 mg zinc daily for 3-6 months, and were not supplemented with copper, became neutropenic and copper deficient.<sup>58</sup> As little as 2 mg copper per day can prevent copper deficiency with 150 mg zinc supplementation.<sup>59</sup>

Zinc reduces absorption of oral iron supplementation, and vice-versa.<sup>60-62</sup> This is clinically relevant when using supplemental iron in pregnancy. The inclusion of zinc in prenatal supplements may reduce the potential for iron supplements to adversely influence zinc status in pregnant women, subsequently reducing the risk of intrauterine zinc deficiency.<sup>62</sup>

## Side Effects and Toxicity

Zinc at doses of 30 mg and above often causes stomach upset, nausea, and possible vomiting, an effect that is reduced when zinc is taken with food. Zinc toxicity with associated copper deficiency has been documented in a case of zinc gluconate supplementation at 850-1,000 mg per day for one year. Symptoms included fatigue and dyspnea on exertion. Objective findings included anemia, neutropenia, pallor, and orthostatic pulse changes.<sup>63</sup>

## Dosage

Doses beyond the RDA of 15 mg/day have not been established. Other dosages are condition-specific. It may be important to note that 30 mg elemental zinc as glycinate chelate in studies with diabetics was unable to raise 5' nucleotidase levels to those of controls and was insufficient to normalize serum zinc levels in diabetics with neuropathy.<sup>40</sup> It appears certain populations of diabetics or individuals with malabsorption may need larger amounts of zinc. It is noteworthy that 660-mg doses of zinc salts were used in diabetics to successfully treat peripheral neuropathy symptoms.<sup>44</sup>

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