

Zinc – Review of Its Present Role in HIV-Infection

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Summary

As micronutrient deficiencies are very common in symptomatic as well as in asymptomatic HIV-infected patients, nutritional interventions can play a major role in comprehensive management of HIV-infection. Also such interventions are feasible and affordable, do not require HIV testing facilities and may even be beneficial to HIV-infected patients without micronutrient deficiency. Current evidence on the role of micronutrients in childhood infections has led to the development and implementation of preventive and therapeutic interventions that reduce infectious disease morbidity and mortality among children in developing countries. Similarly, existing data and data emerging from ongoing and future research could result in interventions to improve micronutrient intake and status which could contribute to a reduction in the magnitude and impact of the global HIV epidemic. In this context, present review discusses importance of zinc in HIV-Infection

Key words: HIV infection, AIDS, Zinc

HIV infection and deficiency of zinc

Multiple studies have documented zinc deficiency to be a common finding in HIV infection.¹ In a survey of 228 in-patients with AIDS, 29% had low and 21% had marginally low serum zinc levels.² The presence of zinc deficiency in these patients significantly increased their chance of getting bacterial infections. While frank zinc deficiencies can occur in AIDS patients as a result of malabsorption, medications, altered metabolic states, and fluid loss from nausea, vomiting, and diarrhea,³ zinc deficiency in both plasma and serum has been observed in HIV+ patients in the asymptomatic state as well.^{4,5,6} Low or marginally low plasma zinc levels were found in 50 percent of 100 healthy, asymptomatic HIV-1 seropositive patients without a history of alcoholism or clinical evidence of nutritional deficiencies.⁴

Although some studies have not seen alterations in HIV patients' serum zinc levels,⁷⁻⁹ others have documented declining plasma and serum levels as the disease progresses, and have found lower zinc levels in more advanced stages of the disease.^{6, 10} Depressions in blood zinc levels in HIV/AIDS may reflect the presence of acute infections; serum zinc levels decrease as hepatic zinc uptake increases, reflecting zinc's role as an acute-phase reactant.¹¹ Opportunistic infections have been shown to lower serum zinc levels, with depressed serum levels lasting long after the infection is resolved.¹² Because of zinc's role in acute infection and its subsequent altered metabolism in chronic infection, it has been argued that serum levels may not be an accurate reflection of immune impairment related to zinc body stores and zinc availability in HIV.¹³ For this thymulin, a thymic hormone which becomes biologically active only after binding with zinc ions, has been proposed as a more sensitive marker.¹⁴ Zinc-binding by thymulin allows recognition by T-lymphocytes and enables T-lymphocyte differentiation; thymulin activity is decreased in cases of zinc deficiency. Thymulin levels in ARC (AIDS-Related Complex, an obsolete term which was used to describe AIDS at the beginning of symptom appearance) patients were demonstrated to be low, while serum zinc levels in the same subjects were within normal limits.¹⁵

Current evidence on role of zinc in HIV infection:

Zinc is a component of both structural and catalytic proteins of HIV. In HIV infection, zinc plays specific roles as an anti-oxidant, immune-modulator, and a possible direct anti-viral agent.^{16,17} Zinc, *in vitro*, has been found to inhibit cell death mediated by tumor necrosis factor (TNF), a cytokine linked to cellular apoptosis and wasting syndrome in HIV.¹⁸ The HIV protease enzyme is necessary to potentiate the production of new HIV copies.¹⁹ Various studies have shown if sufficient zinc ions are bound to the protease it will remain inactive.²⁰ Zinc can also bind to the integrase enzyme via "zinc finger protein" structures and allows for optimal activity of the integrase enzyme. Although the net effect of *in vivo* tissue zinc concentrations on HIV replication has yet to be determined, there is evidence that adding zinc to antiviral medications enhances the medication's effect. Comparable to the *in vitro* anti-viral activity of zidovudine (AZT), the peptide T22 is four-times stronger when bound to zinc ions via cysteine.²¹ Baum demonstrated a need for zinc in an AZT-treated population in which 64 percent of the treated patients were zinc deficient, while only 24 percent of the untreated population had low zinc levels.²² AZT metabolism necessitates a zinc-dependent thymidine kinase for conversion to its active form. The medication may contribute to zinc deficiency, which could lead to decreased effectiveness of the drug in a zinc-deficient patient. Baum also found AZT-treated patients with adequate zinc levels had a significantly greater mitogen response, which was not demonstrated in those who were zinc-deficient.²²

Clinical experience with zinc supplementation in HIV-infected adults and children:

Regardless of the methodological issues of measuring zinc bioavailability, studies looking at zinc supplementation in HIV/AIDS have proven useful. Isa evaluated 11 men with AIDS.²³ In this study, serum and blood cell zinc levels in AIDS patients did not differ significantly from controls, before zinc supplementation. After 10 weeks' supplementation with oral zinc sulfate, providing 0.45mg/kg/day of elemental zinc, there was a significant ($p<0.05$) increase in mean CD4+ cells (from 280 to 390/mm³). Absolute counts of CD3+ lymphocytes also rose significantly. During supplementation, all patients exhibited progressive weight gain, with a mean increase of seven pounds ($p<0.001$), which could not be accounted for by increased calorie intake.

Mocchegiani followed 18 HIV+ patients with CD4+ of 250-400/mm³ on anti-viral medication (AZT alone) who were supplemented with 12 mg elemental zinc daily for 30 days, and found the relative risk for opportunistic infection was significantly higher in the unsupplemented group on AZT.²⁴ In 28 HIV+ patients on HAART (two nucleoside analogues and a protease inhibitor) who were supplemented with the same zinc protocol, no significant risk for opportunistic infections was found in the zinc-unsupplemented HAART group. There was an inverse correlation between serum zinc levels and HIV-RNA (viral load) in both groups. This researcher also observed that triple anti-viral therapy improved zinc absorption and serum zinc levels. Theoretically, zinc absorption might have improved as a result of the anti-inflammatory effect on the gut of a lowered viral load.

Zinc supplementation has also been investigated in pediatric HIV infection. Thirteen stable HIV-infected children (mean, six years of age) were given oral zinc, 1.8-2.2 mg/kg/day.²⁵ Prior to supplementation, nine subjects had low serum zinc levels. After supplementation, six of the nine had normal serum zinc levels. After 3-4 weeks, two patients had significant increases in CD4+ count, and clinical scores improved in four patients. In another small trial of pediatric patients treated with 2 mg zinc/ day for three weeks, significant increases were seen in total lymphocyte count, and a doubling of the CD4/CD8 ratio was observed, indicating a relative rise in CD4+ cell numbers.²⁶

Various clinical studies have shown that zinc supplementation reduces the incidence and severity of diarrhea in children. An in-vitro study has shown evidence to link clinical data regarding beneficial effects of zinc supplementation in HIV-infected children and the pathophysiological mechanism of HIV-related diarrhea. This study showed that zinc, preventing Tat-induced fluid secretion, directly limits a specific mechanism of HIV-1-related diarrhoea. This study emphasized upon the need for a 'zinc approach' in adjunct to specific antiretroviral therapy in HIV-1-infected children.²⁷

Safety concern about zinc supplementation in HIV-infection:

Tang followed a group of 281 HIV-1 positive men for a median 6.8 years in order to determine if dietary and supplemental zinc intake was associated with progression to AIDS.²⁸ At any level above 11.6 mg/day, zinc was associated with an increased relative risk for progression, after controlling for age, symptoms, CD4+ count, energy intake, and medication use. With an intake over 20 mg daily, the relative risk increased to 2.06. Interpretation of this data is difficult, particularly since other findings in this study are confusing; intake of vitamin C between 157-254 mg or intake of niacin between 36.6-61.0 mg/day was associated with a higher risk of progression than either higher or lower levels of either nutrient. Other epidemiological and clinical studies of zinc intake, serum zinc levels, and their relationship to progression to AIDS found no evidence of increased risk of progression with increasing dietary/supplemental zinc intake.^{6, 29} Clearly, more studies looking at zinc regulation of viral replication and dosing studies in HIV are needed, as zinc is clearly a key component of viral replication and inhibition of replication. In light of the adverse effects of zinc deficiency in HIV/AIDS, maintenance of normal physiological levels of zinc appears to be desirable.³⁰

Conclusion

Like other infections, HIV infection impairs micronutrient status, and micronutrient supplementation can reduce HIV transmission, delay disease progression and overall morbidity in HIV-infected patients. Zinc plays important role in HIV-infection. As deficiency of zinc relates to HIV symptomology and progression, a 'zinc approach' (i.e. supplementation of zinc) in adjunct to specific antiretroviral therapy is desirable in the comprehensive management of HIV-infected patients.

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