

Zinc and the stress response¹

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Zinc is an essential trace element required for normal growth, protein metabolism, membrane stability, and the function of over 200 metalloenzymes (1). In the United States, the recommended daily allowance for zinc in healthy adults is 15 mg for men and 12 mg for women. It is assumed that about one-fifth to one-third of ingested zinc is absorbed. Similarly, about 3 mg of zinc a day is required intravenously in stable subjects receiving total parenteral nutrition. Zinc deficiency is believed to occur in some developing countries of the world and in selected populations (eg, the elderly) in developed countries. Zinc deficiency can present itself in multiple fashions, ten of the major manifestations of zinc deficiency (1) being (i) skin lesions, (ii) anorexia (with possible alterations in taste and smell acuity), (iii) growth retardation, (iv) depressed wound healing or protein metabolism, (v) hypogonadism, (vi) altered immune function, (vii) impaired night vision, altered vitamin A metabolism, (viii) diarrhea, (ix) depressed mental function, (x) teratogenesis.

One population frequently overlooked as having a risk for zinc deficiency is patients in a period of stress, trauma, or inflammation. Stress has well defined effects on zinc metabolism, for example, a decrease in the serum zinc concentration, alterations in zinc binding to proteins in the serum, and an increased loss of zinc in the urine (figure 1) (2-4). There is also an internal redistribution of zinc during stress, trauma, or inflammation, zinc being redistributed to some organs, such as the liver, and lost from other tissues, such as the pancreas and intestine. This zinc redistribution presumably occurs to protect high-priority zinc functions, such as the production of acute phase proteins in the liver during the stress response (2). Moreover, a decrease in the serum zinc concentration would make serum a less favorable environment for bacteria to grow (zinc "withholding"). This internal redistribution of zinc is mediated to a great degree by stress hormones such

as ACTH (adrenocorticotrophic hormone), cortisol, catecholamines, and, to a greater extent, cytokines such as interleukin-1, tumor necrosis factor, and interleukin-6 (figure 1). These factors induce the production of metallothionein in the liver, which in turn plays a major role in binding increased amounts of zinc in the liver and thereby achieves an internal redistribution of zinc. However, with this redistribution of zinc, some tissues are "robbed" of zinc in order to supply other tissues with added zinc.

A major research focus of our laboratory has been the evaluation of this internal redistribution of zinc during trauma or inflammation. Our laboratory has sought to define the clinical profile of zinc metabolism following trauma or stress, to determine whether plasma and urine mineral levels reflect mineral status or disease severity or activity, and to evaluate the possible role of zinc supplementation in such stress situations. In 23 patients with burns we demonstrat-

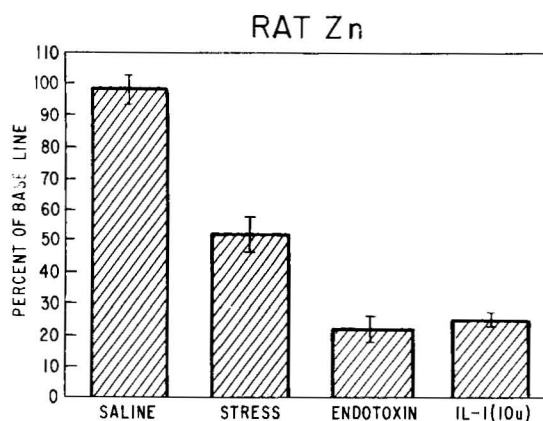


Figure 1. Effects of restraint stress, endotoxin, or interleukin-1 (IL-1) on serum zinc (Zn) concentrations in rat. Blood was obtained from rats for base-line zinc concentrations, and then the rats were injected with saline, endotoxin, or IL-1 or subjected to stress restraint. Blood was withdrawn 6 h later, and all values are reported as the percentage of the base-line serum zinc concentration. The range of the serum zinc concentrations in saline injected into control rats was 96-173 (mean 135) $\mu\text{g} \cdot \text{dl}^{-1}$. Stress restraint produced a reduction in the serum zinc concentration to 53% of the base line, while 25 μg of endotoxin and 10 units of IL-1 both caused dramatic decreases in the serum zinc concentration to 23 and 26% of the base line, respectively. The decrease in zinc induced by stress restraint is probably due to the release of cortisol and other stress hormones. Endotoxin stimulated a release of cytokines, or an injection of IL-1 itself caused a further reduction in the serum zinc concentration.

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ed an initial marked depression in serum zinc concentrations that improved over time irrespective of the form or amount of zinc supplementation (figure 2) (2). The rapidity of improvement in serum zinc concentration correlated inversely with the severity of the burn, as assessed by total burn surface area.

Patients with severe head injury had similar depressions in their serum zinc concentration, but the concentration increased over time in virtually an identical fashion to that observed in the patients with burns (3). Both patient populations also had marked increases in urinary zinc excretion, as shown in the group of head injury patients in figure 3 (3, 4).

Because it was clear that there were marked alterations in zinc metabolism in trauma patients, and since many such patients can lose their total daily intravenous zinc intake (approximately 3 mg a day) through urinary routes, we developed a randomized study of zinc supplementation versus standard zinc therapy in the head injury group of patients. In this study, we sought to evaluate whether zinc supplementation improved either nutritional status or cognitive outcome among these patients. Sixty-eight patients with closed head injuries were randomized to receive either standard zinc therapy (2.5 mg a day while on total parenteral nutrition) followed by a regular diet when tolerating oral intake or 12 mg of zinc a day (while on total parenteral nutrition) followed by an oral diet supplemented with 168 mg of zinc gluconate (equivalent to 22 mg of elemental zinc) a day. Zinc supplementation caused a significant improvement in nutritional status, as assessed by increases in the concentrations of visceral proteins such as retinol binding protein and thyroxine-binding prealbumin, and significantly improved cognitive outcome, as assessed by the Glasgow Coma Scale Score. Thus these preliminary data on 68 moderately to severely head-injured patients suggest that some trauma patients can benefit from zinc supplementation after injury (5).

We conclude the following about zinc metabolism after trauma or inflammation: (i) plasma zinc concentration reflects the disease severity or activity of the patient rather than the overall total body zinc status, (ii) there is an internal redistribution of zinc after trauma or inflammation, (iii) some tissues may become deprived of zinc during this redistribution, and selected patient populations, such as head injury patients, may benefit from additional zinc supplementation.

References

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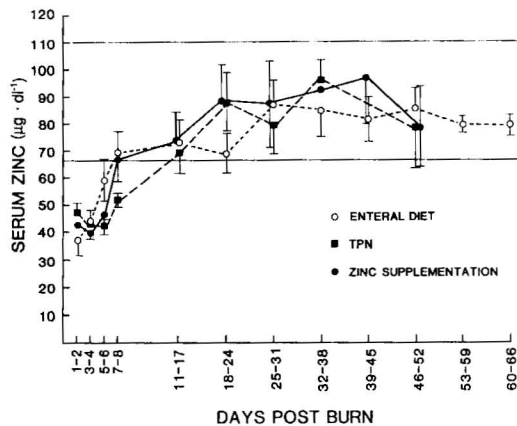


Figure 2. Serum zinc levels (mean and standard errors of the means) in seven patients who received total parenteral nutrition (TPN) during part of their hospitalization, in seven patients who received 220 mg · d⁻¹ of oral zinc sulfate supplementation, and in nine patients who received a regular diet plus enteral nutrition support. Initially, all of the patients had very depressed serum zinc values that improved over the course of their stay in the hospital. There were no statistical differences between the three groups receiving different amounts of zinc via different routes.

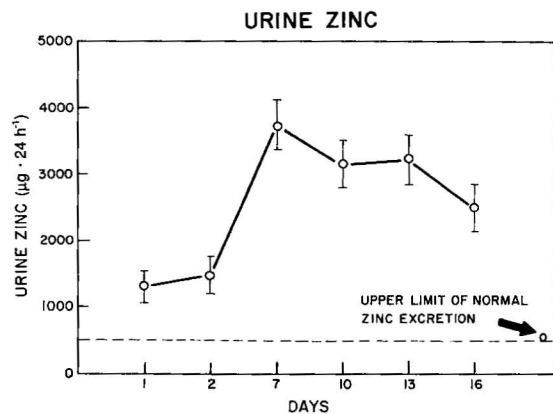


Figure 3. Twenty-four hour urine zinc excretion (mean and standard error of the mean) for 15 head-injured patients over 16 d. The normal upper limit (500 µg · 24 h⁻¹) is shown by the broken line. The patients had increased urinary zinc excretion, which, over time, may contribute to negative zinc balance.

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