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Enteral Zinc Supplementation and Growth in Extremely-Low-Birth-Weight Infants With Chronic Lung Disease

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Abstract

Objective—Zinc deficiency causes growth deficits. Extremely-low-birth-weight (ELBW) infants with chronic lung disease (CLD), also known as bronchopulmonary dysplasia, experience growth failure and are at risk for zinc deficiency. We hypothesized that enteral zinc supplementation would increase weight gain and linear growth.

Methods—A cohort of infants was examined retrospectively at a single center between January 2008 and December 2011. CLD was defined as the need for oxygen at 36 weeks postmenstrual age. Zinc supplementation was started in infants who had poor weight gain. Infants' weight gain and linear growth were compared before and after zinc supplementation using the paired *t* test.

Results—A total of 52 ELBW infants with CLD met entry criteria. Mean birth weight was 682 ± 183 g, and gestational age was 25.3 ± 2 weeks. Zinc supplementation started at postmenstrual age 33 ± 2 weeks. Most infants received fortified human milk. Weight gain increased from 10.9 before supplementation to $19.9 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ after supplementation ($P < 0.0001$). Linear growth increased from 0.7 to 1.1 cm/week ($P = 0.001$).

Conclusions—Zinc supplementation improved growth in ELBW infants with CLD receiving human milk. Further investigation is warranted to reevaluate zinc requirements, markers, and balance.

Keywords

chronic lung disease; extremely-low-birth-weight infant; growth; human milk; preterm infant; zinc

Zinc is an essential micronutrient that plays an important role in growth and development (1). It is involved in multiple cellular and subcellular processes that are essential for cell proliferation, growth, and brain development (2–4). Manifestations of zinc deficiency include poor growth, diarrhea, rash, and immune dysfunction (5).

The rapid growth rate of preterm infants causes a high demand for zinc (5–7). Preterm infants are at increased risk for developing zinc deficiency because they miss the period of increased zinc accretion that occurs in the third trimester (1,8,9). Preterm infants also have immature intestinal tracts and kidneys, resulting in increased zinc losses (10,11). An additional risk factor for zinc deficiency is related to the dramatic decrease in zinc content of human milk during the first few weeks of lactation. This decrease occurs in preterm and term human milk independently of maternal zinc status (12–14).

Extremely-low-birth-weight (ELBW) infants (defined as infants with birth weight <1000 g) constitute a unique group of premature infants who have been surviving in increasing numbers during the last 2 decades (15). Their nutritional requirements, metabolism, and growth patterns are believed to be different from those of premature infants with higher birth weight (16,17).

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia, is a common morbidity affecting up to 40% of ELBW infants (15). Infants with CLD have high rates of postnatal growth failure (18) (defined as body weight <10th percentile for completed weeks of gestation according to model intrauterine growth data or an average weight gain of $<15 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) (19). This common morbidity is tightly linked to neurodevelopmental outcomes in these infants (20). Poor growth in this population could be partially related to a zinc deficiency state because zinc requirements and metabolism in ELBW infants, and those with CLD in particular, are not well understood.

Diagnosis of zinc deficiency states can be difficult because serum zinc level does not accurately reflect total body zinc and biological markers that correlate well with zinc status are lacking (21). Alkaline phosphatase is a zinc-dependent metalloenzyme that has been used as a biological marker of zinc status; alkaline phosphatase levels would presumably be lower in infants with zinc deficiency (21).

We sought to evaluate the effect of enteral zinc supplementation on weight gain and linear growth in ELBW infants with CLD who received volume-restricted fortified human milk.

METHODS

Subjects

After institutional review board approval, we performed a single-center retrospective chart review of ELBW preterm infants with CLD who received enteral zinc supplementation for a minimum of 14 days between January 2008 and December 2011. CLD was defined as the need for supplemental oxygen at 36 weeks postmenstrual age; severe CLD was defined as the need for 30% oxygen and/or positive pressure ventilation at 36 weeks postmenstrual

age (22,23). Subjects with 40% of their weight data missing were excluded from the analysis. There were no other exclusion criteria.

Nutritional Management

Standard guidelines for parenteral and enteral nutrition are followed in the neonatal intensive care unit (NICU) at our institution and consist of administration of parenteral nutrition within the first 24 hours of birth and progression to full enteral feedings (7,24,25). Our institution's standard of care for infants with CLD is that they are advanced to full enteral nutrition and require a protein intake of $3 \text{ to } 4 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ and between $120 \text{ and } 150 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ to maintain growth (26).

The majority of infants receive human milk (donor or mother's own milk). If human milk is not available, infants generally receive the standard premature infant formula Similac Special Care (Abbott Nutrition, Columbus, OH) or Enfamil Premature (Mead Johnson Nutrition, Glenview, IL). Commercial human milk fortifier is added to human milk when the infant tolerates a volume of $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of Enfamil Human Milk Fortifier (Mead Johnson Nutrition) or Similac Human Milk Fortifier (Abbott Nutrition).

Growth standards are established using the Fenton growth curve (27), with an optimal goal for weight gain of $16 \text{ to } 18 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ and linear growth of $0.8 \text{ to } 1.1 \text{ cm/week}$. Weight is recorded daily; infant's length and head circumference are recorded weekly. All of the infants are routinely assessed by a neonatal dietitian.

Zinc Administration

The American Society of Clinical Nutrition recommends that zinc content in parenteral nutrition in preterm infants be $400 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (27). The American Society for Nutritional Sciences recommends that preterm infant formulas provide a concentration of $8 \text{ to } 9 \text{ mg/L}$ of zinc and that human milk be fortified to provide 5 mg/L of zinc (24).

The decision to supplement with zinc was made in infants who had a low rate of weight gain, defined as $<16 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 2 weeks before starting zinc supplementation, despite increasing energy and an adequate protein intake. It is important to note that all of the infants were receiving a minimum of $120 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in enteral feeding for at least 2 weeks before zinc supplementation and none had acute illnesses. Enteral zinc dose was based on that used in studies of zinc supplementation in low-birth-weight infants (28–31).

Statistical Analysis

Paired *t* test was used to compare weight gain, linear growth, and alkaline phosphatase values before and after zinc supplementation. Paired *t* test was calculated with the use of SAS 9.1.3 (SAS Institute, Cary, NC). Mixed model analysis was used to evaluate weight gain over time with the effect of zinc supplementation. Significance was accepted at $P < 0.05$.

RESULTS

Demographics

Our search yielded a total of 55 infants who met entrance criteria. Three infants had incomplete data (because they were transferred to our institution later in life) and were excluded from the analysis. Demographics of the study population are outlined in Table 1.

Nutritional Management

The majority of infants (41, 79%) received fortified human milk at the time of zinc supplementation. The remaining 11 infants received infant formula. Six infants received Similac Special Care, 2 infants received Elecare, 1 infant received Similac Neosure, 1 infant received Portagen for chylothorax, and another infant received Similac 60/40 for renal insufficiency.

Zinc Administration

Supplemental zinc was administered enterally in the form of zinc acetate. The average dose was $1.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ (± 0.6). Based on the zinc content in human milk, human milk fortifier, and infant formula (32), supplementing at these doses represented a 100% to 150% increase above baseline zinc intake. Table 2 outlines the age at initiation, type of feeding, and duration of zinc supplementation.

Weight Gain

After 1 week of zinc supplementation, the average rate of weight gain significantly increased from 10.9 ± 7.8 the week before zinc supplementation to $19.9 \pm 10.1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ($P < 0.0001$). This increase in weight gain remained significant at weeks 3, 5, and 6 after zinc supplementation (Fig. 1). Using mixed-model analysis for repeated measures, weight was shown to significantly increase with passage of time in weeks ($P < 0.0001$). More important, the slope of weight gain is significantly higher after zinc supplementation ($P < 0.0001$) because the interaction term between time and zinc administration has significant effects ($P < 0.0001$). These results suggest that the increase in weight gain is unlikely to be because of passage of time alone.

Linear Growth

Linear growth data were available for 45 infants (86.5%). There was a significant increase in the rate of linear growth after 3 weeks of zinc supplementation, from an average of 0.7 ± 0.5 for 3 weeks before supplementation to $1.1 \pm 0.5 \text{ cm/week}$ ($P = 0.001$). This increase remained significant at 6 weeks after supplementation (Fig. 2), when the average linear growth rate for the 6 weeks before zinc supplementation was 0.69 ± 0.3 and increased significantly to $1.1 \pm 0.26 \text{ cm/week}$ ($P < 0.0001$).

Alkaline Phosphatase

Alkaline phosphatase values were available for 32 (61.5%) infants. Alkaline phosphatase rose in concentration in some infants, but the change was not statistically significant.

DISCUSSION

Zinc is an essential trace mineral that is intricately associated with growth and development (2–4). It is of particular importance in vulnerable populations such as ELBW infants who have rapid growth and periods of critical illness (17,33,34).

In this study, we describe the positive effect of zinc supplementation on growth of ELBW infants with CLD. Few data exist on zinc status and balance in this population of infants that is being encountered more frequently in modern NICUs.

CLD (also known as bronchopulmonary dysplasia) is encountered in approximately 40% of infants in modern NICUs (15). CLD is defined as the need for supplemental oxygen at 36 weeks postmenstrual age (22). Infants with CLD have poor growth and are at increased risk of nutritional deficiencies compared with those without CLD (35,36). Multiple explanations exist for these phenomena, including increased metabolic rate (37) and various therapeutic interventions (fluid restriction, diuretics, and steroids) (18,36). Given their exposure to medications that alter zinc status (diuretics and steroids), fluid restriction, and the lack of clear data on zinc requirements, it is possible that subclinical zinc deficiency contributes to growth failure in infants with CLD. Furthermore, zinc is part of the zinc-copper superoxide dismutase enzyme, an important part of the mechanism by which infants fight oxidant lung damage, thought to be one of the main mechanisms of lung injury in CLD (36). Zinc deficiency can thus, at least theoretically, worsen lung damage and then further worsen CLD and subsequent growth failure.

Zinc supplementation has been shown in many previous studies to improve rates of weight gain in term breast-fed infants (38) and in very-low-birth-weight (VLBW) preterm infants (10,39). Our study group was unique in that it was composed of ELBW infants with CLD.

Friel et al (10) randomized a group of 52 VLBW preterm infants to receive additional zinc in infant formula at an average dose of $2.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or standard infant formula (with no added zinc). These infants were studied for 12 months. The group that was supplemented with zinc had improved linear growth velocity at the end of follow-up. Diaz-Gomez et al (39) randomized VLBW preterm infants to receive additional zinc supplementation in infant formula or placebo for a period of 6 months; infants in the treatment group had significantly improved linear growth velocity. Loui et al (40) performed a zinc balance study in 10 ELBW infants and found that zinc balances were, despite their variability, usually negative. The same group of researchers performed a randomized trial of adding different amounts of trace minerals (including twice the amount of zinc in the standard human fortifier) to human milk (41); the group with increased zinc content had significantly greater increments in weight gain. Our results were consistent with the results of the studies cited above, with a significant increase in weight gain and linear growth.

In addition to improvement in weight gain, our cohort demonstrated an increased rate of linear growth, an outcome thought to be linked to lung development (42). This may suggest a unique benefit of zinc supplementation in infants with CLD.

None of the infants in our study displayed classic signs of zinc deficiency. It is possible, however, that they had subclinical zinc deficiency, a condition that has been of concern in preterm infant nutrition (34,43,44).

The majority of infants in our study received diuretic therapy with furosemide. Of those, 46 (88%) infants received furosemide for a minimum of 4 weeks. Furosemide therapy is commonly used in the management of infants with CLD and has been shown to result in a dose-dependent urinary loss of zinc that is proportional to urine output in animal models (45). Although a similar effect has not been demonstrated in humans (46), furosemide use in premature infants with CLD represents a risk factor for extra losses of zinc.

The diagnosis of subclinical zinc deficiency remains elusive, with serum zinc not being a reflection of total body zinc in addition to the absence of accurate biological makers of zinc status (21). Several biological markers of zinc status have been studied, including alkaline phosphatase, which is a zinc-dependent metalloenzyme that will presumably be at lower levels in zinc deficiency (21). In a zinc-balance study of ELBW infants, Loui et al (40) found that there is a positive correlation between alkaline phosphatase levels and zinc retention, absorption, and linear growth. Additionally, Diaz-Gomez et al found that levels of skeletal alkaline phosphatase were significantly higher at 3 months corrected age in premature infants supplemented with zinc (39); however, in a study by Obladen et al (47) in which a group of VLBW preterm infants were studied over time, half had zinc levels that were below normal limits, but there was no correlation between alkaline phosphatase levels and serum zinc. In 2 reviews of methods of assessment of zinc status in humans (21,48), levels of alkaline phosphatase did not correlate well with zinc status assessed by serum zinc with or without preceding zinc supplementation. In our study, alkaline phosphatase level had no significant correlation with zinc supplementation.

Alkaline phosphatase isozymes are present in several tissues, including osteoblasts. The alkaline phosphatase level in serum can thus be affected by bone mineralization in premature infants (49), making interpretation of levels difficult in this population. Measuring levels of different isozymes of alkaline phosphatase in future studies may elicit a relation to zinc levels.

With zinc supplementation, there is a concern for potential interaction with other nutrients, namely iron and copper, because all 3 of these divalent cations can compete for absorption sites. Previous work by Walravens et al (50) has shown that when given in doses up to 4.5 mg/day in infants, zinc supplementation did not affect copper or iron status.

It is important to note that general nutrition management of infants with CLD in our institution follows standardized guidelines that were implemented in 2008 (26) and have not changed throughout the duration of the study (2008–2011).

The limitations of our study included its retrospective nature and lack of a control group. Given the empiric nature of zinc supplementation in infants with poor growth, it was difficult to find a comparable control group of infants within our institution, and we believed that using infants as their own control group, despite its limitations, would provide a fair comparison. All of the infants were receiving full enteral nutrition for a minimum of 2

weeks at the time of supplementation, which makes the population more homogenous in relation to dietary intervention and makes critical illness an unlikely occurrence and thus not an explanation for the slow growth before zinc supplementation. Zinc content in human milk is variable, and there can be differences between mother's milk and donor milk, which makes estimating zinc intake before supplementation difficult, but zinc was supplemented at doses that were at least 100% higher compared with intake before supplementation. It is unclear whether these results can be applied to ELBW infants without CLD. With these limitations in mind, we believe that the significant increases in weight gain and linear growth in these infants remain provocative.

Zinc supplementation may be a tangible way to improve weight gain and linear growth in ELBW infants with CLD. Alkaline phosphatase may not be a sensitive marker for zinc status in that population. Prospective research is needed to evaluate the relation between zinc status and growth in extremely premature infants and to investigate potential biological markers of zinc status.

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FIGURE 1.

Weight gain before and after zinc supplementation. * $P < 0.001$; ** $P < 0.01$; + $P < 0.05$.

FIGURE 2.

Weight gain before and after zinc supplementation. * $P = 0.001$; ** $P < 0.0001$.

TABLE 1

Demographics of infants receiving zinc supplementation

Sex, n (%)	
Male	30 (58)
Female	22 (42)
Gestational age at birth, wk, mean $\pm$ SD	25.3 $\pm$ 2
Birth weight, g, mean $\pm$ SD	680 $\pm$ 183
Comorbidities, n (%)	
BPD	52 (100)
Severe BPD	48 (92)
Intraventricular hemorrhage	19 (35)
Necrotizing enterocolitis	9 (17)
Received furosemide, n (%)	52 (91)
Received furosemide for at least 4 wk, n (%)	46 (88)

BPD=bronchopulmonary dysplasia; SD=standard deviation.

TABLE 2

Zinc administration

Postmenstrual GA at starting zinc supplementation, wk, mean±SD	33±2
Duration of zinc supplementation, wk, mean±SD	9.6±7.4
Range, wk	2.3–43
Distribution of duration of zinc supplementation, n (%)	
2–6 wk	18 (35)
6–12 wk	23 (44)
>12 wk	11 (21)
Feeding at the time of zinc supplementation, n (%)	
Fortified human milk	41 (79)
Premature infant formula	11 (21)

GA=gestational age; SD=standard deviation.