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Zinc and copper requirements in preterm infants: An examination of the current literature

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ABSTRACT

Background: Zinc and copper are essential for preterm infants, but recommended requirements from different groups vary widely. Recommended zinc intakes have steadily increased over the years. Although this would be expected to impair copper absorption, recommended copper intakes have not risen in parallel.
Objectives: To systematically review the literature on zinc and copper retention in preterm infants; to examine the effect on zinc intake on copper retention; and to estimate the zinc and copper intakes required to meet the levels of zinc and copper retention required for normal growth.
Design: Studies reporting zinc and/or copper retention in preterm infants (<36 weeks of gestation) during the first 120 days of life were identified using PubMed. Only studies reporting net retention were included.
Results: Fourteen studies on zinc retention reporting data on 45 different groups were identified. Eleven studies (32 groups) were identified reporting copper retention. Zinc retention was significantly higher at higher zinc intakes, and higher in formula-based diets than in human milk based diets. Zinc intakes of between 1.8–2.4 mg/kg/d (from formula based diets) and 2.3–2.4 mg/kg/d (from human-milk based diets) were required to achieve adequate zinc retention. Copper retention was significantly positively correlated with copper intake and significantly negatively correlated with zinc intake. At the zinc intakes suggested previously (1.8–2.4, 2.3–2.4 mg/kg/d), copper intakes of between 200 and 250 mcg/kg/d are required to ensure adequate copper retention.
Conclusions: Our results support the higher zinc intakes recommended in recent guidelines. However, they suggest that recommended copper intakes have not kept pace with increasing zinc intakes, and that preterm infants may need higher copper intakes than currently recommended.

1. Introduction

Zinc and copper are essential nutrients for human health [1,2] and both zinc and copper deficiencies are well described in preterm infants [3,4].

Early recommendations for the zinc requirements of preterm infants were based on human milk content [5] or on the content of formulas designed for term infants [6]. Enteral zinc intakes of 0.50–0.55 mg/100 kcal (approximately 0.60–0.75 mg/kg/d) were felt appropriate [5,6]. More recent consensus guidelines have increased the recommended enteral zinc intake to 1 mg/kg/d [7] and subsequently to 1–2 mg/kg/d [8,9], or as high as 3 mg/kg/d for infants of birthweight less than 1 kg [10].

Initial estimates for enteral copper requirements were 90–120 mcg/100 kcal (approximately 110–160 mcg/kg/d) [5,6], and have changed little over the past 25 years. The most recent recommendations are for intakes of between 120 and 150 mcg/kg/d [7,8] or between 100 and 130 mcg/kg/d [9]. However, copper requirements are known to be related to zinc intakes, as zinc interferes with the enteral absorption of copper [1]. It is surprising, therefore, that recommended copper requirements have remained the same when recommended zinc intakes have increased 2- to 4-fold.

One approach to estimating mineral requirement for preterm infants is to try to identify an intake that is likely to meet either the *in utero* accretion rate, or the *ex utero* needs for normal growth. Accretion of zinc by the fetus during the third trimester is between about 300 mcg/kg/d [11] and 850 mcg/kg/d [12]; however the requirement for normal growth is less than this. Klein estimated zinc requirements in preterm infants using a factorial method [13]. According to these calculations, the requirement for retained zinc (i.e. the amount that absorbed zinc must exceed zinc losses) steadily declines with increasing post-conceptional age from about 500 mcg/kg at 27 weeks of post-conceptional age, to 400 mcg/kg

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at 30–32 weeks of post-conceptional age and 200–300 mcg/kg at 35–40 weeks of post-conceptional age [13]. *In utero* copper accretion is between 50 and 56 mcg/kg/d [10,13–15], although accretion rates as high as 80 mcg/kg/d have been suggested [11]. A factorial analysis suggests that a net requirement of about 30 mcg/kg/d is adequate to maintain normal growth [13] in preterm infants.

The objectives of this review are to systematically examine the existing literature on the relationship between zinc and copper intakes and their retention in preterm infants; to identify factors that modify zinc and copper retention; and to devise models that predict the zinc and copper intakes required to meet the *in utero* accretion rate or the *ex utero* requirement for normal growth of 0.3–0.4 mg/kg/d (for zinc) and 30–50 mcg/kg/d (for copper) in preterm infants.

2. Methods

2.1. Selection of studies

Potentially relevant studies were identified by search PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) using combinations of the terms "newborn", "neonate", "preterm infant", "zinc absorption", "copper absorption", "zinc retention", "copper retention", "zinc balance", and "copper balance". The literature cited by each study was examined to identify other potentially relevant studies that had been overlooked in the PubMed search. English language literature published since 1960 was considered.

Studies were included if they (a) examined preterm infants (gestational age at birth <36 weeks), (b) were carried out during the first 120 days of life, and (c) provided estimates of net zinc (or copper) retention. Stable isotope studies that only measured fractional zinc (or copper) absorption but did not permit calculation of total net balance/retention were excluded.

2.2. Data extraction

Summary data were extracted from the published manuscripts. Some manuscripts included data on a single group of infants (e.g. Reference [16]), and so contributed a single data-point to the analysis. Others contained data on different groups of preterm infants, for example groups receiving different copper intakes [17], receiving preterm formula or fortified human milk [18,19], or preterm infants being studied at different post-natal ages [11]. These studies, therefore, contributed more than one data-point to the analysis.

For each distinctly identifiable group from each manuscript, summary data on birthweight, gestational age at birth, post-natal age and post-conceptional age, body weight, diet (human milk or formula) at the time of the metabolic balance, zinc and copper intakes and copper retention were collected.

2.3. Calculation of missing means and standard deviations

A small number of published studies presented data for zinc intake or zinc retention as median and ranges. In these instances, mean and SD were estimated using the method of Hozo et al. [20].

2.4. Data analysis

Determinants of zinc retention were examined using multiple regression analysis. Explorative models including either zinc intake, gestational age, post-natal age, and feed type (formula or human milk), or zinc intake, post-conceptional age, and feed type (formula or human milk) were used to identify likely determinants of zinc retention. Based on the results of these analyses, the best model (with the minimum number of significant independent variables required) was developed. This model was used to estimate the zinc intake required to achieve zinc retention of 0.4 mg/kg/d and 0.3 mg/kg/d (the estimated requirement for infants of 30–32 weeks and 35–40 weeks post-conceptional age, respectively).

Three different methods of weighting the data were used. Data were analyzed using (a) unweighted data (all groups contributed the same amount to the analysis), (b) weighted by sample size (the largest groups were weighed more heavily) or (c) by the reciprocal of the standard error of the mean (SEM, with more precise data was weighed more heavily).

Similar methods were used for copper retention, and the copper intakes required to achieve retention of 30–50 mcg/kg/d were calculated.

Statistical analysis was carried out using JMP version 7.02 (SAS Institute, Raleigh, NC). Data were considered significant at a $P < 0.05$.

3. Results

3.1. Zinc

A total of fourteen studies on zinc retention were identified [11,17–19,21–30] with data on forty-five distinctly identifiable groups (Tables 1 and 2). All studies were identified in the primary PubMed search.

Two studies provided six or more distinct groups, one because zinc balances were carried out at multiple different postnatal ages [11], and one because several different diets were assessed at multiple different ages [21].

Study subjects had a mean birth weight of 1217 g (SD 371) and mean gestational age of 29.9 weeks (SD 4.4). Balance studies were carried out a mean postnatal age of 28 days (SD 44), post-conceptional age of 33.8 weeks (SD 5.1) and weight of 1.48 kg (SD 0.81). The mean zinc intake at the time of the metabolic balance was 1.13 mg/kg/d (SD 1.79, range 0.18 to 2.36 mg/kg/d).

3.2. Zinc retention

Initial inspection of the zinc dataset (Table 2) revealed one obvious outlier. Group 8 had a mean zinc retention of −2.34 mg/kg/d, more

Table 1
Birth demographics of the groups included in the analysis of zinc retention.

Reference	Group	Number per group	Birthweight (g)	Gestational age (weeks)
Dauncey [11]	1–7	29	1191 ± 126	29 ± 1.4
Voyer [21]	8–10	2–3	1262 ± 131	30.0 ± 1.6
Voyer [21]	11–13	6–9	1328 ± 206	31.6 ± 1.1
Voyer [21]	14–16	2–6	1306 ± 159	31.4 ± 1.1
Mendleson [19]	17	6	1152 ± 170	29.1 ± 1.1
Mendleson [19]	18	6	1102 ± 197	28.5 ± 1.0
Mendleson [19]	19	4	1270 ± 171	29.7 ± 1.4
Mendleson [19]	20	6	1108 ± 176	29.2 ± 1.6
Mendleson [19]	21	6	1091 ± 171	29.0 ± 1.5
Mendleson [19]	22	4	1195 ± 128	29.5 ± 0.6
Tyrala [17]	23	5	1478 ± 188	31.2 ± 1.1
Tyrala [17]	24	5	1279 ± 220	30.0 ± 2.5
Higashi [22]	25–28	8–9	NR	<36 weeks
Ehrenkranz [18]	29	7	1275 ± 261	30.3 ± 1.9
Ehrenkranz [18]	30	6	1072 ± 227	28.2 ± 2.3
Ehrenkranz [23]	31	33	1295 ± 238	30.1 ± 1.8
Ehrenkranz [23]	32	7	1189 ± 308	29.0 ± 1.8
Ehrenkranz [23]	33	5	1082 ± 175	29.0 ± 1.8
Ehrenkranz [23]	34	5	1284 ± 220	29.4 ± 1.9
Cooke [24]	35	14	1362 ± 125	32.3 ± 1.7
Wirth [25]	36	8	1223 ± 161	29.4 ± 1.4
Wirth [25]	37	10	1106 ± 70	28.9 ± 1.3
Friel [26]	38	12	1160 ± 290	29 ± 4
Fairly [27]	39	7	1411 ± 87	29.8 ± 0.9
Fairly [27]	40	8	1208 ± 142	29.1 ± 1.1
Wastney [28]	41	9	1440 ± 240	32 ± 3
Loui [29]	42 & 43	10	845 ± 76	25.9 ± 0.6
Martinez [30]	44	20	1189 ± 174	31.8 ± 1.0
Martinez [30]	45	20	1231 ± 210	31.0 ± 0.7