Nutritional Influences on Bone Growth in Children

Nutritional Influences Bone Development from Infancy through Toddler Years

Bonny Specker

Ethel Austin Martin Program in Human Nutrition, South Dakota State University, Brookings, SD 57007

ABSTRACT During the last decade a greater appreciation has developed for determining factors that influence bone accretion in healthy children. Nutritional factors that may contribute to bone accretion in infants and toddlers include maternal nutritional status during pregnancy, type of infant feeding, calcium and phosphorus content of infant formula, introduction of weaning foods, and diet during the toddler and preschool years. Maternal vitamin D deficiency during pregnancy is associated with disturbances in neonatal calcium homeostasis, and maternal calcium deficiency leads to reduced neonatal bone mineral content (BMC). Preterm infants are at increased risk of osteopenia, and, although the use of high mineral formula has reduced the risk of osteopenia in these infants, it has not eliminated it. The reason for the long-term bone deficiency among preterm infants is not clear, although lower physical activity levels have been suggested as a potential cause. Studies find that human milk-fed infants have lower bone accretion than do formula-fed infants; that the greater the mineral content of formula, the greater the bone accretion; and that the inclusion of palm olein oil in infant formula may reduce bone mineral accretion. Bone accretion is not influenced by the timing of the introduction of weaning foods, despite higher serum parathyroid hormone (PTH) concentrations among infants who receive solids earlier. There is evidence of calcium intake-by-gene and calcium intake-by-physical activity interactions among toddlers and young children. The long-term effects of these early nutritional influences on later bone health are unknown. J. Nutr. 134: 691S–695S, 2004.

KEY WORDS: • bone • children • infants • diet • nutrition

During the last decade a greater appreciation has developed for determining what factors influence bone mineral accretion in healthy children. Part of this interest can be attributed to the suggestion that osteoporosis has its origins in childhood. This review focuses on nutritional factors that may contribute to early bone mineral accretion: maternal nutritional status as it relates to fetal and neonatal growth, type of infant feeding, calcium and phosphorus content of infant formula, introduction of weaning foods, and diet during the toddler and preschool years. Nutrition-by-genetics and nutrition-by-physical activity interactions are discussed, as well as the relationship between early diet and bone health later in life.

Maternal nutritional status and early growth

Maternal diet during pregnancy. Numerous observational studies, as well as clinical trials, have been conducted to determine the relationship between maternal vitamin D supplementation during pregnancy and neonatal outcomes. The majority of studies find a relationship between maternal vitamin D status and neonatal calcium metabolism, with a greater risk of hypocalcemia among infants born to vitamin D deficient mothers (1–6). It is thought that maternal vitamin D deficiency leads to secondary hyperparathyroidism, which results in a transitory hypoparathyroidism and hypocalcemia in the neonate (7,8). Despite the numerous studies showing an effect of maternal vitamin D deficiency on neonatal calcium homeostasis, no studies have found a relationship between neonatal bone mineral content (BMC) and maternal vitamin D status.

Several studies have evaluated the effects of maternal calcium intake on neonatal bone mineral accretion. A study in undernourished pregnant mothers who were supplemented with 300 or 600 mg calcium/d during the last trimester showed that these mothers had similar density (BMD) compared to mothers not supplemented, but neonatal BMD was greater (9). Koo and co-workers also reported similar results from a large randomized trial of maternal calcium supplementation for the prevention of preeclampsia (10). A total of 256 pregnant women were enrolled in the randomized, double-blind, placebo-controlled trial. Among mothers in the lowest quintile of

1 Presented at the Nutrition and Bone Health Working Group program at the “American Society of Bone Mineral Research, 25th Annual Meeting,” held in Minneapolis, MN, September 19–23, 2003. The Nutrition and Bone Health Working Group program was organized by Susan J. Whiting and was sponsored by The National Dairy Council. Supplement contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Dairy Council. Guest editors for the supplement publication were Susan J. Whiting, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, and Frances A. Tyulsky, University of Tennessee, The Health Science Center, Memphis, TN.

2 To whom correspondence should be addressed. E-mail: Bonny_Specker@sdstate.edu.

3 Abbreviations used: BMC, bone mineral content; BMD, bone mineral density; 25-OHD, 25-hydroxyvitamin D; DXA, dual energy X-ray absorptiometry; PTH, parathyroid hormone; SPA, single photon absorptiometry; VDR, vitamin D receptor.

0022-3166/04 $8.00 © 2004 American Society for Nutritional Sciences.
calcium intake (<600 mg/d), the infants of those who were randomized to calcium supplementation had higher total body BMC compared to the infants of those mothers who were randomized to placebo. There were no differences in neonatal BMC between placebo and supplemented groups in the upper four quintiles of maternal calcium intake (baseline intakes > 600 mg/d). These studies suggest that there is less fetal bone accretion among mothers who have low calcium intakes (<600 mg/d) compared to higher intakes during pregnancy.

**Preterm birth and decreased intratertineal growth.** The majority of calcium accrued during pregnancy occurs during the last trimester (11), and this increase in fetal demand is met by an increase in maternal intestinal calcium absorption (12). Because of the substantial bone accretion that occurs during the last trimester, infants who are born preterm have lower total body BMC than do term infants (13,14). Preterm infants also are at increased risk of osteopenia (typically diagnosed clinically by radiographs), rickets, and fracture due to postnatal nutrient deficiencies resulting from prolonged exclusive human milk feeding, total parenteral nutrition with low calcium and phosphorus content, and medications or diseases that may influence calcium or vitamin D metabolism (i.e., chronic diuretic use, anticonvulsant use, etc.). Although the use of high-mineral–containing preterm formula has reduced the occurrence of osteopenia in this high-risk group, it has not eliminated it (15,16). Catch-up in radius BMC has been reported in some studies of preterm infants, but not all (17,18). Several studies have shown that former preterm infants tend to be shorter and lighter than their term counterparts are (19,20), and one study of 3- to 5-y-old children found that total body BMC and cortical area of the 20% distal tibia were lower, even after adjusting for current body weight, in former preterm children vs. term children (21). The reason for this long-term bone deficiency among preterm infants is not clear, although lower physical activity levels, with the concomitant decrease in bone loading, have been suggested as a potential cause (21,22)

### Type of infant feeding

Numerous studies have compared changes in BMD or BMC at peripheral bone sites and total body BMC in both preterm and term infants on different feeding regimens (23–31). Studies find that human milk-fed infants have lower bone accretion compared to formula-fed infants. The type of formula also may play an important role in determining bone mass accretion: mineral content of formula, type of formula (soy vs. cow’s milk), and inclusion of palm olein oil in infant formula may influence bone mass accretion during infancy.

**Human milk vs. formula.** Infants exclusively fed human milk have lower total body BMC than do formula-fed infants (31). Both the low vitamin D content of human milk (32) and the decreasing phosphorus concentrations with increasing length of lactation (33,34) are thought to contribute to the lower bone accretion observed among human milk-fed infants.

Theoretically, low vitamin D intake should be associated with decreased BMD due to increased serum parathyroid hormone (PTH) concentrations, which should increase bone resorption. Very few pediatric studies have correlated BMD measurements with serum 25-hydroxyvitamin D (25-OHD) concentrations, and the results are not consistent among those studies that have. In 1981 Greer and co-workers conducted a vitamin D supplementation trial and found that 25-OHD concentrations of 9 human milk-fed infants not receiving supplemental vitamin D decreased during the winter months, whereas the 25-OHD concentrations did not change among the 9 infants randomized to receive 400 IU/d (35). By 12 wk of age, BMC at the 1/3 distal radius [measured by single photon absorptiometer (SPA)], was lower in infants randomized to placebo compared to infants randomized to 400 IU vitamin D/day. By 26 wk of age, the BMC difference between infants receiving vitamin D and those receiving placebo was no longer significant (36). In 1989 these same investigators reported the results of an additional randomized vitamin D supplementation trial among 46 human milk-fed infants from birth to 6 mo of age and found no difference in BMC at the 1/3 distal radius between supplemented and nonsupplemented infants, despite significant differences in serum 25-OHD concentrations (29). Park and co-workers measured BMC of the lumbar spine using dual-energy X-ray absorptiometry (DXA) in 2- to 5-mo-old Korean infants who were either breast-fed without vitamin D supplementation or receiving infant formula containing 400 IU vitamin D/d (37). They found no significant difference in lumbar BMC between the two groups despite a greater serum 25-OHD concentration among the formula-fed compared to the breast-fed infants. Lumbar BMC was not correlated with serum 25-OHD concentrations.

The reason for the lack of a correlation between BMC or BMD and vitamin D status is unclear. In adults with primary hyperparathyroidism, a selective reduction in cortical BMD and preservation of trabecular BMD has been reported (38–41), and it has been suggested that assessment of BMD in relation to PTH requires separation of cortical and trabecular bone (41). Whether these disparate effects of elevated PTH concentrations on trabecular and cortical bone occur in infants with secondary hyperparathyroidism resulting from vitamin D deficiency is not known. In addition, these differing effects may be why bone findings using DXA or single photon absorptiometry in infants with vitamin D deficiency are not consistent. DXA methodology measures areal BMD in 2-dimensions and cannot separate trabecular and cortical bone; this inability to accurately measure these different types of bone may be the reason for discrepant findings on the relationship between BMC or BMD and vitamin D status.

The phosphorus content of human milk may explain the lower bone accretion in breast-fed versus formula-fed infants. Both milk and infant serum phosphorus concentrations decrease with increasing length of lactation and are correlated with each other (34,42). Milk phosphorus concentrations at 1 mo of age are ~140 mg/L and decline to <110 mg/L by 26 wk of age (42). However, by 4 to 6 mo of age, most infants are consuming additional phosphorus from solid foods. After the introduction of these higher phosphorus-containing foods, there is equalization in total body BMC between previously human milk-fed and formula-fed infants (31).

**Mineral content of formula.** The mineral content of infant formula may affect calcium homeostasis and bone accretion. In the neonatal period, a low calcium to phosphorus ratio (Ca:P) formula, which would exist in formulas with a higher phosphorus content, leads to a decrease in serum calcium resulting in an increase in serum PTH concentrations (43). This increase in PTH concentrations should increase bone turnover and may lead to a decrease in bone mineral accretion. However, beyond the neonatal period, higher mineral content formulas lead to a greater bone mass accretion.

A randomized trial in 101 infants was conducted during the 1st y of life (31). The trial was conducted in two phases: Phase I was conducted during the first 6 mo of life when infants were either breast-fed (~300 mg Ca/L and 150 mg P/L) or randomized to either a low mineral formula (430 mg Ca/L and 240 mg P/L) or a moderate mineral-containing formula (510 mg Ca/L and 390 mg P/L). Phase II involved the same infants who were...
re-randomized at 6 mo of age to one of three feeding groups: moderate mineral-containing formula (510 mg Ca/L and 390 mg P/L), high mineral-containing formula (1350 mg Ca/L and 900 mg P/L) or cow's milk (1230 mg Ca/L and 960 mg P/L). Infants who received the moderate mineral containing formula during the first 6 mo had a greater bone mass accretion than did the other two feeding groups (human milk and low mineral-containing formula). During the second period, there was no difference in total body BMC accrual based on the level of mineral content of the formula fed during the second 6 mo. However, the diets the infants received during the first 6 mo were associated with BMC accrual during the second 6 mo (Fig. 1). By 12 mo of age, there were no differences in BMC among either the first or second 6-mo feeding groups. These results indicate that early mineral intake is associated with early bone mass accretion, but when mineral intakes are increased later in infancy, these differences disappear.

**Cow's milk vs. soy milk formula.** Older infant feeding studies found that infants fed soy-based formula had lower radius BMD than did infants fed cow-milk based formula (27,30). However, newer formulations of soy formulas have improved calcium and phosphorus content and availability, and no difference in bone accretion between these newer formulas and cow-milk based formulas has been observed (44).

**Palm olein oil.** Some infant formula companies have added palmitic acid to formula to mimic human milk fatty acid profiles. Formulas with palm olein oil have 22–25% palmitic acid compared to 8–10% in formulas without palm olein oil. The addition of palm olein oil to infant formula has been found to decrease calcium and fat absorption (45–47). A randomized, double-blinded trial conducted in 128 infants from 2 wk to 6 mo of age was conducted to test the hypothesis that infants consuming formula with palm olein would have a lower bone mineral accretion than would infants consuming formula without palm olein (48). Significant differences in total body bone mineral accretion were observed through 6 mo of age, with infants consuming the palm-olein containing formula to have less bone gain than did infants consuming the formula without palm olein (Fig. 2).

**Weaning foods.** The introduction of usual weaning foods into the formula-fed infant's diet does not influence bone mass accretion. Bainbridge and co-workers conducted a trial among 41 infants who were randomly assigned to receive formula alone or formula plus infant cereal beginning at 16 wk of age (49). Although serum PTH concentrations increased significantly by 26 wk of age in the cereal-fed group, there was no difference between groups in BMC changes (1/3 distal radius using SPA). Whether the effect of cereal feeding on serum PTH concentrations was due to higher phosphorus content in the cereal or the binding of calcium to phytates is not known. These results are consistent with those of another randomized trial on the timing of the introduction of solids to an infant's diet. Infants who had solids introduced at age 3 mo had similar total body BMC at 6 and 12 mo of age compared to infants for whom solids were withheld until age 6 mo (50).

**Toddler and preschool years**

Although various studies have explored the relationship between BMC and calcium intake in older children, very few studies have investigated the relationship between bone mass accretion or BMC and nutritional intake in the toddler and preschool years. Lee and co-workers reported in 1993 the results of a longitudinal observational study of 128 children from Hong Kong for whom they had collected extensive dietary intake data during the first 5 y of life (51). They found that BMC at the 1/3 distal radius was associated with the cumulative calcium intake during the first 5 y of life. Calcium intake during the 2nd y of life had the strongest correlation with BMC at 5 y. A trial conducted in 239 children 3 to 5 y of age did not find an effect of calcium supplements on total body bone accretion over the 1-y study period, although the high baseline calcium intake (~900 mg/d) may explain the lack of significant findings (52). This study, however, did find that those children who received calcium supplements had a greater increase in leg BMC with gross motor activity than did those children who did not receive supplemental calcium (see below).

**Nutrient interactions with genetics and physical activity**

**Genetics.** It is not clear whether genetic influences on bone that have been reported are due to a bone-specific effect or due to a general effect on growth. For example, if genes that influence bone also influence early growth, this may lead to early differences in bone size due to increased skeletal loading. Vitamin D receptor (VDR) polymorphisms have been shown to be associated with early growth (53,54), which may be sex-dependent (55), and those differences in early growth may ultimately lead to BMC differences. There are reports that VDR polymorphisms are associated with femoral and vertebral BMC prior to puberty (56), and that prepubertal girls with the BB polymorphism have the lowest BMC but also are the most
responsive to supplemental calcium (57). An association between the occurrence of calcium-deficiency rickets in Nigeria and the Fok I VDR polymorphism, but not the Bsm I, Apa I, or Taq I polymorphisms, has been reported, indicating that the specific VDR polymorphisms may be important in determining an infant’s risk of developing rickets when there is limited calcium intake (58).

**Physical activity.** Nutrients may interact with other environmental factors in their effect on bone growth and mineralization. Increased bone loading through physical activity is one of the major factors influencing regional and total body bone mass accretion during growth (59,60). A 1-y randomized trial on the effect of gross motor versus fine motor activities on infant total body bone mass accretion found evidence that calcium intake during infancy may modify the bone response to activity (61). Gross motor activity had no effect on bone mass accretion among infants receiving moderately high calcium intakes, whereas among infants with moderate to low calcium intakes, gross motor activity actually resulted in less gain in BMC than was shown in the fine motor activity group. Calcium intake was not controlled in this infant study, and these results led to an additional randomized trial in preschool children that formally tested, using a factorial design, the hypothesis that calcium intake modifies the bone response to physical activity in young children.

A randomized trial, involving 239 children aged 3 to 5 y of age, was conducted to determine whether there was a calcium intake-by-physical activity interaction on total body bone gain and tibia geometry (52). Children were randomized to participate in gross motor or fine motor activities for 30 min per day, 5 d per week for one year. Within each group, children were blindly assigned to receive 5 d per week either a placebo or 1,000 mg/d of calcium carbonate. Overall, calcium intake did not influence total body bone mass accretion. However, the difference in leg BMC gain, obtained from the total body scan, between gross motor and fine motor was more pronounced in children receiving calcium vs. placebo. At study completion, children in the gross motor group had greater periosteal and endosteal circumferences at the tibia compared to children in the fine motor group. There also was a significant calcium-by-activity interaction in both cortical thickness and cortical area: among children receiving placebo, thickness and area were smaller with gross motor vs. fine motor activity, but among children receiving calcium, thickness and area were larger with gross motor activity (Fig. 3). These results indicate that the relationship of bone and calcium intake is not simple and may depend upon other environmental factors that influence bone development, such as physical activity.

**Early diet and later bone health**

Although there are early nutritional influences on bone mineral accretion, the long-term effect is not known. Bishop and co-workers reported that preterm infants fed human milk with high mineral fortifier in the neonatal period had lower total body bone mass at 5 y of age compared to preterm infants fed only human milk (62). These findings led to the speculation that there is “early programming,” such that infants who have low mineral intakes early in life develop improved calcium retention later in life. However, a later report by these same authors found no association between childhood total body BMC and early infant feeding practices in a larger number of subjects (20).

Recent studies have reported associations between childhood BMD and both infant vitamin D supplementation and length of breastfeeding. A retrospective study of 106 prepu-


