Zinc deficiency in patients with sickle cell disease\textsuperscript{1,2}

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Zinc deficiency in adult patients with sickle cell disease (SCD) was first reported in 1975\textsuperscript{(1)}. Several clinical manifestations of this disorder were subsequently related to zinc deficiency\textsuperscript{(2)}. These manifestations included growth retardation, hypogonadism in males, hyperammonemia, abnormal dark adaptation, and cell-mediated immune disorder.

The biochemical evidence for diagnosing zinc deficiency in patients with SCD includes low zinc concentrations in plasma, erythrocytes, hair, lymphocytes, and granulocytes and low activities of certain zinc-dependent enzymes, such as carbonic anhydrase in red blood cells, alkaline phosphatase in neutrophils, and thymidine kinase in newly synthesizing skin connective tissue and collagen\textsuperscript{(1, 2)}. A higher than normal activity of plasma ribonuclease in patients with SCD also indicates zinc deficiency because zinc is known to be an inhibitor of this enzyme\textsuperscript{(2)}.

We previously reported hyperammonemia in zinc-deficient humans and experimental animals and related this to an effect of zinc in urea cycle enzymes. We found a decreased activity of ornithine carbamoyltransferase and increased activities of glutamate dehydrogenase and carbamoyl-phosphate synthase-1 in the liver of zinc-deficient rats.

A significant increase in the activity of AMP deaminase—an enzyme involved in the purine catabolic pathway—in the muscle of the zinc-deficient rats was also observed; this alteration may also contribute to hyperammonemia in zinc-deficient animals and humans\textsuperscript{(2, 3)}. Zinc supplementation in patients with SCD resulted in a significant improvement in secondary sexual characteristics, in the normalization of plasma ammonia concentrations, and in the reversal of abnormalities in dark adaptation\textsuperscript{(3)}.

Growth retardation in patients with SCD is a well-known clinical entity\textsuperscript{(4)}. Because zinc deficiency is known to retard growth, we conducted a limited study in SCD patients aged 14–17 y to document the effect of zinc supplementation on growth\textsuperscript{(4)}. We observed a significant beneficial effect on growth after zinc supplementation. In this issue of the Journal, Zemel et al\textsuperscript{(5)} reported the results of their study on the effect of zinc supplementation for 1 y on the growth and body composition of children with SCD. Prepubertal children with SCD aged 4–10 y were enrolled and assigned to receive 10 mg elemental Zn or a placebo daily. Height, sitting height, knee height, and arm circumference z scores increased significantly more in the zinc group than in the control group. These results provide further evidence that zinc deficiency resulting in growth retardation is a major clinical problem in patients with SCD. It is also clear that a simple regimen of oral zinc supplementation corrects zinc deficiency.

It is well known that patients with SCD are susceptible to infection\textsuperscript{(6)}. Infection is the most common cause of death in children with SCD and is predominantly due to lethal pneumococcal sepsis in children aged <3 y. Older patients with SCD have an increased incidence of salmonella infection and increased mortality and morbidity due to tuberculosis. An increased incidence of urinary tract infections due to \textit{Escherichia coli} and clinical pyelonephritis in up to \textless{} 25% of adult patients with SCD has been reported. Susceptibility to \textit{Enterobacter}, \textit{Klebsiella}, and \textit{Mycoplasma pneumoniae} has been reported in patients with SCD. Primary infection with Parvovirus B19 has been reported as a major cause of aplastic crises in patients with SCD. \textit{Mycoplasma} and \textit{Chlamydia pneumoniae} are the most common infections associated with the acute chest syndrome in patients with SCD. It is believed that a large percentage of patients with pulmonary infiltrates probably have associated viral infections\textsuperscript{(6)}. Contributing factors for the increased susceptibility to infections in SCD patients include functional asplenia caused by repeated infarction of the spleen and an opsonophagocytic defect due to an abnormality of the alternate complement pathway with a deficiency of specific circulating antibodies.

Our studies showed that patients with SCD also have cell-mediated immune disorder, which is related to zinc deficiency. In patients with SCD, zinc supplementation corrected anergy, increased natural killer cell activity, increased the ratio of CD4\textsuperscript{+} to CD8\textsuperscript{+}, increased the activity of serum thymulin (a thymic hormone involved in the cell proliferation and differentiation of T-helper cells), and increased the number of CD8\textsuperscript{+}CD73\textsuperscript{+} precytolytic cells\textsuperscript{(7)}.

We studied the effect of zinc supplementation on T-helper cell function and the incidence of infections in 32 adults with SCD. A placebo-controlled trial of the effect of 50–75 mg elemental Zn/d orally for \textless{} 3 y resulted in significant increases in lymphocyte and granulocyte zinc concentrations and interleukin 2 production and fewer documented bacteriologically positive infections, numbers of hospitalizations, and numbers of vaso-occlusive pain crises\textsuperscript{(6)}.

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These effects were seen when zinc was administered in therapeutic doses.

Cytokines appear to be involved in the pathogenesis of vaso-occlusive phenomena in SCD. Cytotoxic cytokines such as interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) induce endothelial cell activation and red blood cell and neutrophil adhesiveness to endothelia (8). Sickle cell monocytes are activated and generate increased concentrations of cytotoxic cytokines such as IL-1β and TNF-α, leading to activation of endothelial cells and vascular inflammation, which play a significant role in the pathophysiology of vaso-occlusive disorders in patients with SCD (8).

We previously showed that the production of IL-1β is higher than normal in zinc-deficient humans (9). Zinc deficiency increases gene expression and production of TNF-α and IL-1β in HL-60, a human malignant monocytic macrophage cell line (A Prasad, B Bao, FWJ Beck, unpublished observation, 2001). Additionally, zinc protects endothelial cells against TNF-α–induced cell injury, probably by down-regulating oxidative stress–sensitive transcription factors (10). Thus, our observation that therapeutic doses of zinc decreased the incidence of vaso-occlusive pain crises in patients with SCD may be related to the decreased induction of cytotoxic cytokines from activated monocytes in patients with SCD.

Zinc deficiency is relatively common in adult patients with SCD, affecting ≈60–70% of the adult SCD patients in our center (2, 6). Our diagnosis of zinc deficiency is based on zinc concentrations in lymphocytes and granulocytes in SCD patients. Hyperzincuria and a high protein turnover due to increased hemolysis significantly increase the daily zinc requirement in SCD patients, which is not met by the usual dietary intake. The role of intestinal absorption and endogenous zinc loss is not known.

REFERENCES