

Zinc Levels and Infections in Hospitalized Patients With AIDS

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ABSTRACT

Impaired cellular and humoral immunity and phagocytic function have been attributed to zinc deficiency. This study examined the association between low serum zinc concentration and opportunistic infections in hospitalized patients with the acquired immune deficiency syndrome (AIDS). We examined the records from all 505 inpatient consultations performed by our Nutrition Service from May 1992 through June 1994. The medical records from all 228 patients with AIDS with known serum zinc levels (determined by atomic absorption spectrophotometry) were reviewed. The length of HIV seropositivity, most recent CD4 count, presence of diarrhea, and degree of malnutrition were noted. The principal diagnosis accounting for the admission was grouped according to the type of infection: *Pneumocystis carinii* pneumonia (PCP), viral, fungal, bacterial, and other. Sixty-seven patients (29%) had abnormally low serum zinc levels (LSZ < 55 $\mu\text{g}/\text{dL}$), 49 patients (21%) had borderline low serum zinc (BSZ ≥ 55 and ≤ 65 $\mu\text{g}/\text{dL}$), and 112 (49%) patients had normal serum zinc levels (NSZ > 65 $\mu\text{g}/\text{dL}$). There was no significant difference among the groups in CD4 count, length of HIV seropositivity, presence of diarrhea, or severity of malnutrition. Patients with zinc deficiency (LSZ) had a significantly higher incidence of bacterial infection than did patients with normal zinc. Patients with borderline zinc levels had an intermediate incidence of bacterial infection. There were no significant differences among the three groups in the incidence of PCP, viral, or fungal infections. Severe zinc deficiency was noted in 29% and borderline levels in an additional 21% of hospitalized AIDS patients. A low zinc level was not associated with the length of HIV seropositivity, CD4 count, or degree of malnutrition. Hypozincemia was associated with an increased incidence of concomitant systemic bacterial infections. *Nutrition* 1996;12:515-518

Key words: acquired immune deficiency syndrome (AIDS), *Pneumocystis carinii* pneumonia (PCP), zinc deficiency

INTRODUCTION

Zinc is an essential mineral that is important for the stabilization and function of numerous metallo-enzymes involved in protein synthesis, protein catabolism, energy metabolism, and both DNA and RNA synthesis.^{1,2} Zinc has an important role in a variety of immune functions including lymphocyte function, natural-killer-cell function, antibody-dependent and cell-mediated cytotoxicity, neutrophil function, lymphokine production, and phagocytosis.³ Zinc deficiency can impair cellular and humoral immunity and phagocytic function.⁴

Total body zinc determinations are not routinely available for clinical use. Serum zinc levels are the most accessible, albeit imperfect marker for zinc deficiency. Hypozincemia is thought

to correlate with low total body zinc stores, although serum zinc levels can vary in the setting of acute infections or fever.

Zinc deficiency has been reported in patients with AIDS^{3,5-8}; however, a causal relationship between the progression of AIDS and zinc deficiency is unknown. Chronic diarrhea, generalized malnutrition, and recurrent infections associated with AIDS may contribute to zinc deficiency.

Zinc deficiency may in turn compound the immune-deficient state, predisposing patients to further complications of HIV disease. Infections due to common bacterial agents or opportunistic agents are common in patients with AIDS. Whether zinc deficiency is associated with distinct infections is a complex issue that has not been evaluated. By retrospective review, we sought to determine whether opportunistic infections in hospitalized patients with AIDS correlated with depressed serum zinc levels.

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TABLE I.

CLINICAL CLASSIFICATION FOR THE DEGREE OF MALNUTRITION (DOM)							
DOM class	Numeric grade	Serum albumin (g/dL)	TSF* (percentile)	MAMC** (percentile)	% IBW†	% UBW‡	Weight loss/time
Mild	1	2.8-3.2	≤25th ≥10th	≤25th ≥10th	80-90%	85-95%	<5%/mo
Moderate	2	2.1-2.7	<10th ≥5th	<10th ≥5th	70-79%	75-84%	<2%/wk <10%/6 mo
Severe	3	<2.1	<5th	<5th	<70%	<75%	>2%/wk >10%/6 mo

*Triceps skin folds.

**Mid arm muscle circumference.

†Ideal body weight.

‡Usual body weight.

METHODS

From May 1992 through June 1994, 505 consultations were performed by our Gastroenterology/Nutrition Service on patients with HIV/AIDS hospitalized at San Francisco General Hospital. Patient evaluations included a complete history and physical examination and a rigorous assessment by our team dietitian. Consultative records from all 505 patients were reviewed, and 228 patients who had had serum zinc determinations during their hospitalization were identified. The medical records from these 228 patients were used to identify primary admitting diagnoses, patients' reports of gastrointestinal symptoms (anorexia, vomiting, weight loss, and/or diarrhea, defined as more than three poorly formed stools/d). The length of time the patient had been HIV seropositive and most recent CD4 count were noted when available.

During the first week of hospitalization, serum zinc and visceral protein (albumin, prealbumin, and transferrin) levels were obtained in patients as part of standard laboratory testing (i.e., after an overnight fast between 6 and 8 a.m.). Serum zinc levels were determined by atomic absorption spectrophotometry. The lower limit of normal for serum zinc in the laboratory was 55 µg/dl.

The classification system outlined in Table I was used to provide a malnutrition score. The classification was based on serum albumin, anthropometric measures compared with age-

adjusted normal individuals, and weight. Based on the predominant severity, a malnutrition score of 1 = mild, 2 = moderate, or 3 = severe was assigned to each patient.

For the analysis, patients were divided into three groups based on serum zinc levels: group 1 (LSZ) had low serum zinc, with a level of less than 55 µg/dL; group 2 (BSZ) had borderline serum zinc, with a level of 55-65 µg/dL; and group 3 (NSZ) had normal serum zinc, with a level higher than 65 µg/dL. The admitting diagnoses were grouped by opportunistic infection: 1) *Pneumocystis carinii* pneumonia (PCP), 2) systemic viral infections (cytomegalovirus or herpes virus), 3) systemic fungal infections (candida esophagitis, cryptococcosis, or histoplasmosis), 4) systemic bacterial infections (pneumonia, bacteremia/sepsis, endocarditis, osteomyelitis, and urosepsis), and 5) other (including patients with lymphoma, neurologic disorders, and no definable diagnosis). In this cohort, the number of patients with identified *Mycobacterium tuberculosis* (6) or *Mycobacterium avium complex* (3) infection was too small to warrant separate analysis, and these patients were grouped in the "other" category.

STATISTICAL ANALYSIS

The results are expressed as mean ± STD. Mean values of continuous variables (mean age, CD4 count, length of HIV

TABLE II.

CHARACTERISTICS OF HOSPITALIZED AIDS PATIENTS		
	Number of Patients with Available Data	Mean ± STD
Zinc (µg/dL)	228	70.2 ± 32.4
CD4	171	65.5 ± 110.1
Years HIV positive	145	4.1 ± 2.8
Serum albumin on administration (g/dL)	228	2.71 ± .57
Degree of malnutrition	228	2.19 ± 0.73

TABLE III.

ZINC LEVELS IN HOSPITALIZED AIDS PATIENTS				
% Patients (228)	Years HIV+	CD4 (cells/mm ³)	DOM (scale 1-3)	Diarrhea
LSZ*	4.2	71.8	2.3	52%
29% (67)	(±2.4)‡	(±139.2)‡	(±0.7)‡	(35/67)
BSZ**	4.5	79.2	2.2	67%
21% (49)	(±3.2)	(±111.0)	(±0.7)	(33/49)
NSZ†	3.9	90.0	2.2	48%
49% (112)	(±2.8)	(±36.0)	(±0.7)	(54/112)
ANOVA	p = NS	p = NS	p = NS	
Chi-square				p = NS

*LSZ = serum zinc < 55 µg/dL.

**BSZ = serum zinc ≥ 55 µg/dL ≤ 65 µg/dL.

†NSZ = serum zinc > 65 µg/dL.

‡ = ±SD.

TABLE IV.

PRIMARY ADMITTING DIAGNOSIS*		
Diagnosis	Number of patients	Percentage
PCP	51	22
Viral	30	13
Fungal	17	7
Bacterial	40	17
Other**	94	41

*Three patients had more than one principal diagnosis on admission.
 **Including lymphoma, failure to thrive, neurologic disorders, mycobacterial infection.

seropositivity, and degree of malnutrition) within the three groups were compared by using one-way analysis of variance (ANOVA). The proportions of opportunistic infections on admission were compared among the three groups by using chi-square analysis. Statistical analysis was performed on the PC program Instat®.

RESULTS

The mean zinc level for all patients was 70.2 (±32.4) µg/dL. The mean CD4 count was 65.5 (±110.1) cells/mm³ in this cohort, and patients had been HIV seropositive for an average of 4.1 (±2.8) yr (Table II). The patients were moderately malnourished (2.2 ± 0.73) based on the general classification system.

Sixty-seven patients (29%) had low serum zinc levels as defined by our laboratory. An additional 49 patients (21%) had borderline serum zinc, and 112 patients (49%) had normal serum zinc levels. There was no significant difference among the three groups in years of HIV seropositivity, mean CD4 count, presence of diarrhea, or degree of malnutrition (Table III).

Two hundred thirty-two primary diagnoses were noted in the 228 patients. Pneumocystis pneumonia was the most common infection identified, present in 22% of the group. Bacterial

infections were the second most common, present in 17% of the total group (Table IV).

Patients with low serum zinc had a significantly higher rate (24%) of bacterial infections than did the groups with borderline (20%) and normal (11%) serum zinc. Combining the borderline group with either the low or normal groups did not change the association between lower serum zinc levels and higher rate of bacterial infection (Fig. 1).

There was no significant difference among the three zinc level groups in the proportion of patients with PCP or "other" admitting diagnoses (Table V). A trend toward a lower proportion of patients with viral and fungal infections in the LSZ group was noted; however, this did not reach statistical significance.

DISCUSSION

Low serum zinc levels are common in hospitalized patients with AIDS: 29% of patients with serum levels below normal and 21% with a borderline low level. Among the three groups of patients with low, borderline, and normal zinc levels, there were no significant differences in CD4 count or length of HIV seropositivity. This lack of correlation suggests that hypozincemia cannot be attributed solely to progression of AIDS.

An association between hypozincemia and severity of malnutrition was also not confirmed by this study. The severity of malnutrition (mild, moderate, and severe) did not differ significantly among the three groups. A history of diarrhea, suggesting possible malabsorption, also did not correlate with abnormally low zinc levels. Serum zinc levels can fluctuate during an acute illness, especially in the presence of fever. In this retrospective study, it was not possible to correlate zinc levels with febrile episodes or severity of acute infection. Among the limited number of patients with multiple serum zinc determinations, the level did not deviate substantially during the hospitalization (data not shown).

Patients with low serum zinc levels had a significantly higher proportion of bacterial infections than did patients with borderline or normal zinc levels. A trend to fewer viral and fungal infections in the LSZ was noted but did not reach statistical significance. The borderline group had an intermediate propor-

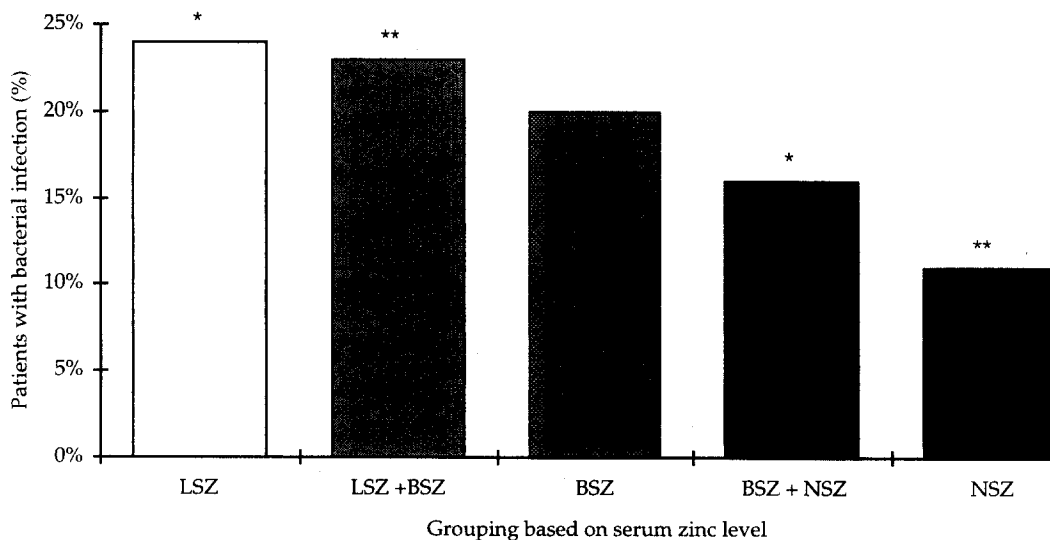


FIG. 1. Serum zinc levels and bacterial infection.

TABLE V.

ADMITTING DIAGNOSES AMONG 3 ZINC LEVEL GROUPS						
Number of patients	PCP	Viral	Fungal	Bacterial	Other	Diarrhea
LSZ* (%) 67	19	6	4	24	44	52 (35/67)
BSZ** (%) 49	22	16	6	20	38	67 (33/49)
NSZ† (%) 112	24	16	10	11	39	48 (54/112)
Chi square	0.53	4.29	1.90	6.83	1.0	5.07
p value	NS	0.12	NS	0.03	NS	0.08

*LSZ = serum zinc < 55 µg/dL.

**BSZ = serum zinc ≥ 55 µg/dL ≤ 65 µg/dL.

†NSZ = serum zinc > 55 µg/dL.

tion of bacterial infection (and viral infection), strengthening the proposed relationship between zinc level and susceptibility to bacterial infection (and a potential inverse relationship to viral infection). The significantly higher proportion among the LSZ group persisted even after combining BSZ and NSZ. The

proportion of patients admitted with PCP and "other diagnoses" did not differ significantly among the three groups of patients.

Impairments in T-cell function accompanying the progression of AIDS are thought to account for increased susceptibility to opportunistic infections, including pneumocystis pneumonia and systemic viral, fungal, and protozoan infections. Bacterial infections account for a significant number of hospitalizations in patients with AIDS, and zinc deficiency may increase the likelihood for or susceptibility to developing these bacterial infections.

Serum zinc appears to be a marker of susceptibility to infections in patients with AIDS, and periodic serum levels may assist health-care providers in risk stratifying patients. The optimal regimen for replacing zinc is controversial. A recent study has suggested that overly aggressive supplementation is actually detrimental.⁹ In addition to a well-balanced diet, we currently recommend a daily multivitamin containing minerals (containing 15–60 mg of zinc oxide or zinc sulfate).

Even though immune function is governed by a wide variety of interdependent factors, this study suggests that low serum zinc may result in an increased risk of bacterial infections. Longitudinal studies with sequential zinc measurements (before, during, and after hospitalization) would be required to establish a causal relationship between zinc deficiency and susceptibility to infections.

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