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

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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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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 postnatal 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].

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>Number per group</th>
<th>Birthweight (g)</th>
<th>Gestational age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voyer [21]</td>
<td>8–10</td>
<td>2–3</td>
<td>1202 ± 131</td>
<td>30.0 ± 1.6</td>
</tr>
<tr>
<td>Voyer [21]</td>
<td>11–13</td>
<td>6–9</td>
<td>1326 ± 206</td>
<td>31.6 ± 1.1</td>
</tr>
<tr>
<td>Voyer [21]</td>
<td>14–16</td>
<td>2–6</td>
<td>1306 ± 159</td>
<td>31.4 ± 1.1</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>17</td>
<td>6</td>
<td>1152 ± 170</td>
<td>29.1 ± 1.1</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>18</td>
<td>6</td>
<td>1102 ± 197</td>
<td>28.5 ± 1.0</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>19</td>
<td>4</td>
<td>1270 ± 171</td>
<td>29.7 ± 1.4</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>20</td>
<td>6</td>
<td>1108 ± 176</td>
<td>29.2 ± 1.6</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>21</td>
<td>6</td>
<td>1091 ± 171</td>
<td>29.0 ± 1.5</td>
</tr>
<tr>
<td>Mendleson [19]</td>
<td>22</td>
<td>4</td>
<td>1195 ± 128</td>
<td>29.5 ± 0.6</td>
</tr>
<tr>
<td>Tyrala [17]</td>
<td>23</td>
<td>5</td>
<td>1478 ± 188</td>
<td>31.2 ± 1.1</td>
</tr>
<tr>
<td>Tyrala [17]</td>
<td>24</td>
<td>5</td>
<td>1279 ± 220</td>
<td>30.0 ± 2.5</td>
</tr>
<tr>
<td>Higashi [22]</td>
<td>25–28</td>
<td>8–9</td>
<td>NR</td>
<td>&lt;36 weeks</td>
</tr>
<tr>
<td>Ehrenkranz [18]</td>
<td>29</td>
<td>7</td>
<td>1275 ± 261</td>
<td>30.3 ± 1.9</td>
</tr>
<tr>
<td>Ehrenkranz [18]</td>
<td>30</td>
<td>6</td>
<td>1072 ± 227</td>
<td>28.2 ± 2.3</td>
</tr>
<tr>
<td>Ehrenkranz [23]</td>
<td>31</td>
<td>33</td>
<td>1295 ± 238</td>
<td>30.1 ± 1.8</td>
</tr>
<tr>
<td>Ehrenkranz [23]</td>
<td>32</td>
<td>7</td>
<td>1189 ± 308</td>
<td>30.0 ± 1.8</td>
</tr>
<tr>
<td>Ehrenkranz [23]</td>
<td>33</td>
<td>5</td>
<td>1082 ± 175</td>
<td>29.0 ± 1.8</td>
</tr>
<tr>
<td>Ehrenkranz [23]</td>
<td>34</td>
<td>5</td>
<td>1284 ± 220</td>
<td>29.4 ± 1.9</td>
</tr>
<tr>
<td>Cooke [24]</td>
<td>35</td>
<td>14</td>
<td>1362 ± 125</td>
<td>32.3 ± 1.7</td>
</tr>
<tr>
<td>Wirth [25]</td>
<td>36</td>
<td>8</td>
<td>1223 ± 161</td>
<td>29.4 ± 1.4</td>
</tr>
<tr>
<td>Wirth [25]</td>
<td>37</td>
<td>10</td>
<td>1106 ± 70</td>
<td>28.9 ± 1.3</td>
</tr>
<tr>
<td>Fried [26]</td>
<td>38</td>
<td>12</td>
<td>1160 ± 290</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>Fairly [27]</td>
<td>39</td>
<td>7</td>
<td>1411 ± 87</td>
<td>29.8 ± 0.9</td>
</tr>
<tr>
<td>Fairly [27]</td>
<td>40</td>
<td>8</td>
<td>1208 ± 142</td>
<td>29.1 ± 1.1</td>
</tr>
<tr>
<td>Wastney [28]</td>
<td>41</td>
<td>9</td>
<td>1440 ± 240</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Lou [29]</td>
<td>42 &amp; 43</td>
<td>10</td>
<td>845 ± 76</td>
<td>25.9 ± 0.6</td>
</tr>
<tr>
<td>Martinez [30]</td>
<td>44</td>
<td>20</td>
<td>1184 ± 174</td>
<td>31.8 ± 1.0</td>
</tr>
<tr>
<td>Martinez [30]</td>
<td>45</td>
<td>20</td>
<td>1231 ± 210</td>
<td>31.0 ± 0.7</td>
</tr>
</tbody>
</table>

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 4.4), 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

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than 7 standard deviations from the mean of the remaining groups. This group was excluded from analysis.

In a univariate analysis, zinc retention was significantly related to zinc intake (Retention = $-0.32 + 0.363 \times \text{Intake}$, $P < 0.001$, $R^2 = 0.30$). When the data for human milk and formula fed groups were analyzed separately, there was a suggestion that zinc retention was higher in feeds based on formula, especially at lower zinc intakes (Fig. 1).

In a multivariate analysis of unweighted data, zinc retention was significantly related to zinc intake ($P = 0.0101$), and to feed type ($P = 0.0039$) but not to gestational age at birth ($P = 0.07$) or post-natal age ($P = 0.60$). When gestational age and postnatal age were replaced by post-conceptional age, zinc retention was significantly related to zinc intake ($P = 0.0055$) and feed type ($P = 0.0126$) but not to post-conceptional age ($P = 0.52$). Similar results were seen in the two weighted analyses.

Three models predicting zinc retention based on feed type (human milk or formula) and zinc intake were constructed (Table 3). The mean zinc intakes required to lead to a zinc retention of 0.4 mg/kg/d from diets based on formula were 1.83 mg/kg/d (from the unweighted data), 1.99 mg/kg/d (weighted by sample size), and 2.44 mg/kg/d (weighted by 1/SEM). In order to retain 0.3 mg/kg/d of zinc, intakes of 1.46 mg/kg/d, 1.45 mg/kg/d or 1.51 mg/kg/d would be required from formula-based diets, and 1.94 mg/kg/d, 2.40 mg/kg/d or 1.95 mg/kg/d from human milk based diets.

### 3.3. Copper

Eleven studies measured copper balance [11, 17–23, 25–27, 30], all of which also reported data for zinc balance. Thirty-two distinct groups were identified (Table 3).

Subjects were born at a mean gestational age of 29.9 weeks (SD 3.3), and weight of 1.22 kg (SD 0.25). Metabolic balances were carried out at a mean postnatal age of 23 days (SD 32), a post-conceptional age of 33.3 weeks (SD 4.5) and a weight of 1.51 kg (SD 0.78) (Table 4).

### 3.4. Copper retention

A scattergram of copper retention against copper intake (Fig. 2) shows that studies of infants fed a human-milk based diet had a narrower range of copper intakes than in those studies of formula-based diets. Furthermore the human-milk based diets had a significantly

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**Table 3**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>N</th>
<th>Age (days)</th>
<th>Diet</th>
<th>HM or formula?</th>
<th>Zinc intake (mg/kg/d)</th>
<th>Zinc retention (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>6</td>
<td>10–12</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.62 ± 0.186</td>
<td>−0.437 ± 0.175</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>6</td>
<td>20–22</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.646 ± 0.149</td>
<td>−0.544 ± 0.389</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>3</td>
<td>30–32</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.641 ± 0.177</td>
<td>−0.415 ± 0.438</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>4</td>
<td>40–42</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.642 ± 0.303</td>
<td>−0.198 ± 0.172</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>5</td>
<td>50–52</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.746 ± 0.291</td>
<td>−0.147 ± 0.315</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>6</td>
<td>60–62</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.598 ± 0.221</td>
<td>0.001 ± 0.050</td>
</tr>
<tr>
<td>Dauncey [11]</td>
<td>16</td>
<td>7</td>
<td>70–72</td>
<td>Unfortified human milk</td>
<td>HM</td>
<td>0.710 (0.653 to 0.770)</td>
<td>0.151 (0.127 to 0.173)</td>
</tr>
</tbody>
</table>

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4. Discussion

Following a systematic examination of the literature, we estimate that preterm infants require between 1.8–2.4 mg/kg/d of zinc from formula based diets, and 2.3–2.4 mg/kg/d from human milk based diets. Assuming an energy intake of 120 kcal/kg/d, these are equivalent to 1.5–2.0 mg/100 kcal. These estimates are at the higher end of the range of recent recommendations [8–10].

There are relatively few randomized controlled trials comparing different levels of zinc intake in preterm infants [29,31–33], only two of which have intakes similar to our estimated requirements [32,33]. Diaz-Gomez [32] compared formulas containing either 0.75 mg/100 kcal of zinc or 1.5 mg/100 kcal of zinc in 36 preterm infants. The infants fed the higher zinc intake had higher serum and red cell zinc concentrations, improved linear growth, and higher serum alkaline phosphatase (a zinc containing enzyme) [32]. A potential adverse effect of higher zinc intakes on copper status was seen, with the serum copper concentration being lower in the zinc supplemented group (perhaps reflecting the difference in zinc:copper ratio of 16.7 mg zinc/mg copper, and 12.5 mg zinc/mg copper in the two formulas). Friel et al. studied 52 very-low birthweight infants randomized to formulas containing either 1.0 mg/100 kcal or 1.64 mg/100 kcal of zinc [33]. The higher zinc intake led to improved linear growth, higher serum zinc concentrations, and improved motor scores [33].

There are very few clinical trials of different copper intakes in preterm infants. Enteral feeding of 41–89 μg/kg/d of copper in preterm infants has been associated with copper deficiency [34]. Tyrala [17] showed no clear benefit of a copper intake of 260 μg/100 kcal compared to 120 μg/100 kcal in preterm infants as assessed by copper balance, serum copper and ceruloplasmin. However, no adverse effects were observed in the high copper group.

We found, as expected, that copper requirements varied as a function of zinc intake. In order to meet the estimated requirements for growth, copper intakes of about 200 μg/kg/d would be required if zinc intakes were 1.8 mg/kg/d, increasing to 250 μg/kg/d if zinc intakes were 2.4 mg/kg/d. These intakes are significantly greater than current recommendations for copper intake in preterm infants of 100 to 150 μg/kg/d [8–10]. However, those recommendations have changed little since the 1980s [5,6] and 1990s [7] when recommended zinc intakes were only 0.5–1.0 mg/kg/d [5–7]. It is noteworthy from Table 3 that those lower copper intakes would be expected to provide adequate copper retention (30–50 μg/kg/d) at those lower zinc intakes. The increased copper requirements we suggest, are therefore, driven by the higher zinc intakes currently recommended.

Our estimates were generated from previously published results. As such, they are limited by the nature of the published data. Many studies were relatively old, and it is likely that they were composed of more mature infants than many NICUs now care for. However, we could not identify any effect of gestational age or birth weight on the relationship between zinc (or copper) intake and retention. This may reflect the fact that, by definition, studies were carried out in infants sufficiently mature to be tolerating full enteral feeds, and sufficiently well to tolerate the metabolic balance procedure.

In addition, there were relatively few studies carried out at higher zinc intakes. Of the 45 identifiable groups in the zinc analysis (Table 2)

![Figure 1. Scattergram of zinc intake and zinc retention in the formula-based groups (black markers) and human milk based diets (gray markers). The area of the symbols is proportional to the sample size of each group. Separate regression lines for the formula-based diets and the human milk based diets are shown.](image-url)

**Table 3**

Results of the three models predicting zinc retention based on zinc intakes (in mg/kg/d) and on feeding type (based on formula = 1, based on human milk = 0).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Intercept Coefficient</th>
<th>P-value</th>
<th>Zinc intake (mg/kg/d) Coefficient</th>
<th>P-value</th>
<th>Feed-type (formula = 1, HM = 0) Coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unweighted model</td>
<td>-0.2210</td>
<td>0.0424</td>
<td>0.2686</td>
<td>0.0042</td>
<td>0.1289</td>
<td>0.0275</td>
</tr>
<tr>
<td>Weighted by N</td>
<td>-0.1472</td>
<td>0.19</td>
<td>0.1861</td>
<td>0.0498</td>
<td>0.1772</td>
<td>0.0054</td>
</tr>
<tr>
<td>Weighted by 1/SEM</td>
<td>-0.0912</td>
<td>0.24</td>
<td>0.2006</td>
<td>0.0057</td>
<td>0.0883</td>
<td>0.0883</td>
</tr>
</tbody>
</table>

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Although stable isotopes are powerful tools to understand mineral absorption in vulnerable populations [36], they have limitations in that they require more time-consuming and difficult metabolic balance studies [16]. However, there seems to be an urgent need for further research especially as recent recommendations are that all preterm infants on human milk than those on formula-based diets. Whether this remains true with more modern human milk formulas is unclear. However, they suggest that copper intake recommendations currently available for preterm infants. Our results support the recent trend towards higher recommendations for copper intakes in preterm infants. However, they suggest that copper intake recommendations have failed to keep pace with the increase in zinc intakes. Higher copper intakes seem required in preterm infants, especially those on higher zinc intakes.

**Conflict of interest**

This work was originally produced as part of a symposium on neonatal nutrition funded by the Mead Johnson Nutrition (Glenview, IL), and authors were paid an honorarium by Mead Johnson Nutritional for participation in the symposium. Mead Johnson Nutrition was not involved in the writing or conclusions of this manuscript. None of the authors have a financial conflict related to the conclusions of this review.
Acknowledgments

Role of co-authors: Drs. Griffin and Domellof were principally responsible for the early drafts of this work. Dr. Griffin was responsible for the literature review, and data analysis and interpretation. All authors were involved in finalizing the recommendations and in correction and editing of the final manuscript.

References


