

Zinc Deficiency in Crohn's Disease

N.W. Solomons, I.H. Rosenberg, H.H. Sandstead and K.P. Vo-Khactu

Department of Medicine, Section of Gastroenterology, The University of Chicago, Chicago, Ill., and Human Nutrition Laboratory, Agricultural Research Service, USDA, Grand Forks, N.Dak.

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Abstract. Zinc nutriture has been studied in 30 patients with Crohn's disease using plasma zinc, hair zinc, and taste acuity as indices. Significant reductions in plasma zinc concentrations and taste acuity were seen in the patient groups as compared with normal controls. Hair zinc content was also generally low with several deficient values encountered among the Crohn's patients. A highly significant correlation between plasma zinc and albumin suggests a possible role of plasma-binding alterations in the depressed plasma zinc levels of patients with Crohn's disease patients and a potential influence on growth and healing in this disease must be considered.

Introduction

Nutritional deficiencies and impaired absorption of nutrients including protein, fat, iron, calcium, folate, vitamin B₁₂ and *D*-xylose have been documented in patients with Crohn's disease (1, 2, 6, 8, 9). The trace metal, zinc, is a nutrient essential for the synthesis of nucleic acids and proteins (27), and for growth (26), and healing (15) in experimental animals. A zinc-responsive human syndrome of dwarfism and hypogonadism has been described (10, 23). In addition, acrodermatitis enteropathica has been found to be responsive to zinc (20, 21). Preliminary studies in patients with sickle cell disease (4) and cystic fibrosis (11) have suggested a possible relationship between conditioned zinc deficiency and the growth retardation and maturation delay which sometimes occurs in adolescents with these diseases. *Sandstead* (24) has described an adolescent patient with regional enteritis and biochemical evidence of zinc deficiency,

who experienced a dramatic clinical response in growth and sexual maturation as well as an improvement in gastrointestinal symptoms after treatment with oral zinc sulfate. In view of the clinical reports cited above and the evidence that zinc has an important role in growth and healing, we have assessed zinc nutriture of adult and adolescent patients with Crohn's disease; some of the latter patients were growth-retarded. Indices of zinc status were plasma zinc, hair zinc, and taste acuity.

Patients and Methods

Patients were studied in the clinics and inpatient services of the Gastroenterology Section of the University of Chicago Hospitals and Clinics. The diagnosis of Crohn's disease had been made by established radiographic, clinical and often pathological criteria. There were 20 adult patients, ranging in age from 20 to 62 years. All had been hospitalized at the time of study for an exacerbation of their disease. 13 were female and 7 were male; 11 were classified as having regional enteritis, 6 had ileocolitis, and 3 had granulomatous colitis. Duration of disease ranged from 2 to 20 years. 11 patients had undergone previous surgical resections and were now presenting with recurrent disease.

10 additional patients were adolescents ranging in age from 10 to 19 years; 5 of these were classified as growth-retarded on the basis of a documented arrest of linear growth for at least 6 months prior to entering the study, and of a height-for-age below the 10th percentile. 1 patient whose height was at the 16th percentile was included in this group because of amenorrhea and delayed sexual maturation. There were 6 females and 4 males among the adolescent groups. 3 had regional enteritis, 6 had ileocolitis and one patient had granulomatous colitis. Duration of disease ranged from 1 month to 5 years, and 1 patient had undergone prior bowel resection.

Adult control subjects, 10 males and 10 females, ranging in age from 20 to 43 years, and without known or suspected bowel disease, were drawn from among hospital technical and professional staff, and patients' spouses and friends. Adolescent controls included 39 healthy subjects, 23 males and 16 females, studied at a private high school. A group of children and adolescents from the Pediatric Endocrine Clinic who presented for evaluation of short stature, and who were classified as constitutionally growth-retarded also served as a control population. All patients and controls consented to participation after full explanation of the study. High school controls had, in addition, the written permission of their parents.

Nonfasting blood samples were collected in plastic containers. Blood was anticoagulated with trace metal-free oxalate. Erythrocytes were removed promptly by centrifugation, and hemolyzed samples were not used for zinc analysis. Zinc was measured by flame atomic absorption spectrometry after the method of *Sinha and Gabrieli* (25). Hair was taken from the occipital scalp with stainless steel scissors. The proximal 2-3 cm were analyzed after being cut into pieces less than 1 mm in length and washed with acetone, ether, and detergent (14). Samples of 15-20 mg were then wet-ashed with nitric and sulfuric acids. The digestate was diluted to 5 ml, and zinc was measured via flame atomic absorption spectrophotometry with 5 vol% H₂SO₄ matrix for both samples and calibration standards. Hair zinc content is expressed in terms of weight of dry, washed hair. Plasma albumin was determined by cellulose acetate protein electrophoresis.

Quantitative determination of taste threshold was performed using the three-drop, forced choice dilution technique of *Hambridge et al.* (12). In this procedure, tastant

solutions representing salty (sodium chloride), sweet (sucrose), bitter (urea), and sour (hydrochloric acid), each in 5 concentrations as previously determined (12) were used. For each dilution, three drops were presented in a changing order on alternate sides of the tongue; two drops contained distilled water, and one drop contained the tastant. The subject was asked to identify the drop which was not water (taste detection) and to identify its flavor correctly (taste recognition). For comparison of groups, a simple taste detection score was used in which a minus one score was given for each of the 20 tastant dilutions which could not be correctly distinguished from water.

The Student's *t* test was used for comparison of the mean between groups. Comparison of paired data within groups was performed by simple linear regression analysis.

Results

Plasma Zinc

Figure 1 illustrates the plasma zinc data for adult Crohn's disease patients and controls. 10 of the 20 patients had plasma zinc values more than 1 SD below the control mean, and 5 had values more than 2 SD below that mean. As compared with a concentration of $74.3 \pm 9.7 \mu\text{g}\%$ (mean \pm 1 SD) for the control

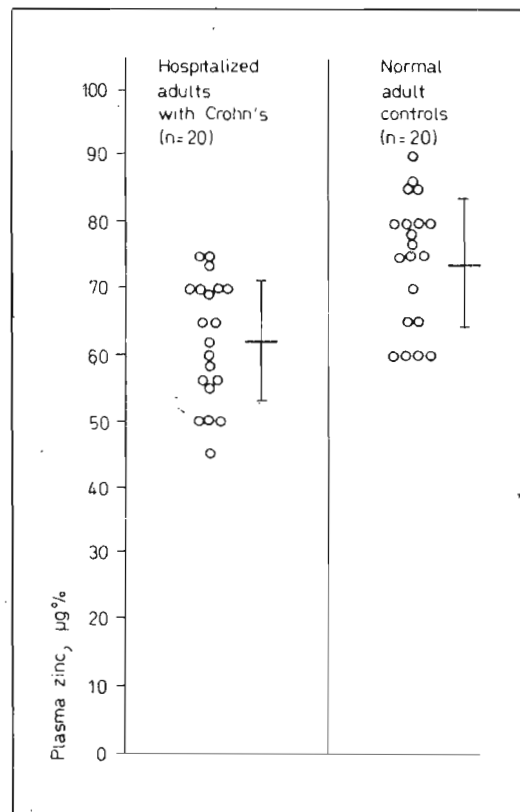


Fig. 1. Scattergram of plasma zinc concentration in adult Crohn's patients and normal adult controls. Bars indicate mean \pm 1 SD.

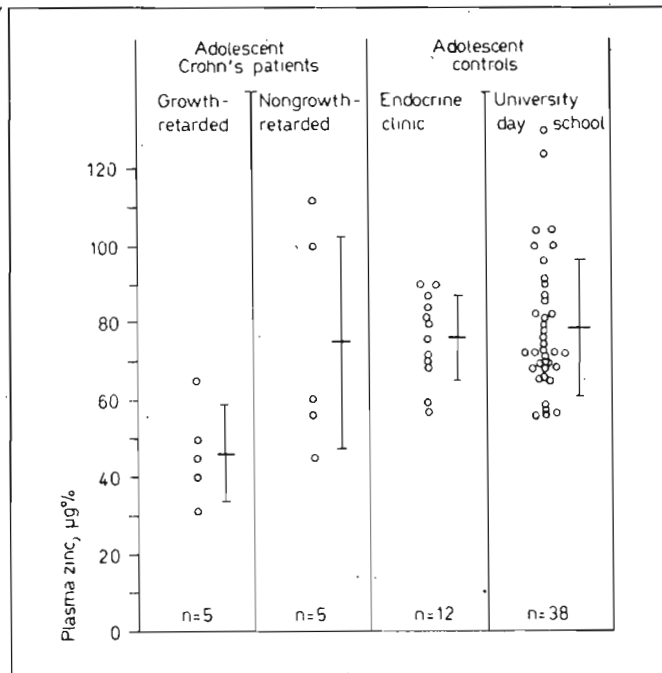


Fig. 2. Scattergram of plasma zinc concentration in the two groups of adolescent Crohn's patients, in constitutionally growth-retarded adolescents, and in normal adolescent controls.

group, the patients had a mean of $62.3 \pm 9.3 \mu\text{g}\%$ ($p < 0.001$). The mean plasma zinc for the 5 adolescent patients with growth retardation or delayed sexual maturation and growth arrest was $46.2 \pm 12.6 \mu\text{g}\%$ as compared with the 5 adolescents with Crohn's disease who maintained normal growth patterns with a mean plasma zinc of $75.2 \pm 27.7 \mu\text{g}\%$. The small number of cases does not allow for meaningful statistical comparison here. However, when compared with the $78.6 \pm 17.6 \mu\text{g}\%$ mean plasma zinc concentration for the normal adolescent controls and the $76.1 \pm 10.3 \mu\text{g}\%$ for the constitutionally growth-retarded controls, the growth-retarded Crohn's adolescents had a significantly depressed mean plasma zinc concentration ($p < 0.001$) (see fig. 2).

Two additional factors, steroid intake and plasma binding, were examined for their possible influence on plasma zinc levels. High dose, parenteral steroids had previously been reported to lower plasma zinc (7), whereas short-term oral doses of 5–10 mg of prednisolone had shown no effect on plasma zinc in another study (5). Among the adult Crohn's patients in the present series, 13 were taking oral steroids and 7 were not taking steroids at the time of the study. No significant difference between the mean plasma concentration of $63.3 \pm 8.6 \mu\text{g}\%$ for the steroid-treated group, and the $58.4 \pm 10.2 \mu\text{g}\%$ for the nonsteroid-treated group were encountered ($p > 0.2$). Moreover, the correlation of plasma zinc vs. daily steroid dose in the former group was poor ($r = 0.015$).

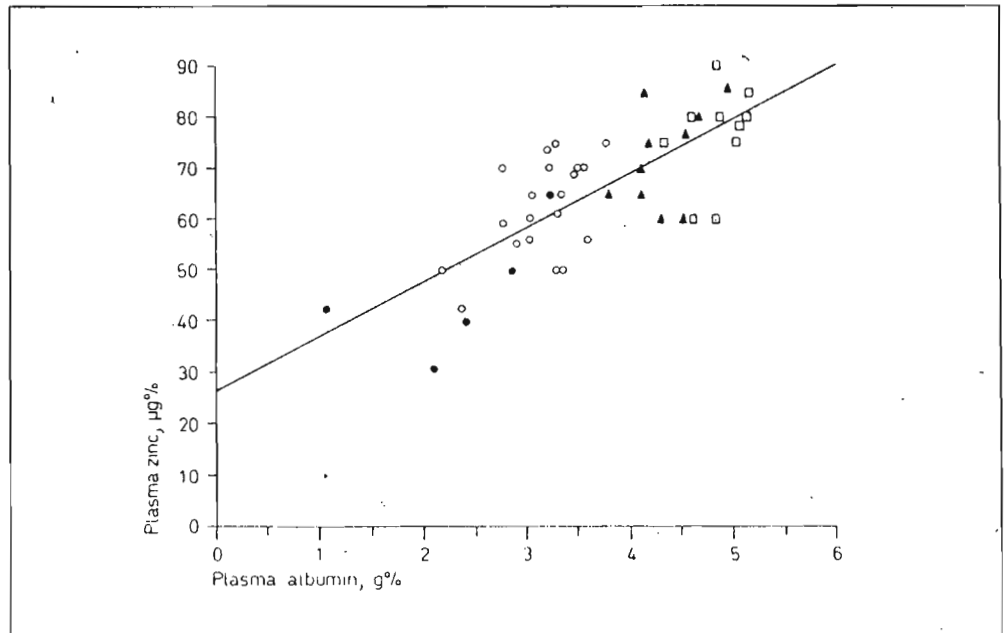


Fig. 3. Regression plot of plasma zinc concentration vs. plasma albumin in adult and growth-retarded adolescent patients and in adult controls. ● = Growth-retarded adolescents with Crohn's; ○ = hospitalized adults with Crohn's; ▲ = normal females; □ = normal males. $r = 0.741$; $p < 0.001$.

Since the majority of plasma zinc is bound to and transported by albumin (13), plasma zinc concentrations have been plotted against plasma albumin levels for the 20 adult controls, 20 hospitalized adult Crohn's patients, and the 5 growth-retarded adolescents with Crohn's disease. As shown in figure 3 a strong correlation was demonstrated ($r = 0.741$, $p < 0.001$).

Hair Zinc

Hair zinc content in Crohn's disease patients tended to be low, but without the statistical significance observed for plasma zinc. Whereas no difference of statistical significance was seen comparing the mean hair zinc concentration of hospitalized adult Crohn's patients, 155 ± 44 ppm, with the local adult controls, 176 ± 30 ppm, of the 20 patients, there were 8 with hair zinc values more than 1 SD below the control mean. Similarly, no differences were found between the mean hair zinc of growth-retarded adolescent patients, 140 ± 67.9 ppm compared with adolescent controls, 168 ± 44 ppm. 1 Crohn's patient, however, clearly had a deficient hair zinc concentration of 36 ppm. The scattergram of hair zinc values for the adult Crohn's patients and growth-retarded adolescent patients is illustrated in figure 4 beside the mean \pm SE for hair zinc concentration from a large series of normal Denver, Colo. residents reported by *Hambidge et al.* (12). The majority (76%) of Crohn's patients had values below the mean.

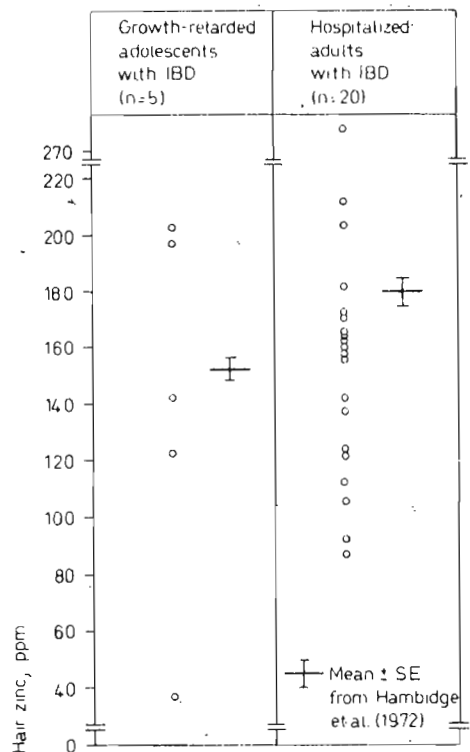


Fig. 4: Scattergram of hair zinc values in growth-retarded adolescent patients and adult patients with inflammatory bowel disease (Crohn's disease). IBD refers to inflammatory bowel disease (Crohn's disease) groups.

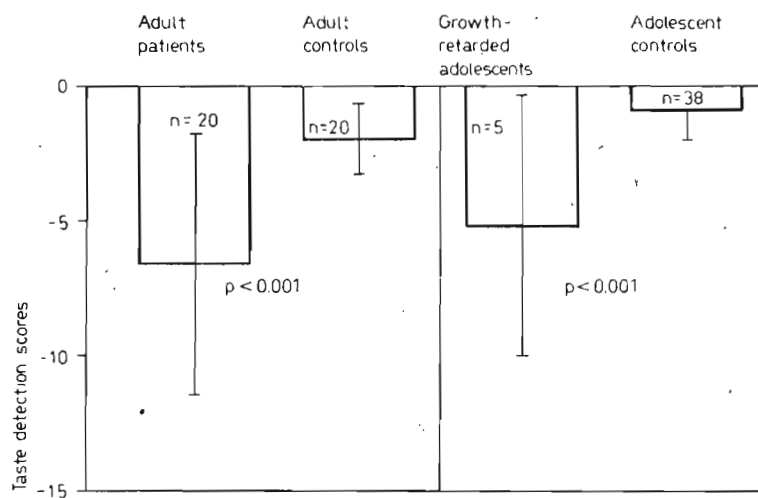


Fig. 5: Taste detection scores in adult and growth-retarded adolescent Crohn's patients and in adult and adolescent controls. Mean values \pm 1 SD are presented.

Taste Acuity

The taste detection scores for adult and adolescent patients and controls are shown in figure 5. The mean for the 20 adult Crohn's patients, -6.6 ± 4.8 was significantly lower than the adult control mean, -2.0 ± 1.5 ($p < 0.001$). Similarly, the mean taste detection score for the 5 growth-retarded adolescents at initial presentation of -5.2 ± 4.8 was impaired compared with the -0.8 ± 1.0 of the control adolescents ($p < 0.001$).

Zinc status data from each index was correlated with paired data from the other indices by linear regression analysis. The correlation of hair zinc vs. plasma zinc had a correlation coefficient, $r = -0.138$, for hair zinc vs. taste acuity, $r = 0.144$, and for plasma zinc vs. taste acuity, $r = 0.199$. None of these individual correlations were significant at the 5% probability level.

Discussion

In this study, we sought to evaluate the nutriture of patients with Crohn's disease with respect to the trace mineral, zinc, to determine whether or not any indications of zinc deficiency could be found. Because a single, unequivocal biochemical or physiological indicator of zinc nutritional status has not yet been agreed upon, we have used three indices: plasma zinc, hair zinc, and taste acuity. Though taste acuity has not been firmly established as a unique index reflecting the adequacy or inadequacy of zinc nutriture, the cause and effect relationship between zinc deficiency and hypogeusia has been a subject of current investigation. Of these indices, plasma zinc and taste acuity are most profoundly depressed in Crohn's disease. Individuals with low and deficient hair zinc content are also encountered among the Crohn's disease group. The lack of mutual correlation among indices of zinc status has been previously noted for plasma zinc and hair zinc by *McBean et al.* (17) and its resolution awaits further basic investigation of biochemical and physiological parameters of zinc nutrition in man. The preliminary conclusion, however, is that zinc deficiency commonly exists in patients with Crohn's disease.

The possible pathogenetic mechanism for zinc deficiency in Crohn's disease include anorexia with reduced intake of zinc, impaired intestinal absorption of zinc, or increased gastrointestinal loss of zinc. The strong correlation between zinc and albumin levels suggests, in addition, that the low plasma zinc concentrations may reflect a reduction of plasma-binding protein, specifically albumin, due to gastrointestinal loss (3) and/or impaired synthesis. Plasma concentrations of zinc, moreover, could be depressed by redistribution and compartmentalization of circulating zinc secondary to leukocyte endogenous mediator (LEM) (22). The influence of LEM on plasma zinc in Crohn's disease is currently under investigation.

The most profound depression in plasma zinc for any group was observed among the 5 growth-retarded adolescents in this study. The cause of growth retardation in Crohn's disease is still largely unexplained (18, 19) and multiple nutritional deficits have been reported in patients with growth arrest (16). Because of the large scatter and small number of adolescent patients, the data are as yet insufficient to conclude that zinc nutriture is a differential factor between growth-retarded and nongrowth-retarded adolescents with Crohn's disease; nor have there been sufficient nutritional studies in Crohn's disease to determine whether zinc, alone or in combination with other nutrients, might be limiting in linear growth and sexual maturation. The observation of zinc deficiency among these patients along with the case report by *Sandstead* (24) of a growth-retarded patient with Crohn's who improved on zinc therapy justifies further investigation of this relationship. In a larger context, moreover, a potential adverse effect on the healing of acute and chronic inflammatory bowel lesions in adult and adolescent patients with a secondary zinc deficiency in Crohn's disease can be considered on the basis of the evidence presented in the present study.

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N. W. Solomons, Institute of Nutrition of Central America and Panama, Carretera Roosevelt, Zona 11, Apartado 11-88, Guatemala City (Guatemala)