Zinc toxicity[1,2]

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ABSTRACT Although consequences of zinc deficiency have been recognized for many years, it is only recently that attention has been directed to the potential consequences of excessive zinc intake. This is a review of the literature on manifestations of toxicity at several levels of zinc intake. Zinc is considered to be relatively nontoxic, particularly if taken orally. However, manifestations of overt toxicity symptoms (nausea, vomiting, epigastric pain, lethargy, and fatigue) will occur with extremely high zinc intakes. At low intakes, but at amounts well in excess of the Recommended Dietary Allowance (RDA) (100–300 mg Zn/d vs an RDA of 15 mg Zn/d), evidence of induced copper deficiency with attendant symptoms of anemia and neutropenia, as well as impaired immune function and adverse effects on the ratio of low-density-lipoprotein to high-density-lipoprotein (LDL/HDL) cholesterol have been reported. Even lower levels of zinc supplementation, closer in amount to the RDA, have been suggested to interfere with the utilization of copper and iron and to adversely affect HDL cholesterol concentrations. Individuals using zinc supplements should be aware of the possible complications attendant to their use. *Am J Clin Nutr* 1990;51:225–7.

KEY WORDS Zinc, zinc toxicity, supplementation

Introduction

For many years most of the nutrition research on zinc has focused on its essential roles in the body. Many studies have examined the consequences of a deficient state on growth, development, and health and the prevalence of deficiency in various population groups. Relatively little attention has been directed toward toxic properties of zinc other than where there has been a clear industrial hazard, such as with metal-fume fever due to inhalation of zinc oxide fumes or as a consequence of severe pollution of a localized environment (1). Indeed, most review texts indicate that zinc is relatively nontoxic and that animals, including humans, exhibit considerable tolerance to high intakes of zinc (2, 3). Although it is true that overt symptoms of toxicity require ingestion of relatively large amounts of zinc, there is increasing evidence that use of zinc supplements by humans, even at fairly modest concentrations, may have adverse consequences under certain circumstances. Such potential consequences will be examined at three somewhat arbitrarily chosen intakes: amounts sufficient to induce acute toxicity, amounts used in pharmacological dosages (100–300 mg Zn/d), and amounts more commonly consumed in self-selected supplements (15–100 mg Zn/d).

Acutely toxic intakes

Most reports of acute toxicity have been in response to food poisoning incidents. Several cases, described by Brown et al (4), resulted from storage of food or drink in galvanized containers. Typically, the food or drink was somewhat acidic in nature and the storage period was fairly long; presumably, sufficient zinc was leached from the galvanized coating to cause the toxic manifestations. It was not possible to quantitate the amount of zinc actually ingested but it was reported that an emetic dose of $ZnSO_4$ is ~1–2 g of the salt, corresponding to 225–450 mg Zn. The presenting symptoms included nausea and vomiting, epigastric pain, abdominal cramps, and diarrhea (frequently bloody). A different set of symptoms was reported for a 16-y-old boy who ingested 12 g of elemental Zn over a 2-d period (5). Symptoms included lethargy, light-headedness, slight staggering of gait, and difficulty in writing; all symptoms disappeared with chelation therapy. Interestingly, no gastrointestinal symptoms were reported in this latter study, suggesting that the form of zinc ingested may strongly influence which manifestations of toxicity will be observed. Fortunately, instances of acute toxicity due to ingestion of very large doses of zinc remain quite uncommon.

Pharmacological intakes

Intakes of zinc in the range of ~100–300 mg Zn/d may be the result of physician's orders to treat various medical problems, of excessive self-supplementation, or of particular experimental protocols. For example, patients being treated with 150 mg Zn/d for sickle cell anemia (6) and for nonresponsive celiac disease (7) developed severe copper deficiency, characterized by the classical symptoms of hypocupremia, anemia, leukopenia, and neutropenia. Normal copper status was restored by cessation of ingestion of the zinc supplements coupled with moderate doses of copper.

Both studies (6, 7) showed that severe copper deficiency can result from prolonged therapy with zinc supplements (23 and 13 mo, respectively) and that cessation of the use of zinc supplements allowed apparent normalization of copper status.

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Received August 23, 1988.

Accepted for publication March 29, 1989.

More recent reports indicate that this problem of induced copper deficiency is still of concern. In a case reported by Hoffman et al (8), a woman given 440–660 mg $ZnSO_4$ (110–165 mg Zn) daily for 10 mo for aphthous ulcers of her mouth and tongue developed copper deficiency with anemia and neutropenia. Interestingly, resolution of the copper deficiency was not accomplished by cessation of the use of the oral zinc supplements and the inclusion of oral copper supplements for 2 mo, but required an intravenous administration of cupric chloride solution over a 5-d period. This would suggest that elimination of excess zinc is slow and that, until such elimination occurs, the intestinal absorption of copper is blocked. A report by Patterson et al (9) of a sideroblastic anemia and leukopenia associated with copper deficiency in a young man consuming large amounts of supplemental zinc for 2 y, corrected by the cessation of the use of zinc supplements, illustrates the dangers inherent in a prolonged period of self-supplementation with large doses of zinc. Studies reporting copper deficiency secondary to the use of zinc supplements have utilized prolonged periods of supplementation ($\geq$ 10 mo) but equivalent dosages for a shorter period of time (6 wk) did not cause hypocupremia in a recent study by Samman and Roberts (10). Interestingly, many subjects in that study did report symptoms of headache, abdominal cramps, nausea, and vomiting—manifestations similar to signs of acute toxicity. Because the study of Samman and Roberts (10) used healthy men and women, it is unclear whether the development of copper deficiency requires longer than 6 wk to manifest or whether it is dependent in some fashion on the health of the subjects.

Other reported consequences of zinc intakes ranging from 100 to 300 mg/d include alterations in immune response and in blood lipid profiles. When 11 healthy male volunteers were given 300 mg Zn/d for 6 wk, several indices of immune function (lymphocyte stimulation index, chemotactic migration, and ingestion of bacteria) were depressed when compared with values obtained just before supplementation (11). However, lower amounts of supplementation (100 mg Zn/d) given to an elderly population for 3 mo did not alter any of the indicators of immune function, including delayed dermal hypersensitivity or in vitro lymphocyte proliferative responses to mitogens and antigens (12).

Because high levels of zinc intake in rats are associated with an increase in serum cholesterol (13), serum lipoprotein concentrations have been examined in those taking zinc supplements. Among the 11 subjects given the 300-mg-Zn/d regimen (11), an increase in low-density-lipoprotein (LDL) cholesterol and a decrease in high-density-lipoprotein (HDL) cholesterol were observed, although triglyceride and total cholesterol concentrations did not vary significantly between baseline and values obtained after 6 wk of supplementation. This reported decrease in HDL cholesterol is in agreement with an earlier observation by Hooper et al (14), whose subjects received 160 mg Zn/d for 6 wk. Thus, there appear to be several potential adverse consequences of such pharmacological doses of zinc, particularly when such intakes are continued for a prolonged period.

Moderately excessive intakes

Several studies indicate that use of zinc supplements between 15 mg/d [the Recommended Dietary Allowance (RDA) for nonpregnant, nonlactating adults (15)] and 100 mg Zn/d, amounts most commonly used with self-supplementation (16), may also have some adverse consequences, problems similar in some ways to those seen with pharmacological dosages. Several investigators (17–20) showed that the amount of zinc in the dietary supply can influence the requirement for copper. By using balance studies with adult men, Sandstead (17) was able to show that as the amount of zinc in the diet increased, so did the amount of copper required to maintain balance. These observations were made at quite modest levels of zinc intake, near the RDA. Other studies also reported increased copper requirements or increased fecal losses of copper as the amount of zinc in the diet increased. Festa et al (18), in their study of young, adult male students, Greger et al (19), in their study of adolescent females, and Burke et al (20), studying elderly persons, all observed increased copper excretion as zinc was increased. Note that the amount of zinc fed in all these studies was near the RDA. However, not all studies have observed this increased copper excretion with increasing zinc intake (21–23). Reasons for the discrepancy in response are not readily apparent but there are substantial differences in experimental design, including differences in the age and sex of subjects, amounts of zinc and copper in the diet, and the duration of the experiment.

If copper excretion or the copper requirement is increased as a function of increased zinc intake, it is logical to suppose that the use of zinc supplements might impair copper status unless there is adequate or perhaps compensatory copper intakes. Few studies have addressed this question. Most of the studies cited above either did not evaluate copper status or failed to observe any significant change in status. The study of Fischer et al (24) did, however, find a decrease in erythrocyte Cu,Zn-superoxide dismutase, a copper metalloenzyme shown to be more sensitive to copper deficiency than are plasma copper or ceruloplasmin concentrations, when healthy adult males were fed two daily doses of 25 mg Zn for 6 wk. Similar results were shown by Yadrick et al (25) when adult females were fed 50 mg Zn/d for 10 wk; erythrocyte superoxide dismutase activity declined to 53% of pretreatment values, although ceruloplasmin concentrations did not differ. In addition, that study also noted an apparent competitive interaction between zinc and iron that lead to a decrease in serum ferritin and hematocrit concentrations by 10 wk in women given zinc supplements without additional iron. Although competitive interactions between zinc and iron were reported for animals (26), the report by Yadrick et al (25) is apparently the first with human subjects under experimental conditions.

Reports of alterations in serum lipoprotein profiles may be related in some fashion to a derangement in copper metabolism as a consequence of zinc supplementation. Black et al (27) observed decreased concentrations of HDL cholesterol when male subjects consumed either 50 or 75 mg Zn/d for 12 wk; with the higher amount of supplementation, HDL cholesterol was also significantly depressed at 6 wk of supplementation. Serum copper concentrations did not vary significantly among treatment groups, although, as noted above (24, 25), this may not be the most sensitive indicator of copper status. Freeland-Graves et al (28) reported only a transient decline in serum HDL cholesterol concentrations in young women given a supplement of 100 mg Zn/d for 8 wk. Using a different experimental approach, Goodwin et al (29) examined how cessation of zinc supplementation affected HDL cholesterol concentra-

tions. In a healthy, elderly population consuming modest supplements (29.1 ± 11.8 mg Zn/d, $\bar{x}$ ± SD), cessation for 8 wk was associated with a significant increase in HDL cholesterol concentrations, a decrease in LDL cholesterol concentrations, and an improvement in the ratio of HDL to LDL. Although not definitively proven, it would appear that consumption of zinc supplements well in excess of the RDA for an extended period would adversely affect HDL cholesterol concentrations.

The mechanism by which zinc could adversely affect copper homeostasis is not well understood. Cousins (30) provided a hypothesis that seems to explain some of this deleterious interaction. Although the mechanisms by which copper and zinc are absorbed into an enterocyte are not known, it is thought that once within the absorptive cell, the metals likely interact within the intracellular pools. Synthesis of metallothionein (a low-molecular-weight, cytosolic protein with high affinity for many heavy-metal ions) is strongly induced by zinc (31). The binding affinity of metallothionein for copper is much greater than it is for zinc; consequently, copper may be sequestered within the absorptive cells of the intestine and thus unavailable for utilization elsewhere in the body. The greater the intake of zinc and the lower the intake of copper (absolutely or relatively), the greater the potential for copper sequestration and, ultimately, copper deficiency. The mechanisms by which high zinc intakes interfere with iron status are less clear, although they may involve competition for similar ligands that facilitate absorption or for similar transport systems.

Ingestion of large amounts of zinc can cause overt toxic manfestations. However, even in the absence of such symptoms, and with amounts frequently consumed by the public, the use of zinc supplements can be seen to interfere with the utilization of other nutrients, particularly copper; to impair immune function; and to adversely affect lipoprotein profiles. Those individuals using zinc supplements, particularly amounts well in excess of the RDA, should be aware of the possible complications attendant to their use.

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