Trace mineral balance during acute diarrhea in infants

Carlos Castillo-Duran, MD, Pablo Vial, MD, and Ricardo Uauy, MD, PhD

From the Institute of Nutrition and Food Technology, University of Chile, Santiago, the Dr. Sotero del Rio Hospital, Santiago, Chile, and the Department of Pediatrics and Human Nutrition Center, University of Texas Southwestern Medical Center, Dallas

To evaluate the magnitude of copper and zinc losses during acute diarrhea requiring hospitalization, we studied 14 infants, 3 to 14 months of age, and compared them with a control group of 15 infants of similar age, birth weight, and nutritional status. Metabolic balance studies were conducted in the study group during an initial 48 hours (period 1) and on days 6 and 7 after admission (period 2). The control group was studied after recovery from respiratory disease. Copper and zinc content of feces, urine, and food samples was measured by atomic absorption spectrophotometry. Mean (±SD) fecal losses were higher for period 1 in the diarrhea group than in control subjects: Cu 55.7 ± 21.2 versus 28.8 ± 6.7 μg/kg/body weight/day (*p* <0.01); Zn 159.4 ± 59.9 versus 47.4 ± 6.4 μg/kg/day (*p* <0.0001). For period 2, Zn losses were similar in both groups, but Cu balance remained negative only in the study group. Retention of Zn for the study group went from −21.2 ± 46.7 in period 1 to 204.5 ± 103.0 μg/kg/day in period 2 (*p* <0.0001), and fecal weight decreased from 70.5 ± 20.6 in period 1 to 36.8 ± 20.0 gm/kg/day in period 2. Fecal weight and fecal losses were correlated: *r* = 0.71 (*p* <0.01) for Cu and *r* = 0.81 (*p* <0.001) for Zn. Plasma mean Cu and Zn levels were low in period 1 but rose in period 2, especially for Zn. A negative correlation was found between fecal Zn losses and plasma Zn: *r* = 0.74 (*p* <0.001). We conclude that acute diarrhea leads to Cu and Zn depletion and that plasma levels and Cu balance remain abnormal a week after admission. (J Pediatr 1988;113:452-7)

Trace mineral deficiencies have been demonstrated in children with acute and chronic diarrhea.[1-5] Repeated bouts of diarrhea and chronic nutrient losses are important causative factors for many nutritional diseases, especially for zinc and copper deficiency.[1,6] Trace mineral deficit may impair host defense mechanisms, early growth, and mental development in infants.[7-10] Limited information is available on the magnitude and duration of copper and zinc losses during acute diarrhea,[3,11,12] and it is scarce for protracted diarrhea.[1-3]

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Reprint requests: Ricardo Uauy, MD, PhD, Department of Pediatrics, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235.

We previously reported low hair copper and zinc content in children with chronic diarrhea[4] and an association between copper deficiency in malnourished infants with a history of recurrent episodes of acute diarrhea.[13] The objectives of our study were (1) to evaluate the magnitude of copper and zinc losses during acute infantile diarrhea that required hospitalization and (2) to estimate copper and zinc balance under these conditions.

METHODS

The study group was composed of 14 male infants (mean age 6.4 months, range 3 to 14 months) admitted to the pediatric ward of Sotero del Rio Hospital because of acute diarrhea (mean 5 days, range 2 to 15 days) and dehydration. All patients received treatment consisting of intravenous fluids during the initial 24 to 48 hours; electrolyte and acid-base abnormalities were corrected.

Patients who required antibiotics were excluded from the study. Oral formula administration was started 8 to 12 hours after admission, with the used diluted cow milk (Leche Purita National Health Service, Chile) with added sucrose 5% (wt/vol). The volume for refeeding started at 50 ml/kg/day and increased to 150 ml/kg (110 kcal/kg) within the first week of recovery according to gastrointestinal tolerance. The control group included 15 male infants (mean age 7.0 months, range 4 to 12 months) recovering from respiratory diseases such as pneumonia or asthma. The control group was similar to the study group in age, birth weight, and nutritional status; mean weight for age was 80% of the National Center for Health Statistics (NCHS) standard for control subjects and 82% for the study group. None had edema or other clinical signs of kwashiorkor. Their balance studies were performed 5 to 10 days after admission, 2 to 3 days before their scheduled discharge from the hospital.

Metabolic balances were conducted in the study group during the first 48 hours after admission (period 1); the balances were repeated in seven randomly selected infants on days 6 and 7 (period 2). Balance studies were also conducted in the 15 control infants; these patients were fed whole cow milk formula (Leche Purita National Health Service, Chile) with added sucrose (74 kcal/dl). Urine was collected daily in trace mineral–free plastic containers to which 10 ml of 10% sulphuric acid was added. Brilliant blue fecal markers were used to indicate initiation and completion of the 48-hour collection. Urine was collected separately from feces by means of an adherent system, after the perineal area was protected with an adhesive skin spray (Skin-Bond, United Medical, Largo, Fla.); feces were collected in trace mineral–free plastic bags during the metabolic balance determinations. Urine and fecal samples were frozen to −20° C until analysis.

Heparinized blood samples (4 ml) were obtained at the end of each metabolic study period in both groups; care was taken to avoid hemolysis and trace mineral contamination. Mineral intakes were estimated from measurements of ingested formula by weighing each bottle before and after every feeding and by quantifying miscellaneous losses. Copper and zinc content of ingredients and random samples of formula was also measured. Trace mineral analysis was conducted by means of atomic absorption spectrophotometry on a Perkin-Elmer model 303 apparatus (Perkin-Elmer Corp., Instrument Group, Norwalk, Conn.). Fecal and food samples were dried to constant weight and subjected to wet digestion with nitric acid before analysis. Fresh stool specimens from the study group were analyzed for the presence of pathogenic bacteria (cultures), parasites (microscopically), and rotavirus (by enzyme-linked immunsorbent assay); the evaluation included specific methods to detect *Cryptosporidium* and *Campylobacter*.

Table I. Copper balance and plasma levels in infants during recovery from acute diarrhea

	Study group		
	Period 1* (n = 14)	**Period 2 (n = 7)**	**Control group (n = 15)**
Intake (μg/kg/day)	6.3 ± 2.7 †	28.0 ± 11.0‡	50.0 ± 10.8
Fecal loss (μg/kg/day)	55.7 ± 21.2	50.1 ± 47.0	28.8 ± 6.7
Urine (μg/kg/day)	0.20 ± 0.06	0.24 ± 0.06	0.21 ± 0.08
Balance (μg/kg/day)	−49.6 ± 21.9§	−21.5 ± 46.7‖	21.0 ± 11.7
Plasma (μg/dl)	63.2 ± 14.4§	90.7 ± 19.5‖	117.1 ± 18.0

*Study group values (intake, fecal loss, balance, plasma) during period 1 versus corresponding control group values: $p < 0.001$.
†Study group during period 1 versus study group intake values during period 2: $p < 0.001$.
‡Study group intake values during period 2 versus control group intake values: $p < 0.0005$.
§Study group values (balance, plasma) during period 1 versus study group values (balance, plasma) during period 2: $p < 0.05$.
‖Study group values (balance, plasma) during period 2 versus control group values (balance, plasma): $p < 0.05$.

Written informed consent was obtained from parents of the infants. The study was previously approved by the ethics committee of the Institute of Nutrition and Food Technology. Data are presented as mean and standard deviation. Simple or paired t tests were applied to selected variables. Regression and correlation analyses were also used.

RESULTS

The mean copper and zinc content of the milk formula used in the study group was 0.22 mg/L and 1.9 mg/L, respectively; the mean copper and zinc content of the formula used for the control group was 0.29 mg/L and 2.6 mg/L, respectively.

Significantly higher fecal losses were found for the study group during period 1 ($p < 0.001$) despite their lower copper intake (Table I). Fecal copper losses remained elevated during period 2. Urinary copper excretion was minimal in both groups; the apparent copper retention was negative, largely because of the high fecal copper loss in period 1. It remained negative for period 2.

We found significantly higher fecal zinc losses in the study group, in comparison with control subjects, during period 1 ($p < 0.001$) (Table II). Zinc losses for the diarrhea group in period 2 were similar to those in control subjects.

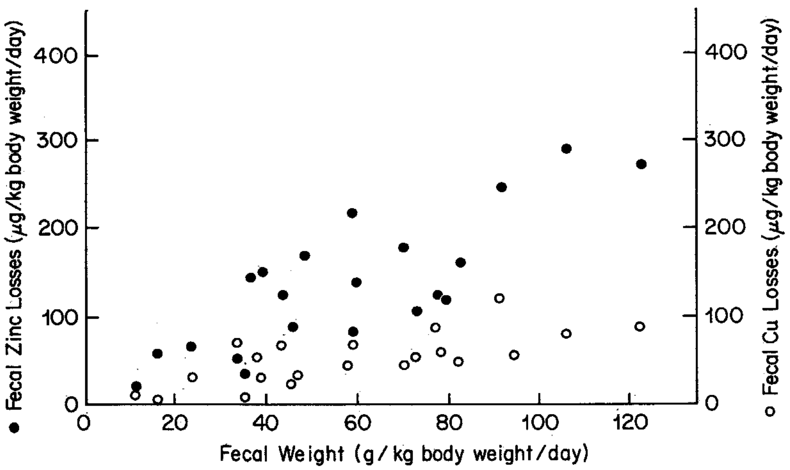

Fig. 1. Relationship between fecal weight and trace mineral fecal losses normalized for body weight in infants with diarrhea. Correlation coefficients were $r = 0.81$ ($p < 0.001$) for zinc and $r = 0.72$ ($p < 0.001$) for copper. Fecal zinc losses increased by 2.1 μg and copper losses by 0.7 μg for each gram increase in fecal weight.

Table II. Zinc balance and plasma levels in infants during recovery from acute diarrhea

	Study group		Control group
	Period 1* (n = 14)	Period 2 (n = 7)	(n = 15)
Intake (μg/kg/day)	51.4±23.3†	254.1±87.4‡	453.0±71.3
Fecal loss (μg/kg/day)	159.4±59.9*	49.6±20.4	47.4±6.4
Urine loss (μg/kg/day)	Undetectable	Undetectable	0.3±2.3
Balance (μg/kg/day)	−108.0±67.5†	204.5±103.0‡	405.3±60.8
Plasma (μg/dl)	57.7±19.0§	101.4±20.7‖	123.6±25.6

*Study group values (intake, fecal loss, balance, plasma) during period 1 versus corresponding conrol group values and study group fecal loss value during period 2: $p < 0.001$.
†Study group values (intake, balance) during period 1 versus study group values (intake, balance) during period 2: $p < 0.0005$.
‡Study group values (intake, balance) during period 2 versus control group values (intake, balance): $p < 0.001$.
§Study group plasma values during period 1 versus study group plasma values during period 2: $p < 0.05$.
‖Study group plasma values during period 2 versus control group plasma values: $p < 0.05$.

Zinc retention was negative during period 1 but became positive during period 2, although it remained lower than that observed for the control group.

Fecal weight decreased significantly in the study group from 70.5 ± 20.6 gm/kg body weight/day in period 1, to 36.8 ± 20.0 gm/kg/day in period 2 ($p < 0.0005$). A significant correlation was found in the study group between fecal weight and both fecal copper losses ($r = 0.72$; $p < 0.001$) and fecal zinc losses ($r = 0.81$, $p < 0.001$) (Fig. 1). No correlation was found between mineral losses and fecal weight in the control group.

Half of the infants had plasma copper levels below the normal limit of 90 μg/dl on day 8. In contrast, only one infant had low plasma zinc levels on day 8 (57 μg/dl). Plasma zinc levels for both periods correlated negatively with fecal zinc excretion during periods 1 and 2 ($r = -0.74$; $p < 0.001$) (Fig. 2). Fecal weight and zinc losses decreased in period 2; concomitantly, plasma zinc levels increased.

The microbiologic analysis of feces in the study group revealed that six infants had enteropathogenic *Escherichia coli*, two infants had rotavirus, and one infant had *Salmonella enteritidis* serotype *typhimurium*. No microorganisms were detected in the other five infants.

DISCUSSION

Studies that evaluate mineral losses in infants during and after episodes of acute diarrhea are scarce, despite the global importance of this problem. Cordano and Graham[6] demonstrated that severe copper deficiency is associated with a history of chronic diarrhea, whole cow milk feeding, and malnutrition. These investigators also reported a relationship between malabsorption syndrome, malnutrition, and copper deficiency.[12,13] Parker et al.[1] demonstrated abnormal fat and nitrogen absorption, as well as increased fecal copper and zinc losses, in infants with protracted diarrhea. Rothbaum et al.[2] showed a decrease in serum zinc and alkaline phosphatase levels in infants receiving parenteral nutrition because of prolonged diarrhea; both

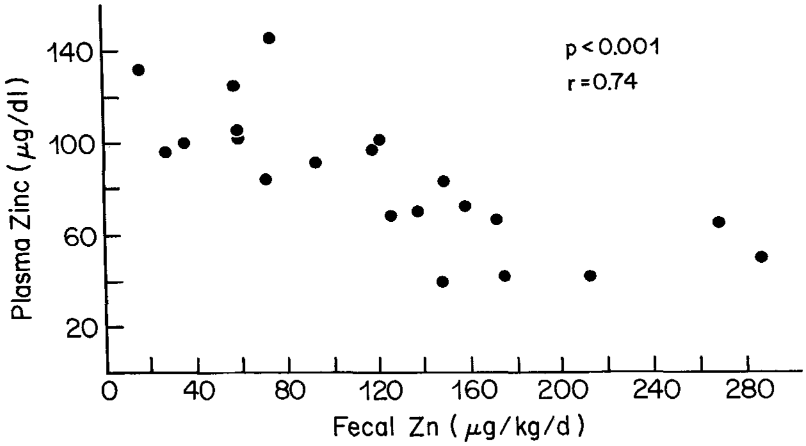

Fig. 2. Relationship between fecal zinc losses and plasma zinc levels for infants with diarrhea. Correlation coefficient was $r = -0.74$ ($p < 0.001$). Plot represents values for periods 1 and 2.

measurements tended to normalize if parenteral zinc supplementation was increased. Our finding of zinc losses during the early stages of recovery from diarrhea is in agreement with the increase in zinc requirements suggested by Rothbaum et al.[2] Naveh et al.[3] found decreased plasma zinc levels in acute diarrhea and a negative correlation between duration of diarrhea and plasma zinc levels in infants. Coello-Ramirez and Diaz-Bensussen[14] also described decreased serum zinc levels in malnourished children with protracted diarrhea or acute gastroenteritis. Sarker et al.[15] showed low plasma zinc levels during the acute phase of diarrhea in children 9 months to 6 years of age, with moderate to severe malnutrition; these values tended to normalize after 2 weeks of recovery.

Our study showed large fecal copper and zinc losses during the early stages of recovery from acute diarrhea. Fecal losses for copper remained elevated 1 week after admission to the hospital, whereas zinc losses during the second period of balance were normal. Even though we do not have reliable data on zinc retention in normal "healthy" infants, our control group had a higher mineral retention than the estimated normal accretion rate for this age group, adjusted for the digestibility of minerals in cow milk.[16] The zinc content of whole cow milk is closer to the estimated zinc requirements for normal infants.

The zinc content of mineral supplemented formulas infants ranges from 3 to 5.5 mg/L.[16] If the absorbed zinc requirement is considered to be 100 μg/kg/day, and if this amount is adjusted by the zinc bioavailability for cow milk formulas (20% to 25%), an infant would require about 2.5 mg/day under normal conditions.[17] Infants recovering from diarrhea might benefit from zinc-supplemented formula or other weaning foods rich in zinc to achieve faster repletion after diarrhea, especially if they are preterm or malnourished and have higher copper and zinc requirements.[18,19]

Copper balance remained negative despite the decline in copper fecal losses, perhaps because of insufficient copper intake provided by the cow milk feeding and by the diluted formula given to these infants.[20] If the copper lost during the days of diarrhea before hospital admission and the high copper output during the early stages of recovery are considered, it is virtually impossible to replace all the fecal copper losses by feeding whole cow milk (copper content 0.2 to 0.3 mg/L). If copper-supplemented formulas (0.4 to 0.7 mg/L) were used, 2 or 3 weeks would be necessary to replace cumulative fecal copper losses and provide for maintenance copper needs.[17]

A significant correlation was found between fecal weight and daily fecal zinc or copper output. It may be important to study fecal mineral concentrations in specific types of diarrheal disease, such as secretory or osmotic diarrhea, and to investigate the proportion of these losses that correspond to endogenous and dietary origin.

Low plasma copper and zinc levels were found during the first balance period; zinc levels were almost normal, and copper levels improved partially during the second balance. Plasma copper concentrations may reflect nutritional copper status, but plasma zinc values are not a good index of zinc body status, especially during acute changes in zinc balance.[21,22] The correlation between fecal zinc losses and plasma zinc levels indicates the possible importance of fecal zinc losses in determining plasma zinc levels during diarrhea, despite the reported endogenous redistribution and the decrease in plasma zinc levels during infection.[23,24]

Multiple factors may influence copper and zinc retention in acute diarrhea. There may be a decrease in food intake.[25,26] Increased losses may be related to intestinal cellular damage caused by the infectious agent or by milk protein hypersensitivity.[27,28] Losses may even be influenced by a specific trace mineral deficit per se, as observed during copper or zinc deficiency in the rat.[29,30] Diarrhea induces increased intestinal, hepatic, and pancreatic secretions, rich in copper and zinc, which may not be reabsorbed, thus further increasing fecal losses.[23] The exudation of protein-mineral complexes to the intestinal lumen has been demonstrated in rats; the formation of insoluble complexes of copper or zinc with fat, phosphates, calcium, and fiber is also possible.[31,32] Finally, in experimental animals, net secretion of calcium, magnesium, and zinc can be observed after feeding hypertonic glucose solutions.[33] We did not obtain evidence of these mechanisms, but all infants had diminished formula intake and most had enteropathogenic microorganisms associated with the diarrhea.

We conclude that acute diarrhea and dehydration may lead to marked copper and zinc depletion and to abnormally low plasma trace mineral levels. Infants recovering from acute diarrhea may require trace mineral supplementation if factors predisposing them to mineral deficiency are present.

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