# Zinc[1]

Zinc was recognized as an essential trace metal for humans during the studies of Iranian adolescent dwarfs in the early 1960s. Zinc metal existing as $Zn^{2+}$ is a strong electron acceptor in biological systems without risk of causing oxidant damage to cells. $Zn^{2+}$ functions in the structure of proteins and is a catalytic component of >300 different enzymes, encompassing almost every aspect of biology, including growth, immune defense, cognitive function, and bone health. Because the zinc ion plays such a fundamental role in the survival of organisms, including humans, its concentration in the body must be adequate and well controlled.

Body zinc homeostasis is regulated by 2 families of zinc transporters, solute-linked carrier (SLC)[2] proteins SLC30A [also called Zinc Transporter (ZNTs)] and SLC39A [also called Zrt- and Irt-like protein (ZIPs)], as well as metallothioneins. In humans, the SLC30A zinc transporter family includes 10 members that transport zinc ions across cell membranes into the extracellular space or move zinc ions across organelle membranes from the cytosol to the organelle. The SLC39A zinc transporter family has 14 members that function in an opposite direction of the SLC30A proteins. Metallothioneins are small cysteine-rich metalloproteins that tightly bind to heavy metal ions, protecting cells from metal toxicity. These proteins work together in concert to balance dietary zinc uptake and endogenous zinc excretion, maintaining cellular zinc concentrations within a narrow physiologic range.

## Deficiencies

Zinc deficiency can result from low dietary intake of zinc, inadequate zinc absorption, increased zinc excretion, or an increased need for zinc (e.g., children and pregnant women). Zinc deficiency is associated with stunted growth, poor appetite, dermatitis, alopecia, hypogonadism, and impaired immune function that can lead to frequent diarrhea and/or upper respiratory tract infection. Severe zinc deficiency caused by low dietary zinc intake is uncommon in the developed world; however, it is seen in patients with inherited or acquired conditions. Individuals with the rare genetic disorder acrodermatitis enteropathica (AE) experience severe zinc deficiency from birth because of mutations in *ZIP4*, which encodes a major intestinal zinc uptake protein. Additionally, lactating mothers who carry mutations in *ZNT2* are not able to provide adequate zinc in breast milk, leading to zinc deficiency in nursing infants. Severe zinc deficiency can also result from certain malabsorption syndromes and from conditions that increase excretion of the mineral, such as prolonged diarrhea. Moreover, severe zinc deficiency has been seen in those undergoing total parenteral nutrition without adequate zinc and in alcoholics.

A milder form of zinc deficiency may be relatively common worldwide; however, the lack of a sensitive and specific biomarker of zinc status hinders scientific study of marginal zinc deficiency in human health. Individuals at risk of zinc deficiency are listed in **Table 1**.

## Diet Recommendations

Updated in 2001, dietary requirements of zinc are based on the amount of dietary zinc needed to match endogenous excretion of the mineral and are calculated through use of a factorial modeling approach. The daily intake requirement, the estimated average requirement, was used to establish the RDA. The estimated average requirement and RDA recommendations are presented in **Table 2** by age and gender group (1).

## Food Sources

Zinc is present in a wide variety of foods, with rich sources being shellfish and red meat. Zinc bioavailability from animal sources is relatively high because of the absence of compounds that inhibit its absorption and the presence of certain amino acids that enhance absorption. Beans, nuts, and whole-grain products are also good sources of zinc, although zinc bioavailability from plant sources is lower because of the presence of phytic acid, which binds zinc and inhibits its absorption.

## Clinical Uses

***Diagnosis of zinc deficiency.*** Zinc deficiency is diagnosed by clinical manifestations, such as dermatitis, alopecia, poor appetite, frequent diarrhea and/or upper respiratory infection, stunted growth in children, and hypogonadism. Low serum zinc concentration is an indicator of zinc deficiency, albeit not a sensitive one.

***Diarrhea (children).*** Zinc supplementation helps reduce the severity and duration of diarrhea in poorly nourished children who are usually zinc deficient.

***AE.*** Zinc supplementation is the only effective treatment for this fatal disease. AE patients are treated with either oral or intravenous zinc, depending on the severity of zinc deficiency, and require lifelong therapeutic zinc supplementation (100 mg/kg per day). The major side effect of long-term, high-dose oral zinc supplementation is zinc-induced copper deficiency and copper deficiency–induced anemia caused by zinc interfering with dietary copper absorption.

***Wilson's disease.*** Wilson's disease is a genetic disorder of copper metabolism. Patients with Wilson's disease have a defect in endogenous copper excretion. Thus, copper accumulates in tissues, such as liver and brain, causing neurologic or


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**TABLE 1 Individuals at risk of zinc deficiency**

| |
|---|
| Malnourished individuals |
| Individuals with severe or persistent diarrhea |
| Premature or low-birth-weight infants |
| Children and adolescents |
| Pregnant and lactating women |
| Individuals with malabsorption syndromes |
| Individuals with inflammatory bowel disease (Crohn's disease, ulcerative colitis) |
| Patients with chronic kidney disease, especially those on hemodialysis |
| Individuals with sickle cell anemia |
| Patients who have undergone gastric by-pass surgery |
| Alcoholics |
| Vegetarians |
| Adults ≥65 y of age |

psychiatric symptoms and liver disease. Therapeutic zinc supplementation has been used for the treatment of Wilson's disease because zinc can compete with copper for absorption in the gut.

***Patients with kidney failure.*** Regular hemodialysis results in endogenous zinc loss. Zinc supplements, along with other minerals like copper and iron, are commonly prescribed to hemodialysis patients.

***Other conditions.*** Zinc supplementation is used in patients with severe burns or sickle cell anemia. Zinc generally enhances immune function and decreases incidence of infections.

## Toxicity

Zinc toxicity is rare because of homeostatic regulation of body zinc concentrations at sites of dietary zinc absorption (small intestine) and endogenous zinc excretion (pancreatic exocrine acini, intestinal tract, and kidneys). However, long-term zinc supplementation over the tolerable upper intake level (40 mg/d for adults) can interfere with copper absorption and cause copper deficiency.

## Recent Research

Zinc has been implicated in all aspects of human biology. Here, we briefly highlight recent progress of zinc research in immune function, diabetes, and cancer.

***Zinc and immune function.*** Zinc is essential for normal development and function of the immune system because zinc is a cofactor for many proteins involved in immune regulation (2). Abnormal zinc homeostasis in immune cells also increases the risk of infection. A substantial body of work has been performed in adaptive immunity, where zinc deficiency affects the thymus, resulting in decreased T-cell maturation/activation and altered Th1/Th2 response. Zinc deficiency also negatively affects humoral immunity by impairing B-cell development and differentiation in response to immune stimuli. The zinc transporter ZIP10 plays a critical role in B-cell antigen receptor signal transduction and early B-cell development (3). More recently, the role of zinc in inflammatory cells has also been established. Intracellular zinc concentrations are vital in the maturation of dendritic cells, a subpopulation of immune cells involved in the inflammatory response. ZIP6 has been shown to play a role in this activation of dendritic cells. In humans, zinc supplementation has been associated with decreased inflammatory responses in populations susceptible to zinc deficiency, including sickle cell patients and the elderly.

***Zinc, insulin, and susceptibility to diabetes.*** The insulin-producing pancreatic β-cell, which contains some of the highest concentrations of zinc in the body, functions in insulin synthesis, maturation, secretion, and signaling. Decreased pancreatic zinc concentrations have been found in diabetic patients and in mouse models of type 2 diabetes (T2D) (4). Notably, maternal zinc deficiency increases offspring susceptibility to increased body mass, glucose intolerance, and impaired insulin secretion. Together, these data have prompted significant interest in the relation between zinc and T2D. Genome-wide association studies have identified variants in *ZNT8* with increased risk of T2D. ZNT8 is responsible for transporting zinc into the insulin secretory granule, and other studies have confirmed that the Arg325 *ZNT8* variant could play a role in the development of autoimmune type 1 diabetes. However, a more recent study identified some rare loss-of-function *ZNT8* mutations in humans that are associated with protection against T2D (5), suggesting the role of ZNT8 as a therapeutic target and early risk identifier is more complex than originally thought.

***Zinc, oxidative stress, and cancer.*** Decreases in serum zinc concentrations are found in several types of cancer patients, including head and neck, lung, breast, liver, stomach, and prostate. In addition to the function of zinc in antioxidant and DNA damage defense, zinc plays a crucial role in pathways involving inflammation, cell signaling, apoptosis, and cell

**TABLE 2** DRIs for zinc (mg/d)[1]

| | EAR, mg/d | | RDA, mg/d | | | |
|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | AI | UL |
| Age | | | | | | |
| 0–6 mo | — | — | — | — | 2 | 4 |
| 7–12 mo | 2.5 | 2.5 | 3 | 3 | — | 5 |
| 1–3 y | 2.5 | 2.5 | 3 | 3 | — | 7 |
| 4–8 y | 4 | 4 | 5 | 5 | — | 12 |
| 9–13 y | 7 | 7 | 8 | 8 | — | 23 |
| 14–18 y | 8.5 | 7.3 | 11 | 9 | — | 34 |
| ≥19 y | 9.4 | 6.8 | 11 | 8 | — | 40 |
| Pregnant, ≤18 y | — | 10 | — | 12 | — | 34 |
| Pregnant, 19–50 y | — | 9.5 | — | 11 | — | 40 |
| Lactating, ≤18 y | — | 10.9 | — | 13 | — | 34 |
| Lactating, 19–50 y | — | 10.4 | — | 12 | — | 40 |

[1] AI, adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

invasion. In particular, zinc may be important during prostate cancer malignancy (6). The prostate contains the highest concentrations of zinc of all soft tissues, and these concentrations dramatically decrease during the development of prostate cancer. The reduction of intraprostatic zinc concentrations in prostate cancer tissue is concomitant with decreases in ZIP1, ZIP2, and ZIP3 expression. Despite early in vitro and preclinical studies using zinc supplementation, the benefit of increasing zinc intake to protect against prostate cancer in humans remains controversial and has yielded conflicting results. However, measuring zinc concentrations in prostatic secretions has shown promise as a tool for early prostate cancer detection with greater specificity and sensitivity than prostate-specific antigen screening (7).

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Liping Huang
USDA/Agricultural Research Service/Western Human Nutrition Research Center, University of California Davis, Davis, CA

Victoria J Drake
Linus Pauling Institute, Oregon State University, Corvallis, OR

Emily Ho*
Moore Family Center and Linus Pauling Institute, Oregon State University, Corvallis, OR

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[2]Abbreviations used: AE, acrodermatitis enteropathica; SLC, solute-linked carrier; T2D, type 2 diabetes; ZIP, Zrt- and Irt-like protein; ZNT, Zinc Transporter.

*To whom correspondence should be addressed. E-mail: emily.ho@oregonstate.edu.

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