

Zinc: An Essential Micronutrient

ROBERT B. SAPER, MD, MPH, and REBECCA RASH, MA, *Boston University School of Medicine, Boston, Massachusetts*

Zinc is an essential micronutrient for human metabolism that catalyzes more than 100 enzymes, facilitates protein folding, and helps regulate gene expression. Patients with malnutrition, alcoholism, inflammatory bowel disease, and malabsorption syndromes are at an increased risk of zinc deficiency. Symptoms of zinc deficiency are nonspecific, including growth retardation, diarrhea, alopecia, glossitis, nail dystrophy, decreased immunity, and hypogonadism in males. In developing countries, zinc supplementation may be effective for the prevention of upper respiratory infection and diarrhea, and as an adjunct treatment for diarrhea in malnourished children. Zinc in combination with antioxidants may be modestly effective in slowing the progression of intermediate and advanced age-related macular degeneration. Zinc is an effective treatment for Wilson disease. Current data do not support zinc supplementation as effective for upper respiratory infection, wound healing, or human immunodeficiency virus. Zinc is well tolerated at recommended dosages. Adverse effects of long-term high-dose zinc use include suppressed immunity, decreased high-density lipoprotein cholesterol levels, anemia, copper deficiency, and possible genitourinary complications. (*Am Fam Physician*. 2009;79(9):768-772. Copyright © 2009 American Academy of Family Physicians.)

Zinc is the second most abundantly distributed trace element in the body after iron.¹ Zinc catalyzes enzyme activity, contributes to protein structure, and regulates gene expression.² It is found in a variety of foods, such as beef, poultry, seafood, and grains.^{2,3} Commercial zinc supplements contain 7 to 80 mg of elemental zinc, and are commonly formulated as zinc oxide or salts with acetate, gluconate, and sulfate. In the 2002 National Health Interview Survey, 2.5 percent of adults reported using zinc supplements in the previous year.⁴ Multivitamins were used by 62 percent of adults and contain 7.5 to 15 mg of elemental zinc.⁴ Zinc supplements are commonly used to alleviate a number of conditions, including zinc-deficient states, diarrhea, age-related macular degeneration, upper respiratory infection (URI), wound healing, and human immunodeficiency virus (HIV).

Pharmacology

Zinc is absorbed in the small intestine. Prolonged, severe decreases or increases in zinc intake are necessary to substantially affect zinc stores.⁵ Zinc is a cofactor for polymerases and proteases involved in many cellular functions (e.g., wound repair,⁶ intestinal epithelial cell regeneration).⁷ Zinc is also a cofactor for thymulin, a thymic hormone essential for T-cell maturation.⁸ Zinc has antioxidant

properties and may protect against macular degeneration from oxidative stress.⁹

Uses and Effectiveness

ZINC DEFICIENCY

Zinc deficiency caused by malnutrition is the 11th major risk factor in the global distribution of disease burden and is associated with 1.8 million deaths annually.¹⁰ Serum zinc levels are not a reliable measure of zinc stores and, therefore, are not recommended for routine screening. A presumptive diagnosis of zinc deficiency can be made in the context of zinc-deficiency symptoms, signs of malnutrition (e.g., underweight, hypoalbuminemia), or conditions commonly associated with zinc deficiency (*Table 1*).^{1,2} A meta-analysis of 33 randomized controlled trials (RCTs) enrolling prepubertal children from North and South America, Europe, Africa, and Asia who were at risk of zinc deficiency showed that zinc supplementation modestly enhanced linear growth and weight gain (effect sizes of 0.35 and 0.31, respectively) compared with the control group.¹¹

DIARRHEA

A meta-analysis of 22 RCTs of zinc supplements versus placebo for the treatment of diarrhea in children from developing countries found an 18 percent reduction of diarrhea symptoms compared with placebo.¹² A meta-analysis of 15 prevention studies

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Zinc reduces the severity and duration of acute and chronic diarrhea in children from developing countries.	A	12, 13
Zinc acetate is an effective maintenance therapy for Wilson disease.	B	35, 36
Clinical zinc deficiency in adults should be treated with zinc supplements at two to five times the recommended dietary allowance.	C	40, 41
Zinc in combination with vitamins C and E, and beta-carotene may slow the progression of intermediate and advanced age-related macular degeneration.	B	14

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

demonstrated that zinc supplementation conferred a 14 percent reduced risk in the incidence of diarrheal episodes compared with placebo.¹³ It is uncertain if zinc's effect on diarrhea is because of an independent effect or repletion of zinc deficiency. No data are available for zinc and childhood diarrhea in industrialized countries.

AGE-RELATED MACULAR DEGENERATION

The evidence supporting zinc and antioxidants for slowing the progression of age-related macular degeneration comes predominantly from the Age-Related Eye Disease Study (AREDS).^{14,15} AREDS randomized 3,640 mostly well-nourished adults 55 to 80 years of age with age-related macular degeneration to oral zinc oxide, antioxidants (vitamin C, vitamin E, beta-carotene), zinc plus antioxidants, or placebo. For participants with intermediate age-related macular degeneration (i.e., many medium-sized drusen or at least one large drusen) or advanced age-related macular degeneration (i.e., breakdown of

light-sensitive cells and support tissues with or without blood vessel fragility and edema ["wet" or "dry" age-related macular degeneration, respectively]), the zinc plus antioxidant group had a modest reduced risk of worsening visual acuity compared with placebo (27 percent, $P = .008$). However, there were increased hospitalizations because of urinary tract infections and nephrolithiasis in the two zinc arms versus non-zinc arms (11.1 versus 7.6 percent; $P = .003$).¹⁶ It would be prudent for smokers at risk of advanced age-related macular degeneration to refrain from taking the beta-carotene component because of the increased risk of lung cancer in smokers taking this supplement.¹⁷ The value of zinc plus antioxidants is unknown in persons younger than 55 years, those with a family history of age-related macular degeneration, and those with a different nutritional status.

There are no published RCTs addressing zinc for the primary prevention of early age-related macular degeneration.¹⁸ Results of prospective cohort studies are mixed. A meta-analysis of four such studies found an odds ratio of 0.91 (95% confidence interval [CI], 0.74 to 1.11) for the association between high zinc intake and early age-related macular degeneration.¹⁹ A subsequent cohort study found the highest decile of zinc intake for Australian adults to be associated with a 44 percent reduction in the risk of age-related macular degeneration.²⁰

URI

A meta-analysis including 12 RCTs with a total of 5,512 children in developing countries found a reduction in URI incidence in those using zinc supplements compared with placebo (8 percent; 95% CI, 1 to 15 percent).¹³ Regarding treatment, a meta-analysis of eight RCTs with 890 predominantly adult participants with URI in industrialized countries who were treated with zinc lozenges found no

Table 1. Characteristics of Zinc Deficiency

Symptoms

Growth retardation, delayed puberty, erectile dysfunction, diarrhea, alopecia, glossitis, nail dystrophy, hypogonadism (in males), decreased immunity^{1,2}

Associated diseases

Crohn disease, celiac disease, chronic alcoholism, cirrhosis, sickle cell disease, acrodermatitis enteropathica

Associated conditions

Pregnancy, lactation, prolonged intravenous feeding, vegan diet, short bowel syndrome, history of intestinal surgery (e.g., gastric bypass)

Information from references 1 and 2.

Zinc

evidence of a statistically significant reduction in duration.²¹ Methodologic problems included poor blinding, small sample size, high drop-out rates, and variability in zinc dosage and formulation. Subsequent studies in adults²²⁻²⁵ and children^{26,27} showed similarly mixed results. Overall, robust data are lacking for the effectiveness of zinc lozenges in reducing the duration or severity of URI.

WOUND HEALING

Zinc deficiency is associated with impaired wound healing.²⁸ Although zinc is a common ingredient in topical products used to treat skin conditions such as ulcers, diaper rash, and hemorrhoids, relatively few studies support its use for accelerating wound healing. An RCT of 46 infants with diaper dermatitis found no significant difference in resolution between zinc oxide ointment and ointment base alone.²⁹ A meta-analysis of 181 participants from six RCTs of oral zinc sulfate versus placebo for venous or arterial leg ulcers found no significant difference in time to ulcer resolution.³⁰ An RCT comparing surgical mesh impregnated with zinc oxide ointment versus mesh with ointment base alone found no statistically significant difference in time to secondary closure of pilonidal surgery wounds.³¹

OTHER USES

Zinc deficiency is associated with the rapid progression of HIV.³² However, most RCTs of zinc in persons who are HIV positive have shown no increase in CD4 cell counts or decrease in viral load.^{33,34} Wilson disease can be successfully treated with zinc because of its ability to compete with copper for binding sites.³⁵ Zinc acetate has been shown to be effective in the long-term treatment of Wilson disease and is approved by the U.S. Food and Drug Administration for maintenance therapy.³⁶ Although oral zinc has been used for acne, minocycline (Dynacin) is twice as effective.³⁷

Contraindications, Adverse Effects, and Interactions

Chronic ingestion of zinc supplements up to the tolerable upper intake level (40 mg elemental zinc per day in adults) is generally considered safe. Use of zinc supplements above the tolerable upper intake level in well-nourished pregnant and lactating women is contraindicated.² Common adverse effects of excessive zinc intake include metallic taste, nausea, vomiting, abdominal cramping, and diarrhea (*Table 2*).² Prolonged exposure to amounts greater than the tolerable upper intake level

Table 2. Key Points About Zinc Supplements

Effectiveness	Probably effective: zinc deficiency; Wilson disease Possibly effective: slow progression of age-related macular degeneration; childhood diarrhea and URI in developing countries Probably ineffective: URI, wound healing, human immunodeficiency virus
Adverse effects	Metallic taste, nausea, vomiting, abdominal cramping, diarrhea, suppressed immunity, reduced levels of high-density lipoprotein cholesterol, decreased copper stores, urinary tract infection, nephrolithiasis
Interactions	Penicillamine (Cuprimine), tetracyclines, quinolones; decreased copper absorption
Contraindications	Use with caution in pregnant and lactating women
Dose*	Zinc deficiency: two to five times the recommended dietary allowance† (depending on severity) for six months Diarrhea: 5 to 20 mg Age-related macular degeneration: 80 mg of elemental zinc with 2 mg of copper, 500 mg of vitamin C, 400 IU of vitamin E, 15 mg of beta-carotene Dose should not exceed the tolerable upper intake level‡ for prolonged periods
Cost	\$4 to 15 for three-month supply
Bottom line	Safe at doses less than or equal to the tolerable upper intake level‡; useful for zinc deficiency, Wilson disease, and childhood diarrhea in malnourished populations; possibly useful in combination with antioxidant supplements for slowing the progression of age-related macular degeneration

URI = upper respiratory infection.

*—All doses are for milligrams of elemental zinc per day.

†—Recommended dietary allowance² (by age) = 0 to 6 months: 2 mg; 7 months to 3 years: 3 mg; 4 to 8 years: 5 mg; 9 to 13 years: 8 mg; 14 to 18 years: 11 mg (boys), 8 mg (girls); older than 19 years: 11 mg (men), 8 mg (women); pregnancy: 11 mg; lactation: 12 mg.

‡—Tolerable upper intake level per day² (by age) = 0 to 6 months: 4 mg; 7 to 12 months: 5 mg; 1 to 3 years: 7 mg; 4 to 8 years: 12 mg; 9 to 13 years: 23 mg; 14 to 18 years: 34 mg; older than 18 years: 40 mg.

may suppress immunity, decrease high-density lipoprotein cholesterol levels, and cause hypochromic microcytic anemia and copper deficiency.³⁸ Furthermore, the Health Professionals Follow-up Study of 46,974 adult men found a 2.3 increased relative risk of advanced prostate cancer in men using elemental zinc in amounts of 100 mg per day or more.³⁹ Zinc may inhibit absorption of penicillamine (Cuprimine), tetracyclines, and quinolones. Iron supplements and phytates, found in grains and legumes, can inhibit zinc absorption and should be taken at least two hours apart from zinc supplements.

Dosage

Mild zinc deficiency should be treated with zinc supplementation at two to three times the recommended dietary allowance (RDA), whereas moderate to severe deficiency can be treated at four to five times the RDA.^{40,41} Treatment should last for six months. For acute diarrhea in malnourished children six to 36 months of age, 20 mg per day of elemental zinc has been used.¹² To slow the progression of age-related macular degeneration, 80 mg of elemental zinc with 2 mg copper should be used daily in combination with 500 mg of vitamin C, 400 IU of vitamin E, and 15 mg of beta-carotene.¹⁴ Table 3 lists common oral zinc preparations.

Bottom Line

Despite zinc's many essential roles in human physiology, no robust data support zinc supplementation alone for persons with a normal zinc status. However, zinc in combination with antioxidants may be modestly effective in slowing the progression of age-related macular degeneration. In children living in developing areas of the world, zinc supplementation may be an

effective preventive measure for diarrhea and URI, and an adjunct treatment for diarrhea. Zinc has been shown to be an effective treatment for Wilson disease. No consistent benefit of zinc has been found for treatment of URI, wound healing, or HIV. Ongoing zinc supplementation up to the tolerable upper intake level is generally safe. Higher doses should be limited to short-term use because of an increased risk of gastrointestinal adverse effects, copper deficiency, anemia, and genitourinary complications.

Members of various family medicine departments develop articles for "Complementary and Alternative Medicine." This is one in a series coordinated by Sumi Sexton, MD, and Benjamin Kligler, MD, MPH.

The Authors

ROBERT B. SAPER, MD, MPH, is an assistant professor of family medicine at Boston University School of Medicine, Boston, Mass., and director of integrative medicine in the Department of Family Medicine at Boston Medical Center. Dr. Saper received his medical degree from Harvard Medical School, Boston, Mass., and completed a family medicine residency at the University of California, San Francisco. He completed a research fellowship in complementary and alternative medicine at Harvard Medical School and Harvard School of Public Health.

REBECCA RASH, MA, earned her master of arts degree in medical nutrition sciences from the Department of Family Medicine at Boston University School of Medicine.

Address correspondence to Robert B. Saper, MD, MPH, Boston Medical Center, Department of Family Medicine, One Boston Medical Center Place, Dowling 5 South, Boston, MA 02118 (e-mail: robert.saper@bmc.org). Reprints are not available from the authors.

Author disclosure: Dr. Saper received a Career Development Award (K07 AT002915-03) from the National Center for Complementary and Alternative Medicine, National Institutes of Health.

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Table 3. Common Oral Zinc Preparations

Zinc preparation	Elemental zinc (mg)
Zinc acetate, 30% zinc, 25 mg	7.5
Zinc acetate, 30% zinc, 50 mg	15
Zinc gluconate, 14.3% zinc, 50 mg	7
Zinc gluconate, 14.3% zinc, 100 mg	14
Zinc sulfate, 23% zinc, 110 mg	25
Zinc sulfate, 23% zinc, 220 mg	50
Zinc oxide, 80% zinc, 100 mg	80

NOTE: The standard ingredient labels for dietary supplements provide the name of the form of zinc in the product (e.g., zinc [as zinc sulfate]) and the amount of elemental zinc in milligrams.

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