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# Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations

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## ABSTRACT

Given the recent spate of reports of vitamin D deficiency, there is a need to reexamine our understanding of natural and other sources of vitamin D, as well as mechanisms whereby vitamin D synthesis and intake can be optimized. This state-of-the-art report from the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society was aimed to perform this task and also reviews recommendations for sun exposure and vitamin D intake and possible caveats associated with these recommendations. *Pediatrics* 2008;122:398–417

VITAMIN D IS a prohormone that is essential for normal absorption of calcium from the gut, and deficiency of vitamin D is associated with rickets in growing children and osteomalacia in adults. Rickets is the failure of mineralization of growing bone and cartilage. Initial descriptions of rickets were provided by Daniel Whistler and Francis Glisson in England as early as the 17th century. At the turn of the 20th century, with industrialization, this disease became endemic until it was discovered that exposure to sunlight and cod liver oil could both prevent and treat rickets.<sup>1,2</sup> Once vitamin D was identified and easy ways to supplement foods were developed, nutritional rickets almost disappeared from industrialized countries.<sup>1–3</sup> However, there has been a reappearance of rickets from vitamin D deficiency in recent decades as a result of multiple factors, which we will discuss in the course of this review. Dark-skinned infants who are exclusively breastfed and infants born to mothers who were vitamin D deficient through pregnancy seem to be at particularly high risk. However, rickets is also being reported in older children.

In North America and the United Kingdom, there are no current definitive prevalence estimates available for vitamin D–deficiency rickets because recent publications have been mainly case reports or case series obtained from hospital admissions records. The 2 largest series reported 126 cases over a period of 10 years in Australia<sup>4</sup> and 104 cases over 2 years in Canada.<sup>5</sup> Reported and published cases of nutritional rickets in the United States increased from 65 between 1975 and 1985 to 166 between 1986 and 2003.<sup>6</sup> Since then, 3 reports added another 62 cases to the American literature.<sup>7–9</sup> It should also be recognized that in other parts of the world, nutritional rickets remains a public health problem.<sup>10–13</sup>

In 2003, the American Academy of Pediatrics (AAP) recommended a vitamin D supplement for (1) breastfed infants who do not consume at least 500 mL of a vitamin D–fortified formula/beverage<sup>14</sup> and (2) nonbreastfed infants who do not consume >500 mL of vitamin D–fortified beverages. The supplementation should start during the first 2 months of life and continue throughout childhood and adolescence. The rationale for this timing is that vitamin D stores in the newborn, which are obtained through transplacental passage from the vitamin D–replete mother, should last for at least 8 weeks after delivery given that the half-life of serum 25(OH)-vitamin D [25(OH)-D] is ~2 to 3 weeks.<sup>15</sup> In a term infant born to a vitamin D–replete mother, the supply of vitamin D may last even longer (8–12 weeks) given the storage of vitamin D in fat. In the United States, all infant formulas are mandated to contain 40 to 100 IU of vitamin D per 100 kcal (1 kcal = 4.2 kJ) of formula (258–666 IU of vitamin D per L of a 20 kcal/oz formula<sup>14,16</sup>) and, in fact, all contain at least 400 IU/L of vitamin D.<sup>17</sup> Thus, daily intake of at least 500 mL of vitamin D–fortified formula would ensure the required minimum daily intake of vitamin D of 200 IU/day. However, despite current guidelines for vitamin D supplementation, rickets continues to be reported.

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This review was developed to be of educational value to practitioners; it should not be construed as indicating official policy or guidelines of the Lawson Wilkins Pediatric Endocrine Society.

### Key Words

food fortification, breastfeeding, calcium, supplements, vitamin D

### Abbreviations

AAP—American Academy of Pediatrics  
25(OH)-D—25(OH)-vitamin D  
UVR—ultraviolet radiation  
PTH—parathyroid hormone  
1,25(OH)<sub>2</sub>-D—1,25-dihydroxy vitamin D  
ALP—alkaline phosphatase  
DBP—vitamin D–binding protein  
24,25(OH)<sub>2</sub>-D—24,25-dihydroxy vitamin D  
MED—minimum erythema dose  
mAb—monoclonal antibody  
HPLC—high-pressure liquid chromatography  
SPF—sun protection factor

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**TABLE 1 Biochemical Manifestations of Different Stages of Vitamin D Deficiency**

	Plasma Ca <sup>++</sup>	Plasma PO <sub>4</sub>	ALP	PTH	25(OH)-D	1,25(OH) <sub>2</sub> -D	Radiograph Changes
Early	N/↓	N/↓	↑	↑	↓	N	Osteopenia
Moderate	N/↓	↓	↑↑	↑↑	↓↓	↑	Rachitic changes +
Severe	↓↓	↓↓	↑↑↑	↑↑↑	↓↓↓	↑/N/↓	Rachitic changes ++

N indicates normal; ↑, increase; ↓, decrease. + mild changes, ++ moderate to severe changes

Adapted with permission from Levine M, Zapalowski C, Kappy M. Disorders of calcium, phosphate, PTH and vitamin D metabolism. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:762.

It is important to recognize that vitamin D is primarily made in the skin after exposure to ultraviolet radiation (UVR), and <10% is derived from dietary sources.<sup>18</sup> Modern conditions of dress, lifestyle, and recommendations regarding sun avoidance to reduce risks of skin cancer may prevent a large proportion of the population from making healthy amounts of this vitamin. Over the last 2 decades, our understanding of vitamin D synthesis and its functions has increased markedly. This improved understanding and the many reports of vitamin D–deficiency rickets require us to reexamine traditional concepts and current recommendations for vitamin D supplementation and sun exposure and to develop revised management strategies. In this review we discuss the causes of vitamin D deficiency, particularly in relation to natural and artificial sunblocks and maternal vitamin D status, and current knowledge regarding prevention and treatment of vitamin D deficiency.

### EFFECT OF VITAMIN D DEFICIENCY

#### Calcium and Phosphorus Metabolism and Bone

In a vitamin D–sufficient state [25(OH)-D levels of >50 nmol/L (20 ng/mL)], net intestinal calcium absorption is up to 30%, although calcium absorption can reach 60% to 80% during periods of active growth. In a vitamin D–deficient state, intestinal calcium absorption is only ~10% to 15% and there is a decrease in the total maximal reabsorption of phosphate. In conditions of vitamin D deficiency,<sup>19</sup> low ionized calcium levels stimulate parathyroid hormone (PTH) secretion, which (1) increases calcium reabsorption in renal tubules and (2) increases 1- $\alpha$ -hydroxylase activity, which causes increased 1,25-dihydroxy vitamin D [1,25(OH)<sub>2</sub>-D] synthesis. Increased PTH levels also cause phosphorus loss in urine. Decreased levels of phosphorus (and also calcium) and decreased calcium\*phosphorus product result in decreased bone mineralization. In addition, the low phosphorus levels cause a failure of the expected apoptosis of hypertrophied chondrocytes, with cellular “ballooning” and disorganization of the growth plate. Failure or delay of calcification of osteoid leads to osteomalacia in mature bones. Osteomalacia in immature bones is referred to as rickets. The term rickets also describes the abnormal organization of the cartilaginous growth plate and the accompanying impairment of cartilage mineralization.

The clinical presentation of vitamin D–deficiency rickets includes symptoms and signs of bone deformity and/or pain and may be associated with hypocalcemia and associated clinical features.<sup>20</sup> The disease can be divided into 3 stages (Table 1). The first stage is charac-

terized by osteopenia and subclinical or overt hypocalcemia (usually very transitory and, therefore, undocumented), which is followed in the second stage by rising levels of PTH. Increases in PTH levels cause calcium mobilization from bone and correction of hypocalcemia. Demineralized collagen matrix is prone to hydration and swelling, which causes the periosteal covering to expand outward, and bone pain occurs, mediated by periosteal sensory pain fibers. In the final stage, bone changes become more severe, and hypocalcemia once again becomes evident.

Symptoms of rickets can range from none to varying degrees of irritability, delay in gross motor development, and bone pain. Signs include widening of the wrists and ankles, genu varum or valgum, prominence of the costochondral junctions (rachitic rosary), delayed closure of fontanelles, craniotabes, and frontal bossing. Tooth eruption may be delayed and tooth enamel may be of poor quality if vitamin D deficiency occurs in utero or in early infancy, increasing the risk for caries. Rickets also may be associated with poor growth (a manifestation of associated bone disease) and an increased susceptibility to infections.

Vitamin D deficiency that presents as hypocalcemic seizures or tetany is reported more frequently in infancy and adolescence than in childhood. At these periods of increased growth velocity, the increased demand for calcium cannot be met in a timely fashion, and the patient may present with hypocalcemia even before bone demineralization or radiologic signs of rickets are observed.<sup>21,22</sup> During childhood, lower metabolic demand allows the body to avoid symptomatic hypocalcemia by drawing on bone stores of calcium secondary to hyperparathyroidism in the second stage of the disease. However, this occurs at the expense of depleting bone of its calcium, which results in signs of demineralization and subsequent bone deformity.<sup>22</sup> Children with vitamin D deficiency who are hypocalcemic may manifest clinical features associated with hypocalcemia per se such as apneic spells, stridor or wheezing, hypotonia, muscular weakness, and brisk reflexes. Severe vitamin D deficiency also may be associated with cardiomyopathy related to hypocalcemia, which normalizes with treatment.<sup>23</sup>

The diagnosis of rickets depends on presence of the clinical features mentioned above and radiologic and laboratory features. Radiologic images may indicate osteopenia and cortical thinning of long bones, stress fractures, and metaphyseal widening and fraying. The earliest sign is usually osteopenia followed by a widening of

**FIGURE 1**

Vitamin D–deficiency rickets at presentation (upper) and 3 months after vitamin D and calcium therapy (lower) in a 1-year old black boy. At presentation, radiographs of the wrist (left) and knee (right) showed evidence of splaying, fraying, cupping, and demineralization of the distal radial and ulnar metaphyses, the distal metaphysis of the femur, and proximal metaphyses of the tibia and fibula. There was widening of the physis. After therapy, the child showed evidence of near-complete resolution of metaphyseal fraying with interval development of a dense provisional zone of calcification in the metaphysis consistent with healing rickets.



the growth plate from proliferation of uncalcified cartilage and osteoid, followed by metaphyseal widening, splaying, cupping, and fraying (Fig 1). A coarse trabecular pattern is observed of the metaphysis. The earliest rachitic change is a loss of demarcation between the metaphysis and growth plate and loss of the provisional zone of calcification.<sup>20</sup> A 10-point radiographic scoring system was developed to aid in assessment of the severity of rickets on the basis of knee and wrist findings<sup>24</sup> (Table 2). Laboratory findings include hypophosphatemia, varying degrees of hypocalcemia, increased alkaline phosphatase (ALP), and increased PTH levels. Low levels of 25(OH)-D confirm the diagnosis but may not be necessary when other clinical, radiologic, and laboratory findings are unequivocal. Levels of 1,25(OH)<sub>2</sub>-D may become elevated as PTH levels rise, with a concomitant increase in 1- $\alpha$ -hydroxylase activity. Table 1 summarizes laboratory findings in the 3 stages of vitamin D–deficiency rickets.<sup>25</sup>

#### **Extraskeletal Effects of Vitamin D**

The vitamin D receptor is present in the small intestine, colon, osteoblasts, activated T and B lymphocytes,  $\beta$  islet cells, and most organs in the body such as the brain, heart, skin, gonads, prostate, breast, and mononuclear cells. Epidemiologic studies over the last 2 decades have suggested important effects of vitamin D on the immune system and in preventing certain cancers; these findings are summarized below. Although these findings have generated great interest, the possibility of confounding

variables needs to be considered. It is important to note that adjusted attributable risk calculated from multivariate models remains considerable for many cancers in conditions of vitamin D deficiency.<sup>26</sup> Long-term prospective studies examining the effects of vitamin D supplementation in preventing immune-mediated conditions and cancers that may be related to vitamin D deficiency are awaited.

#### *Skin*

Keratinocytes express the vitamin D receptor, and when these cells are exposed to vitamin D, their growth is inhibited and they are stimulated to differentiate.<sup>27</sup> This has led to the use of topical vitamin D analogs to treat psoriasis.<sup>28</sup>

#### *Immune Effects*

Vitamin D modulates B- and T-lymphocyte function.<sup>29,30</sup> Epidemiologic evidence exists of vitamin D deficiency being associated with autoimmune diseases such as type 1 diabetes and multiple sclerosis.<sup>31,32</sup> One-year-old vitamin D–deficient children have been reported to be at a fourfold higher risk of developing type 1 diabetes than vitamin D–sufficient children.<sup>33</sup> Also, the risk for multiple sclerosis is higher in people who live above 35° latitudes than in those who live below this latitude,<sup>34</sup> and an inverse relationship has been reported between vitamin D concentrations and risk of multiple sclerosis.<sup>35</sup>

**TABLE 2 Radiographic Features of Rickets (a 10-Point Scoring System)**

Wrist <sup>a</sup> : Score both the radius and the ulna separately	
Grade	Radiographic features
1	Widened growth plate, irregular metaphyseal margins, but without concave cupping
2	Metaphyseal concavity with fraying of margins
2 bones × 2 points = 4 points possible	
Knee <sup>a</sup> : Score both the femur and tibia separately	
Multiply grade in A by the multiplier in B for each bone, and then add femur and tibia scores	
A	
Grade	Degree of lucency and widening of zone of provisional calcification
1	Partial lucency, smooth margin of metaphysis visible
2	Partial lucency, smooth margin of metaphysis not visible
3	Complete lucency, epiphysis appears widely separated from distal metaphysis
B	
Multiplier	
0.5	≤1 condyle or plateau
1	2 condyles or plateaus
2 bones × 1 point × 3 points = 6 points possible	
Total: 10 points possible	

<sup>a</sup> Score the worst knee and the worse wrist.

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Data suggest that vitamin D–sufficient states in the mother and infant may protect against type 1 diabetes<sup>36</sup> and multiple sclerosis.<sup>37</sup> Protective effects of vitamin D supplementation have also been demonstrated against rheumatoid arthritis<sup>38</sup> and inflammatory bowel disease.<sup>39</sup>

### Cancer

Vitamin D concentrations of >75 nmol/L (30 ng/mL) keep cell growth in check and prevent cells from becoming autonomous and developing into unregulated cancer,<sup>40–42</sup> and vitamin D deficiency has been related to breast, prostate, and colon cancer.<sup>43–48</sup>

### Psychiatric Conditions

Adequate vitamin D levels in pregnancy are associated with decreased risk of schizophrenia<sup>49</sup>; conversely, low levels of sun exposure are associated with seasonal affective disorder<sup>50</sup> and mood disturbances.<sup>51</sup> It is unclear, however, whether it is decreased sun exposure or deficiency of vitamin D that is related to the latter conditions. Vitamin D–sufficient states in the mother and infant are thought to be associated with a lower risk of bipolar disorder.<sup>52</sup> Low maternal vitamin D levels may have an impact on fetal brain maturation, given that vitamin D is also involved in development and functioning of the nervous system.<sup>53</sup>

### SOURCES OF VITAMIN D

Most circulating vitamin D is synthesized from skin exposure to ultraviolet B (UV-B) radiation.

### Cutaneous Vitamin D Synthesis

Vitamin D synthesis by the skin is the main source of this prohormone for most people. Vitamin D<sub>2</sub> (ergocalciferol) is plant derived, whereas vitamin D<sub>3</sub> (cholecalciferol)

is synthesized by animals. Fig 2 reviews the process of vitamin D synthesis. 7-Dehydrocholesterol (provitamin D) is a relatively rigid, 4-ringed structure present in the lipid bilayer of the plasma membrane of epidermal keratinocytes and dermal fibroblasts.<sup>54</sup> The highest concentrations of 7-dehydrocholesterol are found in the stratum basale and stratum spinosum of the epidermis; thus, these layers have the greatest capability of provitamin D synthesis.<sup>55</sup> Exposure to UV-B in the wavelengths of 290 to 315 nm initiates the synthesis of vitamin D by causing double bonds in the B ring of provitamin D to rearrange, which leads its B ring to open and, thus, converting it to the less rigid provitamin D. Provitamin D isomerizes to vitamin D and then is transferred to extracellular space and dermal capillaries, where it binds with vitamin D–binding protein (DBP). This binding ensures efficient conversion of provitamin D to vitamin D by shifting the equilibrium toward vitamin D. The complex of DBP with vitamin D is transported to the liver for 25-hydroxylation to 25(OH)-D (calcidiol). Although 25(OH)-D is 2 to 5 times as potent as vitamin D, it is not biologically active at physiologic concentrations. 25(OH)-D is released into the circulation and transported to the kidney bound to DBP for 1- $\alpha$ -hydroxylation to 1,25(OH)<sub>2</sub>-D and for 24-hydroxylation to 24,25-dihydroxy vitamin D [24,25(OH)<sub>2</sub>-D].<sup>56</sup> 1,25(OH)<sub>2</sub>-D (calcitriol) is the active form of vitamin D, whereas 24,25(OH)<sub>2</sub>-D has limited, if any, physiologic activity. Nuclear receptors for 1,25(OH)<sub>2</sub>-D are present in >30 tissues. Although specific intracellular binding proteins for 24,25(OH)<sub>2</sub>-D have been identified in healing bone tissue and cartilage at sites of fractures, a role in fracture healing has not yet been demonstrated.<sup>57</sup> Studies have indicated that 1- $\alpha$ -hydroxylation may also occur at sites other than the kidney, such as the alveolar macro-

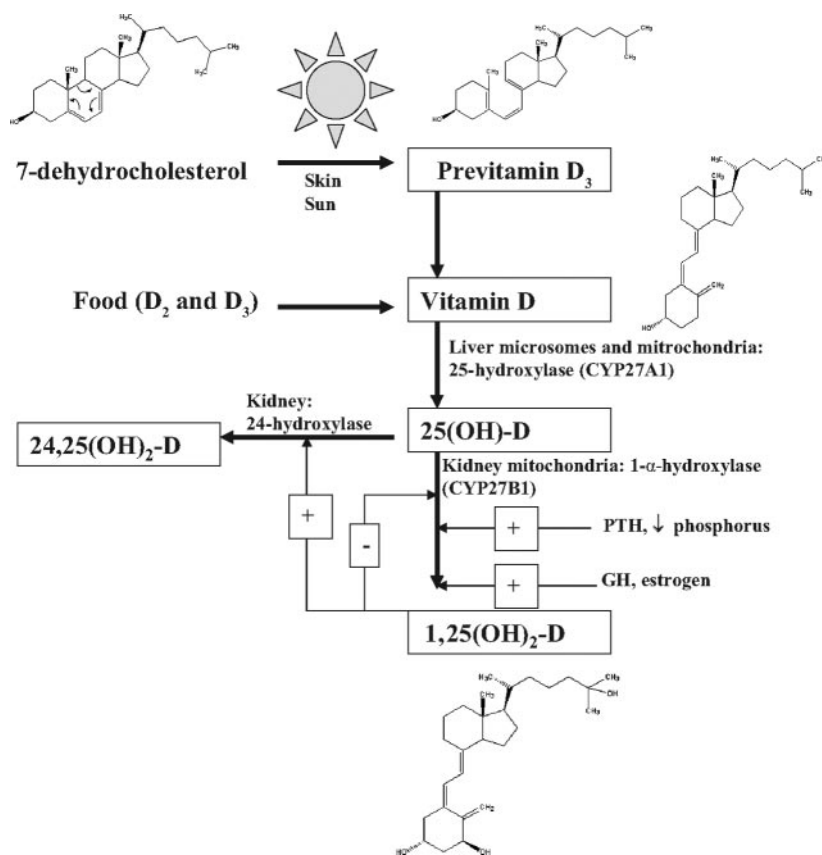


FIGURE 2

Vitamin D synthesis and processing. GH indicates growth hormone. (Adapted with permission from Levine M, Zapalowski C, Kappy M. Disorders of calcium, phosphate, parathyroid hormone and vitamin D metabolism. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:716, 719.)

phages, lymph nodes, placenta, colon, breasts, osteoblasts, activated macrophages, and keratinocytes, which suggests an autocrine-paracrine role for 1,25(OH)<sub>2</sub>-D.

Epidermal melanin is a natural sunscreen that regulates skin color and is synthesized from tyrosine by the enzyme tyrosinase. After exposure to UV-B radiation, melanin granules are transferred from melanocytes in the epidermis to adjacent epidermal cells migrating to the cell surface, which causes darkening of the skin. It takes ~2 weeks for a cell to migrate from the stratum basale to stratum corneum and another 2 weeks for stratum corneum cells to slough off. The concentration of melanin in skin regulates how much UV-B penetrates to reach the epidermal layers with the highest concentrations of 7-dehydrocholesterol (ie, stratum basale and spinosum).<sup>55</sup> Therefore, melanin protects against the risk of skin cancer induced by excessive exposure to UVR and also prevents UVR-induced photolysis of folate, a metabolite necessary for normal development of the embryonic neural tube and spermatogenesis. Therefore, it imparts an evolutionary advantage to dark-skinned people who live in areas of excessive sun exposure.<sup>58</sup> However, a high melanin concentration can cause decreased vitamin D synthesis by preventing UV-B from reaching the stratum basale and spinosum of the epidermis, and this risk becomes manifest in situations of inadequate sun exposure. It is important to note that women of all populations have lighter skin than men, presumably because of increased vitamin D and calcium needs during pregnancy and lactation.<sup>59</sup>

UVR exposure to the skin is measured as the minimum erythema dose (MED) or the amount of UVR exposure that will cause minimal erythema (slight pinkness) of the skin. The amount of UVR exposure that is equivalent to 1 MED depends on skin pigmentation, and duration of exposure is factored into the MED. An entire-body exposure to 1 MED is estimated to result in release of 10 000 to 20 000 IU of vitamin D into the circulation in 24 hours<sup>60,61</sup> (reviewed in ref 56). Exposure of 40% of the body to one-fourth MED will result in generation of ~1000 IU of vitamin D per day, the minimum amount of vitamin D synthesis necessary to maintain concentrations in the reference range.<sup>56</sup>

UV-B (290–315 nm) has a shorter wavelength than UV-A (320–400 nm) and is prone to scatter with oblique rays earlier or later in the day; thus, little vitamin D is produced in the skin at these times even in the summer months.<sup>62</sup> At solar noon (when the sun is at its zenith), the ratio of UV-B to UV-A light is the highest, and the only time that enough UV-B photons reach the earth's surface to produce vitamin D in the skin is between 1000 and 1500 hours in the spring, summer, and the fall. Thus, safe sun exposure at these times is important. Exposure time in the southern United States to achieve 1 MED at solar noon in the summer months is 4 to 10 minutes for pale skin, and 60 to 80 minutes for dark skin.<sup>56</sup> It should be noted that children, and particularly infants, may require less sun exposure to produce sufficient quantities of vitamin D because of greater surface area for size and greater capacity to produce vitamin D

than older people.<sup>63</sup> In 1985, Specker et al<sup>64</sup> reported that 30 minutes of sun exposure per week for infants in diapers and 2 hours of sun exposure per week for fully clothed infants without a hat maintained vitamin D levels of >27.5 nmol/L (11 ng/mL) in Cincinnati, Ohio. However, the duration of UVR exposure that is necessary for infants and children to maintain vitamin D levels at >50 nmol/L (20 ng/mL), the currently accepted level for vitamin D sufficiency in children, particularly in relation to the time of day, season, or skin pigmentation remains to be determined.

Effects of natural sunblocks such as skin pigmentation and geography-related factors (eg, latitude, season, time of day, shade, air pollution) on cutaneous synthesis of vitamin D will be described at greater length under causes of vitamin D deficiency, as will the effects of artificial sunblocks such as clothing and sunscreens. It should be noted that excessive exposure to sunlight does not further increase vitamin D production. Instead, previtamin D<sub>3</sub> is degraded into inert products such as lumisterol-3 and tachysterol-3, and vitamin D<sub>3</sub> photoisomerizes to suprasterol and other inert products, with no effects on calcium metabolism. Previtamin D<sub>3</sub> accumulation is limited to 10% to 15% of the original 7-dehydrocholesterol concentrations because of this photoisomerization during prolonged sun exposure.

The disadvantage of UVR exposure for vitamin D generation is the induction of certain cancers and other health conditions. The risk for skin cancers is increased with excessive sun exposure,<sup>65-69</sup> and the AAP recommends that children younger than 6 months be kept out of direct sunlight to reduce the risks of skin cancer.<sup>70</sup> It is important to note that malignant melanoma and basal cell carcinoma of the skin are more likely to occur after excessive UV-A rather than UV-B exposure.<sup>71-73</sup> Therefore, in contrast to common belief, exposure to the mid-day sun is less likely to cause these skin cancers than similar exposure to the sun early or late in the day. Conversely, actinic keratosis and squamous cell carcinoma are related to lifetime exposure to UV-B. Sunscreens have greater protection against UV-B than UV-A and, thus, protect against the latter skin conditions more so than the former.<sup>74</sup> Chronic sun exposure also damages the elastic structure of the skin, which increases the risk of wrinkling.<sup>75</sup> Of the total global burden of disease, 0.1% is attributable to death and disability resulting from UVR-induced skin cancer, cataracts, cancers and pterygia of the eye, sunburn, and reactivation of viral infections<sup>76</sup> and amounts to an economic burden of \$5 to \$7 billion per year. However, the economic burden from vitamin D deficiency is estimated to be as high as \$40 to \$53 billion in the United States per year<sup>77</sup>; this estimate takes into account the burden of disease from rickets and osteomalacia, associated deformities, bone fractures, muscle weakness, and pneumonia, as well as multiple sclerosis and common cancers associated epidemiologically with vitamin D deficiency such as prostate, colon, and breast cancers.<sup>76</sup> Grant et al<sup>77</sup> estimated that 50 000 to 70 000 US citizens die prematurely each year as a result of cancer related to insufficient vitamin D alone. Thus, economic costs related to vitamin D deficiency

**TABLE 3 Vitamin D Content of Foods**

Food	Vitamin D Content, IU
Cow's milk	3-40/L
Fortified milk/infant formulas	400/L
Fortified orange juice/soy milk/rice milk	400/L
Butter	35/100 g
Margarine, fortified	60/tablespoon
Yogurt (normal, low fat, or nonfat)	89/100 g
Cheddar cheese	12/100 g
Parmesan cheese	28/100 g
Swiss cheese	44/100 g
Cereal fortified	40/serving
Tofu fortified (1/2 block)	120
Fresh shitake mushrooms	100/100 g
Dried shitake mushrooms (nonradiated)	1660/100 g
Egg yolk	20-25 per yolk
Shrimp	152/100 g
Calf liver	15-50/100 g
Canned tuna/sardines/salmon/mackerel in oil	224-332/100 g
Canned pink salmon with bones in oil	624/100 g
Cooked salmon/mackerel	345-360/100 g
Atlantic mackerel (raw)	360/100 g
Atlantic herring (raw)	1628/100 g
Smoked herring	120/100 g
Pickled herring	680/100 g
Codfish (raw)	44/100 g
Cod liver oil	175/g; 1360/tablespoon

Adapted from [www.nal.usda.gov/fnic/foodcomp/Data/Other/vitLd99.pdf](http://www.nal.usda.gov/fnic/foodcomp/Data/Other/vitLd99.pdf).

around the world may be phenomenal, but the well-known hazards of UVR need to be balanced against many possible benefits.

### Dietary Sources of Vitamin D

#### Natural Sources

Natural sources of vitamin D include oily fish such as salmon, mackerel, and sardines, cod liver oil, liver and organ meats (which, however, have a high cholesterol content), and egg yolks (which have a variable amount of vitamin D). Note that the method used for cooking food can have significant effects on its vitamin D content. For example, frying fish reduces active vitamin D content by ~50%, whereas baking does not affect the vitamin D content of fish. Also, with regards to fish, farm-raised fish may have higher vitamin D content than free-living fish. Table 3 describes the amount of vitamin D available in various foods. In addition, dietary sources of calcium are described in Table 4. Unfortunately, most natural (unfortified) sources of vitamin D are not commonly consumed by children; therefore, fortifying food with vitamin D becomes important if there is inadequate sun exposure.

#### Vitamin D in Breast Milk

Although human milk is the best source of nutrition for term infants, vitamin D content of breast milk is insufficient to meet the recommended intake of vitamin D. Vitamin D content in breast milk averages ~22 IU/L (range: 15-50 IU/L) in a vitamin D-sufficient mother.<sup>78</sup> Assuming an average consumption of 750 mL/day,<sup>79</sup> exclusive breastfeeding without sun exposure would provide only 11 to 38 IU/day of vitamin D, which is far

**TABLE 4 Calcium Content of Foods**

	Serving	Calcium Content, mg
Whole milk	244 g (1 cup)	276
2% reduced-fat milk	244 g (1 cup)	285
1% low-fat milk	244 g (1 cup)	290
Fortified orange juice	1 cup	300
Mozzarella/cheddar/Swiss cheese	30 g (1 oz)	204–224
Cottage cheese, 2% milk fat	226 g (1 cup)	156
Cottage cheese, 1% milk fat	226 g (1 cup)	138
Yogurt, plain, whole milk	227 g (8 oz)	275
Yogurt, plain, low fat	227 g (8 oz)	415
Yogurt, plain, skim milk	227 g (8 oz)	452
Tofu (firm, ¼ block)	81 g	163
Tofu (soft)	120 g (1 piece)	133
Sardines including bones, canned in oil	85 g (3 oz)	325
Pink salmon including bones, canned in oil	85 g (3 oz)	181
Brown or white bread	3 large slices	100
Whole-meal bread	3 large slices	55
Baked beans, canned with sauce	253 g (1 cup)	142
Spinach/collard greens/soybean greens cooked, boiled, drained without salt	180–190 g (1 cup)	245–266
Broccoli/kale cooked, boiled, drained, without salt	130–156 g (1 cup)	62–94
Canned beans such as black-eyed peas, kidney beans, black beans, garbanzo beans	½ cup	35–70
Almonds, dry roasted, whole	⅓ cup	126

Adapted from [www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w301.pdf](http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w301.pdf).

below the recommended minimum intake of 200 IU/day.<sup>14</sup>

#### Food Fortified With Vitamin D

Food-fortification practices vary around the world. Infant formulas in the United States are mandated to contain 40 to 100 IU of vitamin D per 100 kcal, because this range of vitamin D content would be sufficient to meet the recommended daily intake of vitamin D for most infants.<sup>80</sup> In Canada, fortification with vitamin D is mandatory for designated foods such as milk and margarine. However, in the United States, vitamin D fortification of foods is not usually a requirement but is necessary if the label indicates that the food is fortified. Therefore, whereas Canada requires that all milk be vitamin D fortified, in the United States only milk labeled as “vitamin D fortified” is required to contain vitamin D. For milk and orange juice, vitamin D content after fortification should include 400 IU/L. Unfortunately, (1) milk is not uniformly consumed in the United States, (2) given the current and appropriate emphasis on breastfeeding, infant formulas are also not uniformly consumed, and (3) the push to reduce juice consumption as a measure against the rising prevalence of obesity means that orange juice is not as uniformly consumed as it used to be. Therefore, fortification of milk and orange juice does not necessarily imply adequate vitamin D supplementation for the population at large. Calvo et al<sup>81</sup> reviewed the fortification of food with vitamin D in the United States and demonstrated that many food items, including

many dairy products perceived to be fortified with vitamin D, in fact are not fortified. Adding to the variability of vitamin D content of food is (1) the variation in naturally occurring vitamin D depending on season and climatic conditions, (2) the state of flux in fortification of foods in the marketplace, and (3) variations in the procedures used to fortify milk (storage conditions for the vitamin preparation, method used to add vitamin D to milk, point during processing at which point the vitamin D is added).<sup>82</sup> Surveys of compliance of various dairies with vitamin D-fortification regulations in the United States have indicated that many samples are not in compliance, mostly being underfortified.<sup>24,82–84</sup> In Europe, margarine and some cereals are also fortified with vitamin D, and in the United States, mandatory and uniform fortification of cheese, breads, and cereals is being considered.

#### Supplements

Vitamin D supplements with 200 to 1000 IU per pill are available, as are preparations that provide much higher doses. Both vitamin D<sub>2</sub> (ergocalciferol, plant derived) and D<sub>3</sub> (cholecalciferol, animal derived) are used in supplements. Although traditionally D<sub>2</sub> and D<sub>3</sub> have been considered to be equipotent, at least 2 studies have suggested some differences in their potencies. In 1 study in which patients were administered 4000 IU of vitamin D<sub>2</sub> or D<sub>3</sub> for 14 days, 25(OH)-D levels were 1.7 times higher after D<sub>3</sub> than D<sub>2</sub> administration.<sup>85</sup> Another recent study demonstrated longer periods of sustained 25(OH)-D levels after a single large dose (50 000 IU) of vitamin D<sub>3</sub> than vitamin D<sub>2</sub>, attributable in large measure to greater affinity of DBP for 25(OH)-D<sub>3</sub> compared with 25(OH)-D<sub>2</sub>. On the basis of these data, the authors suggested that vitamin D<sub>3</sub> may be at least 3 times more potent than vitamin D<sub>2</sub>.<sup>86</sup> Although most commercial multivitamin preparations contain vitamin D<sub>2</sub> (Drisdol, most children’s chewable multivitamins including Flintstones and Garfield, prenatal and women’s multivitamins), some, such as Poly-Vi-Sol, contain vitamin D<sub>3</sub>. Supplements that contain cholecalciferol may be preferable to those that contain ergocalciferol, particularly when used as a single large dose.

#### RANGES FOR NORMAL AND ABNORMAL BLOOD VITAMIN D CONCENTRATIONS

Unreliability of commonly used vitamin D assays and lack of agreement regarding the definition of a “normal” population has led to some difficulty in the establishment of reference ranges for serum 25(OH)-D concentrations. 25(OH)-D is the major circulating form of vitamin D, and its levels are the best available indicator of total body vitamin D status. The half-life of 25(OH)-D is 2 to 3 weeks, much longer than that of the active metabolite, 1,25(OH)<sub>2</sub>-D, which has a half-life of only 4 hours. The latter is not a good indicator of vitamin D stores, unlike 25(OH)-D, because (1) subtle decreases in calcium concentrations in vitamin D deficiency cause PTH elevations that induce increased 1- $\alpha$ -hydroxylase activity, which results in normal or elevated levels of



1,25(OH)<sub>2</sub>-D, and (2) it normally circulates at concentrations that are 100- to 1000-fold less abundant than 25(OH)-D.

### Pitfalls of Using Standard Reference Ranges Given Currently Available Vitamin D Assays

For recommended reference ranges to be universally applicable, 25(OH)-D assays need to be accurate, reproducible, and internationally standardized. It is also important to interpret reported 25(OH)-D concentrations correctly. A complete description of 25(OH)-D assays is well beyond the scope of this review, and only salient features are mentioned here. Cutaneous vitamin D and most natural food sources of vitamin D are derived from cholecalciferol or vitamin D<sub>3</sub>. Conversely, vitamin D generated from irradiating yeast is ergocalciferol (vitamin D<sub>2</sub>) as is the vitamin D obtained from most supplements in the United States. Both forms are used to fortify food. Therefore, assays used to assess 25(OH)-D levels should be capable of measuring both D<sub>2</sub> and D<sub>3</sub> derivatives. Potential for incorrect diagnosis of deficiency and subsequent overtreatment exists if the assay measures only the natural D<sub>3</sub> derivative. This is particularly so because medicinal vitamin D is usually (although not always) the D<sub>2</sub> form.

Currently used immunoassays with highly specific monoclonal antibodies (mAbs) to 25(OH)-D have proven to be more accurate than older competitive protein-binding assays, which had problems with interference and cross-reactivity (reviewed in refs 87 and 88). Different competitive protein-binding assays used different sources of DBPs, variable extraction and preliminary purification procedures, and incubation environment and, therefore, led to variable results. These assays often resulted in higher 25(OH)-D values than other methods, likely because a chromatographic separation step was lacking.<sup>89,90</sup> The chemiluminescent protein-binding assay uses a reagent to separate vitamin D from its binding proteins and, similar to the older protein-binding assays, has no chromatographic separation step.<sup>91</sup> Like many of the protein-binding assays, this assay was found to result in higher 25(OH)-D levels than radioimmunoassays and high-pressure liquid chromatography (HPLC) in 1 study.<sup>88</sup> Radioimmunoassays using mAbs initially compared well with HPLC; however, even these have been shown to have some variability,<sup>88</sup> likely because some antibodies detect both 25(OH)-D<sub>2</sub> and 25(OH)-D<sub>3</sub> metabolites, whereas others underestimate the D<sub>2</sub> metabolite.<sup>92</sup> Greater than 30% to 50% variability for detecting the 25(OH)-D<sub>2</sub> and 25(OH)-D<sub>3</sub> metabolites has been reported with typical laboratory assays. HPLC or tandem mass spectroscopy have been variably reported as the gold standard for vitamin D metabolite assays. Whereas the mAb assays have significant preferential affinity for the D<sub>2</sub> or D<sub>3</sub> analytes and may cause gross overestimation or underestimation of total levels depending on the standards used, HPLC and mass spectroscopy have the advantage of successfully separating the D<sub>2</sub> and D<sub>3</sub> metabolites. However, HPLC is time consuming, with limited clinical applicability, and neither HPLC nor mass spectroscopy are universally available.

**TABLE 5 Vitamin D Status in Relation to 25(OH)-D Levels**

Vitamin D Status	25(OH)-D Level, nmol/L (ng/mL)
Severe deficiency	≤12.5 (5)
Deficiency	≤37.5 (15)
Insufficiency	37.5–50.0 (15–20)
Sufficiency	50–250 (20–100) <sup>a</sup>
Excess	>250 (100) <sup>b</sup>
Intoxication	>375 (150) <sup>104</sup>

<sup>a</sup> Adult data indicate that a level of >80 nmol/L (>32 ng/mL) is desirable.

<sup>b</sup> An admittedly arbitrary designation.

Table 5 classifies states of vitamin D deficiency, sufficiency, and excess on the basis of 25(OH)-D levels. In determining the reference range for 25(OH)-D levels, data that are considered include biomarkers such as changes in ALP, bone density, and calcium absorption at varying concentrations of 25(OH)-D, as well as evidence of rickets.

#### Severe Vitamin D Deficiency

Currently, severe deficiency is somewhat arbitrarily defined as a 25(OH)-D level of ≤12.5 nmol/L (5 ng/mL).<sup>63</sup> One study indicated that 86% of the children studied who had 25(OH)-D levels of <20 nmol/L (8 ng/mL) had rickets, and 94% of the hypocalcemic children with vitamin D deficiency had levels of <20 nmol/L (8 ng/mL).<sup>4</sup> Presumably, these proportions would have been higher with a cutoff of 12.5 nmol/L (5 ng/mL).

#### Vitamin D Deficiency and Insufficiency

For children, it has been recommended that a serum 25(OH)-D level of ≤37.5 nmol/L (15 ng/mL) be considered indicative of deficiency and >50 nmol/L (20 ng/mL) as indicative of vitamin D sufficiency.<sup>93</sup> A detailed description of studies that formed the basis of these recommendations is beyond the scope of this review, and only a few are described here. In 1 study of 14- to 16-year-old Finnish girls, bone density at the forearm was low in girls with 25(OH)-D levels of ≤40 nmol/mL (16 ng/mL).<sup>94</sup> However, nutritional rickets with documented radiologic changes occurs in black breastfed infants at 25(OH)-D levels as high as 40 to 45 nmol/L (16–18 ng/mL),<sup>95,96</sup> and ALP levels are noted to rise at serum 25(OH)-D levels of <50 nmol/L (20 ng/mL).<sup>97,98</sup>

#### Vitamin D Sufficiency

Although a lower limit of 50 nmol/L (20 ng/mL) for 25(OH)-D levels is still considered indicative of vitamin D sufficiency in children, data in adults suggest a somewhat higher cutoff on the basis of studies that reported impaired calcium absorption<sup>99</sup> and lower bone density (100) at 25(OH)-D levels of <80 nmol/L (32 ng/mL).<sup>60,99–101</sup> On the basis of these and other data, a lower limit of 80 nmol/L (32 ng/mL) is increasingly becoming accepted as the lower limit of normal for 25(OH)-D levels in adults. More studies examining associations of ALP, calcium absorption, and bone mineral density with 25(OH)-D levels in infants and children are necessary to determine if the higher cutoff for sufficiency now being used in

**TABLE 6 Causes of Vitamin D Deficiency**

Decreased vitamin D synthesis
Skin pigmentation
Physical agents blocking UVR exposure
Sunscreen, clothing
Shade
Geography
Latitude, season
Air pollution, cloud cover, altitude
Decreased nutritional intake of vitamin D
Decreased maternal vitamin D stores and exclusive breastfeeding
Malabsorption (celiac disease, pancreatic insufficiency [cystic fibrosis], biliary obstruction [biliary atresia])
Decreased synthesis or increased degradation of 25(OH)-D (chronic liver disease and drugs such as rifampicin, isoniazid, anticonvulsants)

Adapted with permission from Levine M, Zapalowski C, Kappy M. Disorders of calcium, phosphate, parathyroid hormone and vitamin D metabolism. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:760.

adults should be applied to children as well. In addition, it is important to identify other biomarkers that may indicate a state of vitamin D insufficiency or deficiency in children. Better and more standardized assays are essential, given the great degree of variability in the assays in current use.<sup>88</sup>

#### *Vitamin D Excess and Intoxication*

At the other end of the spectrum, individuals with 25(OH)-D levels of >250 nmol/L (100 ng/mL) have been arbitrarily designated as having vitamin D excess and as being at risk for vitamin D intoxication.<sup>102</sup> Some laboratories use an upper limit of normal of 200 nmol/L (80 ng/mL). However, sunbathers and lifeguards achieve 25(OH)-D levels of >250 nmol/L (100 ng/mL) without evidence of vitamin D intoxication, and administration of vitamin D supplements leading to 25(OH)-D levels of 250 nmol/L (100 ng/mL) is not associated with harmful effects.<sup>103</sup> Conversely, hypercalcemia is definitely associated with 25(OH)-D levels of >325 nmol/L (150 ng/mL).<sup>104</sup>

### **CAUSES OF VITAMIN D DEFICIENCY**

Table 6 describes various causes of vitamin D deficiency.

#### **Decreased Vitamin D Synthesis**

The important role of ultraviolet light in the UV-B range on cutaneous vitamin D synthesis was described in "Cutaneous Vitamin D Synthesis." The reemergence of vitamin D–deficiency rickets in northern Europe and North America is primarily associated with dark-skinned children on strict vegetarian diets, cult or fad diets, dark-skinned infants exclusively breastfed beyond 3 to 6 months of age, premature infants, and infants born to vitamin D–deficient mothers. Excessive use of sunscreen may also contribute to decreased cutaneous vitamin D synthesis. Worldwide, rickets persists in infants who are breastfed for a prolonged period of time or kept out of sunlight for prolonged periods, as in India, China, and the Middle East. Fetuses of pregnant women who have severe vitamin D deficiency from wearing the traditional veil can develop rickets in utero and present with hy-

pocalcemia and tetany at birth (congenital rickets). All this has prompted an in-depth look at factors that affect vitamin D synthesis such as skin pigmentation, exposure to sunlight, geography, and infant-feeding patterns. The emphasis on sun-blocking agents and sun avoidance to decrease the risk of skin cancer is being called into question, at least in darker-skinned individuals, given the associated risk of decreased vitamin D synthesis. Benefits of judicious UVR exposure need to be balanced against the risks of vitamin D deficiency, at least in certain populations. In this section we review factors that affect vitamin D synthesis in the skin.

#### *Vitamin D Deficiency in Relation to Skin Pigmentation*

Skin pigmentation determines the duration of sun exposure necessary to achieve a certain concentration of vitamin D. However, when UV-B exposure is not limited to a fixed amount of energy (of UV-B radiation) but is expressed as MED (the amount of UV-B required to produce slight pinkness of the skin), exposure to the equivalent MED of whole-body UV-B results in similar vitamin D levels. It should be noted that more UV-B is necessary to produce a MED in darker-skinned people; therefore, dark-skinned people require a longer duration of sun exposure than light-skinned people for a similar response.<sup>105</sup> Overall, an Asian Indian person is thought to require 3 times, and a black person 6 to 10 times, as much UV-B exposure as a light-skinned person to achieve equivalent vitamin D concentrations.<sup>60,106</sup>

Lower 25(OH)-D levels have been reported in black compared with white (1) infants <6 months old in Cincinnati,<sup>64</sup> (2) prepubertal girls in the southeastern United States,<sup>107</sup> and (3) postmenarchal adolescent girls,<sup>108</sup> particularly in the winter months. Thirty six percent of black teenagers in 1 study from Boston, Massachusetts, had 25(OH)-D levels of <37.5 nmol/L (15 ng/mL).<sup>93</sup> In 2 studies of children with rickets, 83% to 91% of the children with rickets who were 2 to 45 months old<sup>109</sup> and 4 to 54 months old<sup>6</sup> were black, and all 9 children with rickets in a report from Texas were dark skinned.<sup>7</sup> This last study strikes a cautionary note in that living in a geographical area with abundant sunlight does not guarantee protection from development of nutritional rickets in dark-skinned children. Vitamin D deficiency is also being reported outside the United States in relation to skin pigmentation. In a prospective study from the United Kingdom in children aged 0 to 5 years,<sup>110</sup> vitamin D–deficiency rickets was most common in children of black African or African Caribbean descent, followed by children of South Asian descent and white children. Of 17 children with rickets who were referred to a children's hospital in Toronto, Ontario, Canada, between 1988 and 1993, 12 were born to dark-skinned parents.<sup>111</sup>

#### *Vitamin D Deficiency in Relation to Physical Agents Blocking UVR exposure*

##### *Clothing*

The amount of skin that is exposed to the sun is important. Exposure of the whole body versus only the face, hands, and arms is associated with marked differ-

ences in vitamin D synthesis.<sup>60</sup> For example, a fully clothed infant without a hat requires 4 times as much sun exposure as an infant in only a diaper to achieve similar 25(OH)-D concentrations.<sup>64</sup> At least 20% of the body's surface should be exposed to UV-B for blood vitamin D concentrations to increase. Women and children in Saudi Arabia who wear traditional outfits, therefore, are at great risk for vitamin D deficiency. Subclinical vitamin D deficiency is also common in veiled Kuwaiti women, and some have frank osteomalacia.<sup>112</sup> The nature of clothing is important, such that black wool is twice as effective in absorbing and thus preventing transmission of incident UV-B radiation to the skin as white cotton.<sup>113</sup> In addition, more tightly woven fabric causes greater UV-B attenuation.<sup>114</sup> In addition to clothing, the heat of the summer months in certain parts of the world leads to sun-avoidant behavior and, therefore, inadequate sunlight exposure.<sup>115,116</sup>

#### *Sunscreen*

Sunscreen absorbs UV-B and some UV-A light and prevents it from reaching and entering the skin. A sunscreen with a sun protection factor (SPF) of 8 can decrease vitamin D<sub>3</sub> synthetic capacity by 95%, and SPF 15 can decrease it by 98%<sup>117</sup> (reviewed in ref 56). In adults who apply sunscreen properly (2 mg/cm<sup>2</sup>), the amount of vitamin D<sub>3</sub> produced is decreased 95%. However, the effect of sunscreens on vitamin D production may also be affected by geography, with adequate vitamin D production despite sunscreen application in areas of excessive sunlight exposure.<sup>118</sup> Farrerons et al<sup>119</sup> demonstrated lower vitamin D levels in people using SPF 15 sunscreens than in those not using sunscreen; however, these lower levels were not sufficient to cause PTH level elevations. For adequate vitamin D synthesis, exposure to the midday sun (between 1000 and 1500 hours) for 10 to 15 minutes in the spring, summer, and fall is considered sufficient for light-skinned people, providing ~25% of the MED. After this extent of exposure, application of a sunscreen with an SPF of ≥15 is recommended to prevent damaging effects of chronic excessive exposure to sunlight.<sup>62,120-123</sup> It is notable that in a 2003 study, 48% of white girls aged 9 to 11 years living in Maine had 25(OH)-D levels of <50 nmol/L (20 ng/mL) at the end of winter, and 17% continued to have vitamin D insufficiency at the end of summer because of sunscreen use and the practice of complete sun protection.<sup>124</sup>

#### *Shade*

Increased urbanization and increased time spent indoors at work may lead to decreased time spent outdoors and, therefore, decreased vitamin D synthesis, even in light-skinned populations. Shade reduces the amount of solar radiation by 60%, and windowpane glass blocks UVR.<sup>125</sup> A third of students at Boston University who stayed indoors for long periods and always wore sun protection were vitamin D insufficient [25(OH)-D levels ≤ 50 nmol/L (20 ng/mL)] at the end of winter.<sup>126</sup> Similarly, disabled children and children who stay indoors may not receive a summertime boost in vitamin D levels.<sup>127</sup>

### *Vitamin D Deficiency in Relation to Geography*

#### *Latitude and Season*

Vitamin D-deficiency rickets is more commonly reported in white children from the northern than the southern United States.<sup>6</sup> This is attributed to a decrease in incident UVR with increasing latitude, because the oblique angle at which sunlight reaches the atmosphere leads to a greater path being traversed through the atmosphere and ozone layer, with greater resultant scatter and absorption of UVR.<sup>128</sup> Similarly, in the winter months, the rays of the sun enter the atmosphere at an oblique angle, UV-B photons have to pass through a greater distance of the atmosphere, and more UV-B photons are efficiently absorbed by ozone. Therefore, fewer photons per unit area strike the earth. Above 37° north latitude, in the winter months, the number of UV-B photons reaching the earth's atmosphere is decreased by 80% to 100%, and as a consequence, little vitamin D<sub>3</sub> is produced in the skin.<sup>56</sup> A minimum amount of UV-B is necessary for vitamin D production, and this may not be reached at a latitude of above 40° in winter even with prolonged sun exposure.<sup>129</sup> There are, therefore, 4 to 5 months in winter when vitamin D cannot be produced from UV-B in places such as Boston (42.5° north).<sup>130</sup> Vitamin D levels reach their nadir in February and March in the northern hemisphere.<sup>130</sup>

Children of all ages are more susceptible to low vitamin D levels during the winter compared with the summer months. A report from Iowa (41° north) indicated that during winter, 78% of unsupplemented breastfed infants of different skin pigmentations had 25(OH)-D levels of <27.5 nmol/L (11 ng/mL), as opposed to only 1% of such infants during summer.<sup>131</sup> Infants with florid rickets are known to first present in the late winter or early spring at 6 to 12 months of age with hypocalcemia and associated clinical features, often frank tetany or convulsions, also known as "spring tetany." In Edmonton, Alberta, Canada (52° north), the prevalence of 25(OH)-D levels of <40 nmol/L (18 ng/mL) at the end of winter was 22% and 8% in boys and girls 2 to 8 years old and 69% and 35% in boys and girls 9 to 16 years old, respectively.<sup>132</sup>

Summertime vitamin D levels are usually adequate, and 1 question is whether sufficient sun exposure during spring, summer, and fall suffices to maintain normal vitamin D concentrations during winter. In other words, could vitamin D produced in the summer and other months be stored in body fat and potentially released and used in the winter? However, studies have demonstrated inverse associations between body fat and circulating 25(OH)-D levels, suggesting that sequestration of vitamin D in adipose tissue in obese individuals or increased storage capacity for vitamin D in fat may prevent appropriate release of vitamin D, leading to deficient states.<sup>133,134</sup> Therefore, in northern latitudes, despite sun exposure during summer, vitamin D supplementation may be necessary to maintain optimal vitamin D levels during winter.

### *Cloud Cover, Air Pollution, and Altitude*

Cloud cover, increasing water vapor, and industrial pollution can reduce the amount of UV-B that reaches the earth's surface, and industrial pollution has been associated with a greater prevalence of vitamin D–deficiency rickets.<sup>135</sup> In contrast, higher altitudes (as in the Rocky Mountains) are associated with greater UVR because of the thinner atmosphere and lower stratospheric ozone, thus protecting against vitamin D deficiency even in otherwise northern latitudes.

### **Decreased Nutritional Intake of Vitamin D**

Lower intake of vitamin D–fortified foods, particularly milk and fortified cereals, may result in vitamin D–deficiency rickets in certain populations, particularly in dark-skinned people who live in higher latitudes and in the winter months. The decreased intake may be from choice or from necessity in societies poor enough to be unable to afford these foods. Reduced intake of fortified milk is common among adolescents and young women of childbearing age, which results in decreased vitamin D concentrations in blood.

### **Maternal Vitamin D Status, Prematurity, and Exclusive Breastfeeding**

#### *Vitamin D Deficiency Resulting From Poor Maternal Vitamin D Status*

In 1 US study, 12% of women 20 to 29 years old (peak childbearing years) had serum 25(OH)-D levels below the accepted threshold of deficiency (37.5 nmol/L [15 ng/mL]),<sup>136</sup> and in another study, vitamin D deficiency was reported to be more common in black (42%) than white (4%) women.<sup>137</sup> High rates of vitamin D deficiency have been reported in darker-skinned pregnant women,<sup>138,139</sup> particularly in the winter months and at higher latitudes,<sup>140</sup> and low vitamin D levels during pregnancy have been associated with intrauterine growth retardation, premature labor, and hypertension, all of which increase the risk of low birth weight.<sup>141–143</sup> Indeed black and Asian American mothers have higher rates of low birth weight infants in the United States than do Americans of European or Hispanic descent.<sup>144–146</sup> Decreased vitamin D levels in the mother result in decreased transplacental transfer of vitamin D and reduced stores at birth. Serum 25(OH)-D levels in infants correlate with maternal serum 25(OH)-D.<sup>64</sup>

#### *Vitamin D Deficiency Resulting From Prematurity*

Prematurely born infants have a shorter duration in which to accumulate vitamin D stores from transplacental transfer from the mother and also have a higher requirement for vitamin D than term infants.<sup>147</sup> Therefore, they are more likely to be vitamin D deficient. They have been reported to be more likely to have enamel defects in both primary and permanent teeth, because vitamin D sufficiency is necessary for normal fetal tooth development.<sup>148,149</sup>

#### *Vitamin D Deficiency Resulting From Exclusive Breastfeeding*

We have previously indicated that, assuming an average consumption of 750 mL/day,<sup>79</sup> exclusive breastfeeding

without sun exposure would provide only 11 to 38 IU/day of vitamin D.<sup>14</sup> It is important to note that the vitamin D content of breast milk varies on the basis of skin color, with lower vitamin D concentrations in breast milk of black compared with white women.<sup>150</sup> Therefore, breastfed infants need to obtain additional vitamin D through either sun exposure or supplementation. The amount of sun exposure for infants and young children described earlier in this review (see “Cutaneous Vitamin D Synthesis”) as recommended by Specker et al<sup>64</sup> is sufficient to maintain serum 25(OH)-D concentrations of >27.5 nmol/L (11 ng/mL). However, this recommendation has its limitations, particularly because 25(OH)-D levels need to be >50 nmol/L (20 ng/mL) according to current recommendations, and some may even argue that a lower limit of 80 nmol/L (32 ng/mL) is more physiologic. Whereas synthesis of vitamin D in the skin is a major source of vitamin D in infants and children, current recommendations of the AAP that limit sun exposure for infants <6 months old because of harmful effects on the skin by UV-B radiation<sup>151</sup> make breastfed infants more vulnerable to developing vitamin D deficiency.

Exclusive breastfeeding without adequate sun exposure or vitamin D supplementation is an important risk factor for vitamin D deficiency.<sup>95,152–156</sup> In a review of 65 clinical cases of rickets in children aged 2 to 45 months published between 1975 and 1985 in 11 publications, Cosgrove and Dietrich<sup>109</sup> noted that the children were either still breastfeeding or were on a milk-free vegetarian diet at the time of diagnosis. Weisberg et al<sup>6</sup> then reviewed 166 published cases of rickets in children aged 4 to 54 months between 1986 and 2003 in 22 publications and reported that 96% were breastfed. Of the breastfed infants, only 5% were receiving vitamin D supplements. Exclusively breastfed infants born in winter in Wisconsin had mean 25(OH)-D levels of <25 nmol/L (10 ng/mL) at 6 months of age if they were not given any supplements,<sup>157</sup> and 98% of infants in Alaska noted to have 25(OH)-D levels of <62.5 nmol/L (25 ng/mL) were exclusively breastfed.<sup>158</sup> Thus, breastfed infants need to obtain additional vitamin D through supplementation (infant or maternal<sup>159,160</sup>) or adequate sun exposure.

#### *Vitamin D Deficiency in Formula-Fed Infants*

Although vitamin D deficiency is common in exclusively breastfed infants, it may also occur in formula-fed infants. In a prospective study from the United Kingdom in children aged 0 to 5 years, 50% of children with rickets presenting with hypocalcemic convulsions were formula fed.<sup>110</sup> Thus, the vitamin D content of formulas may be insufficient to compensate for the impact of antenatal maternal vitamin D deficiency.

### **Malabsorption Can Cause Rickets by Reducing Vitamin D, Calcium, and/or Phosphate Absorption**

Vitamin D absorption is chylomicron dependent; consequently, children with diseases that interfere with fat absorption are at risk of developing vitamin D deficiency. Rickets caused by malabsorption can be found in chil-

dren with celiac disease,<sup>161</sup> with food allergies,<sup>162</sup> after gastric and small-bowel resection, and with pancreatic insufficiency including cystic fibrosis, Crohn disease, and cholestatic hepatopathies. A complete discussion on vitamin D deficiency that occurs as a consequence of malabsorption is beyond the scope of this review. We also will not discuss vitamin D deficiency that can occur as a result of chronic use of medications such as anticonvulsants or glucocorticoids.

#### **LIMITATIONS OF CURRENT RECOMMENDATIONS OF VITAMIN D INTAKE**

Whether the recommended 200 IU/day intake of vitamin D (based on the 2003 guidelines of the AAP) is sufficient for all breastfed infants regardless of vitamin D status of the mothers during pregnancy, skin pigmentation, use of sunscreen, geographical latitude, clothing habits, or dietary calcium intake is very questionable. The premise for this recommendation is that the intake of 200 IU of vitamin D per day is sufficient to maintain serum 25(OH)-D concentrations of >27.5 nmol/L (11 ng/mL) to prevent rickets. However, a level of 27.5 nmol/L (11 ng/mL) is not sufficient for preventing all cases of florid rickets,<sup>95,96,163</sup> and rickets can occur at 25(OH)-D concentrations between 25 and 50 nmol/L (10–20 ng/mL).<sup>95,96</sup> In infants aged 7 to 12 months, daily intake of 200 IU of vitamin D allows 25(OH)-D levels to be maintained at >25 nmol/L (10 ng/mL); however, these concentrations are less than that achieved in unsupplemented infants in the summertime.<sup>164</sup> As discussed previously, 25(OH)-D levels of >50 nmol/L (20 ng/mL) (vitamin D sufficiency) need to be aimed for<sup>165,166</sup> to prevent increases in ALP levels,<sup>97,98</sup> and historical data indicate that a daily intake of 400 IU of vitamin D as cod liver oil is sufficient to prevent rickets by maintaining 25(OH)-D levels above this range and is not harmful.<sup>167,168</sup> In 1998, AAP had recommended supplementation with 400 IU/day of vitamin D for deeply pigmented breastfed infants<sup>169</sup>; however, this recommendation was not reaffirmed in the 2003 AAP guidelines. Current recommendations for vitamin D intake do not take into account skin pigmentation or the effects of geography. It should be noted that the Canadian Paediatric Society recommends 800 IU/day of vitamin D for breastfed infants during the winter months<sup>5,170</sup> on the basis of the high prevalence of vitamin D deficiency among Canadian mothers and their infants (46% and 36%, respectively).<sup>171</sup> Thus, dietary requirements for vitamin D may be higher in northern latitudes, particularly in winter, perhaps closer to the recommended vitamin D intake by the Canadian Paediatric Society.

#### **PREVENTION AND TREATMENT OF NUTRITIONAL VITAMIN D-DEFICIENCY RICKETS**

##### **Prevention**

##### *Exposure to Sunlight (Cutaneous Vitamin D Synthesis From Solar UV-B Exposure)*

Exposure to sunlight is the principal source of vitamin D for most children and adolescents. However, the limited

ability of the skin to synthesize vitamin D in the winter months, particularly at latitudes above 37.5° and for dark-skinned people, makes vitamin D supplementation necessary. A balance is necessary, therefore, between limiting sun exposure to avoid risks of skin cancer and allowing enough exposure to optimize vitamin D levels and prevent rickets, as well as development of immune-mediated diseases and future cancer. More studies are necessary to reexamine the risks versus benefits of UVR in terms of not only health care costs but also human suffering and to develop new recommendations for safe sun exposure of infants, children, and adolescents on the basis of skin color, geography, culture, and breastfeeding practices.

Current AAP recommendations include keeping infants <6 months old out of direct sunlight, selecting children's activities that minimize sunlight exposure, and using protective clothing and sunscreen.<sup>70</sup> These recommendations may still hold for light-skinned children in lower latitudes, particularly in the summer months. However, the effects of UV-B exposure on dark-skinned infants, children, and adolescents who live in higher latitudes need to be explored, and studies are necessary to determine the duration of safe sun exposure that will allow sufficient vitamin D generation to maintain 25(OH)-D levels >50 nmol/L (20 ng/mL) at these higher latitudes and in infants and children with darker skin pigmentation.

##### *Fortification of Food With Vitamin D*

There are few foods that naturally contain vitamin D, and because most of these are meat or fish based, they may not be acceptable to cultures that favor a vegetarian diet. Currently, few foods are fortified with vitamin D. Routine vitamin D fortification should be considered for milk and other food products, particularly at high latitudes.

Food-fortification strategies in current practice may not be sufficient to prevent vitamin D deficiency in dark-skinned individuals, particularly in the winter months and at higher latitudes. Because milk and "ready-to-eat" cereal consumption is lower in black compared with white populations in the United States, dietary practices also need to be taken into consideration in determining the adequacy of fortification practices. A plan for fortification of food based on skin pigmentation and geography, and taking into account cultural norms, would be useful, given that requirements for dietary supplementation with vitamin D are higher for dark-skinned populations and at higher latitudes. Until this plan is available, we endorse at least the current mandate that infant formulas contain 40 to 100 IU of vitamin D per 100 kcal of formula.

Consideration needs to be given to monitoring the vitamin D status of dark-skinned women residing in higher latitudes during pregnancy and recommending additional vitamin D supplementation if women are vitamin D deficient. Periods of rapid growth such as infancy and adolescence are important periods during which to ensure vitamin D supplementation,<sup>14,172</sup> partic-

ularly in dark-skinned children and children who live in higher latitudes.

### Use of Supplements

Given that (1) 200 IU of vitamin D is insufficient to maintain 25(OH)-D levels of  $>50$  nmol/L (20 ng/mL), the cutoff for vitamin D insufficiency, whereas 400 IU of vitamin D is sufficient to prevent rickets and maintain levels of  $>50$  nmol/L (20 ng/mL), (2) 25(OH)-D levels are very low in breastfed infants who do not receive supplements, and (3) sun exposure sufficient to maintain 25(OH)-D levels in the recommended range may not be possible at higher latitudes and in the winter months, we recommend that all breastfed infants, and nonbreastfed infants and children who do not ingest at least 1 L of vitamin D-fortified milk per day, receive 400 IU vitamin D per day as a supplement.<sup>172</sup> Consumption of 1 L of fortified formula daily is possible in older, exclusively formula-fed infants but unlikely in breastfed infants who are also formula fed; therefore, supplementation with 400 IU/day is necessary for all breastfed infants. We recommend that supplementation begin within days of birth, given that vitamin D deficiency can start early in life and even in utero when the mother is vitamin D deficient. This amount of vitamin D supplementation is not associated with adverse effects, and associated costs are not significant. Zipitis et al<sup>173</sup> have reported that the cost of primary prevention of vitamin D deficiency in a high-risk population in the United Kingdom compares favorably both medically and financially with treatment of established disease. Similar studies are necessary in other parts of the world to assess the cost/benefit ratio of supplementing with higher-than-currently-recommended doses of vitamin D.

Dark-skinned infants who are exclusively breastfed should receive at least 400 IU/day of vitamin D as a supplement, but they may require more. Preterm infants should be supplemented from birth with 400 to 800 IU/day because of inadequate transfer of maternal vitamin D stores and issues associated with prematurity such as poor feeding, gastrointestinal difficulties impairing absorption, and, sometimes, liver and kidney impairment. Consideration should be given to recommendations of the Canadian Paediatric Society, which suggests supplementation with 800 IU/day for breastfed infants during the winter months. This would be particularly important for exclusively breastfed infants of dark-skinned mothers who live at higher latitudes. Infants and children who receive higher doses of vitamin D as supplements should be monitored at least yearly for 25(OH)-D levels. Note that there is a growing body of evidence that suggests that for adults in the United States, the recommended daily intake of vitamin D should be close to 1000 IU. Studies are necessary to determine if these recommendations should also apply to children.

Recent data indicate that administration of high doses of vitamin D (4000–6400 IU daily) to breastfeeding mothers is capable of raising 25(OH)-D levels in the infant to levels similar to those seen with infant supplementation without causing hypervitaminosis D in the mother and increases

**TABLE 7 Treatment of Vitamin D–Deficiency Rickets: Vitamin D and Calcium Supplementation and Monitoring of Therapy**

Vitamin D (ergocalciferol)
Double-dose vitamin D: 20 $\mu$ g (800 IU)/d $\times$ 3–4 mo; or
Pharmacological doses of vitamin D: 25–125 $\mu$ g (1000–10 000 IU) per day $\times$ 8–12 wk depending on the age of the child, then maintain at 10–25 $\mu$ g (400–1000 IU) per day; or
Stoss therapy: $\sim$ 2.5–15.0 mg or 100 000–600 000 IU of vitamin D orally (over 1–5 d), then maintain at 10–25 $\mu$ g (400–1000 IU) of vitamin D per day, or 1.25 mg or 50 000 IU of vitamin D <sub>2</sub> weekly for 8 wk orally (teenagers and adults)
Calcium
30–75 mg/kg per d of elemental calcium in 3 divided doses (start at a higher dose, and wean down to the lower end of the range over 2–4 wk)
Monitoring of therapy
At 1 mo: calcium, phosphorus, ALP
At 3 mo: calcium, phosphorus, magnesium, ALP, PTH, 25(OH)-D, urine calcium/creatinine ratio (frequency depends on severity of rickets and hypocalcemia); recheck radiologic findings in 3 mo
At 1 y and annually: 25(OH)-D

Adapted with permission from Levine M, Zapalowski C, Kappy M. Disorders of calcium, phosphate, parathyroid hormone and vitamin D metabolism. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:741.

antirachitic activity of breast milk.<sup>159,160</sup> High-dose vitamin D supplementation in nursing mothers, therefore, is another possible strategy for improving the vitamin D status of purely breastfeeding infants.

### Screening

Pediatricians should have a low threshold for screening for vitamin D deficiency (1) in the presence of nonspecific symptoms such as poor growth, gross motor delays, and unusual irritability, (2) for dark-skinned infants who live at higher latitudes in the winter and spring months, (3) for children on anticonvulsants or chronic glucocorticoids, and (4) for children with chronic diseases that are associated with malabsorption, such as cystic fibrosis and inflammatory bowel disease. Another possible group to consider screening for vitamin D deficiency is children with frequent fractures and low bone mineral density, in whom maintaining an optimal vitamin D level would be important for maximizing calcium absorption. A screening tool for vitamin D–deficiency rickets is serum ALP,<sup>174</sup> which if elevated for age should be followed with measurements of serum 25(OH)-D, calcium, phosphorus, and PTH, along with radiologic examination of the distal ends of (1) the radius and ulna (wrist anteroposterior view) or (2) tibia and femur (knee anteroposterior view) depending on the age of the child.<sup>96</sup> ALP levels are usually  $<500$  IU/L in neonates and  $<1000$  IU/L in children up to 9 years of age and decrease after puberty<sup>175</sup>; however, the range varies depending on the method used for the assay. Some studies, however, indicate that whereas all children with radiographic evidence of rickets have low vitamin D levels, not all have high ALP levels, and the wrist radiograph may be the most reliable test for detecting subclinical rickets.<sup>176,177</sup>

## Treatment

Table 7 details treatment protocols for vitamin D deficiency using vitamin D.

## When to Treat

Vitamin D therapy is necessary for infants and children who manifest clinical features of hypocalcemia as a result of vitamin D deficiency or rickets and when vitamin D levels are in the deficient range.

## Vitamin D and Calcium Replacement

Vitamin D given in daily doses of 25 to 250  $\mu\text{g}$  (1000–10 000 IU) (depending on the age of the child) can be used for a 2- to 3-month period to normalize 25(OH)-D levels and replenish stores. Our recommendation is to use doses of 1000 IU/day for infants <1 month old, 1000 to 5000 IU/day for infants 1 to 12 months old, and >5000 IU/day for children >12 months old.<sup>63</sup> With therapy, radiologic evidence of healing is observed in 2 to 4 weeks, after which the dose of vitamin D can be reduced to 400 IU/day. Lack of compliance is an important cause of lack of response, and an option after the first month of life is to administer high doses of vitamin D in a single administration (100 000–600 000 IU over 1–5 days),<sup>178,179</sup> instead of smaller doses over a longer period, followed by maintenance dosing. High-dose vitamin D may need to be intermittently repeated (usually every 3 months) if poor compliance persists with maintenance dosing. When high doses of vitamin D need to be administered (“stoss” therapy, from the German *stossen* meaning “to push”), caution is necessary if oral vitamin D preparations containing propylene glycol such as Drisdol are used, because propylene glycol can be toxic at very high doses. Possible approaches for small children include (1) soaking a 50 000-IU capsule in a small amount of water to soften it and administering the intact capsule in blended food such as applesauce<sup>178</sup> or (2) crushing a 25 000-IU or 50 000-IU vitamin D tablet before administration to avoid excessive administration of propylene glycol. Shah and Finberg have successfully administered 100 000 IU of vitamin D every 2 hours over a 12-hour period.<sup>178</sup> In teenagers and adults, 50 000 IU of vitamin D has been successfully administered orally once per week for 8 weeks.<sup>165</sup>

Hypocalcemia should be treated with calcium supplements (Table 7). Parenteral calcium as calcium gluconate (10–20 mg of elemental calcium per kg intravenously slowly over 5–10 minutes, usually given as 1–2 mL/kg of 10% calcium gluconate) becomes necessary in case of manifest tetany or convulsions. Repeat boluses may also be necessary on occasion, as may calcium administration with intravenous fluids. Calcium levels should then be maintained with oral calcium supplements. Even for children who are not frankly hypocalcemic, calcium supplements are important for avoiding subsequent hypocalcemia from a decrease in bone demineralization and an increase in bone mineralization as PTH levels normalize (“hungry-bone” syndrome), particularly with stoss therapy. Recommended doses of elemental calcium are 30 to 75 mg/kg per day in 3 divided doses. In addition

**TABLE 8 Available Vitamin D, Calcium, and Phosphorus Preparations**

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Vitamin D and its analogs
Vitamin D <sub>2</sub> (ergocalciferol): available in 3 forms
200 $\mu\text{g}$ /mL (8000 IU/mL) solution in propylene glycol solution
1250 $\mu\text{g}$ (50 000 IU) gelcaps
625- and 1250- $\mu\text{g}$ (25 000- and 50 000-IU) tablets have been available
Trade names: Calciferol, Drisdol, most children’s chewable multivitamins including Flintstones and Garfield, prenatal and women’s multivitamins
Vitamin D <sub>3</sub> (cholecalciferol): may be 3 times as potent as vitamin D <sub>2</sub>
Trade names: Delta-D, Poly-Vi-Sol
1.0 $\mu\text{g}$ of vitamin D = 40 IU; 1.0 mg of vitamin D = 40 000 IU
Calcium preparations
Calcium gluconate: 10% injection, preservative-free solution, 100 mg/mL; elemental calcium 9 mg/mL
Calcium chloride: 10% injection, preservative-free solution, 100 mg/mL; elemental calcium 27.2 mg/mL
Calcium carbonate: oral suspension 1250 mg/5 mL (elemental calcium 500 mg/5 mL); chewable tablets (400 mg elemental calcium per gram of calcium carbonate); trade names: Tums, Viactiv, Caltrate, OsCal, and others
Calcium glubionate: oral solution 1800 mg/5 mL (elemental calcium 115 mg/5 mL); trade name: Calcionate
Tribasic calcium phosphate: caplet containing 600 mg of calcium and 280 mg of phosphorus (390 mg of elemental calcium per gram of tribasic calcium phosphate); Trade names: Posture

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tion to calcium supplements, calcitriol may be necessary in doses of 20 to 100 ng/kg per day in 2 to 3 divided doses until calcium levels normalize. High doses of calcium are necessary early in the course of therapy, after which doses are reduced by half for the next 1 to 2 weeks. Once vitamin D supplementation has been reduced to 400 IU/day with normal PTH and 25(OH)-D levels, calcium supplementation is usually not necessary.

## Available Forms of Vitamin D and Calcium

Commonly used preparations of vitamin D and calcium are described in Table 8. Injectable vitamin D is an excellent option for stoss therapy but is no longer commercially available. It has been successfully prepared, however, by local compounding pharmacies when necessary. Pharmaceutical companies should be encouraged to manufacture this parenteral vitamin D preparation given its usefulness in situations of poor compliance. Calcitriol is not preferred for stoss therapy. It is expensive, has a short half-life, and does not build up vitamin D stores. Therefore, its use in nutritional deficiency of vitamin D is not optimal and is limited to treating associated hypocalcemia alone. In addition, calcitriol when given in large doses may cause hypercalcemia because of its rapid onset of action, which limits the amount that can be administered. Similarly, dihydrotachysterol can only treat hypocalcemia associated with vitamin D deficiency but does not build up vitamin D stores.

Commonly used calcium preparations are described in Table 8. It should be noted that increased 1- $\alpha$ -hydroxylase activity from high PTH levels in the second phase of rickets may cause transient hypercalcemia after vitamin D treatment because of elevation of 1,25(OH)<sub>2</sub>-D levels to well above the upper limit of the reference range.

### Monitoring Therapy

It is important to obtain calcium, phosphorus, and ALP levels 1 month after initiating therapy. With stoss therapy, a biochemical response occurs in 1 or 2 weeks, the first sign of which is an increase in phosphate. It is important to remember that ALP levels may actually increase in the short term as bone formation rates increase. In addition, there is usually an initial increase in  $1,25(\text{OH})_2\text{-D}$  levels. Subsequently, ALP and  $1,25(\text{OH})_2\text{-D}$  levels decrease to normal, and  $25(\text{OH})\text{-D}$  levels increase to within the reference range. Complete radiologic healing may take months, but changes are evident in 1 week. In 3 months, it is important to obtain calcium, phosphorus, magnesium, ALP,  $25(\text{OH})\text{-D}$ , and PTH levels, and one may consider obtaining a urine sample to determine the calcium/creatinine ratio. A radiograph should also be repeated at 3 months. Subsequently,  $25(\text{OH})\text{-D}$  levels should be monitored yearly.

### When to Refer

If radiographic evidence of some healing is not observed with vitamin D and calcium replacement in 3 months, considerations should include malabsorption, liver disease, or a lack of compliance with replacement therapy. One should also rule out the use of medications that may affect vitamin D levels. For patients who develop vitamin D deficiency as a consequence of malabsorption, higher doses of vitamin D are required than those recommended for vitamin D deficiency (as much as 4000–10 000 IU/day). This is usually administered as an aqueous solution such as Drisdol with oral calcium supplementation. A high dose of vitamin D given as an intramuscular injection in oil is effective in conditions of malabsorption. However, availability of this injection is variable, which limits its use. Higher vitamin D dosing for treatment or supplementation is also necessary for children who are receiving anticonvulsants or glucocorticoids.

Indications for considering other causes of rickets are reviewed in detail by Wharton and Bishop<sup>175</sup> and are summarized here. These include radiologic evidence of rickets at <6 months of age and between 3 and 10 years of age. At very young ages, vitamin D deficiency is more likely to present as hypocalcemia than rickets, and vitamin D requirements are not as marked in the childhood years as in the pubertal years. Radiographs that show a periosteal reaction and a moth-eaten metaphysis rather than the findings described earlier in this review (see “Calcium and Phosphorus Metabolism and Bone” and Fig 1) should raise concerns of conditions other than vitamin D–deficiency rickets. Similar, normal levels of ALP and  $25(\text{OH})\text{-D}$ , very low or very high levels of  $1,25(\text{OH})\text{-D}$ , and high serum urea nitrogen and creatinine levels are red flags for considering other causes of rickets. Other causes of rickets include calcium and phosphorus deficiency, inherited forms of hypophosphatemic rickets, and vitamin D receptor mutations. These conditions are not reviewed here but are important to consider.

### CONCLUSIONS

The increasing numbers of reports of rickets in Western industrialized nations are related to the practice of exclusive breastfeeding without concomitant vitamin D supplementation in northern latitudes, decreased UV-B exposure (particularly in dark-skinned people), and the excessive use of sunscreen. Recommendations for vitamin D supplementation in breastfed infants should take into account skin pigmentation and geography. Recommendations for fortification of commonly used foods with vitamin D are necessary in keeping with various cultural norms of food intake and geography. Current recommendations of sun exposure and vitamin D supplementation are limited because of a paucity of studies in children, nonuniformity of  $25(\text{OH})\text{-D}$  assays used in research studies, and lack of uniformity in the description of normal and abnormal ranges for  $25(\text{OH})\text{-D}$  levels in children. More studies are necessary in children using standard assays to determine safe levels of sun exposure and resultant vitamin D levels, as well as the  $25(\text{OH})\text{-D}$  levels below which pathologic changes begin. A low threshold for assessing vitamin D sufficiency in infants, children, and adolescents is recommended given the growing knowledge about effects of vitamin D not only on bone mineral metabolism but also on the immune system and in preventing various kinds of cancer. Data indicate greater health care costs from diseases related to vitamin D deficiency than from those caused by excessive exposure to UVR, indicating the need for a reexamination of recommendations for sun-avoidant behavior, including the use of sunscreens.

### SUMMARY AND GUIDELINES

1. The risk of vitamin D deficiency is higher in dark-skinned populations, children who live at higher latitudes, exclusively breastfed infants and children, infants born to vitamin D–deficient mothers, and premature infants and may also be affected by cultural practices (including nature of clothing and use of sunscreen).
2.  $25(\text{OH})\text{-D}$  levels should be maintained at least above 50 nmol/L (20 ng/dL) (cutoff for vitamin D sufficiency) in infants and children, and studies are necessary to determine if a level of 80 nmol/L (32 ng/mL) should be considered the cutoff for vitamin D sufficiency in a pediatric population, as is recommended for an adult population.
3. Risks associated with exposure to UVR (such as skin cancer) need to be balanced against the risks associated with deficient cutaneous vitamin D synthesis (rickets, immune system effects, and certain cancers), particularly if intake of vitamin D in food and as supplements is insufficient. Currently recommended sun exposure for infants is insufficient to maintain vitamin D levels in the recommended range for dark-skinned infants and children, particularly at higher latitudes and during the winter months. We recommend more studies to assess the duration of safe sun exposure that will allow sufficient vitamin D synthesis in these situations.



4. When obtaining 25(OH)-D levels, it is important to ascertain that the assay being used measures both vitamin D<sub>2</sub> and D<sub>3</sub> derivatives. Vitamin D<sub>3</sub> (cholecalciferol) is derived from cutaneous synthesis and animal sources. Vitamin D<sub>2</sub> (ergocalciferol) is derived from plant sources. Both vitamin D<sub>2</sub> and D<sub>3</sub> are used for food fortification, and the majority of supplements contain vitamin D<sub>2</sub>. Vitamin D<sub>3</sub> may be almost 3 times as potent as vitamin D<sub>2</sub>, but both contribute to vitamin D status.
5. Although we endorse the current mandate that infant formulas contain 40 to 100 IU of vitamin D per 100 kcal of formula, we recommend research into strategies for fortifying other kinds of food including all forms of milk and milk products, cereals, and bread. Current food-fortification practices are insufficient to maintain optimal 25(OH)-D levels in most children, particularly dark-skinned children who live at higher latitudes and in the winter months.
6. Supplementation with 400 IU of vitamin D should be initiated within days of birth for all breastfed infants, and for nonbreastfed infants and children who do not ingest at least 1 L of vitamin D-fortified milk daily.
7. Premature infants, dark-skinned infants and children, and children who reside at higher latitudes (particularly above 40°) may require larger amounts of vitamin D supplementation, especially in the winter months, and consideration should be given to supplementing with up to 800 IU of vitamin D per day. A high index of suspicion for vitamin D deficiency should be maintained for these infants and children.
8. ALP may be used to screen for rickets, with the caveat that rickets has sometimes been reported with normal ALP levels. When a high index of suspicion exists, a wrist or knee radiograph should be obtained. The best way to assess vitamin D status is to measure 25(OH)-D levels.
9. We recommend treating infants and children who are vitamin D insufficient or deficient with 1000 IU/day of vitamin D for infants <1 month old, 1000 to 5000 IU/day for children 1 to 12 months old, and >5000 IU/day for children >12 months old. Vitamin D levels should subsequently be maintained with 400 IU of vitamin D supplementation per day. For patients who demonstrate poor compliance, a high dose of vitamin D may be given as a single dose or repeated intermittently. It is important to recognize that (1) simultaneous calcium supplementation is necessary because of the risk of hypocalcemia from decreased demineralization of bone and increased remineralization as PTH levels normalize, (2) symptomatic hypocalcemia requires parenteral calcium replacement, and (3) calcitriol and dihydrotachysterol can help treat hypocalcemia associated with rickets but do not build up vitamin D stores.

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## Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations

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