Building Bones in Babies: Can and Should We Exceed the Human Milk-Fed Infant’s Rate of Bone Calcium Accretion?

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Increasing calcium absorption and bone calcium accretion to levels above those achieved by human milk-fed, full-term infants is possible with infant formulas. However, no data support such a goal or suggest that it is beneficial to short- or long-term bone health. Small differences in the bioavailability of calcium between infant formulas are unlikely to have long-term consequences. Long-term studies of the effects of infant feeding type on ultimate bone mass are needed. For now, the vitamin-replete breast-fed infant’s rate of calcium accretion during the first year of life should be the standard targeted for infant formulas.

Key words: bone mineral content, calcium absorption, human milk, minerals

INTRODUCTION

Osteoporosis is a major public health crisis in the United States. Reasonable evidence supports the concept that low peak bone mass is associated with an increased lifetime risk of low bone mass and ultimately osteoporotic fractures. Therefore, it has been reasonable to adopt a public policy of enhancing bone mass accumulation of young people with a goal of optimizing peak bone mass. However, it remains unclear exactly what optimal calcium intake is at any given age to achieve this goal and whether catch-up is possible throughout the period (up to about 30 years of age) during which bone mineral mass is being acquired.

This goal of optimizing bone mineral accumulation throughout childhood and young adulthood, however, can potentially be in conflict with other nutritional concepts. This includes the fundamental concept that the body composition of exclusively breast-fed infants in the first 6 months of life is the ideal standard for all full-term infants. It is recognized by the World Health Organization that human milk provides all of the calcium needed for the first 6 months of life, and most of the calcium needed to support adequate bone growth and mineralization during the second 6 months of life.

Questions that remain are: 1) what are the differences in bone mineral accumulation between breast- and formula-fed infants? and 2) what are the potential consequences of these differences?

MEASURING BONE IN INFANTS: CALCIUM BALANCE VERSUS BONE MINERAL MASS MEASUREMENT

In general, to determine the effects of any feeding type on bone mineral calcium accumulation during growth—which can be referred to as calcium retention or calcium accretion—one of two methods is used. The first is the calcium balance method. This method can be done one of two ways. In the first, the classical balance method...
(which is also referred to as the mass balance method), the difference between calcium intake and output is measured by dietary fecal and urine collections. The second method is to use isotopes, usually stable isotopes, to trace the amount of calcium absorbed, usually in infants from a single feeding. These two approaches differ in multiple ways, including the end point being measured, the dietary regulation needed, and the ease of performing the measurement. In general, the classical balance method is more likely to overestimate absorbed calcium due to its reliance on potentially incomplete fecal collections.

Classical balance tests performed at home are particularly prone to incomplete fecal collections despite attempts to adjust for this, and for this reason these tests have fallen out of favor in recent years. Most studies have used the stable isotope method due to its simplicity and lack of reliance on fecal collections. To determine overall calcium retention from the isotope method usually involves some estimate for endogenous secretion of calcium, but this is a very small factor in infants, and variability associated with estimation would not lead to appreciable error in a group of subjects. This method is not readily subject to overestimating the amount retained unless a technical error is made in administering the isotopes.

The second method to determine calcium accretion, which may be used in populations with rapidly growing bones, is to compare the total body bone mineral content (TBBMC) before and after an intervention or time period and divide the total increment by the average number of days between measurements. Currently, dual-energy X-ray absorptiometry (DEXA) is usually used for these measurements. This method relies on the assumption, experimentally verified in several populations, that 32.2% of the measured bone mineral is calcium. Small variations in this value and body composition changes in infancy are unlikely to lead to substantial error with this method. There are no direct comparisons in infants of any of these methods, and thus no single method can be considered a gold standard.

One issue with the use of bone mineral mass changes over the entirety of infancy is that it cannot differentiate the source of the calcium; calcium from solid foods cannot be distinguished as being from human milk or infant formula.

### Table 1. Calcium Concentration and Daily Calcium Intake of Human Milk and of Selected Infant Formulas Marketed in the United States*

<table>
<thead>
<tr>
<th>Calcium Concentration (mg/dL)</th>
<th>Calcium Intake (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human milk (Western countries)</td>
<td>26</td>
</tr>
<tr>
<td>Similac Advance†</td>
<td>52</td>
</tr>
<tr>
<td>Enfamil Lipil‡</td>
<td>52</td>
</tr>
<tr>
<td>Good Start Supreme§</td>
<td>43</td>
</tr>
<tr>
<td>Parent’s Choice</td>
<td>42</td>
</tr>
<tr>
<td>Similac PM 60/40†</td>
<td>37</td>
</tr>
</tbody>
</table>

*Shown are label contents for infant formulas, actual content is often slightly above listed amount. Human milk from mothers in developing countries is often about 20% lower than listed amounts. Feeding volume is estimated as 780 mL/d in breast-fed infants and 850 mL/d in formula-fed infants.† Manufactured by Ross Laboratories, Columbus, OH. ‡ Manufactured by Mead-Johnson, Evansville, IN. § Manufactured by Nestlé USA, Glendale, CA. /H14067 Manufactured by PBM Nutritionals, Gordonsville, VA. 

Data are available for human milk-fed infants from both mass-balance and isotope-based studies. The isotope-based studies are limited in that the infants included were older and a few had a small amount of solid food in their diet. However, results have consistently been very similar from tracer and balance studies for mineral absorption and retention from human milk. In general, about 60% to 70% of calcium is absorbed from human milk, leading to a net of about 90 to 100 mg daily calcium retention during the first 6 months of exclusive human milk feeding (Table 2). More recent data are consistent with studies performed as early as 1944.

There are surprisingly few studies in which TBBMC has been measured longitudinally in breast-fed, full-term infants. There are no studies in which the published report indicates that all infants received only human milk and no infant formula or solid foods for the entire study period. One study included formula intake in nearly all of the breast-fed infants by 6 months of age and another...
only took measurements at 0.5, 12, and 24 months, with exclusive breast-feeding only required for 4 months. A third study did not identify the feeding method but it was unlikely to be primarily breast milk. Therefore, it is likely that the calculations based on these data overestimate the calcium accretion associated with exclusive breast-feeding during the first 6 months of life. Balance data may therefore be a more accurate reflection of calcium accretion from exclusive human milk feeding during this time period, especially given the consistency of results from multiple methods over 60 years.

These data can, however, provide some further information regarding breast-feeding and bone calcium accretion. Based on the TBBMC results, Butte\textsuperscript{6} found that an average of 119 mg calcium is accreted daily during the first year of life—about 110 mg daily in girls and 130 mg daily in boys. Data from Specker\textsuperscript{14} give a slightly higher estimate of about 140 mg daily, but are difficult to interpret due to the variable intake of infant formulas in the human milk-fed infants. It is impossible to determine the effects of solid food or formula intake on these data or to identify the exact rate of calcium accretion specifically during the first 6 months of life, but given a usual calcium intake from solids after 6 months of age of about 60 to 80 mg/d,\textsuperscript{2} one could reasonably estimate an average of about 100 mg daily calcium accretion during exclusive breast-feeding and about 140 mg daily on mixed feedings. Thus, it appears that these TBBMC data are consistent with the classical and isotopic balance studies. Ultimately, further studies using both isotopes (in younger infants) and multiple body composition techniques (in exclusively breast-fed infants) are needed.

### Table 2. Calcium Absorption Fraction and Daily Retention (Accretion by Full-Term Infants as Assessed Using Balance Studies or Total Body Bone Mineral Content (TBBMC) Measurement)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Calcium Absorption (%)</th>
<th>Calcium Retention mg/d</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human milk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical balance</td>
<td>58</td>
<td>94</td>
<td>Fomon and Nelson, 1993\textsuperscript{11}</td>
</tr>
<tr>
<td>Isotope balance</td>
<td>61</td>
<td>82</td>
<td>Abrams et al.\textsuperscript{12}</td>
</tr>
<tr>
<td>TBBMC</td>
<td>n/a</td>
<td>119</td>
<td>Butte et al., 2000\textsuperscript{6}</td>
</tr>
<tr>
<td>Infant Formula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical balance</td>
<td>39–48</td>
<td>152–191</td>
<td>Nelson et al., 1996\textsuperscript{17}</td>
</tr>
<tr>
<td></td>
<td>37–57</td>
<td>143–233</td>
<td>Nelson et al., 1998\textsuperscript{18}</td>
</tr>
<tr>
<td>Isotope balance</td>
<td>56–66</td>
<td>195–234</td>
<td>Abrams et al., 2002\textsuperscript{16}</td>
</tr>
<tr>
<td>TBBMC</td>
<td>n/a</td>
<td>213–240</td>
<td>Koo et al., 2003\textsuperscript{19}</td>
</tr>
<tr>
<td></td>
<td>n/a</td>
<td>148</td>
<td>Butte et al., 2000\textsuperscript{6}</td>
</tr>
</tbody>
</table>

*For isotope-based studies, net calcium absorption shown was based on a body weight of 6.0 kg with endogenous excretion of calcium estimated as 3/mg/k/d.\textsuperscript{9} Urinary calcium for all balances was estimated as 24 mg/d.\textsuperscript{11} Feeding volume was estimated as 780 mL/d for human milk-fed infants and 850 mL for formula-fed infants.\textsuperscript{2,6} For bone mass studies, daily differences in TBBMC were multiplied by 0.322 to obtain the average daily calcium retention.

### CALCIUM ACCRETION IN FORMULA-FED INFANTS

A number of studies have been done using both classical balance and isotope techniques.\textsuperscript{16–18} Results of selected studies using cow’s milk-based formulas are summarized in Table 2. The classical balance studies shown\textsuperscript{17,18} involved relatively small numbers of infants, and many of the balance studies were done at home. Fractional absorption has tended to range between 40% and 60% in most studies. Differences in results among formulas and investigations cannot simply be attributed to single components such as the fat source of the formulas, and there have been no studies using currently marketed formulas that include long-chain polyunsaturated fatty acids. A few data are available for specialized formulas such as those made from soy and casein hydrolysates, but the data are limited from these studies and are not representative of most marketed infant formulas and thus are not considered here.\textsuperscript{11}

Data from the TBBMC studies can be used to calculate an estimate of calcium absorption as a function of intake. This can reasonably be done, for example, with data from a study in which changes over 6 months in infants receiving one of two formulas that principally differed in fat composition were compared.\textsuperscript{19} These calculations demonstrate a difference in calcium absorption of about 6% between formulas (Table 3). This difference is much less than that suggested by mass-balance studies of similar formulas. This comparison demonstrates the potential limitations in classical balances, especially those performed at home, in identifying...
Overall, in the first year of life, available data suggest an average of about 30 to 40 g of bone calcium accretion during the first year of life in breast-fed infants and 50 to 80 g in formula-fed infants. These values are higher than the second year of life, but lower than the peak rate during adolescence.6,24 (Table 4).

Assuming the breast-fed infant to be the standard, then about 3% to 4% of adult bone mass is formed in the first year of life. This compares to about 12% to 14% annually during the peak 2 years of adolescence and about 50% during all of adolescence.24 The effects on calcium absorption related to variations in infant formulas represent about 1% of adult bone mass.

These differences between human milk and formula (and between formula types) of 1% to 3% in adult bone balance are likely due to the differences in calcium concentrations; however, they do not appear to cause calcium absorption thresholds above which additional calcium cannot be absorbed. Using classical balances, it was concluded that calcium retention of up to 400 mg daily, which is 300% to 400% of the breast-fed infant, is feasible if it was truly beneficial to maximize calcium accretion.

**HUMAN MILK COMPARED WITH FORMULA**

Direct comparisons of calcium accretion using mass or isotopic balances from exclusively human milk-fed compared with formula-fed infants receiving currently marketed formulas do not exist. However, the data in Table 2 provide the range of data from multiple studies, and can reasonably be used as a basis for a comparison. Limitations in this cross-sectional analysis due to vastly different study methodologies, such as limitations in proposed meta-analysis of absorption data, must nevertheless be recognized.21

**Table 3. Calculation of Estimated Fractional Calcium Absorption from Changes in Total Body Bone Mineral Content (TBBMC) During the First 6 Months of Life**20

| Formula A | Calcium intake: 1109 mL/d * 0.527 mg/mL = 584 mg/d
| Calcium retention (from TBBMC data): 213 mg/d
| Net calcium absorption = 213 + 6(4) = 237 mg/d
| Net absorption fraction = net calcium absorption/calcium intake = 237/584 = 40.6% |

| Formula B | Calcium intake: 1072 mL/d * 0.527 mg/mL = 565 mg/d
| Calcium retention (from TBBMC data): 240 mg/d
| Net calcium absorption = 240 + 6(4) = 264 mg/d
| Net absorption fraction = net calcium absorption/calcium intake = 264/565 = 46.7% |

*Calcium retention of 213 mg/d from formula A and 240 mg/d from formula B was determined by subtracting the initial TBBMC from the final TBBMC provided and multiplying by 0.322 as the fraction of calcium in bone and then dividing by 182 to represent the number of days in 6 months. Net absorption is derived assuming 24 mg/d (4 mg/kg/d) urine calcium. Feeding volumes and calcium concentration are as provided in Koo et al., 2003 using the value at 3 months, the midpoint of the study. Formulas are each listed as providing 0.527 mg/mL of calcium.

These data demonstrate a slightly greater fractional absorption of calcium in human milk-fed infants and a much greater total calcium absorption and retention of calcium in formula-fed infants in the United States. Total calcium absorption in infants, as with adults, is dose dependent.20 Since formula calcium concentration greatly exceeds that of human milk, it is not at all certain that the actual intrinsic bioavailability of calcium in currently marketed formulas is different from that from human milk. Such a direct comparison, at identical mineral compositions, is extremely unlikely to ever be performed due to the guidelines for infant formula in the United States and elsewhere mandating calcium concentrations far above those of human milk.

One investigation performed a number of years ago in Europe reported very slightly lower bone mineral mass in some formula-fed infants compared with breast-fed infants.22 However, no baseline data were available, and the formulas marketed may have had substantially poorer bioavailability than currently or previously marketed formulas in the United States.23 The direct comparisons reported in the United States,6,14 although limited by methodological issues as well as the available calcium balance data (Table 2), are consistent with much greater calcium accretion by formula-fed infants than breast-fed infants in the first year of life.

The magnitude of the difference between human milk-fed and formula-fed infants is less clear. Using numbers typical of the entire first year of life (Table 2) might lead to a daily retention of 120 mg from human milk and 180 mg from formula. This would lead to about 22 g of additional calcium being accreted during the first year into the bones of formula-fed infants compared with human-milk fed infants.

**HOW DOES THIS DIFFERENCE TRANSLATE TO THE ENTIRETY OF PEAK BONE MASS ACCUMULATION?**

Overall, in the first year of life, available data suggest an average of about 30 to 40 g of bone calcium accretion during the first year of life in breast-fed infants and 50 to 80 g in formula-fed infants. These values are higher than the second year of life, but lower than the peak rate during adolescence.6,24 (Table 4).
mass are comparable to the differences found in studies of adolescents given short-term calcium supplementation. 1-3 These differences have not been found to be maintained over long-term follow-up. 3 A catch-up phenomenon is likely throughout adolescence and early adulthood, and small initial differences associated with calcium supplementation may not be biologically important. 3,25 The only study that has looked at the effect of calcium intake throughout early childhood found that calcium intake during the second year of life, but not the first year, was associated with bone mineral content of the distal radius of 5 year-old children in Hong Kong. 26

LONG-TERM DATA?

A reasonable question is, what are the short and long-term data associated with the use of human milk or formula and bone growth in infants? It has been suggested that...calcium intakes by breast-fed infants may be quite near the requirement. As determined by evolutionary forces, the provision of calcium to the breast-fed infant may represent the best compromise between the joint goals of meeting the infant’s needs and protecting the mother against undue depletion of her body stores of calcium. 11

More recently, in a review of calcium absorption from infant formulas, this perspective was supported with the comment that: “in this era of evidence-based medicine, the development of human milk substitutes must be based on achieving optimal physiological outcome measures rather than superficially replicating the nutrient content of human milk.” 21

There are remarkably few data defining concepts such as “optimal physiological outcome” related to bone during the first year of life. There are no convincing data that there are short- or long-term benefits or risks of achieving a higher bone mass than breast-fed infants. There are, in fact, no studies in which groups of infants fed an infant formula marketed in the United States were studied longitudinally from infancy through later childhood to determine the effects of infant feeding type on long-term bone mass.

Nor are there even any studies in which infants fed two different types of formula were studied longitudinally from infancy through a reasonable time point later in childhood. A single study evaluating bone mineral mass in 4-year-old children found no difference based on infant feeding type (based on the fat composition of the infant formula or human milk versus formula), but there was no baseline data from this study, and 4 years is an inadequate amount of time in which to assess long-term outcomes. 27 Nonetheless, these data are consistent with the lack of an effect of early feeding method on bone mineral content later in childhood.

Consistent with this perspective are the results of a study evaluating bone mineral density at 8 years of age in 330 children in Tanzania who had been breast-fed or formula-fed. 28 Breast-feeding, especially for 3 months or more, was associated with a greater bone mineral density than formula feeding. The nature of the formulas used and their bioavailability relative to human milk is not known.

Animal data also cannot be relied upon to evaluate these issues. The limited available data suggest that a lower bone mineral mass in early life leads to greater bone mass later in life, but available data are not definitive. 29 An excess of calcium intake in large-breed puppies is well recognized to be associated with later skeletal abnormalities in the dogs, including osteochondrosis. 30 Similar to the results shown in infants, relatively high intakes of calcium are not associated with the achievement of threshold absorption values in dogs. 20

The concept of catch-up bone mineral mass accumulation is clearly identified as feasible and even likely based on data in premature infants. 31-33 In full-term infants, TBBMC appeared to increase at a faster rate in the second 6 months of life in infants with lower mineral intake during the first 6 months of life. 34 In one comparison of preterm and full-term infants, the former increased their total body BMC more than full-term infants after hospital discharge although both groups were “predominantly” fed human milk. 35 This suggests that increasing absorption to very high levels upon demand may be likely in at-risk groups.

Finally, concern may be expressed that even if a catch-up occurs at or prior to adolescence, the child may be at risk of fractures in early childhood from lower bone mass in infancy related to breast-feeding. However, this

Table 4. Bone Calcium Accretion (g/yr) during Different Life Periods

<table>
<thead>
<tr>
<th>Period</th>
<th>Human Milk-Fed</th>
<th>Formula-Fed</th>
<th>Male</th>
<th>Female</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy (0–12 mo)</td>
<td>30–43</td>
<td>54–88</td>
<td></td>
<td></td>
<td>See Table 2</td>
</tr>
<tr>
<td>1–2 yrs</td>
<td>25</td>
<td>22</td>
<td></td>
<td></td>
<td>Butte et al., 20006</td>
</tr>
<tr>
<td>Adolescence (9–18 yrs)</td>
<td>58</td>
<td>42</td>
<td></td>
<td></td>
<td>Whiting et al., 200424</td>
</tr>
<tr>
<td>Peak puberty</td>
<td>131</td>
<td>104</td>
<td></td>
<td></td>
<td>Whiting et al., 200424</td>
</tr>
</tbody>
</table>
is also extremely unlikely. Recent data do not support a relationship between bone mineral density and fractures in prepubertal children. There are no reports of an increased incidence of fractures or rickets in early childhood in children who had been vitamin D-replete, breast-fed infants.

**IS BREAST MILK CALCIUM LIMITED TO PROTECT THE MOTHER’S BONES?**

The concept of an evolutionary limit in breast milk calcium would imply that mothers are placed at short- or long-term risk of low bone mineral mass associated with breast-feeding, and that mothers who over a lifetime produce more milk have lower bone mineral mass or osteoporosis. Available data suggest the opposite: that breast-feeding is ultimately beneficial to maternal bone status. Interestingly, even the highest risk groups such as adolescent mothers have not been shown to place their bones at risk by lactation, and there is no evidence that nursing twins (or, more specifically, nursing two infants at the same time as has been done by wet nurses throughout human history) is a risk factor for osteoporosis or fractures in women.

Evidence that there is no benefit to the infant in increasing maternal mineral status is provided by studies of calcium supplementation in women in The Gambia. A large calcium supplement was given to pregnant women at very high risk of nutritional inadequacy. No effect was seen on breast milk calcium concentration or infant bone mineral status at birth. A slower rate of increase in infant whole-body bone mineral content was seen in the supplemented group. Calcium supplements have previously been shown to have no benefits on bone status in women during lactation. These results are not consistent with the suggestion that breast milk calcium is low to protect the mother or that improved maternal mineral status would be used to increase available minerals to the infant.

**CHANGES IN FORMULA COMPOSITION?**

Infant formulas are constantly evolving, and earlier studies of their mineral bioavailability do not reflect current practices and potential improvements in composition. In considering comparisons of different formulas and comparisons of formula with human milk, it is important to recognize that no studies have been done in the recent era in which long-chain polyunsaturated fatty acids have been added to infant formulas, and these may further increase mineral bioavailability. Additionally, the use of prebiotics, which increase calcium absorption in older children, may have a similar effect when added to infant formulas. Ultimately, however, manufacturers can readily increase calcium accretion to levels far above that seen in breast-fed infants simply by increasing the calcium content of formulas.

**CONCLUSION: WHAT IS THE STANDARD FOR BONE GROWTH?**

It is tempting to target the greatest bone mass at any age in life so as to decrease the risk of osteoporosis and fractures. However, to do so in infants would require the conclusion that the human milk-fed infant is not optimally mineralized. This would have considerable public-policy consequences and would logically imply a need to provide calcium supplements to breast-fed infants, presumably from birth. This view is inconsistent with the perspectives related to nutrient adequacy of breast-feeding and the importance of breast-feeding for infant health. Mothers would be advised not to allow their premature infants to exclusively breast-feed after hospital discharge due to their substantial bone deficit.

There are no data to suggest such a course of action. The very limited available data, although not definitive, suggest that breast milk is an entirely adequate source of calcium and related minerals. Infant formulas are not engineered to mimic human milk in content, only in physiological outcomes. As such, they all provide more calcium and phosphorus than human milk does. The question is not how can infant formulas be made to provide the most calcium or greatest bone mineral mass; rather, we must ask whether the target for bone mineral accretion in formula-fed infants should be that of the breast-fed, full-term infant. This requires that we readjust our thinking away from “more is better,” even when it comes to calcium and bones.

**REFERENCES**

5. Gartner LM, Morton J, Lawrence RA, et al.; American Academy of Pediatrics Section on Breastfeed-