Pharmacology and therapeutics

Evidence supporting zinc as an important antioxidant for skin

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Abstract

Antioxidants play a critical role in keeping skin healthy. The antioxidant benefits of vitamin C and E are well known, but the importance of the trace mineral, zinc, has been overlooked. This article reviews the evidence supporting zinc's antioxidant role in protecting against free radical-induced oxidative damage. Zinc protects against UV radiation, enhances wound healing, contributes to immune and neuropsychiatric functions, and decreases the relative risk of cancer and cardiovascular disease. All body tissues contain zinc; in skin, it is five to six times more concentrated in the epidermis than the dermis. Zinc is required for the normal growth, development and function of mammals. It is an essential element of more than 200 metalloenzymes, including the antioxidant enzyme, superoxide dismutase, and affects their conformity, stability, and activity. Zinc also is important for the proper functioning of the immune system, and for glandular, reproductive and cell health.

Abundant evidence demonstrates the antioxidant role of zinc. Topical zinc, in the form of divalent zinc ions, has been reported to provide antioxidant photoprotection for skin. Two antioxidant mechanisms have been proposed for zinc: zinc ions may replace redox active molecules, such as iron and copper, at critical sites in cell membranes and proteins; alternatively, zinc ions may induce the synthesis of metallothionein, sulfhydryl-rich proteins that protect against free radicals. No matter how they work, topical zinc ions may provide an important and helpful antioxidant defense for skin.

Introduction

In this article we review the role of zinc in the body, manifestations of severe and mild zinc deficiency, the role of zinc as an antioxidant, the potential mechanisms of this antioxidant function, and evidence that it protects skin.

Zinc and the body

Zinc is present in all organs, tissues, and fluids of the body. The skin and appendages are rich in zinc: containing approximately 20% of the body's total.[1,2] Zinc binds to a number of biologic molecules and influences their conformation, stability and activity. Zinc serves as a catalyst for enzymes responsible for DNA replication, gene transcription, and RNA and protein synthesis. At the cellular level, zinc is critical for cell survival and affects signal transduction, transcription and replication.[3,4] Zinc is important for several human functions, including growth and development, bone metabolism, neuropsychiatric and immune functions, and wound healing.[1] In addition, zinc decreases the relative risk of cancer and cardiovascular disease[5] and protects against ultraviolet radiation.[2]

Zinc was not considered an essential human nutrient until 1974 when the National Research Council set a recommended daily allowance for oral intake of 15 milligrams.[6] Interestingly, 40 years earlier zinc was reported to be required for normal growth and development in rats.[7]

In humans, zinc is absorbed in the jejunum and ileum. Body control mechanisms make it difficult to ingest too much zinc.[1] However, negative zinc balances are possible, and in rats only a few days of a zinc-deficient diet are needed before a rapid reduction in DNA synthesis occurs.[8] Approximately 99% of the total body's zinc is intracellular. In plasma, zinc is almost completely protein bound.[9] Good food sources of zinc include seafood, beef, lamb, eggs, whole grains, nuts and yogurt.[10] To maximize absorption, oral supplements should contain zinc with methionein, an amino acid that is easily absorbed; vitamin B_6 (pyridoxine) also helps with zinc assimilation. Calcium can retard zinc absorption, so calcium and zinc supplements should be taken at different times of the day.

International Journal of Dermatology 2002, 41, 606–611

Severe zinc deficiency: acrodermatitis enteropathica

Acrodermatitis enteropathica is a rare inherited disorder caused by an inability to absorb sufficient zinc from diet. Before its discovery in 1973 by Moynahan and Barnes, acrodermatitis enteropathica was typically fatal in infancy or early childhood; subsequently, dietary supplementation with zinc salts were used to alleviate symptoms with dramatic and rapid improvement. Acrodermatitis enteropathica is the model of severe zinc deficiency and has helped in the recognition of severe zinc deficiency in other clinical situations.[9,12]

The clinical manifestations of zinc deficiency affect multiple organ systems. Symptoms are nonspecific, and often go unrecognized. The presence of the classic tetrad of neuropsychiatric abnormalities, circumorificial and acral dermatitis, alopecia and diarrhea should alert the clinician to zinc deficiency.[13]

One of the earliest features of severe zinc deficiency is anorexia. Smell and taste dysfunction, mood changes, and cognitive impairment are subsequent neuropsychiatric manifestations of acute zinc loss.[9,14] Indeed some adults with acrodermatitis enteropathica have been misdiagnosed with psychiatric illnesses described as "schizoid" and "depressive".[15,16] Likewise, zinc-deficient infants are irritable and difficult to console.

Growth impairment or failure to thrive is a common feature of children with acrodermatitis enteropathica.[13] Impaired growth is also a notable feature in other causes of zinc deficiency, and acceleration in growth rate is observed after zinc replacement therapy.[12,16–18]

The dermatologic features of zinc deficiency are characteristic and allow early diagnosis of the condition. The earliest cutaneous change is erythema and scaling in the nasolabial and retro-auricular folds. Later, the neck, inguinal, axillary and perineal skin become involved. At the same time, angular cheilitis, stomatitis and glossitis may be present. Areas including the knees, elbows, heels and occipital scalp, which are prone to friction and trauma, are frequently involved.[13] Characteristically, the rash is symmetric and consists of orange-brown, erosive and crusted, well-demarcated patches or plaques. With time, these plaques may be hyperkeratotic and resemble psoriasis.[13,19] Vesicular or bullous lesions may occur on the fingertips and palms. Nail changes may be observed with brown discoloration and paronychia commonly reported.[19] Beau's lines, transverse depressions across the nail plates, have been reported in acrodermatitis enteropathica and may occur with white transverse bands.[19]

Ocular abnormalities also have been reported in severe zinc deficiency and include conjunctivitis, xerosis and keratomalacia, blepharitis and corneal edema leading to clouding and opacities.[13] Gastrointestinal symptoms of bulky, frothy, watery stools are seen less often today because of earlier diagnosis of zinc deficiency.[13] Relief of bowel symptoms ensues with zinc supplementation.[11,13]

Immunologic deficits have been documented in zinc deficiencies. In both animals and humans, zinc deficiency has been associated with a decreased number of T lymphocytes, decreased T-cell mitogen response, and diminished T helper and NK-cell cytotoxic function. In both animals and humans with zinc deficiency, depression of delayed-type hypersensitivity has been observed, and improvement noted with zinc supplementation.[20,21]

Mild zinc deficiency

The existence and definition of "mild" zinc deficiency is controversial.[21] Isolated zinc deficiency has been documented during periods of rapid growth such as infancy, childhood, and adolescence.[13,21] During pregnancy, there is a significant gradual decrease in plasma zinc that is not explained by the physiologic alterations of the pregnant state.[22,23] Several studies have demonstrated associations between low plasma zinc and complications of pregnancy or abnormal fetal development.[21] However, these studies lack consistency, often involve populations at high risk for zinc deficiency and obstetric complications (e.g. low income, adolescent populations), and are not double blind.

Elderly patients typically have low body stores of zinc. In a randomized controlled trial, the impact of supplemental zinc on immunity in an elderly population was evaluated.[24] Elderly patients who received daily zinc supplementation (20 mg/day) demonstrated improved humoral responses after vaccination.[24]

Mild zinc deficiency has also been reported in various disease states, including those that involve[1] absorption abnormalities, such as cystic fibrosis and inflammatory bowel disease;[2] conditions of excessive zinc loss via urine and hemolysis, such as alcoholism, insulin-dependent diabetes and sickle cell anemia;[3] increased zinc requirements, such as growth hormone replacement therapy.[21,25]

Unlike severe zinc deficiency, epithelial tissues are not affected prominently in states of mild deficiency. It is important to note, however, that the epidermis contains five to six times more zinc than the dermal layer.[7] Nonetheless, xerotic or roughened skin and impaired wound healing have been reported in association with mild zinc deficiency, implicating changes in skin.[21]

Antioxidant role of zinc: systemic effects

Multiple studies in humans suggest that zinc may have a protective effect against free radical generation and oxidative stress. Zinc levels influence many conditions mediated by oxidative damage, including cutaneous and rheumatologic inflammatory diseases, alcoholism and liver cirrhosis, and cardiovascular diseases.

Reactive oxygen species are a major cause of tissue injury in inflammatory conditions. Evidence supports the benefits of zinc in certain inflammatory disorders including rheumatoid arthritis, acne, acne rosacea, and dissecting cellulitis of the scalp. Decreased plasma zinc levels have been reported in rheumatoid arthritis patients when compared with normal controls.[26,27] Numerous studies have shown the benefits of either topical or oral zinc in the treatment of acne, possibly through anti-inflammatory effects.[28] High doses of oral zinc therapy have been reported to completely resolve dissecting cellulitis of the scalp in at least one patient.[29]

Free radical injury has been proposed as a cause of liver damage and cirrhosis, with decreased zinc levels and increased oxidized lipid levels observed in many cirrhotic patients.[30] These findings further support the hypothesis that zinc deficiency is associated with oxidative damage. In rats, zinc has been shown to protect against carbon tetrachloride-induced liver damage, which is mediated via a free radical pathway.[31] Alcohol increases lipid peroxidation, and zinc has been shown to reduce alcohol-induced liver damage in mice.[32] In animal studies, the antioxidant function of zinc has also been shown to prevent toxicity to lung and renal tissue, as well as to platelets, erythrocytes and leukocytes.[33] In rats, the carcinogenic effects of subcutaneous injected cadmium in rat testes were reduced (50%) with subcutaneous zinc administration and almost eliminated (92%) with oral zinc treatment.[34] In mice, whole body radiation induces a systemic pro-oxidant effect, the toxicity of which may be prevented by the administration of zinc.[35] Zinc may exert this protective antioxidant effect by stabilizing lipid membranes and preventing lipid peroxidation by free radicals.

Free radical injury also plays a major role in the development of arteriosclerosis, cardiovascular disease, and cancer. In humans, several studies suggest zinc has a role in protecting against oxidative damage. Compared with healthy controls, patients with coronary artery disease exhibited significantly lower plasma zinc levels.[36,37] In a study of 178 elderly Italian patients, those who received zinc supplements (25 mg) had decreased serum lipid peroxides.[37] In a large cohort of 10,532 Dutch patients who were followed for 6–9 years, a decrease in the relative risk for cancer and cardiovascular disease was noted in those patients whose serum zinc was in the highest quintile.[5] Another study demonstrated an inverse association between zinc intake and coronary artery disease in rural and urban populations in India. The study showed a positive correlation between lower intake of dietary zinc, lower serum zinc levels and the prevalence of coronary artery disease and diabetes.[38]

Reactive oxygen species have been shown to have a significant role in UV radiation-induced injury. In cultured skin fibroblasts exposed to UVA and UVB, zinc was protective against cytotoxicity and lipid peroxidation.[38–40] When zinc was added to an immortalized human keratinocyte cell line, it decreased both the amount of DNA damage following UVB exposure and also the number of nucleosomes observed, a marker of apoptosis or cell death. Apoptosis, as detected by increased nucleosomes, increased with the addition of a cell-diffusible zinc chelator.[41]

In a mouse model of UV immunosuppression, oral zinc supplements reduced the immunosuppression to contact hypersensitivity caused by three minimal erythema doses of UVB light. Immunohistologic studies of skin revealed increased epidermal metallothionein in zinc-supplemented animals. When similar studies were conducted in transgenic mice with null mutations in metallothionein-I and metallothionein-II genes, significantly more UV immunosuppression was demonstrated, and this effect was not altered by zinc supplements. These studies were compatible with the hypothesis that zinc induction of metallothionein in skin is protective against UV immunosuppression.[2,42]

Antioxidant role of zinc: topical effects

Topical zinc ions traverse skin and can be found in dermis and blood.[43,44] A recent study demonstrated zinc concentrations in skin could be increased eightfold by topical application of $ZnSO_4$. A concentration of 3% was optimal. Topical zinc sulfate induced mRNA for metallothionein.[45] Zinc oxide is extremely insoluble and would not be expected to be similarly active. Topical application of 1% $ZnCl_2$ has been shown to protect mouse skin against UVA- and UVB-induced sunburn cell formation.[46] Percutaneous absorption of zinc salt was demonstrated by increased zinc concentrations in skin. Topical application of zinc ions has been shown to induce metallothionein, which may account for its photoprotective effect.[47] Induction of metallothionein by subcutaneous injection of $CdCl_2$, an inducer of metallothionein similar to zinc ion, protected skin from UVB-induced injury, measured by sunburn cells.[48]

Mechanism of action theories

The mechanism of action for zinc's antioxidant effects is unknown. However, two options are suggested: redox stable Zn^{++} may replace redox reactive metals such as iron and copper at critical cellular or extracellular sites, and/or Zn^{++} may induce metallothionein synthesis, forming a zinc-thiolate moiety that functions as a preferred sacrificial site for oxidant attacks, preserving skin and its components. Figure 1 outlines these two options.

In the first theorized mechanism, zinc demonstrates site-specific antioxidant effects when binding to cell membranes and some proteins by competing with and displacing redox-active metals, such as iron and copper.[48] Iron and copper are able to transfer electrons and produce reactive oxygen species including HO· and O_2^-. Zinc, on the other hand, has a single

Mechanism 1:

Replacement of redox reactive metals Fe^{++} and Cu^{+} by redox nonreactive Zn^{++}

Example is given for Fe^{++} but similar reactions occur with Cu^{+}. Although free Fe^{++} and Cu^{+} are unusual in vivo (i.e., they are bound strongly by binding proteins), they can be present in ligand binding to DNA or cell membranes. In the presence of H_2O_2 (which can be produced directly by oxidases or through the dismutation of superoxide generated by ultraviolet radiation or inflammation), the highly destructive hydroxyl radical HO· may be produced resulting in structural damage or DNA mutation.[55]

$$Fe^{++}\text{-ligand} + H_2O_2 \rightarrow Fe^{+++}\text{-ligand} + OH^{-} + HO\cdot$$

When Zn^{++} replaces Fe^{++} in the ligand, the destructive reaction is precluded. Moreover, the resultant free Fe^{++} can then be captured by protective binding proteins ferritin in the intracellular space and transferrin in the extracellular compartment.

$$Fe^{++}\text{-ligand} + Zn^{++} \rightarrow Zn^{++}\text{-ligand} + Fe^{++}$$

$$Fe^{++} + \text{ferritin, transferrin} \rightarrow \text{Fe-ferritin, -transferrin}$$

Mechanism 2:

Zn^{++} induces the synthesis of metallothionein, a sulfhydryl rich family of proteins

The zinc-thiolate moiety resulting from the binding of zinc to metallothionein appears to be a preferential target of oxidant injury.[56,57] Zinc-metallothionein may function as a preferred sacrificial substrate for oxidant attacks providing protection for cells and surrounding tissues.

Figure 1 Proposed mechanism of action theories for the antioxidant role of zinc

ionization state at physiologic pH and is redox stable.[50] Zinc competes with iron and copper for binding ligands and thus may decrease free radical production at the ligand-binding site.[51] Iron and copper are inactivated by binding specific proteins when displaced from ligand binding; iron is bound by ferritin or transferrin, and copper is bound by copper chaperone protein or ceruloplasmin.[49]

In the other theorized mechanism, the protective effect of zinc in photo-oxidative stress may be related to zinc's induction of and binding to metallothionein. Metallothionein is a family of at least 16 low molecular weight proteins (6000–10,000 Da) with high cysteine content (approximately 1/3).[51] Heavy metals, IL-1, EGF, interferon, glucocorticoid, and ionizing radiation induce its expression.[48,52,53] Metallothionein has a demonstrated role in heavy metal detoxification, zinc and copper homeostasis, and as a free radical scavenger.[54] Ultraviolet B radiation has been shown to induce metallothionein synthesis in epidermis, apparently as a protective mechanism against further free radical attacks.[53]

Conclusion

Zinc is essential for human development and function. It provides conformational stability to numerous metalloenzymes. Zinc deficiency is associated with oxidative damage in numerous diseases, including cancer, cirrhosis, coronary artery disease, diabetes and some skin disorders. Studies of zinc deficiency have elucidated broad clinical ramifications. Zinc protects against UV radiation, enhances wound healing, contributes to immune and neuropsychiatric functions, and decreases the relative risk of cancer and cardiovascular disease. Abundant evidence demonstrates the antioxidant role for zinc. Topical zinc, in the form of divalent zinc ions, has been reported to provide antioxidant photoprotection for skin. Two antioxidant mechanisms have been proposed for zinc. Zinc may replace redox active molecules, such as iron and copper, at critical sites in cell membranes and proteins. Alternatively, zinc may induce the synthesis of metallothionein, sulfhydryl-rich proteins that protect against free radicals. No matter how they work, topical zinc ions may provide an important and helpful antioxidant defense for skin.

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