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Carol L. Wagner, Frank R. Greer and the Section on Breastfeeding and Committee on Nutrition

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CLINICAL REPORT

Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Guidance for the Clinician in Rendering
Pediatric Care

Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

ABSTRACT

Rickets in infants attributable to inadequate vitamin D intake and decreased exposure to sunlight continues to be reported in the United States. There are also concerns for vitamin D deficiency in older children and adolescents. Because there are limited natural dietary sources of vitamin D and adequate sunshine exposure for the cutaneous synthesis of vitamin D is not easily determined for a given individual and may increase the risk of skin cancer, the recommendations to ensure adequate vitamin D status have been revised to include all infants, including those who are exclusively breastfed and older children and adolescents. It is now recommended that all infants and children, including adolescents, have a minimum daily intake of 400 IU of vitamin D beginning soon after birth. The current recommendation replaces the previous recommendation of a minimum daily intake of 200 IU/day of vitamin D supplementation beginning in the first 2 months after birth and continuing through adolescence. These revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D per day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer. The new data may eventually refine what constitutes vitamin D sufficiency or deficiency. *Pediatrics* 2008;122:1142–1152

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words

vitamin D, vitamin D deficiency, rickets, vitamin D requirements, infants, children, adolescents, 25-hydroxyvitamin D, vitamin D supplements

Abbreviations

AAP—American Academy of Pediatrics
25-OH-D—25-hydroxyvitamin D
1,25-OH₂-D—1,25-dihydroxyvitamin D
PTH—parathyroid hormone

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INTRODUCTION

This statement is intended to replace a 2003 clinical report from the American Academy of Pediatrics (AAP),¹ which recommended a daily intake of 200 IU/day of vitamin D for all infants (beginning in the first 2 months after birth), children, and adolescents. The new recommended daily intake of vitamin D is 400 IU/day for all infants, children, and adolescents beginning in the first few days of life.

BACKGROUND

Rickets attributable to vitamin D deficiency is known to be a condition that is preventable with adequate nutritional intake of vitamin D.^{2–6} Despite this knowledge, cases of rickets in infants attributable to inadequate vitamin D intake and decreased exposure to sunlight continue to be reported in the United States and other Western countries, particularly with exclusively breastfed infants and infants with darker skin pigmentation.^{4,7–14} Rickets, however, is not limited to infancy and early childhood, as evidenced by cases of rickets caused by nutritional vitamin D deficiency being reported in adolescents.¹⁵

Rickets is an example of extreme vitamin D deficiency, with a peak incidence between 3 and 18 months of age. A state of deficiency occurs months before rickets is obvious on physical examination, and the deficiency state may also present with hypocalcemic seizures,^{16–18} growth failure, lethargy, irritability, and a predisposition to respiratory infections during infancy.^{16–22} In a retrospective review of children presenting with vitamin D deficiency in the United Kingdom,¹⁶ there were 2 types of presentations. The first was symptomatic hypocalcemia (including seizures) occurring during periods of rapid growth, with increased metabolic demands, long before any physical findings or radiologic evidence of vitamin D deficiency occurred. The second clinical presentation was that of a more chronic disease, with rickets and/or decreased bone mineralization and either normocalcemia or asymptomatic hypocalce-

TABLE 1 Vitamin D Deficiency: Stages and Clinical Signs**1. Stages of vitamin D deficiency**

Stage I

25-OH-D level decreases, resulting in hypocalcemia and euphosphatemia; 1,25-OH₂-D may increase or remain unchanged

Stage II

25-OH-D level continues to decrease; PTH acts to maintain calcium through demineralization of bone; the patient remains eucalcemic and hypophosphatemic and has a slight increase in the skeletal alkaline phosphatase level

Stage III

Severe 25-OH-D deficiency with hypocalcemia, hypophosphatemia, and increased alkaline phosphatase; bones have overt signs of demineralization

2. Clinical signs of vitamin D deficiency

- Dietary calcium absorption from the gut decreases from 30%–40% to 10%–15% when there is vitamin D deficiency
- Low concentrations of 25-OH-D trigger the release of PTH in older infants, children, and adolescents in an inverse relationship not typically seen with young infants; the increase in PTH mediates the mobilization of calcium from bone, resulting in a reduction of bone mass; as bone mass decreases, the risk of fractures increases
- Rickets
 - Enlargement of the skull, joints of long bones, and rib cage; curvature of spine and femurs; generalized muscle weakness
- Osteomalacia and osteopenia
- Abnormal immune function with greater susceptibility to acute infections and other long-latency disease states (see below)

3. Potential latent disease processes associated with vitamin D deficiency

- Dysfunction of the innate immune system is noted with vitamin D deficiency
 - Immunomodulatory actions may include
 - Potent stimulator of innate immune system acting through Toll-like receptors on monocytes and macrophages
 - Decrease threshold for long-latency diseases such as cancers (including leukemia and colon, prostate, and breast cancers), psoriasis, diabetes mellitus, and autoimmune diseases (eg, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus)

mia. (For a more complete review of nutritional rickets and its management, please refer to the recent publication in *Endocrinology and Metabolism Clinics of North America* on the topic.²³)

There are 2 forms of vitamin D: D₂ (ergocalciferol, synthesized by plants) and D₃ (cholecalciferol, synthesized by mammals). The main source of vitamin D for humans is vitamin D₃ through its synthesis in the skin when UV-B in the range of 290 to 315 nm converts 7-dehydrocholesterol to previtamin D₃. Through the heat of the skin, previtamin D₃ is further transformed into vitamin D₃, which then binds to the vitamin D-binding protein and is transported to the liver and converted to 25-hydroxyvitamin D (25-OH-D) by the action of 25-hydroxylase. 25-OH-D, the nutritional indicator of vitamin D, undergoes a second hydroxylation in the kidney and other tissues to become 1,25-dihydroxyvitamin D (1,25-OH₂-D). Vitamin D is an important prehormone with active metabolites (25-OH-D and 1,25-OH₂-D) that are involved in many metabolic processes beyond bone integrity and calcium homeostasis.²⁴ More-detailed reviews of vitamin D physiology and metabolism are available from Hathcock et al,²⁵ Holick,²⁶ Webb,²⁷ and Misra et al.²³

It is important to note that measuring the concentration of 1,25-OH₂-D instead of 25-OH-D for assessment of vitamin D status can lead to erroneous conclusions, because 1,25-OH₂-D concentrations will be normal or even elevated in the face of vitamin D deficiency as a result of secondary hyperparathyroidism (see Table 1). Prevention of vitamin D deficiency and achieving adequate intake of vitamin D and calcium throughout childhood may reduce the risk of osteoporosis as well as other long-latency disease processes that have been associated with vitamin D-deficiency states in adults.^{28–31}

The presence of vitamin D as a natural ingredient in food in most diets is limited, occurring in relatively sig-

nificant amounts only in fatty fish and certain fish oils, liver and fat from aquatic mammals, and egg yolks of chickens fed vitamin D.³² In adults, new evidence suggests that vitamin D plays a vital role in maintaining innate immunity³³ and has been implicated in the prevention of certain disease states including infection,^{34,35} autoimmune diseases (multiple sclerosis,^{28,33,36,37} rheumatoid arthritis³⁸), some forms of cancer (breast, ovarian, colorectal, prostate),^{24,30,39–42} and type 2 diabetes mellitus.^{43–45} Results from prospective observational studies also suggest that vitamin D supplements in infancy and early childhood may decrease the incidence of type 1 diabetes mellitus.^{46–50}

RECOMMENDED DAILY INTAKE OF VITAMIN D FOR INFANTS AND CHILDREN

In partnership with the Institute of Medicine, the National Academy of Sciences Panel for Vitamin D recommended in 1997 a daily intake of 200 IU vitamin D to prevent vitamin D deficiency in normal infants, children and adolescents.⁵¹ This recommendation was endorsed by the AAP in a previous clinical report.¹ The National Academy of Sciences guidelines for infants were based on data primarily from the United States, Norway, and China, which showed that an intake of at least 200 IU/day of vitamin D prevented physical signs of vitamin D deficiency and maintained the concentration of 25-OH-D at or above 27.5 nmol/L (11 ng/mL).[†] These recommendations were made despite 50 years of clinical experience demonstrating that 400 IU of vitamin D (the concentration measured in a teaspoon of cod liver oil) not only prevented rickets but also treated it.^{52–55} Primarily on the basis of new information in adults linking

[†]Universal units of measure for 25-OH-D and 1,25-OH₂-D are nmol/L. Conversion to ng/mL is made by dividing the value expressed in nmol/L by 2.496. Thus, 80 nmol/L becomes 32 ng/mL.

other biomarkers (parathyroid hormone [PTH], insulin resistance, bone mineralization, and calcium absorption studies) to vitamin D deficiency, there is a growing concern that the previous recommendation of 200 IU/day as an adequate intake of vitamin D is not sufficient, even for infants and children.^{53,56-61}

This new information has resulted in defining vitamin D deficiency in adults as a 25-OH-D concentration of <50 nmol/L and vitamin D insufficiency as a 25-OH-D concentration of 50 to 80 nmol/L.^{25,26,62-67} At the present time, however, consensus has not been reached with regard to the concentration of 25-OH-D to define vitamin D insufficiency for infants and children.⁶⁶⁻⁶⁹ Although there may not be a precise definition of what constitutes vitamin D insufficiency in infants and children, it is known that 200 IU/day of vitamin D will not maintain 25-OH-D concentrations at >50 nmol/L in infants, the concentration attributed to vitamin D sufficiency in adults.^{62,67,70-74} On the other hand, 400 IU/day of vitamin D has been shown to maintain serum 25-OH-D concentrations at >50 nmol/L in exclusively breastfed infants.⁷³ It is also of note that liquid vitamins and vitamin D-only preparations available in the United States conveniently supply 400 IU/day, not 200 IU/day, in either drop or milliliter preparations.

SUNLIGHT EXPOSURE AND VITAMIN D

Historically, the main source of vitamin D has been via synthesis in the skin from cholesterol after exposure to UV-B light. Full-body exposure during summer months for 10 to 15 minutes in an adult with lighter pigmentation will generate between 10 000 and 20 000 IU of vitamin D₃ within 24 hours; individuals with darker pigmentation require 5 to 10 times more exposure to generate similar amounts of vitamin D₃.⁷⁵⁻⁷⁸ The amount of UV exposure available for the synthesis of vitamin D depends on many factors other than just time spent outdoors. These factors include the amount of skin pigmentation, body mass, degree of latitude, season, the amount of cloud cover, the extent of air pollution, the amount of skin exposed, and the extent of UV protection, including clothing and sunscreens.^{56,77,79-81} The Indoor Air Quality Act of 1989 reported that Americans spent an average of 93% of their time indoors,⁸² supporting the higher prevalence of lower 25-OH-D concentrations among adult Americans.^{83,84} More recently, vitamin D deficiency (as defined by concentrations of 25-OH-D < 25 nmol/L) among school-aged children and adolescents has been reported, reflecting modern-day lifestyle changes.^{3,6,9,58,85-96}

The multitude of factors that affect vitamin D synthesis by the skin,²⁷ the most important of which is degree of skin pigmentation, make it difficult to determine what is adequate sunshine exposure for any given infant or child.⁹⁷⁻⁹⁹ Furthermore, to limit exposure to UV light, the Centers for Disease Control and Prevention, with the support of many organizations including the AAP and the American Cancer Society, launched a major public health campaign in 1998 to increase public awareness about sunlight exposure

and the risks of various skin cancers.¹⁰⁰ Indirect epidemiologic evidence now suggests that the age at which direct sunlight exposure is initiated is even more important than the total sunlight exposure over a lifetime in determining the risk of skin cancer.¹⁰¹⁻¹⁰⁵ Among dermatologists, there is active discussion about the risks and potential benefits of sun exposure and/or oral vitamin D supplementation^{97,99,106}; however, the vast majority would agree with the current AAP guidelines for decreasing sunlight exposure, which include the advice that infants younger than 6 months should be kept out of direct sunlight. Although the AAP encourages physical activity and time spent outdoors, children's activities that minimize sunlight exposure are preferred, and when outdoors, protective clothing as well as sunscreens should be used.¹⁰⁵ In following these guidelines, vitamin D supplements during infancy, childhood, and adolescence are necessary.

PREGNANCY, VITAMIN D, AND THE FETUS

The Institute of Medicine in 1997⁵¹ and a Cochrane review in 2002¹⁰⁷ concluded that there are few data available regarding maternal vitamin D requirements during pregnancy, despite the fact that maternal vitamin D concentrations largely determine the vitamin D status of the fetus and newborn infant. With restricted vitamin D intake and sunlight exposure, maternal deficiency may occur, as has been documented in a number of studies.¹⁰⁷⁻¹¹³

Recent work has demonstrated that in men and non-pregnant women, oral vitamin D intake over a 4- to 5-month period will increase circulating 25-OH-D concentrations by approximately 0.70 nmol/L for every 40 IU of vitamin D ingested,^{114,115} which is consistent with earlier work performed in pregnant women. In those studies, as predicted by vitamin D kinetics, supplements of 1000 IU/day of vitamin D to pregnant women resulted in a 12.5 to 15.0 nmol/L increase in circulating 25-OH-D concentrations in both maternal and cord serum compared with nonsupplemented controls.¹⁰⁸⁻¹¹⁰ Maternal 25-OH-D concentrations ranged from a mean of approximately 25 nmol/L at baseline to 65 ± 17.5 nmol/L at 230 days of gestation in the group of women who received 1000 IU of vitamin D per day during the last trimester. In comparison, 25-OH-D concentrations were 32.5 ± 20.0 nmol/L in the unsupplemented control group. These data suggest that doses exceeding 1000 IU of vitamin D per day are necessary to achieve 25-OH-D concentrations of >50 nmol/L in pregnant women.¹⁰⁸⁻¹¹⁵ The significance of these findings for those who care for the pediatric population is that when a woman who has vitamin D deficiency gives birth, her neonate also will be deficient.

It is important to note that women with increased skin pigmentation or who have little exposure of their skin to sunlight are at a greater risk of vitamin D deficiency and may need additional vitamin D supplements, especially during pregnancy and lactation.⁷¹ In a study by van der Meer et al,¹¹⁶ >50% of pregnant women with darker pigmentation in the Netherlands were vitamin D

deficient, as defined by a 25-OH-D concentration of <25 nmol/L.

Studies in human subjects have shown a strong relationship between maternal and fetal circulating (cord blood) 25-OH-D concentrations.^{117–120} With severe maternal vitamin D deficiency, the fetus may rarely develop rickets in utero and manifest this deficiency at birth.⁷¹ Supplementation with 400 IU of vitamin D per day during the last trimester of pregnancy has minimal effect on circulating 25-OH-D concentrations in the mother and her infant at term.¹¹² An unsupplemented infant born to a vitamin D–deficient mother will reach a state of deficiency more quickly than an infant whose mother was replete during pregnancy.⁷¹

Adequate nutritional vitamin D status during pregnancy is important for fetal skeletal development, tooth enamel formation, and perhaps general fetal growth and development.¹²¹ There is some evidence that the vitamin D status of the mother has long-term effects on her infant. In a recent Canadian study by Mannion et al comparing growth parameters in newborn infants with the maternal intakes of milk and vitamin D during pregnancy, investigators found an association between vitamin D intake during pregnancy and birth weight but not infant head circumference or length at birth.¹²² With every additional 40 IU of maternal vitamin D intake, there was an associated 11-g increase in birth weight. Another study of the intrauterine effect of maternal vitamin D status revealed a significant association between umbilical cord 25-OH-D concentrations and head circumference at 3 and 6 months' postnatal age that persisted after adjustment for confounding factors.^{109,111} A study performed in the United Kingdom during the 1990s demonstrated that higher maternal vitamin D status during pregnancy was associated with improved bone-mineral content and bone mass in children at 9 years of age.¹²³

Given the growing evidence that adequate maternal vitamin D status is essential during pregnancy, not only for maternal well-being but also for fetal development,^{71,122,124,125} health care professionals who provide obstetric care should consider assessing maternal vitamin D status by measuring the 25-OH-D concentrations of pregnant women. On an individual basis, a mother should be supplemented with adequate amounts of vitamin D₃ to ensure that her 25-OH-D levels are in a sufficient range (>80 nmol/L).^{25,26,64,66,67} The knowledge that prenatal vitamins containing 400 IU of vitamin D₃ have little effect on circulating maternal 25-OH-D concentrations, especially during the winter months, should be imparted to all health care professionals involved in the care of pregnant women.^{26,64,71,115}

THE EFFECT OF MATERNAL VITAMIN D SUPPLEMENTATION DURING LACTATION ON THE VITAMIN D STATUS OF THE BREASTFED INFANT

The vitamin D content of human milk (parental vitamin D compound plus 25-OH-D) is related to the lactating mother's vitamin D status.^{71–74,126} In a lactating mother supplemented with 400 IU/day of vitamin D, the vitamin

D content of her milk ranges from <25 to 78 IU/L.^{73,74,126–129} Infants who are exclusively breastfed but who do not receive supplemental vitamin D or adequate sunlight exposure are at increased risk of developing vitamin D deficiency and/or rickets.^{7,10–12,14,18,81,130} Infants with darker pigmentation are at greater risk of vitamin D deficiency,¹³¹ a fact explained by the greater risk of deficiency at birth¹³² and the decreased vitamin D content in milk from women who themselves are deficient.¹²⁷

A small number of studies have examined the effect of higher maternal supplements of vitamin D on the 25-OH-D concentrations in breastfed infants. Supplements of 1000 to 2000 IU of vitamin D per day to nursing mothers have little effect on the breastfeeding infant's vitamin D status as measured by infant 25-OH-D concentrations.^{81,133,134} In 2 recent pilot studies that involved lactating women supplemented with high-dose vitamin D (up to 6400 IU/day), the vitamin D content of the mothers' milk increased to concentrations as high as 873 IU/L without any evidence of maternal vitamin D toxicity.^{73,74} The 25-OH-D concentrations in breastfed infants of mothers who received 6400 IU/day of vitamin D increased from a mean concentration of 32 to 115 nmol/L. These results compared favorably with infants receiving 300 to 400 IU of vitamin D per day, whose 25-OH-D concentrations increased from a mean of 35 to 107 nmol/L. Although vitamin D concentrations can be increased in milk of lactating women by using large vitamin D supplements, such high-dose supplementation studies in lactating women must be validated and demonstrated to be safe in larger, more representative populations of women across the United States. Recommendations to universally supplement breastfeeding mothers with high-dose vitamin D cannot be made at this time. Therefore, supplements given to the infant are necessary.

VITAMIN D SUPPLEMENTATION FOR BREASTFEEDING INFANTS

Although it is clear and incontrovertible that human milk is the best nutritive substance for infants during the first year,^{135–137} there has been concern about the adequacy of human milk in providing vitamin D.^{70,138} As such, the AAP published its 2003 vitamin D supplementation statement,¹ recommending that all breastfed infants start to receive 200 IU of vitamin D per day within the first 2 months after delivery.

With improved understanding of the detrimental effects of insufficient vitamin D status before the appearance of rickets, studies in North America are continuing to examine the vitamin D status of children and appropriate 25-OH-D serum concentrations. A 2003 report of serum 25-OH-D status in healthy 6- to 23-month-old children in Alaska revealed that 11% had concentrations of <37 nmol/L and 20% had concentrations of 37 to 62 nmol/L.^{139,140} Thirty percent of the infants were still breastfeeding, and these infants were more likely to have serum 25-OH-D concentrations of <37 nmol/L. After this study, the Alaskan Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) began an initiative to actively identify breastfeeding chil-

TABLE 2 Oral Vitamin D Preparations Currently Available in the United States (in Alphabetical Order)

Preparation ^a	Dosage
Bio-D-Mulsion (Biotics Research Laboratory, Rosenberg, TX; www.bioticsresearch.com)	1 drop contains 400 IU ^b ; also comes in a preparation of 2000 IU per drop ^b ; corn oil preparation
Carlson Laboratories (Arlington Heights, IL; www.carlsonlabs.com)	1 gel cap contains 400 IU; also comes in 2000-IU and 4000-IU gel caps and in single-drop preparations of 400-IU, 1000-IU, and 2000-IU ^b ; safflower oil preparation
Just D (Sunlight Vitamins Inc [Distributed by UnitDrugCo, Centennial, CO]; www.sunlightvitamins.com)	1 mL contains 400 IU; corn oil preparation
Multivitamin preparations: polyvitamins (A, D, and C vitamin preparations) ^c	1 mL contains 400 IU; variable preparations that include glycerin and water; may also contain propylene glycol and/or polysorbate 80

Note that higher-dose oral preparations may be necessary for the treatment of those with rickets in the first few months of therapy or for patients with chronic diseases such as fat malabsorption (cystic fibrosis) or patients chronically taking medications that interfere with vitamin D metabolism (such as antiepileptic medications).

^a A study by Martinez et al¹⁶² showed that newborn and older infants preferred oil-based liquid preparations to alcohol-based preparations.

^b Single-drop preparation may be better tolerated in patients with oral aversion issues, but proper instruction regarding administration of these drops must be given to the parents or care provider, given the increased risk of toxicity, incorrect dosing, or accidental ingestion.

^c The cost of vitamin D-only preparations may be more than multivitamin preparations and could be an issue for health clinics that dispense vitamins to infants and children. The multivitamin preparation was the only preparation available until recently; therefore, there is a comfort among practitioners in dispensing multivitamins to all age groups.

dren and provide free vitamin supplements for them and a vitamin D fact sheet for their mothers. Another recent study by Ziegler et al¹⁴¹ assessed the vitamin D status of 84 breastfeeding infants in Iowa (latitude 41°N). In the 34 infants who received no supplemental vitamin D, 8 (23%) infants had a serum 25-OH-D concentration of <27 nmol/L at 280 days of age. Of these 8 low measurements, 7 were made in the winter months (November through April). Thus, at this time it is prudent to recommend that all breastfed infants be given supplemental vitamin D₃.

The 2003 AAP statement recommended supplements of 200 IU of vitamin D per day to all breastfed infants within the first 2 months of life, after breastfeeding was well established.¹ This was in agreement with a 1997 report from the Institute of Medicine.⁵¹ This report's recommendation of 200 IU/day was largely based on a study that showed that among breastfed infants in northern China supplemented with 100 or 200 IU of vitamin D per day, there were no cases of rickets.¹⁴² However, 17 of 47 infants and 11 of 37 infants receiving 100 or 200 IU of vitamin D per day, respectively, had serum concentrations of 25-OH-D at <27 nmol/L. Although corollary maternal serum concentrations were not measured, on the basis of vitamin D pharmacokinetics, maternal vitamin D status is assumed to have been abnormally low, thereby preventing adequate transfer of vitamin D in human milk. When the breastfeeding mother has marginal vitamin D status or frank deficiency, infant 25-OH-D concentrations are very low in unsupplemented infants, particularly in the winter months in latitudes further from the equator. It is clear that 25-OH-D concentrations of >50 nmol/L can be maintained in exclusively breastfed infants with supplements of 400 IU/day of vitamin D, which is the amount contained in 1 teaspoon of cod liver oil^{52,54} and for which there is historic precedence of safety and prevention and treatment of rickets.^{5,6,143}

Thus, given the evidence that (1) vitamin D deficiency can occur early in life, especially when pregnant women are deficient, (2) 25-OH-D concentrations are very low in unsupplemented breastfeeding infants, par-

ticularly in the winter months when mothers have marginal vitamin D status or are deficient, (3) that the amount of sunshine exposure necessary to maintain an adequate 25-OH-D concentration in any given infant at any point in time is not easy to determine, and (4) serum 25-OH-D concentrations are maintained at >50 nmol/L in breastfed infants with 400 IU of vitamin D per day, the following recommendation is made: A supplement of 400 IU/day of vitamin D should begin within the first few days of life and continue throughout childhood. Any breastfeeding infant, regardless of whether he or she is being supplemented with formula, should be supplemented with 400 IU of vitamin D, because it is unlikely that a breastfed infant would consume 1 L (~1 qt) of formula per day, the amount that would supply 400 IU of vitamin D.

FORMS OF VITAMIN D SUPPLEMENTS

There are 2 forms of vitamin D that have been used as supplements: vitamin D₂ (ergocalciferol, which is plant derived) and vitamin D₃ (cholecalciferol, which is fish derived). It has been shown that vitamin D₃ has greater efficacy in raising circulating 25-OH-D concentrations under certain physiological situations.¹⁴⁴ Most fortified milk products and vitamin supplements now contain vitamin D₃. Vitamin D-only preparations are now available in the United States, in addition to the multivitamin liquids supplements, to provide the appropriate concentrations of 400 IU/mL (see Table 2). Some also contain 400 IU per drop, but such preparations must be prescribed with caution; explicit instruction and demonstration of use are essential because of the greater potential for a vitamin D overdose if several drops are administered at once.

The new vitamin D-only preparations are particularly appropriate for the breastfed infant who has no need for multivitamin supplements. The cost of purchase and administration of vitamin D either alone or in combination with vitamins A and C (as it is currently constituted) is minimal. Pediatricians and other health care professionals should work with the Special Supplemental Nutrition Program for Women, Infants, and Children

clinics to make vitamin D supplements available for breastfeeding infants. Current preparations, assuming correct administration of dosage by caregivers, place the infant at little risk of overdosage and vitamin D toxicity, although this must be considered. Care must be taken by health care professionals to provide explicit instructions regarding the correct dosage and administration.¹⁴⁵ Preparations that contain higher concentrations of vitamin D should only be prescribed in the setting of close surveillance of vitamin D status and for those who have such a demonstrated requirement (eg, those who suffer from fat malabsorption or who must chronically take antiseizure medication).

FORMULA-FED INFANTS AND VITAMIN D SUPPLEMENTS

All infant formulas sold in the United States must have a minimum vitamin D concentration of 40 IU/100 kcal (258 IU/L of a 20 kcal/oz formula) and a maximum vitamin D₃ concentration of 100 IU/100 kcal (666 IU/L of a 20 kcal/oz formula).¹⁴⁶ All formulas sold in the United States have at least 400 IU/L of vitamin D₃.¹⁴⁷ Because most formula-fed infants ingest nearly 1 L or 1 qt of formula per day after the first month of life, they will achieve a vitamin D intake of 400 IU/day. As mentioned earlier, infants who receive a mixture of human milk and formula also should get a vitamin D supplement of 400 IU/day to ensure an adequate intake. As infants are weaned from breastfeeding and/or formula, intake of vitamin D–fortified milk should be encouraged to provide at least 400 IU/day of vitamin D. Any infant who receives <1 L or 1 qt of formula per day needs an alternative way to get 400 IU/day of vitamin D, such as through vitamin supplements.

VITAMIN D SUPPLEMENTS DURING LATER CHILDHOOD AND ADOLESCENCE

As was mentioned earlier, there is active debate among vitamin D experts as to what constitutes vitamin D “sufficiency,” “insufficiency,” and “deficiency” in adults and children as defined by 25-OH-D serum concentrations.‡ Vitamin D deficiency is not limited to infancy and early childhood but covers the life span, with periods of vulnerability that mirror periods of accelerated growth or physiologic change. In fact, vitamin D deficiency in older children and adolescents continues to be reported worldwide.§ Recent studies of vitamin D status have shown that 16% to 54% of adolescents have serum 25-OH-D concentrations of ≤ 50 nmol/L.^{9,85–88,90,94,150–152} In 1 study that used the adult definition of insufficiency of a serum 25-OH-D concentration of <80 nmol/L, 73.1% of adolescents demonstrated values below this concentration.¹⁵³ In examining the prevalence of vitamin D deficiency in adolescents, studies across North America have shown that serum 25-OH-D concentrations of <30 nmol/L occur in as few as 1% to as many as 17% of adolescents, depending on the subjects themselves and the latitude and season of measurement.^{3,86,87,151,152} All of these studies found black adolescents to have signifi-

cantly lower 25-OH-D status than individuals who are not black. Although there have been no large series of adolescents with vitamin D–deficiency rickets, cases continue to occur.¹⁵

The inverse relationship of increasing PTH with decreasing 25-OH-D concentrations has been demonstrated in older children and adolescents.^{9,152} A study of vitamin D insufficiency in 6- to 10-year-old preadolescent black children in Pittsburgh, PA, revealed that serum PTH concentrations decreased with increasing serum 25-OH-D concentrations and reached a plateau when the serum 25-OH-D concentration was ≥ 75 nmol/L.¹⁵⁰ In Boston, MA, Gordon et al¹⁵² found that 24.1% of healthy teenagers in their cross-sectional cohort were vitamin D deficient (25-OH-D concentration ≤ 37 nmol/L), of whom 4.6% were severely deficient (25-OH-D concentration ≤ 20 nmol/L) and 42% were vitamin D insufficient (25-OH-D concentration ≤ 50 nmol/L). There was an inverse correlation between serum 25-OH-D and PTH concentrations ($R = -0.29$). Concentrations of 25-OH-D also were related to season, ethnicity, milk and juice consumption, BMI, and physical activity, which were independent predictors of vitamin D status.

Similar results were found by Cheng et al⁸⁹ in their cohort of pubertal and prepubertal Finnish girls. These investigators also found a significantly lower cortical volumetric bone-mineral density of the distal radius and tibial shaft in girls with vitamin D deficiency (as defined by 25-OH-D concentrations ≤ 25 nmol/L). These results are supported by the work of Viljakainen et al⁵⁸ in their study of 212 Finnish early-adolescent (aged 11–12 years) girls who were randomly assigned to receive 0, 200, or 400 IU of vitamin D per day for 12 months. After 1 year, bone-mineral augmentation of the femur was 14.3% and 17.2% higher in the girls receiving 200 and 400 IU of vitamin D, respectively, compared with those in the placebo group.

The extent of vitamin D deficiency has been suggested by reports from other regions of the world, including children and adolescents living in northern Greece⁹⁴ and Germany⁵⁷ and adolescents in Beijing,¹⁵³ Turkey,⁸⁸ Finland,⁵⁸ and Ireland.⁹⁵ With lower 25-OH-D concentrations correlating with increased PTH concentrations, vitamin D deficiency could result in secondary hyperparathyroidism. This condition would deplete the bone of mineral, especially during periods of accelerated bone growth, and lead to long-term detrimental effects.

In evaluating bone mineralization as a function of vitamin D status in adolescents, several studies in the United States and Europe have demonstrated an unfavorable effect of lower 25-OH-D concentrations on bone health.^{58,89,154,155} Adolescent girls with serum 25-OH-D concentrations of >40 nmol/L have demonstrated increased radial, ulnar, and tibial bone-mineral densities,¹⁵² although studies have demonstrated inconsistent findings in other body sites.¹⁵⁴ Additional studies are needed to identify the serum 25-OH-D status that promotes optimal bone health in older children and adolescents.

Although consuming 1 qt (32 oz) of vitamin D–forti-

‡Refs 6, 9, 56, 64, 66, 67, 94, 132, and 148–150.

§Refs 9, 57, 58, 85–89, 94–96, and 150–154.

fied milk will provide 400 IU of vitamin D₃ per day, it is clear that in the adolescent population, the intake of vitamin D–fortified milk is much less.^{155–157} In the United States, milk intake decreased by 36% among adolescent girls from 1977–1978 to 1994–1998.¹⁵⁶ Fortified cereals (½-cup dry) and 1 egg (yolk) will each provide approximately 40 IU of vitamin D₃. Given the dietary practices of many children and adolescents, a dietary intake of 400 IU of vitamin D is difficult to achieve.¹⁵⁷ Thus, for older children and adolescents, a daily multivitamin or vitamin D–only preparation containing 400 IU of vitamin D would be warranted. Additional studies are needed to evaluate what the optimal vitamin D status in older children and adolescents is and whether this level can be achieved consistently through diet and a vitamin D supplement of 400 IU/day.

Along with adequate vitamin D intake, dietary calcium intake to achieve optimal bone formation and modeling must be ensured.⁸⁷ A dietary history is essential in assessing the adequacy of dietary intake for various vitamins, minerals, and nutrients, including vitamin D and calcium.^{3,91} Children and adolescents at increased risk of developing rickets and vitamin D deficiency, including those with increased skin pigmentation, decreased sunlight exposure, chronic diseases characterized by fat malabsorption (cystic fibrosis, etc), and those who require anticonvulsant medications (which induce cytochrome P450 and other enzymes that may lead to catabolism of vitamin D) may require even higher doses than 400 IU/day of vitamin D.^{158–161}

SUMMARY GUIDELINES

To prevent rickets and vitamin D deficiency in healthy infants, children, and adolescents, a vitamin D intake of at least 400 IU/day is recommended. To meet this intake requirement, we make the following suggestions:

1. Breastfed and partially breastfed infants should be supplemented with 400 IU/day of vitamin D beginning in the first few days of life. Supplementation should be continued unless the infant is weaned to at least 1 L/day or 1 qt/day of vitamin D–fortified formula or whole milk. Whole milk should not be used until after 12 months of age. In those children between 12 months and 2 years of age for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk would be appropriate.¹⁶³
2. All nonbreastfed infants, as well as older children who are ingesting <1000 mL/day of vitamin D–fortified formula or milk, should receive a vitamin D supplement of 400 IU/day. Other dietary sources of vitamin D, such as fortified foods, may be included in the daily intake of each child.
3. Adolescents who do not obtain 400 IU of vitamin D per day through vitamin D–fortified milk (100 IU per 8-oz serving) and vitamin D–fortified foods (such as fortified cereals and eggs [yolks]) should receive a vitamin D supplement of 400 IU/day.

4. On the basis of the available evidence, serum 25-OH-D concentrations in infants and children should be ≥50 nmol/L (20 ng/mL).
5. Children with increased risk of vitamin D deficiency, such as those with chronic fat malabsorption and those chronically taking antiepileptic medications, may continue to be vitamin D deficient despite an intake of 400 IU/day. Higher doses of vitamin D supplementation may be necessary to achieve normal vitamin D status in these children, and this status should be determined with laboratory tests (eg, for serum 25-OH-D and PTH concentrations and measures of bone-mineral status). If a vitamin D supplement is prescribed, 25-OH-D levels should be repeated at 3-month intervals until normal levels have been achieved. PTH and bone-mineral status should be monitored every 6 months until they have normalized.
6. Pediatricians and other health care professionals should strive to make vitamin D supplements readily available to all children within their community, especially for those children most at risk.

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