letters

Immunobiology of zinc and zinc therapy

In a recent article in *Immunology Today*, Wellinghausen *et al.*[1] reviewed the various interactions between zinc and the immune system. The authors clearly pointed out that zinc (zinc ions and/or chelated zinc) plays an important role in the maintenance of immune function. Zinc deficiency results in hypoplasia of the immune system, impaired immune response, poor wound healing, diminished T-cell dependent reactions, and attenuated chemotaxis by neutrophils and monocytes. It should be underlined, however, that zinc therapy has to be discussed very carefully and a number of important factors have to be addressed.

Recent observations indicate that zinc doses as low as 50 mg/day over a prolonged period in healthy individuals can induce subtle impairment of immunologic responses[2]. The pharmacological interaction of zinc with the immune system has implications for the long-term administration of zinc supplements. In a study of 11 healthy young men, 150 mg zinc given twice daily decreased the lymphocyte proliferation response to phytohemagglutinin and reduced the chemotaxis and phagocytosis of neutrophils[3]. In a clinical trial in which elderly subjects were given 100 mg zinc per day, the delayed-hypersensitivity response was reduced[4].

Our studies show that zinc affects DNA synthesis and cytokine production [interleukin 2 (IL-2), IL-6, IL-10] by pokeweed mitogen-stimulated peripheral blood mononuclear cells in a concentration-dependent manner[5]. Both functions of immune cells were strongly suppressed by zinc at a concentration of 0.2 mM. These findings are in accordance with the observations of Wellinghausen *et al.* (toxic dose for T cells: 96–128 μM; for monocytes: 38–512 μM)[1].

Furthermore, we found that zinc levels higher than 0.5 mM – equivalent to a daily dose of ~45 mg zinc salt – had a toxic effect on immune cells[5]. Prasad[6] suggests that orally ingested zinc at doses up to 45 mg/day (elemental zinc) is virtually nontoxic in adults.

We have also examined the effect of long-term, low-dose zinc supplementation [zinc-hydrogenaspartate; UNIZINK 50 three times daily (29.76 mg/day)] on serum levels of IL-6 and IL-10 in 16 patients with chronic liver disease: all had reduced serum zinc levels, in most due to liver cirrhosis[5]. The liver, which plays an important role in zinc metabolism, contains two pools of exchangeable zinc in the cells, one rapidly exchangeable, the other slowly exchangeable. A reduction in liver zinc content can hinder both regeneration and recovery of liver cells. Patients with chronic liver disease, particularly liver cirrhosis, frequently have endotoxemia, increased serum concentrations of cytokines, notably IL-6, and reduced serum zinc levels. In liver disease, the decline in serum zinc levels is due to diminished hepatic extraction, portosystemic shunts, alcohol-induced disturbed absorption and is possibly influenced by cytokines, such as IL-6 (Ref. 5). In our study, we showed that in most patients zinc supplementation decreases serum levels of certain cytokines, especially IL-6, but also IL-10, and leads to a normalization of serum zinc concentrations.

In conclusion, our results show that zinc affects a functional activation or inhibition of isolated immune cells in a concentration-dependent manner. The critical concentration is 0.5 mM, equivalent to a daily dose of ~45 mg zinc salt. In patients with diminished serum zinc levels due to chronic liver disease, zinc supplementation also appears to influence cell growth and cytokine production. These findings suggest new uses for zinc supplementation, but they also reveal the potential risks of zinc therapy.

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Reply to Reinhold *et al.*

In a recent *Trends* article[1] we described the significance of zinc in the immune system. We briefly discussed all facets of the immunobiology of zinc but could not explain all the mechanisms of action in detail due to limited space. The reply from Reinhold *et al.*, as well as those from Radulescu[2] and Weiss *et al.*[3], add some detail to the immunobiology of zinc; however, their results do not contradict ours. Furthermore, all three studies support our conclusion that immune function is delicately regulated by the concentration of zinc[1].

We clearly argued that administration of zinc should be based on the particular requirements of an individual and controlled by the plasma zinc level (not exceeding 30 μM to avoid immunosuppressive effects[4–6]). High-dose zinc treatment (above 150 mg/day) can result in extreme side-effects, such as anaemia[7,8], decreased high-density lipoprotein cholesterol levels[9] or bleeding gastric erosion[10]. Reinhold *et al.*[11] suggested 0.5 mM as the critical concentration for leukocyte function; however, our studies[4,6] and those of the authors themselves[11], showed that zinc concentrations above 50–100 μM could have immunosuppressive effects. Above 500 μM, zinc is toxic for all leukocyte subsets, even for the zinc-tolerating monocytes. Therefore, the zinc dose has to be controlled and must be adjusted to the individual patient, especially as the resorption of zinc is influenced by various diseases and by aging. In conclusion, zinc treatment should be controlled by the plasma level, as discussed previously[1], because the adsorption of orally administered zinc is difficult to estimate. The same will be true if zinc is used for immunosuppression[1,4]. The range