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A.S.P.E.N. Clinical Guidelines: Nutrition Support of Neonatal Patients at Risk for Metabolic Bone Disease

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Abstract

Background: Premature infants are at increased risk for metabolic bone disease, with resulting delayed bone growth, osteopenia, and rickets. *Method:* A systematic review of the best available evidence to answer a series of questions regarding neonatal patients at risk of metabolic bone disease receiving parenteral or enteral nutrition was undertaken and evaluated using concepts adopted from the Grading of Recommendations, Assessment, Development and Evaluation working group. A consensus process was used to develop the clinical guideline recommendations prior to external and internal review and approval by the American Society for Parenteral and Enteral Nutrition Board of Directors. *Questions:* (1) What maternal risk factors predispose the neonate to metabolic bone disease? (2) What is the optimal type of feeding to promote neonatal bone health? (3) When and how should vitamin D supplements be administered? (4) Does parenteral nutrition (PN) predispose a neonate to metabolic bone disease, and if so, are there PN formulation recommendations to minimize this risk? (*JPEN J Parenter Enteral Nutr*. 2013;37:570-598)

Keywords

neonates; parenteral nutrition; minerals/trace elements

Background

More than 30 years ago, it was observed that premature infants, especially those with very low birth weight (<1500 g), are at increased risk for metabolic bone disease, including delayed longitudinal growth, osteopenia, and rickets.[1-3] Since that time and with the continuous advances in neonatal intensive care, the incidence of the condition has continued to rise with recent studies reporting poor mineralization in up to 55% of infants <1000 g and 23% of infants <1500 g at birth.[4,5] Approximately 80% of bone mineral stores occur during the last trimester of intrauterine development. Preterm neonates are largely bereft of this critical period of bone growth, which puts them at higher risk for metabolic bone disease.[6] The mineral deficit these infants have at birth is often worsened by the practical difficulties of ensuring an adequate mineral intake during the neonatal period. Metabolic bone disease, however, is not a condition limited to the preterm infant, and there are factors that place even term infants at risk for this condition.

Accurate diagnosis and evaluation coupled with a solid understanding of the factors associated with the disease are necessary to accurately identify high-risk patients in order to effectively focus preventive efforts. Specific bone mineral density studies that have been used to assess the status and adequacy of therapy in the infant include dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (CT), and quantitative ultrasound (US). It must be highlighted that these studies are not standard of care for neonates and infants, and normative data are not available for all age groups and particularly for the preterm infant. However, these studies have been used within research study protocols and provide some quantitative data with regard to the effect of different variables on neonatal bone health. Certainly, the validation of these imaging studies and the determination of normative values for neonates and infants are imperative before these

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studies can be recommended for the evaluation of bone health in this population.

In the current guidelines, we aim to identify maternal and neonatal factors that place infants at risk for metabolic bone disease and provide a rationale for nutrition strategies to prevent and treat the condition.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization composed of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.[7-18] A.S.P.E.N. evaluates in an ongoing process when individual Clinical Guidelines should be updated.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

A.S.P.E.N. Clinical Guidelines has adopted concepts of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group.[19-22] A full description of the methodology as adapted by A.S.P.E.N. has been published.[23] Briefly, specific clinical questions where nutrition support is a relevant mode of therapy are developed and key clinical outcomes are identified. A rigorous search of the published literature is conducted, each included study is assessed for research quality, tables of findings are developed, the body of evidence for the question is evaluated, and a recommendation for clinical practice that is based on both the best available evidence and the risks and benefits to patients is developed by consensus. Recommendations are graded as strong when the evidence is strong and/or net benefits outweigh harms. Weak recommendations may be based on weaker evidence and/or important tradeoffs to the patient. When limited research is available to answer a question, no recommendation can be made.

Results

For the current Clinical Guideline, a PubMed search was performed to identify pertinent studies using the search terms *bone* AND *neonate* OR infant**. The search was further focused by identifying studies containing at least 1 of the following additional key terms: *aluminum; breastfed; breast fed; breast-fed; breast milk; calcium; copper; cysteine; diet; feeding; formula; human milk; magnesium; maternal; mineral; nutrition; parenteral nutrition; phosphorus; preterm formula; rickets; risk factor; total parenteral nutrition; trace element; Vitamin D or Vitamin K*. Studies were excluded if they contained 1 or more of the following key terms: *bone marrow transplant; bone marrow transplantation; cancer; dialysis; hyperparathyroidism; hypoparathyroidism; osteopetrorickets; renal failure; renal tubular acidosis or transplant*, which allowed for the exclusion of studies addressing bone disease in the setting of these other medical conditions that were not consistent with the aims of the current Clinical Guidelines. In addition, the following limits regarding the type of study were used: humans; clinical trial; randomized controlled trial (RCT); clinical trial: phase I, phase II, phase III, phase IV; comparative study; controlled clinical trial; guideline; journal article; multicenter study; English language; and published within the last 10 years. The search was conducted on July 22, 2011. A total of 941 abstracts were reviewed, of which 29 papers met the inclusion criteria of the Clinical Guidelines and were included. The questions are summarized in Table 1.

Practice Guidelines and Rationales

Question 1. What maternal risk factors predispose the neonate to metabolic bone disease?

Recommendation: Maternal vitamin D deficiency is a risk factor for neonatal vitamin D deficiency and abnormal bone health, and we suggest that pregnant women be screened for vitamin D deficiency and those that are deficient be supplemented (Weak). Insufficient data are available to determine the effect of maternal magnesium sulfate and folic acid use on neonatal bone health (Further research needed).

Evidence Grade: Low (Tables 2 and 3)

Rationale: Fetal bone development and growth occur during pregnancy with maximal accretion rates for both calcium and phosphorus occurring during the third trimester, making it important for one to consider the maternal factors that may have an impact on the development of the fetal skeleton and neonatal bone health.[6] Our literature review identified a few salient maternal nutrition factors that have been studied in relation to neonatal bone health, including maternal vitamin D deficiency, the administration of intravenous (IV) magnesium sulfate as a tocolytic agent, and maternal folic acid intake.

Table 1. Nutrition Support Guideline Recommendations in Metabolic Bone Disease of the Neonate.

Question	Recommendation	Grade
1. What maternal risk factors predispose the neonate to metabolic bone disease?	Maternal vitamin D deficiency is a risk factor for neonatal vitamin D deficiency and abnormal bone health, and we suggest that pregnant women be screened for vitamin D deficiency and those that are deficient be supplemented.	Weak
	Insufficient data are available to determine the effect of maternal magnesium sulfate and folic acid use on neonatal bone health.	Further research needed
2. What is the optimal type of feeding to promote neonatal bone health?	When available, we suggest human milk with nutrient fortifier for the preterm infant.	Weak
	When human milk is not available, we suggest that nutrient-enriched formula be used.	Weak
3. When and how should vitamin D supplements be administered?	We suggest vitamin D supplementation for healthy breastfed infants and those with malnutrition and/or rickets.	Weak
	Further studies are needed to determine the optimal dose, route, and duration of supplementation in each of these conditions.	Further research needed
4. Does parenteral nutrition (PN) predispose a neonate to metabolic bone disease, and if so, are there PN formula recommendations to minimize this risk?	We suggest that PN predisposes the infant to metabolic bone disease.	Weak
	We suggest the use of PN solutions with high-dose calcium and phosphorus supplementation.	Weak
	PN containing aluminum is a risk factor for metabolic bone disease of the neonate, and we suggest that future efforts be made to reduce aluminum content of PN.	Strong

Several studies have attempted to correlate maternal vitamin D status with neonatal bone health. Five observational studies met inclusion criteria and were reviewed.[24-28] Taken together, the available data suggest that maternal vitamin D deficiency is a risk factor for neonatal vitamin D deficiency, with the potential deleterious effects on both neonatal and later childhood bone health.

Magnesium sulfate continues to be widely used as a tocolytic agent despite a paucity of evidence supporting its efficacy,[29] and there has been recent concern regarding the effect of prolonged administration of this drug on both maternal and neonatal health. Given the paucity of data and the poor quality of the available data,[30,31] it is difficult to determine whether the prolonged administration of magnesium sulfate as a tocolytic agent has a detrimental effect on neonatal bone health, and thus, future prospective studies are necessary before any definitive recommendation can be made.

Folic acid is known to play an important role in normal growth and likely also plays a role in normal bone formation and growth. Furthermore, data exist suggesting that folic acid supplementation has beneficial effects on bone status in certain adult populations.[32] Our literature search identified only 1 study that evaluated the effect of the duration of folic acid supplementation during pregnancy on neonatal bone metabolism. The authors found no difference in any neonatal biomarkers of bone metabolism between neonates born to mothers who took folic acid supplementation until the end of the second vs the third trimester of pregnancy.[33] Based on the paucity of available data, we cannot comment on the effect of extending folic acid supplementation through the third trimester of pregnancy—a period of rapid bone development—on neonatal bone health, and further studies are necessary.

Question 2. What is the optimal type of feeding to promote neonatal bone health?

Recommendation: When available, we suggest human milk with nutrient fortifier for the preterm infant (Weak). When human milk is not available, we suggest that nutrient-enriched formula be used (Weak).

Evidence Grade: Low (Tables 4 and 5)

Rationale: The goal in nourishing premature infants is to minimize nutrient deficits and promptly address deficits that are encountered. The best practices for accomplishing this, particularly early after hospital discharge, have yet to be defined. Although feeding human milk to premature infants is widely acknowledged as being superior to formula feedings because of immunological and developmental benefits, human milk–fed infants often accrue the greatest nutrition deficits by the time of hospital discharge.[34-37] We sought to identify studies that evaluated the effect of different types of feeds on metabolic bone disease of the neonate.

Table 2. Evidence Table Question 1: What maternal risk factors predispose the neonate to metabolic bone disease?

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Maternal Vitamin D Deficiency					
Viljakainen, 2010[28]	OBS	Healthy pregnant Caucasian women (20–40 years) with an uneventful singleton full-term child were recruited at 35 weeks' gestation	To determine the association between maternal vitamin D status and neonatal bone variables	Neonates divided into groups based on maternal 25-OHD below or above the median value of 42.6 nmol/L	Did provide a direct measure of neonatal bone health using quantitative CT
	Cross-sectional study with longitudinal follow-up	Helsinki and Uusimaa (Finland)	*Outcome measures:* Maternal (first trimester and 2 days postpartum) and neonatal (umbilical cord) 25-OHD, PTH, and quantitative tibial CT (BMD, BMC, CSA)	Tibial BMC was 0.047 (95% CI, 0.011–0.082) g/cm higher ($P = .01$) and CSA was 12.3 (95% CI, 2.0–22.6) mm^2 larger with no difference in BMD in neonates with mothers with a 25-OHD above the median compared with below the median	No correlation between bone measures and clinical pathology
	Attrition rate: 1/125	N = 124 (mother and neonate pairs)			Moderate sample size
Dijkstra, 2007[25]	OBS	Neonates of healthy mothers with either dark skin and/or concealing clothing (risk group) or light skin (control group)	To determine the prevalence of vitamin D deficiency in neonates of mothers at risk of vitamin D deficiency (dark skin, concealing clothing) compared with those not presumed to be at risk	42.5% of neonates had vitamin D deficiency (25-OHD <25 nmol/L)	Not controlled for use of vitamin supplements and type of feeds
	Prospective	Rotterdam (the Netherlands)	*Outcome measures:* maternal (end of third trimester) and neonatal (umbilical cord) 25-OHD, ionized Ca, Phos, ALP, PTH	There was a positive correlation between maternal and neonatal 25-OHD ($r = 0.88$)	The clinical implications of neonatal vitamin D deficiency not evaluated
	Attrition rate: 38/125	N = 87 (mother and neonate pairs; n = 49 high-risk group, n = 38 low-risk group)		Pearson correlations of neonatal 25-OHD with ionized Ca, Phos, ALP, and PTH were nonsignificant	Moderate sample size and high attrition rate

(continued)

Table 2. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Javaid, 2006[26]	OBS	Pregnant white women (>16 years of age, <17 weeks' gestation) with singleton gestations born at term. Divided into groups based on maternal 25(OH)-vitamin D concentration: vitamin D replete (>20 μg/L), insufficient (11–20 μg/L), and deficient (<11 μg/L)	To investigate the effect of maternal vitamin D status during late pregnancy on childhood skeletal growth	49 of 198 (31%) mothers had vitamin D insufficiency (25-OHD 11-20 μg/L) and 28 of 198 (18%) had vitamin D deficiency (25-OHD <11 μg/L) during pregnancy	Did provide a direct measure of neonatal bone health using DXA
	Prospective cohort study with longitudinal follow-up	Southampton (United Kingdom)	*Outcome measures:* DXA at 9 years of age (whole body and lumbar spine BMC, BMD, bone area)	Low maternal 25-OHD was associated with reduced whole-body BMC ($P = .0088$), BMD ($P = .0063$), and bone area ($P = .0269$) in addition to reduced lumbar spine BMC ($P = .0300$) and BMD ($P = .0094$) in children 9 years of age	Provided a measure of bone health later in childhood (9 years of age)
	Attrition rate: 398 of 596 (original cohort of 596 with 461 invited to participate in 9-year follow-up based on geographic location at time of follow-up and 198 participated)	N = 198 (mother and child pairs)			No correlation between bone measures and clinical pathology
Thomson, 2004[27]	OBS	Pregnant women with 25-OHD deficiency (<30 nmol/L) and their infants ages 4–10 months	To determine the postnatal vitamin D status and bone health of women identified as vitamin D deficient in pregnancy and their infants	All 47 women had vitamin D insufficiency (25-OHD <50 nmol/L) and 39 of 47 (83%) were vitamin D deficient (25-OHD <30 nmol/L)	Large sample size Variability with age at which data were collected on the children (ie, 4–10 months)

(continued)

Table 2. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Retrospective audit with prospective recruitment and additional data collection	Melbourne (Australia)	*Outcome measures:* maternal and infant serum 25-OHD, ALP, Ca, Phos, PTH; x-ray results in children with clinical or laboratory findings suggestive of rickets	18 of 45 (40%) infants were vitamin D insufficient and 14 of 45 (31%) were vitamin D deficient	The clinical implications of neonatal vitamin D deficiency not evaluated
	Attrition rate: 0 of 47 women; 2 of 47 infants (unable to obtain blood sample)	N = 47 (mother and newborn pairs)		12 of 16 (75%) of breastfed infants compared with only 2 of 29 (6.9%) formula-fed infants had vitamin D deficiency 12 infants were offered an x-ray (low 25-OHD and high ALP and/or raised PTH) and 10 attended, with 1 of 10 having rickets	Small sample size
Andiran, 2002[24]	OBS	Healthy breastfed newborns and their mothers (aged 18–39 years) who had not previously received vitamin D supplementation	To evaluate the vitamin D status and risk factors for vitamin D deficiency in healthy breastfed newborns and their mothers	46 of 54 (85%) mothers had vitamin D insufficiency (25-OHD <40 nmol/L) and 25 of 54 (46%) had vitamin D deficiency (25-OHD <25 nmol/L)	Study only evaluated breastfed newborns
	Retrospective audit with prospective recruitment and additional data collection	Ankara (Turkey)	*Outcome measures:* serum 25-OHD, Ca, Phos, ALP	43 of 54 (80%) of newborns had vitamin D deficiency	The clinical implications of neonatal vitamin D deficiency not evaluated
	Attrition rate: 0 of 54	N = 54 (mother and neonate pairs)		There was a significant correlation between maternal and neonatal 25-OHD levels ($r = 0.63$; $P = .01$) and the most important risk factor for low neonatal 25-OHD was a maternal level <25 nmol/L (OR = 15.2; $P = .002$)	Moderate sample size

(continued)

Table 2. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Maternal Magnesium Sulfate					
Yokoyama, 2010[31]	OBS	Neonates whose mothers either received prolonged IV $MgSO_4$ (>5 days) (cases) or did not receive IV $MgSO_4$ (controls)	To assess the effects of prolonged (>5 days) maternal IV $MgSO_4$ on neonatal bone health	Mean duration of maternal $MgSO_4$ administration = 18.3 ± 11.3 days (range, 5–44 days)	Radiographic bone abnormalities were identified in only 2 of 117 patients overall, making a determination of the effect of prolonged maternal IV $MgSO_4$ on radiographic evidence of neonatal bone disease difficult to determine
	Retrospective case-control study	Togichi (Japan)	*Outcome measures:* neonatal Mg, Ca, Phos, ALP, radiography at birth (evaluating for osteopenia at the metaphyseal line)	Mean serum Mg, Phos, and ALP levels significantly higher and Ca levels significantly lower ($P <$ .001 in all cases) among neonates born to mothers who received prolonged IV MgSO4	Moderate sample size
	Attrition rate: NA	N = 117 (n = 58 cases; n = 59 controls)		Radiographic bone abnormalities evident in 2 of 58 cases and 0 of 59 controls at birth (P = .496)	
Nassar, 2006[30]	OBS	Pregnant women who received IV $MgSO_4$ administration for >48 hours (cases) or for ≤48 hours (controls)	To determine the effect of prolonged (>48 hour) IV $MgSO_4$ administration on maternal and neonatal outcome	No difference in neonatal Ca level between groups (8.5 ± 1.1 mg/dL in both)	Imaging studies not routinely performed on all neonates exposed to prolonged maternal IV $MgSO_4$ so unable to compare groups with regard to the incidence abnormal bone mineralization
	Retrospective chart review	Beirut (Lebanon)	*Outcome measures:* maternal adverse effects, neonatal adverse effects (birth weight, Apgar scores, Mg and Ca levels, nursery stay, hypotonia, morbidity, mortality)	Abnormal bone mineralization seen in neonates of 3 of 78 cases vs 0 of 77 controls (no P value)	No follow-up images or long-term outcomes provided for the 3 patients with radiographic evidence of abnormal bone mineralization

(continued)

Table 2. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Attrition rate: NA	N = 155 (mother and neonate pairs; n = 78 cases, n = 77 controls)		No difference between groups in any measure of neonatal morbidity or mortality	Moderate sample size
Maternal Folic Acid					
Hossein-Nezhad, 2011[33]	OBS	Pregnant women 8–12 weeks' gestation and aged 15–42 years of age who took folic acid (1 mg/d) from the beginning of pregnancy to the end of the second trimester (group I) or until delivery (group II)	To evaluate the effect of folic acid supplementation taken until the end of the second vs third trimester on maternal and fetal markers of bone turnover	No significant difference in any neonatal biomarkers of bone metabolism or any fetal anthropometric characteristics between groups	Moderate sample size
	Prospective cohort study	Tehran (Iran)	*Outcome measures*: maternal and neonatal (cord) serum levels of markers of bone metabolism (25-OHD, PTH, OC, crosslaps); fetal anthropometric measures		
	Attrition rate: not specified	N = 113 (n = 54 group I; n = 59 group II)			

ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; CI, confidence interval; CSA, cross-sectional area; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; IV, intravenous; Mg, magnesium; $MgSO_4$, magnesium sulfate; NA, not available; Phos, phosphorus; PTH, parathyroid hormone; OBS, observational study; OC, osteocalcin; OR, odds ratio; 25-OHD, 25-hydroxyvitamin D.

Table 3. GRADE Table Question 1: What maternal risk factors predispose the neonate to metabolic bone disease?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome
Maternal vitamin D deficiency and neonatal vitamin D deficiency[24,25,27]	**Biochemical:** 25-OHD	3 OBS[24,25,27]	**Biochemical:** Lower[24,25,27]	Low
Maternal vitamin D deficiency and neonatal[28] or childhood (9 years of age)[26] bone health	**Bone:** BMC BMD CSA	2 OBS[26,28]	**Bone:** Lower[26] No difference[28] Lower[26] Lower[28]	Low
Prolonged (>48 hour) vs short-term (≤48 hour)[30] or prolonged (>5 day) vs no maternal IV $MgSO_4$ administration[31]	**Biochemical:** Ca ALP, Mg, Phos **Bone:** Radiographic bone abnormality	2 OBS[30,31]	**Biochemical:** No difference[30] Lower[31] Higher[31] **Bone:** No difference[30,31]	Low
Folic acid supplementation through second vs third trimester of pregnancy[33]	**Biochemical:** 25-OHD, PTH, OC, crosslaps	1 OBS[33]	**Biochemical:** No difference	Low

25-OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; CSA, cross-sectional area; IV, intravenous; Mg, magnesium; $MgSO_4$, magnesium sulfate; Phos, phosphorus; PTH, parathyroid hormone; OBS, observational study; OC, osteocalcin.

The available data suggest that exclusive breastfeeding is associated with lower bone mineralization in both the preterm and term infant[38-41] and that fortification has beneficial effects on bone health for the human milk–fed preterm neonate[42,43]; however, further studies are necessary to determine the optimal type, amount, and duration of nutrient fortification.

For the formula-fed infant, the available data suggest that a nutrient-enriched preterm formula administered to preterm infants from hospital discharge to approximately term has beneficial effects on growth and bone health.[44-48] Of note, all of these studies looked at relatively healthy preterm infants, and thus sufficient data are not available to make a recommendation for the sicker and smaller preterm infant. In addition, the available data are insufficient to allow for a recommendation regarding the use of a nutrient-enriched preterm formula beyond approximate expected term, and thus further studies are necessary to address this time period.

Question 3. When and how should vitamin D supplements be administered?

Recommendation: We suggest vitamin D supplementation for healthy breastfed infants and those with malnutrition and/or rickets (Weak). Further studies are needed to determine the optimal dose, route, and duration of supplementation in each of these conditions (Further research needed).

Evidence Grade: Low (Tables 6 and 7)

Rationale: Current recommendations for vitamin D intake differ, and we sought to identify studies that provided guidance with regard to indications and methods for vitamin D supplementation in the neonate.

The available data suggest that vitamin D supplementation is beneficial in healthy term[40,49,50] and preterm[51] breastfed infants in addition to children with established malnutrition and rickets,[52-54] but further studies are necessary to determine the optimal dose, route of administration, and duration of treatment; thus, specific recommendations cannot be made at this time. There is also disagreement among professional organizations with regard to vitamin D dose in infants. The American Academy of Pediatrics[55] recommends 400 IU (10 μg) per day, as does the Institute of Medicine with a goal 25-hydroxyvitamin D level >20 ng/mL.[56] However, the Endocrine Society[57] recommends that infants require at least 400 IU and that 1000 IU daily may be needed to obtain an optimal 25-hydroxyvitamin D level (>30 ng/mL) for nonskeletal health benefits.

Question 4. Does PN predispose a neonate to metabolic bone disease, and if so, are there PN formulation recommendations to minimize this risk?

Recommendation: We suggest that PN predisposes the infant to metabolic bone disease (Weak). We suggest using PN

Table 4. Evidence Table Question 2: What is the optimal type of feeding to promote neonatal bone health?

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Human Milk vs Formula					
Kim, 2010[66]	OBS	Healthy term infants divided into 3 groups: A (formula fed), B (breastfed only without supplementation) and, S (breastfed with vitamin D supplementation at 200 IU daily in the form of Poly-Vitamin Drops from 2–12 months of age)	To evaluate the vitamin D status of Korean infants and to determine the vitamin D nutrition status and bone mineralization in term breastfed infants who were formula fed, breastfed only, or breastfed with vitamin D supplementation (200 IU/d)	*6-month follow-up:* 25-OHD different among groups with A > S > B ($P < .001$)	No difference among groups in demographic characteristics, baseline laboratory values, or lifestyle characteristics
	Prospective cohort study	Chungbuk National University (Cheongju, Korea)	*Outcome measures:* serum 25-OHD, Ca, Phos, ALP, PTH and DXA (BMD, BMC) at birth, 6 months, and 12 months of age	Prevalence of vitamin D deficiency (25-OHD <11 ng/mL) and insufficiency (25-OHD 11–30 ng/mL) was 0% and 12%, 11% and 68%, and 0% and 45% for groups A, B, and S, respectively	Multivitamin solution used contained vitamins in addition to vitamin D (vitamins A, C, and E; thiamin; riboflavin; niacin; pyridoxine; iron; fluoride)
	Attrition rate: 13 of 74 (reason not specified)	N = 74 (n = 25 group A; n = 28 group B; n = 21 group S)		Ca and ALP not different but Phos with A > S > B ($P < .001$) and PTH higher in group B with B > A = S ($P = .001$) BMD and BMC higher in group A with A > B = S ($P < .05$) *12-month follow-up:* (n = 30 group A; n = 16 group B; n = 15 group S) 25-OHD higher in groups A and S with A = S > B ($P < .001$) No infants vitamin D deficient, although 50% of infants in group B vitamin D insufficient	Small sample size

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
				Ca and ALP not different but serum Phos lower in group S than in A with A > S (P = .0009) but A = B and B = S and PTH higher in group S than in A with S > A (P = .025) and A = B and B = S BMD higher in group A than in groups B and S (P = .010, A > B = S) and BMC higher in group A than in group S (P = .025, A > S, A = B, B = S)	
Harvey, 2009[39]	OBS	Infants born to women previously enrolled in Southampton Women's Survey (a study of lifestyle factors, diet, and anthropometrics among nonpregnant women ages 20–34 years)	To evaluate the relationship between childhood bone size and density at 4 years with the duration and type of milk-feeding in infancy and compliance with infant feeding guidance	Duration of breastfeeding did not predict any measure of bone size or density in children at 4 years of age	Data regarding feeds based on maternal recall, introducing significant potential bias
	Prospective cohort	Southampton General Hospital (Southampton, United Kingdom)	*Outcome measures:* DXA (BMC, BMD) at 4 years	No difference in bone mineral at age 4 years between predominantly breastfed and formula-fed infants	Unclear whether breastfed group received fortifier
	Questionnaire-based study design	N = 599			Large sample size
	Attrition rate: 22 of 621				
Young, 2005[38]	OBS	Healthy 4-year-old children born at term	To determine whether the type of feeding during the first 4 months of life affects bone mineral density at 4 years of age	BMC, BMD, and anteroposterior spine z scores not significantly different between groups at 4 years of age	Groups did not differ with respect to age, sex, or body mass index but the HM group had more Caucasians (P = .05)
	Prospective cohort	University of Nebraska Medical Center (Omaha, Nebraska)	*Outcome measures:* DXA (BMC, BMD) and anteroposterior spine z scores at 4 years of age		Primarily Caucasian subjects (>50%)

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Attrition rate: 20 of 198 (did not complete DXA imaging)	N = 178 (n = 57 breastfed; n = 56 formula without palm olein; n = 65 formula with palm olein)			Unclear whether breastfed group received fortifier Moderate sample size
Kurl, 2003[41]	OBS	Preterm infants (<32 weeks gestational age)	To (1) evaluate how nutrition status of preterm infants (judged by growth measured and biochemical values) evolves during the initial hospitalization when infants are fed according to the available recommendations, (2) determine the effect of feeding on growth after discharge, and (3) identify risk factors associated with low lumbar BMC later in infancy	Exclusively breastfed infants with larger weight for length than formula-fed infants ($P = .003$)	All infants fed HM (mother's or banked HM) predischarge
	Prospective cohort	Kuopio University Hospital (Kuopio, Finland)	*Outcome measures:* anthropometrics at birth and discharge; lumbar spine DXA (BMC) when weight 5–7 kg	Infants exclusively breastfed postdischarge with 7.0 (95% CI, 1.2–41.7)–fold higher risk of low BMC ($P = .046$)	When infants reached milk intake of 100 mg/kg/d, milk fortification with hydrolyzed whey protein started, after which multivitamins were added
	Nonblinded	N = 64 (n = 38 formula feeding initiated within 1 week postdischarge; n = 13 formula feeding initiated 2–14 weeks postdischarge, n = 13 breastfed for entire study period)			Milk fortifier, mineral supplements, and vitamin C continued until 2.5 kg and vitamin D and iron continued throughout study period
	Attrition rate: 19 of 83 (transfer of care to other institution or failure to follow-up)				Milk/formula intake postdischarge not quantified Solid foods added between 3 and 6 months Small sample size

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
HM Fortification					
Aimone, 2009[42]	RCT	Preterm (<33 weeks gestational age, 750–1800 g birth weight) infants who received ≥80% energy from HM pre–hospital discharge	To evaluate the impact of fortifying HM with a multinutrient HM fortifier (approximately 50% of feeds fortified) for 12 weeks postdischarge on bone mineralization, body composition, and HM use measured at 4 and 12 months' corrected age	HM-alone group trended toward higher gestational age ($P = .06$) and fewer males ($P = .07$)	Infants on HM alone received vitamin A 1500 IU/d, vitamin D 400 IU/d, vitamin C 30 mg/d, iron 15 mg/d. Infants on fortified HM received 200 IU/d vitamin D and 15 mg/d iron
	Blinded (details of blinding not provided)	Multiple neonatal intensive care units in greater Toronto area (Toronto, Canada)	*Outcome measures*: anthropometrics; DXA (BMC, BMD) at 4 and 12 months' corrected age	Infants with fortified HM had increased weight ($P = .07$) and length ($P = .02$) at the end of the 12-week feeding intervention and both weight ($P = .0035$) and length ($P = .001$) higher 12 months' corrected age	Duration of HM feeding did not differ between groups, but the volume of HM consumed was higher for the HM-alone group at 6 months ($P = .035$) but not at 12 months' corrected age
	Attrition rate: 9 of 39 (lost to follow-up)	N = 39 (n = 20 HM alone; n = 19 fortified HM)		BMC at 4 and 12 months' corrected age higher in infants on fortified HM ($P = .02$) but when corrected for length, effect disappeared ($P = .25$) BMD was not different between groups at 4 or 12 months' corrected age	Intent-to-treat analysis Small sample size
De Schepper, 2005[43]	OBS	Preterm infants (<34 weeks gestational age, birth weight 800–2210 g)	To determine whether whole-body bone mineralization is different at hospital discharge between preterm infants fed a commercial preterm formula and those fed with fortified HM	Whole-body bone mass percentage at hospital discharge (median day of life 40) not different between the 3 different feeding regimens (28 ± 7 preterm formula; 27 ± 6 fortified HM; 33 ± 9 mixed feeds)	Only evaluated bone mass at discharge from the hospital

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Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Prospective cohort study	Academic Hospital of the Free University of Brussels (Brussels, Belgium)	*Outcome measures:* DXA (whole-body bone mineral mass) and anthropometrics at hospital discharge (median 40 days of age)	Significant correlation between bone mass and birth weight ($r = 0.42$; $P < .05$) and body weight at discharge ($r = 0.35$; $P < .05$)	Both preterm formula and fortified HM groups received Ca 150 mg/kg/d and Phos 75 mg/kg/d
	Attrition rate: 0 of 34	N = 34 (n = 15 preterm formula; n = 10 fortified HM; n = 9 mixed)			All infants supplemented with vitamin D 400 IU/d Very small sample size
Infant Formula Fortification					
Picaud, 2008[48]	RCT	Healthy formula-fed preterm infants (gestational age <33 weeks, birth weight <1750 g)	To compare bone mineralization and growth in preterm infants fed an enriched preterm formula vs a standard term formula for the first 2 months after hospital discharge (all infants fed standard term formula from 2–4 months after hospital discharge)	BMC and BMD at 2 months higher in enriched formula group ($P = .05$ and $P = .01$, respectively)	All infants received HM prior to hospital discharge
	Double-blind	Multicenter including Lyon and Montpellier, France	*Outcome measures:* DXA (BMC, BMD); anthropometrics	BMC and BMD at 4 months higher in enriched formula group ($P = .01$ and $P = .002$, respectively)	No solid foods introduced during study period
	Attrition rate: 7 of 49	N = 49 (n = 26 standard formula; n = 23 enriched formula)		Body weight at 2 and 4 months postdischarge higher in enriched formula group ($P = .06$ and $P = .03$, respectively)	Amount of dietary intake measured Energy intake similar between groups but protein, Ca, and Phos intake significantly higher in the enriched formula group Moderate sample size

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Litmanovitz, 2007[47]	RCT	Preterm healthy formula-fed infants (birth weight <1550 g and appropriate for gestational age)	To evaluate differences in bone strength between preterm infants fed a nutrient-enriched formula compared with a standard term formula from 40 weeks' corrected gestational age to 6 months of age (all infants received the nutrient-enriched formula until 40 weeks' corrected age)	No difference between groups in SOS, weight, length, or head circumference at term or 3 or 6 months' corrected age	All infants received the nutrient-enriched formula until 40 weeks' corrected age
	Blinded (details of blinding not provided)	Meir Medical Center (Kfar Saba, Israel)	*Outcome measures:* tibial QUS (SOS); osteoblastic bone activity (BS-ALP); osteoclastic bone resorption activity (ICTP); anthropometrics at 3 and 6 months' corrected age	Significant increase in bone SOS in both groups from term to 6 months' corrected age ($P < .001$ for both groups)	QUS not a validated technique of measuring bone health in infants
	Attrition rate: not specified	N = 20 (n = 10 standard formula; n = 10 enriched formula)		No difference between groups in serum markers of bone turnover at term or 3 or 6 months' corrected age	No additional food intake Very small sample size
Koo, 2006[45]	RCT	Healthy preterm formula-fed infants (gestational age 24–34 weeks, birth weight 630–1620 g)	To evaluate differences in growth, bone mass, and body composition in preterm infants fed a nutrient-enriched formula compared with a standard term formula from discharge until 1 year of age	Infants on term formula with higher weight, length, and head circumference *z* scores ($P < .05$ for all comparisons) at 2, 4, 6, 9, and 12 months postdischarge	Details regarding predischarge formula not provided
	Double-blind	Wayne State University (Detroit, MI)	*Outcome measures:* DXA (BMC) at 2, 4, 6, 12 months after discharge; anthropometrics at 2, 4, 6, 9, 12 months after discharge	BMC higher in term formula-fed infants compared with enriched formula-fed infants ($P \leq .01$) at 2, 4, 6, and 12 months postdischarge	Subjects started solid foods during study period

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Attrition rate: 22 of 89 (did not complete 1-year follow-up, each replaced by next eligible subject)	N = 89 (n = 45 standard formula; n = 44 enriched formula)			Details on amount of formula and solid food intake not measured Not isocaloric formulas Longer follow-up period (1 year of age) Moderate sample size
Lapillonne, 2004[46]	RCT	Healthy formula-fed preterm infants (gestational age 28–32 weeks, birth weight 1000–1600 g) on full enteral nutrition by 3 weeks of age	To evaluate differences in bone mineralization in preterm infants fed an nutrient-enriched preterm formula vs an isocaloric control formula from the age when full enteral feedings were tolerated through expected term (3 months of age)	BMC of infants on enriched formula 23% ($P = .039$) and 35% ($P = .002$) higher at hospital discharge and expected term, respectively, than control	All infants received vitamin D 800 IU/d
	Double-blind	Edouard Herriot Hospital (Lyon, France)	*Outcome measures:* serum Ca, Phos, ALT, 25-OHD, OC; DXA (BMC); growth	Mean gain in BMC between hospital discharge and expected term significantly higher in enriched formula group (53.6 ± 21.7 vs 38.9 ± 17.7 g, $P = .037$)	Isocaloric formulas
	Attrition rate: 4 of 41 (n = 2 early feed intolerance; n = 1 worsening bradycardia/apnea/cyanosis unrelated to feedings; n = 1 family request)	N = 41 (n = 20 standard formula; n = 21 enriched formula)		Laboratory values similar between groups, except mean 25-OHD at expected term higher in enriched formula group ($P = .002$) Mean weight gain between entry into the study and expected term higher in enriched formula group ($P = .016$)	Formula intake and thus energy intake did not differ between groups Ca and Phos intake was higher (25% and 40%, respectively) in the enriched formula group Short-term follow-up (~3 months of age) Small sample size

(continued)

Table 4. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
De Curtis, 2002[44]	RCT	Healthy formula-fed preterm infants (gestational age <35 weeks, birth weight <1750 g)	To evaluate differences in growth and weight gain composition in preterm infants fed standard term formula vs enriched formula after discharge from the hospital during the first 2 months of life	No difference in growth or whole-body composition between standard and enriched postdischarge formula-fed groups at birth, at discharge from the hospital, or at 2 months of age	Details regarding predischarge formula not provided
	Blinded (details of blinding not provided)	University of Liege (Liege, Belgium)	*Outcome measures:* whole-body DXA (BMC); anthropometrics at discharge from the hospital and 2 months of age	Mean BMC increased from 9.4 ± 0.8 to 10.2 ± 0.6 mg/cm^3 in the standard term formula group and from 9.4 ± 0.9 to 10.3 ± 1.1 mg/cm^3 in the enriched formula group ($P < .01$)	Study powered to detect a bone mineral content gain of 30 mg/kg/d
	Attrition rate: 0 of 33	N = 33 (n = 17 standard formula; n = 16 enriched formula)			Not isocaloric formulas Short-term follow-up (2 months of age) Very small sample size

ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; BS-ALP, bone-specific alkaline phosphatase; Ca, calcium; DXA, dual-energy x-ray absorptiometry; HM, human milk; ICTP, cross-linked carboxy-terminal telopeptide of type I collagen; OBS, observational study; OC, osteocalcin; Phos, phosphorus; PTH, parathyroid hormone; QUS, quantitative ultrasound; RCT, randomized controlled trial; SOS, speed of sound; 25-OHD, 25-hydroxyvitamin D.

Table 5. GRADE Table Question 2: What is the optimal type of feeding to promote neonatal bone health?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome
Breast vs formula feeding healthy term[38-40] or preterm[41] infants during the first year of life	**Biochemical:** 25-OHD Ca, ALP Phos PTH **Growth:** Weight **Bone:** BMC BMD	1 OBS[66] 1 OBS[41] 4 OBS[38-41]	**Biochemical:** Lower (6, 12 mo)[66] No difference (6, 12 mo)[66] Lower (6 mo), no difference (12 mo)[66] Higher (6 mo), no difference (12 mo)[66] **Growth:** Higher[41] **Bone:** Lower[40,41] Lower (6, 12 mo)[40] No difference (48 mo)[38,39]	Low
Nutrient-fortified vs nonfortified HM in preterm infants for 12 weeks after hospital discharge[42]	**Growth:** Weight **Bone:** BMC BMD	1 RCT[42]	**Growth:** Higher (12 wk, 12 mo)[42] **Bone:** Higher (4, 12 mo)[42] No difference (4, 12 mo)[42]	Moderate
Fortified HM vs preterm formula in preterm infants before hospital discharge[43]	**Bone:** Whole-body BM%	1 OBS[43]	**Bone:** No difference[43]	Low
Enriched formula vs standard formula for preterm infants from hospital discharge to 2,[44] 3,[46] or 4[48] months of age; 6 months gestational age[47]; and 1 year of age[45]	**Growth:** Weight **Bone:** BMC BMD SOS **Biochemical:** BS-ALP ICTP	5 RCT[44-48]	**Growth:** No difference[44,47] Higher[46,48] Lower[45] **Bone:** No difference[46] Higher[45,48] Lower[47] Higher[45,48] No difference[47] **Biochemical:** No difference[47] No difference[47]	Moderate

ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; BM%, bone mass percentage; BS-ALP, bone-specific alkaline phosphatase; Ca, calcium; HM, human milk; ICTP, cross-linked carboxy-terminal telopeptide of type I collagen; OBS, observational study; OC, osteocalcin; Phos, phosphorus; PTH, parathyroid hormone; RCT, randomized controlled trial; QUS, quantitative ultrasound; SOS, speed of sound; 25-OHD, 25-hydroxyvitamin D.

formulations with high-dose calcium and phosphorus content (Weak). PN aluminum is a risk factor for metabolic bone disease of the neonate (Strong), and we suggest that future efforts be made to reduce the aluminum content of PN.

Evidence Grade: Low/Moderate (Tables 8 and 9)

Rationale: Preterm and low birth weight infants are at increased risk for low bone mass and metabolic bone disease because they miss the period of greatest mineral accretion that occurs during the last trimester of pregnancy. Most of these infants are unable to tolerate full enteral feedings within the first days or weeks after birth, and nutrients need to be delivered via PN. Unfortunately, the threshold for calcium and phosphorus precipitation limits the delivery of appropriate amounts of these minerals via PN. Given that the recommended range of calcium and phosphorus delivered by PN in preterm infants is wide, 40–120 mg/kg/d for calcium and 31–71 mg/kg/d for phosphorus,[58,59] we sought to identify studies that provided guidance with regard to PN formulations for preterm neonates.

The available data suggest that PN does predispose the infant to metabolic bone disease[60] and that PN formulations with high-dose calcium and phosphorus content should be used.[61]

We did not identify a study that addressed the vitamin D content of PN formulations. PN formulations are routinely supplemented with vitamin D; however, the optimal dose is not

Table 6. Evidence Table Question 3: When and how should Vitamin D supplements be administered?

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Siafarikas, 2011[67]	RCT	Healthy breastfed infants with intermediately pigmented skin (skin photo types I and II) born during summer and winter moths	To compare the efficacy of 250 IU vs 500 IU of oral vitamin D supplementation daily and to quantify sun exposure and analyze maternal factors	Most infants with vitamin D insufficiency at initial postnatal visit, and all values normalized with no difference between groups at 6 weeks ($P = .48$)	Breastfed infants only
	Not blinded	Hospital Berlin-Lichtenberg	*Outcome measures:* serum 25-OHD, ALP, Ca, Phos, serum albumin, creatinine at day 5 and 6 weeks; clinical signs of rickets	Ca levels increased from day 5 to week 6 ($P = .0001$) and at 6 weeks higher for infants on 250 IU/d than those on 500 IU/d of vitamin D ($P = .048$)	All infants had minimal UV-B exposure
	Not placebo controlled	(Berlin, Germany)		Phos was different between groups and did not increase significantly between day 5 and week 6	Measured maternal dietary intake
	Attrition rate: 12 of 40 (insufficient blood samples)	N = 40 (n = 10 summer born on 250 IU/d; n = 10 winter born on 250 IU/d; n = 10 summer born on 500 IU/d; n = 10 winter born on 500 IU/d)		ALP within normal range for all infants but increased between day 5 and week 6 independent of supplementation group and season ($P < .05$)	Short period of follow-up
				Reported average time of daily sun or UV-B exposure not different between groups, although sunshine exposure score higher in the 250-IU/d compared with 500-IU/d group ($P = .048$)	Very small sample sizes

(continued)

Table 6. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Savino, 2011[68]	OBS	Healthy Caucasian exclusively breastfed infants <12 months with normal skeletal status and who had not received any calcium supplementation and whose mothers were not taking calcium or vitamin D supplements were divided into 2 groups: group 1 (breastfed with vitamin D supplementation at 400 IU/d starting at birth) and group 2 (breastfed without vitamin D supplementation)	To access bone status using QUS of the second metacarpus and to determine the effect of vitamin D supplementation from birth to 1 year of age on bone mineralization	mcSOS and mcBTT lower in group 2 compared with group 1 ($P = .001$ and $P = .015$, respectively)	Excluded maternal supplement factor by excluding mothers taking any calcium or vitamin D supplements
	Cross-sectional study	Regina Margherita Children's Hospital (Turin, Italy)	*Outcome measures:* QUS of the second metacarpus (mcSOS, mcBTT)	*z* score of mcSOS for age, *z* score of BTT for age, and the *z* score of BTT for length also lower in group 2 ($P = .003$, $P = .026$, and $P = .029$, respectively)	No laboratory measures
	Attrition rate: 0 of 77	N = 77 (n=38 group 1, n = 39 group 2)			New and unvalidated measure of bone health and no reference values for QUS parameters
	Analysis using Mann-Whitney *U* test and Spearman's correlation				Small sample size
Kim, 2010[66]	OBS	Healthy term infants divided into 3 groups: A (formula fed), B (breastfed only without supplementation), and S (breastfed with vitamin D supplementation at 200 IU daily in the form of Poly-Vitamin Drops from 2–12 months of age)	To evaluate the vitamin D status of Korean infants and to determine the efficacy of vitamin D supplementation (200 IU/d from 2–12 months) on vitamin D nutrition status and bone mineralization in term breastfed infants	*6-month follow-up*: 25-OHD different among groups with A > S > B ($P < .001$)	No difference among groups in demographic characteristics, baseline laboratory values, or lifestyle characteristics

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Table 6. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	Prospective cohort study	Chungbuk National University (Cheongju, Korea)	*Outcome measures:* serum 25-OHD, Ca, Phos, ALP, PTH, and DXA (BMD, BMC) at birth, 6 months, and 12 months of age	Prevalence of vitamin D deficiency (25-OHD <11 ng/mL) and insufficiency (25-OHD 11–30 ng/mL) 0% and 12%, 11% and 68%, and 0% and 45% for groups A, B, and S, respectively	Only evaluated vitamin D supplementation at 200 IU/d, which may not be sufficient (some studies suggest 400–800 IU/d is necessary in late infancy)
	Attrition rate: 13 of 74 (reason not specified)	N = 74 (n = 25 group A, n = 28 group B, n = 21 group S)		Ca and ALP not different but Phos with A > S > B (P < .001) and PTH higher in group B with B > A = S (P = .001)	Multivitamin solution used contained vitamins in addition to vitamin D (vitamins A, C, and E; thiamin; riboflavin; niacin; B_6; iron; fluoride)
	Funded by the Korean government			BMD and BMC higher in group A with A > B = S (P < .05)	No data provided on maternal calcium or vitamin D supplementation but maternal sunlight exposure and dietary intake were estimated
				12-month follow-up: (n = 30 group A, n = 16 group B, n = 15 group S)	DXA is not a validated measure of bone health in infants, and there are no accepted normal ranges
				25-OHD higher in groups A and S with A = S > B (P < .001)	Small sample size
				No infants vitamin D deficient, although 50% of infants in group B vitamin D insufficient	
				Ca and ALP not different but serum Phos lower in group S than in group A with A > S (P = .0009) but A = B and B = S and PTH higher in group S than in group A with S > A (P = .025) and A = B and B = S	

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Table 6. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
				BMD higher in group A than in groups B and S (P = .010, A > B = S) and BMC higher in group A than in group S (P = .025, A > S, A = B, B = S)	
Soliman, 2010[69]	OBS	Children <3 years of age with nutrition rickets	To evaluate the clinical, biochemical, and radiographic response to a single intramuscular dose of vitamin D (10,000 IU/kg) in children with vitamin D deficiency rickets	25-OHD, Ca, and Phos higher 3 months following treatment (P < .05 in all)	Type of feed not controlled for but majority of infants (35/40) exclusively breastfed >6 months with 36 of 40 being breastfed at baseline and 24 of 40 still being breastfed at 6-month follow-up
	Prospective	Hamad Medical Centre (Doha, Qatar)	*Outcome measures:* serum 25-OHD, Ca, Phos, ALP, PTH, serum albumin; anthropometric parameters	PTH and ALP lower 3 months following treatment (P < .05 in both)	Small sample size
	Attrition rate: not specified	N = 40		39 of 40 children with a decrease in 25-OHD to below 20 ng/mL at 6 months following treatment Radiographic (epiphyseal and diaphyseal) changes normalized in 95% of cases 3 months following treatment	
Kislal, 2008[70]	RCT	Preterm infants (<33 weeks) fed breast milk or formula without vitamin D randomly assigned to vitamin D supplementation groups: group 1 (200 IU/kg), group 2 (400 IU/kg), or group 3 (800 IU/kg)	To compare the efficacy of 3 different doses of vitamin D (200 IU/kg, 400 IU/kg, 800 IU/kg) in maintaining normal vitamin D status in preterm infants	Ca and Phos were not different before and after treatment in any group	Given no difference between groups in OC levels, 200 IU/d of vitamin D seems to be as effective as 800 IU/d with regard to OC

(continued)

Table 6. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
	No statement regarding blinding		*Outcome measures:* biochemical measures of bone turnover (serum Ca, Phos, ALP, OC, and urinary DPD) at baseline and following 15 days of vitamin D supplementation	ALP increased following therapy in group 1 (P = .033) and group 3 (P = .016) but not group 2 (P = .460)	The significant increase in DPD excretion with 800 IU/d of vitamin D suggests that high vitamin D doses may accelerate bone turnover and resorption in the preterm infant
	Not placebo controlled	Zekai Tahir Burak Maternity Teaching Hospital (Ankara, Turkey)		OC increased following treatment in groups 1, 2, and 3 (P = .006, P = .020, and P = .045, respectively)	Only addresses preterm infants
	Attrition rate: 11 of 48	N = 37 (n = 11 group 1, n = 15 group 2, n = 11 group 3)		There was a linear correlation between vitamin D dose and urinary DPD excretion, but the difference trended toward significance only in group 3 (P = .059)	Small sample size
Alp, 2006[71]	OBS	Caucasian children aged 3–19 months with no history of bone disease (controls) or with moderate to severe malnutrition without rachitic manifestations (cases) who were treated with a high protein diet and either 400 IU or 800 IU daily vitamin D supplementation (randomly assigned) for 3 months	To compare BMD of lumbar spine before and after vitamin D therapy in children with malnutrition without rachitic manifestations and to compare these with healthy children in the same community	Baseline BMD lower in children with malnutrition than controls (P < .01) and lower in children with severe than with moderate malnutrition (P < .01)	Only addressed malnourished children without rickets
	Case-controlled study	Ataturk University (Erzurum, Turkey)	*Outcome measure:* lumbar spine DXA (BMD)	Both groups of malnourished children with increased BMD with treatment (P < .05 for 400 IU/d group, P < .01 for 800 IU/d group)	Establish correlation between malnutrition and BMD
	Attrition rate: 28 of 41	N = 62 (n = 41 malnourished, n = 21 healthy controls)		Increased BMD over the 3-month study period significantly greater in malnourished children receiving 800 IU vs 400 IU of daily vitamin D supplementation (P < .05)	Small sample size

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Table 6. (continued)

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Akcam, 2006[72]	OBS	Term breastfed otherwise healthy infants aged 5–13 months with nutrition rickets divided into 2 groups based on vitamin D therapy: group 1 (single high-dose vitamin D 600,000 IU orally) or group 2 (20,000 IU orally daily for 30 days)	To compare the increase in BMD in 2 different therapy regimens of vitamin D in infants with vitamin D deficient rickets (VDR)	Ca, Phos, and ALP levels following treatment not different between groups	Excluded infants born to mothers taking calcium or vitamin D supplements during pregnancy or lactation
	Prospective	Isparta Children's Hospital (Isparta, Turkey)	*Outcome measures:* serum Ca, Phos, ALP; lumbar spine DXA (BMD) prior to and following 31 days of treatment	Posttreatment BMD not different between groups ($P = .940$)	Limited and contradictory data on the relationship between BMD and rickets
	Attrition rate: 0 of 20	N = 20 (n = 10 group 1, n = 10 group 2)		BMD increased from pretreatment values in both groups 1 and 2 ($P = .005$ and $P = .047$, respectively)	Very small sample size
				All patients in both groups with healing of rickets following treatment	

ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; DPD, deoxypyridinoline; DXA, dual-energy x-ray absorptiometry; mcBTT, bone transmission time; mcSOS, speed of sound; Phos, phosphorus; OBS, observational study; OC, osteocalcin; PTH, parathyroid hormone; QUS, quantitative ultrasound; 25-OHD, 25-hydroxyvitamin D.

Table 7. GRADE Table Question 3: When and how should Vitamin D supplements be administered?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome
In breastfed infants:	**Biochemical:**	1 OBS[66]	**Biochemical:**	Low to moderate
Vitamin D oral supplementation (200 IU/d)[66] or (400 IU/d)[68] vs no supplementation from 2–12 months	25-OHD	1 RCT[26]	Higher (6, 12 mo),[66] no difference[67]	
Low (250 IU) vs high (500 IU) dose daily oral vitamin D supplementation during the initial 6 weeks of life[67]	Ca		No difference (6, 12 mo),[66] higher[67]	
	Phos		Higher (6 mo), no difference (12 mo),[66] 6 weeks[67]	
	ALP		No difference (6, 12 mo),[66] 6 weeks[67]	
	PTH		Lower (6 mo), no difference (12 mo)[66]	
	Bone:		**Bone:**	
	BMD		No difference (6, 12 mo)[66]	
	BMC		No difference[68]	
	mcSOS			
	mcBTT			
In preterm infants:	**Biochemical:**	1 RCT[70]	**Biochemical:**	Moderate
Change in vitamin D status with 200 IU/kg/d (1), 400 IU/d (2), or 800 IU/d (3) oral vitamin D supplementation from 15–30 days of life[70]	Ca		No difference (1, 2, 3)[70]	
	Phos		Higher (1, 3), no difference (2)	
	ALP		Higher (1, 2, 3)	
	OC		No difference (1, 2), higher (3)	
	Urinary DPD			
In malnourished children:	**Bone:**	1 OBS[71]	**Bone:**	Low
High-dose (800 IU) vs low-dose (400 IU) daily oral vitamin D supplementation for 3 months[71]	BMD		Lower[71]	
In rachitic children:	**Biochemical:**	2 OBS[69,72]	**Biochemical:**	Low
Low daily oral dose (20,000 IU) for 30 days vs single oral dose (600,000 IU) vitamin D therapy,[72] after single 10,000-IU/kg IM injection of vitamin D[69]	Ca		No difference,[71] higher[69]	
	Phos		No difference,[71] higher [69]	
	ALP		No difference,[71] lower[69]	
	25-OHD		Higher[69]	
	PTH		Lower[69]	
	Bone:		**Bone:**	
	BMD		No difference[71]	

ALP, alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; DPD, deoxypyridinoline; DXA, dual-energy x-ray absorptiometry; IM, intramuscular; mcBTT, bone transmission time; mcSOS, speed of sound; OBS, observational study; OC, osteocalcin; Phos, phosphorus; PTH, parathyroid hormone; RCT, randomized controlled trial; QUS, quantitative ultrasound; 25-OHD, 25-hydroxyvitamin D.

known at this time. It is common practice to provide approximately 200 international units (5 mcg) vitamin D per day[62]; however, further research is necessary to determine the ideal vitamin D for neonates requiring PN therapy.

Beyond calcium, phosphorus, and vitamin D content, the aluminum content of standard PN formulations deserves attention when discussing metabolic bone disease of the neonate. Aluminum is a contaminant of PN components, and high doses of aluminum have been shown to negatively affect both cognitive development and short-term bone health.[63] In animals and adult humans, excess aluminum has been shown to accumulate at mineralization fronts and is associated with reduced bone formation.[62] In addition, Sedman et al[64] reported that bone aluminum concentrations were 10-fold higher in preterm infants who received PN for >3 weeks as compared with control subjects. It has been recently demonstrated that the currently available PN products in the United States have an aluminum content that makes it impossible to meet the new Food and Drug Administration rule of <5 mcg/kg per day of aluminum exposure in patients <50 kg.[65] Thus, it is imperative that manufacturers develop new methods to reduce the aluminum contamination in their products and healthcare professionals be aware of the aluminum exposure in our PN-dependent neonates.

Table 8. Evidence Table Question 4: Does PN predispose a neonate to metabolic bone disease? Are there PN formula recommendations to minimize this risk?

Lead Author (Reference No.), Year	Study Design, Quality	Population, Setting, N	Study Objective	Results	Comments
Pereira-da-Silva, 2011[61]	RCT	Healthy preterm neonates (≤33 weeks gestational age) on PN for >1 week assigned to receive low-dose Ca and Phos (45 mg/kg/d Ca; 26.5 mg/kg/d Phos) or high-dose Ca and Phos (75 mg/kg/d Ca; 44.1 mg/kg/d Phos) by PN	To assess whether early higher Ca and Phos intake delivered via PN can prevent bone strength decline in preterm infants during the first weeks of life	SOS values for low-dose groups decreased significantly over first 6 weeks of life ($P = .027$), whereas the values for the high-dose group did not ($P = .976$)	Phos was added to PN as a fixed Ca:Phos ratio of 1.7:1
	Triple-blind	Hospital Dona Estefania (Lisbon, Portugal)	*Outcome measures:* tibial QUS (SOS) weekly from birth to discharge	By the fifth and sixth weeks of life, the SOS values were lower for the low-dose groups ($P = .035$ and $P = .011$, respectively)	Same enteral feeding regimen used for both groups
	Attrition rate: 5 of 91 (interrupted PN administration during first week of life)	N = 86 (n = 40 low dose; n = 46 high dose)			Long-term outcomes not assessed Moderate sample size
Fewtrell, 2009[63]	RCT	Previously preterm (<34 weeks gestational age, <1850 g birth weight) adolescents (13–15 years old) previously randomly assigned to aluminum-depleted vs standard PN solutions during the neonatal period	To assess whether neonatal aluminum exposure affects long-term bone mass	Lumbar spine BMC and BA higher in low-aluminum group ($P = .017$ and $P = .031$, respectively)	Composition of PN solutions identical other than aluminum and chloride content
	Double-blind	Multiple hospitals (Cambridge and Norwich, United Kingdom)	*Outcome measures:* lumbar spine and whole-body DXA (BMC, BMD, BA)	Whole-body BMC, BA, BMD, and BMD *z* scores and lumbar spine BMD *z* score trended higher in low-aluminum group	Questionnaires used to quantify calcium intake, weight-bearing activity, and overall activity level
	Attrition rate: 0 of 59 (33% of eligible initial subjects participated)	N = 59 (n = 26 standard aluminum; n = 33 low aluminum)			Only 33% of eligible subjects from initial study participated in this follow-up study Moderate sample size
Rohana, 2007[60]	OBS	Infants with a birth weight <1500 g	To determine the correlation between bone mineral content and biochemical markers in very low birth weight (<1500 g) infants	Longer duration PN support associated with lower BMC ($P = .03$)	Ca and Phos content of PN solutions not provided
	Cross-sectional study	Hospital Universiti Kebangsaan Malaysia (Kuala Lampur, Malaysia)	*Outcome measures:* DXA (BMC) (mean postnatal day 46.5 ± 19.4)		Moderate sample size
	Attrition rate: NA (41/151 of eligible infants enrolled)	N = 41			

BA, bone area; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; DXA, dual-energy x-ray absorptiometry; NA, not available; OBS, observational study; Phos, phosphorus; PN, parenteral nutrition; RCT, randomized controlled trial; QUS, quantitative ultrasound; SOS, speed of sound.

Table 9. GRADE Table Question 4: Does PN predispose a neonate to metabolic bone disease? Are there PN formula recommendations to minimize this risk?

Comparison	Outcome	Quantity, Type Evidence	Findings	GRADE of Evidence for Outcome
Long- vs short-duration PN,[60] early high-dose Ca, Phos (75 mg/kg/d Ca; 44.1 mg/kg/d Phos) vs low-dose Ca, Phos (45 mg/kg/d Ca; 26.5 mg/kg/d Phos) via PN[61]	**Bone:** BMC SOS	1 OBS[60] 1 RCT[61]	**Bone:** Lower[60] Higher[61]	Weak to moderate
Aluminum-depleted vs standard PN[63]	**Bone:** LS BMC, LS BA LS BMD, WB BMC, WB BMD, WB BA	1 RCT[63]	**Bone:** Higher[63] No difference[63]	Moderate

Abbreviations: BA, bone area; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; LS, lumbar spine; OBS, observational study; Phos, phosphorus; PN, parenteral nutrition; RCT, randomized controlled trial; SOS, speed of sound; WB, whole body.

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References

1. Steichen JJ, Gratton TL, Tsang RC. Osteopenia of prematurity: the cause and possible treatment. *J Pediatr*. 1980;96(3, pt 2):528-534.
2. Greer FR, McCormick A. Bone growth with low bone mineral content in very low birth weight premature infants. *Pediatr Res*. 1986;20(10):925-928.
3. James JR, Congdon PJ, Truscott J, Horsman A, Arthur R. Osteopenia of prematurity. *Arch Dis Child*. 1986;61(9):871-876.
4. Koo WW, Sherman R, Succop P, et al. Fractures and rickets in very low birth weight infants: conservative management and outcome. *J Pediatr Orthop*. 1989;9(3):326-330.
5. McIntosh N, De Curtis M, Williams J. Failure of mineral supplementation to reduce incidence of rickets in very-low-birthweight infants. *Lancet*. 1986;2(8513):981-982.
6. Hosking DJ. Calcium homeostasis in pregnancy. *Clin Endocrinol (Oxf)*. 1996;45(1):1-6.
7. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr*. 2002;26(1)(suppl):1SA-138SA.
8. Guidelines for use of total parenteral nutrition in the hospitalized adult patient. A.S.P.E.N. Board of Directors. *JPEN J Parenter Enteral Nutr*. 1986;10(5):441-445.
9. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 1993;17(4)(suppl):1SA-52SA.
10. Arsenault D, Brenn M, Kim S, et al. A.S.P.E.N. clinical guidelines: hyperglycemia and hypoglycemia in the neonate receiving parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2012;36(1):81-95.
11. Goldner WS, Stoner JA, Lyden E, et al. Finding the optimal dose of vitamin D following Roux-en-Y gastric bypass: a prospective, randomized pilot clinical trial. *Obes Surg*. 2009;19(2):173-179.
12. Jaksic T, Hull MA, Modi BP, Ching YA, George D, Compher C. A.S.P.E.N. clinical guidelines: nutrition support of neonates supported with extracorporeal membrane oxygenation. *JPEN J Parenter Enteral Nutr*. 2010;34(3):247-253.
13. Jesuit C, Dillon C, Compher C, Lenders CM. A.S.P.E.N. clinical guidelines: nutrition support of hospitalized pediatric patients with obesity. *JPEN J Parenter Enteral Nutr*. 2010;34(1):13-20.
14. Knox LS, Crosby LO, Feurer ID, Buzby GP, Miller CL, Mullen JL. Energy expenditure in malnourished cancer patients. *Ann Surg*. 1983;197(2):152-162.
15. Mehta NM, Compher C. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr*. 2009;33(3):260-276.
16. Mueller C, Compher C, Ellen DM. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. *JPEN J Parenter Enteral Nutr*. 2011;35(1):16-24.
17. Sabery N, Duggan C. A.S.P.E.N. clinical guidelines: nutrition support of children with human immunodeficiency virus infection. *JPEN J Parenter Enteral Nutr*. 2009;33(6):588-606.
18. Brown RO, Compher C. A.S.P.E.N. clinical guidelines: nutrition support in adult acute and chronic renal failure. *JPEN J Parenter Enteral Nutr*. 2010;34(4):366-377.
19. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines, 1: introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
20. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines, 2: framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395-400.
21. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines, 4: rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-415.

22. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines, 3: rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
23. Druyan ME, Compher C, Boullata JI, et al. Clinical guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients: applying the GRADE system to development of A.S.P.E.N. clinical guidelines. *JPEN J Parenter Enteral Nutr*. 2012;36(1):77-80.
24. Andiran N, Yordam N, Ozon A. Risk factors for vitamin D deficiency in breast-fed newborns and their mothers. *Nutrition*. 2002;18(1):47-50.
25. Dijkstra SH, van Beek A, Janssen JW, de Vleeschouwer LH, Huysman WA, van den Akker EL. High prevalence of vitamin D deficiency in newborn infants of high-risk mothers. *Arch Dis Child*. 2007;92(9):750-753.
26. Javaid MK, Crozier SR, Harvey NC, et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet*. 2006;367(9504):36-43.
27. Thomson K, Morley R, Grover SR, Zacharin MR. Postnatal evaluation of vitamin D and bone health in women who were vitamin D-deficient in pregnancy, and in their infants. *Med J Aust*. 2004;181(9):486-488.
28. Viljakainen HT, Saarnio E, Hytinantti T, et al. Maternal vitamin D status determines bone variables in the newborn. *J Clin Endocrinol Metab*. 2010;95(4):1749-1757.
29. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2002;(4):CD001060.
30. Nassar AH, Sakhel K, Maarouf H, Naassan GR, Usta IM. Adverse maternal and neonatal outcome of prolonged course of magnesium sulfate tocolysis. *Acta Obstet Gynecol Scand*. 2006;85(9):1099-1103.
31. Yokoyama K, Takahashi N, Yada Y, et al. Prolonged maternal magnesium administration and bone metabolism in neonates. *Early Hum Dev*. 2010;86(3):187-191.
32. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA*. 2005;293(9):1082-1088.
33. Hossein-Nezhad A, Mirzaei K, Maghbooli Z, Najmafshar A, Larijani B. The influence of folic acid supplementation on maternal and fetal bone turnover. *J Bone Miner Metab*. 2011;29(2):186-192.
34. Aggett PJ, Agostoni C, Axelsson I, et al. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2006;42(5):596-603.
35. Greer FR. Post-discharge nutrition: what does the evidence support? *Semin Perinatol*. 2007;31(2):89-95.
36. Griffin IJ. Postdischarge nutrition for high risk neonates. *Clin Perinatol*. 2002;29(2):327-344.
37. O'Connor DL, Jacobs J, Hall R, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. *J Pediatr Gastroenterol Nutr*. 2003;37(4):437-446.
38. Young RJ, Antonson DL, Ferguson PW, Murray ND, Merkel K, Moore TE. Neonatal and infant feeding: effect on bone density at 4 years. *J Pediatr Gastroenterol Nutr*. 2005;41(1):88-93.
39. Harvey NC, Robinson SM, Crozier SR, et al. Breast-feeding and adherence to infant feeding guidelines do not influence bone mass at age 4 years. *Br J Nutr*. 2009;102(6):915-920.
40. Kim MJ, Na B, No SJ, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. *J Korean Med Sci*. 2010;25(1):83-89.
41. Kurl S, Heinonen K, Lansimies E. Pre- and post-discharge feeding of very preterm infants: impact on growth and bone mineralization. *Clin Physiol Funct Imaging*. 2003;23(4):182-189.
42. Aimone A, Rovet J, Ward W, et al. Growth and body composition of human milk–fed premature infants provided with extra energy and nutrients early after hospital discharge: 1-year follow-up. *J Pediatr Gastroenterol Nutr*. 2009;49(4):456-466.
43. De Schepper J, Cools F, Vandenplas Y, Louis O. Whole body bone mineral content is similar at discharge from the hospital in premature infants receiving fortified breast milk or preterm formula. *J Pediatr Gastroenterol Nutr*. 2005;41(2):230-234.
44. De Curtis M, Pieltain C, Rigo J. Body composition in preterm infants fed standard term or enriched formula after hospital discharge. *Eur J Nutr*. 2002;41(4):177-182.
45. Koo WW, Hockman EM. Posthospital discharge feeding for preterm infants: effects of standard compared with enriched milk formula on growth, bone mass, and body composition. *Am J Clin Nutr*. 2006;84(6):1357-1364.
46. Lapillonne A, Salle BL, Glorieux FH, Claris O. Bone mineralization and growth are enhanced in preterm infants fed an isocaloric, nutrient-enriched preterm formula through term. *Am J Clin Nutr*. 2004;80(6):1595-1603.
47. Litmanovitz I, Eliakim A, Arnon S, et al. Enriched post-discharge formula versus term formula for bone strength in very low birth weight infants: a longitudinal pilot study. *J Perinat Med*. 2007;35(5):431-435.
48. Picaud JC, Decullier E, Plan O, et al. Growth and bone mineralization in preterm infants fed preterm formula or standard term formula after discharge. *J Pediatr*. 2008;153(5):616-621, 621.e1-2.
49. Savino F, Viola S, Tarasco V, et al. Bone mineral status in breast-fed infants: influence of vitamin D supplementation. *Eur J Clin Nutr*. 2011;65(3):335-339.
50. Siafarikas A, Piazena H, Feister U, Bulsara MK, Meffert H, Hesse V. Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants. *Arch Dis Child*. 2011;96(1):91-95.
51. Kislal FM, Dilmen U. Effect of different doses of vitamin D on osteocalcin and deoxypyridinoline in preterm infants. *Pediatr Int*. 2008;50(2):204-207.
52. Akcam M, Yildiz M, Yilmaz A, Artan R. Bone mineral density in response to two different regimes in rickets. *Indian Pediatr*. 2006;43(5):423-427.
53. Alp H, Orbak Z, Kermen T, Uslu H. Bone mineral density in malnourished children without rachitic manifestations. *Pediatr Int*. 2006;48(2):128-131.
54. Soliman AT, El-Dabbagh M, Adel A, Al Ali M, Aziz Bedair EM, Elalaily RK. Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. *J Trop Pediatr*. 2010;56(1):19-26.
55. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142-1152.
56. Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr*. 2011;14(5):938-939.
57. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
58. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28(6):S39-S70.
59. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. 1. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr*. 2005;41(suppl 2):S1-S87.
60. Rohana J, Hasmawati J, Zulkifli SZ. Risk factors associated with low bone mineral content in very low birth weight infants. *Singapore Med J*. 2007;48(3):191-194.
61. Pereira-da-Silva L, Costa A, Pereira L, et al. Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. *J Pediatr Gastroenterol Nutr*. 2011;52(2):203-209.
62. Klein GL. Metabolic bone disease of total parenteral nutrition. *Nutrition*. 1998;14(1):149-152.
63. Fewtrell MS, Bishop NJ, Edmonds CJ, Isaacs EB, Lucas A. Aluminum exposure from parenteral nutrition in preterm infants: bone health at 15-year follow-up. *Pediatrics*. 2009;124(5):1372-1379.

64. Sedman AB, Klein GL, Merritt RJ, et al. Evidence of aluminum loading in infants receiving intravenous therapy. *N Engl J Med*. 1985;312(21): 1337-1343.
65. Poole RL, Hintz SR, Mackenzie NI, Kerner JA Jr. Aluminum exposure from pediatric parenteral nutrition: meeting the new FDA regulation. *JPEN J Parenter Enteral Nutr*. 2008;32(3):242-246.
66. Kim MJ, Na B, No SJ, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. *J Korean Med Sci*. 2010;25(1):83-89.
67. Siafarikas A, Piazena H, Feister U, Bulsara MK, Meffert H, Hesse V. Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants. *Arch Dis Child*. 2011;96(1):91-95.
68. Savino F, Viola S, Tarasco V, et al. Bone mineral status in breast-fed infants: influence of vitamin D supplementation. *Eur J Clin Nutr*. 2011;65(3):335-339.
69. Soliman AT, El-Dabbagh M, Adel A, Al Ali M, Aziz Bedair EM, Elalaily RK. Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. *J Trop Pediatr*. 2010;56(1):19-26.
70. Kislal FM, Dilmen U. Effect of different doses of vitamin D on osteocalcin and deoxypyridinoline in preterm infants. *Pediatr Int*. 2008;50(2): 204-207.
71. Alp H, Orbak Z, Kermen T, Uslu H. Bone mineral density in malnourished children without rachitic manifestations. *Pediatr Int*. 2006;48(2):128-131.
72. Akcam M, Yildiz M, Yilmaz A, Artan R. Bone mineral density in response to two different regimes in rickets. *Indian Pediatr*. 2006;43(5):423-427.