Review Article

A Review on Vitamin D Deficiency Treatment in Pediatric Patients

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Vitamin D is essential for calcium absorption and for maintaining bone health in the pediatric population. Vitamin D deficiency may develop from nutritional deficiencies, malabsorption, enzyme-inducing medications, and many other etiologies. It may present as hypocalcemia before bone demineralization at periods of increased growth velocity (infancy and adolescence) because the increased calcium demand of the body cannot be met. In children, inadequate concentrations of vitamin D may cause rickets and/or symptomatic hypocalcemia, such as seizures or tetany. In this review, we will discuss the pharmacology behind vitamin D supplementation, laboratory assessments of vitamin D status, current literature concerning vitamin D supplementation, and various supplementation options for the treatment of vitamin D deficiency in the pediatric population.

INDEX TERMS cholecalciferol, ergocalciferol, pediatric, vitamin D deficiency

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INTRODUCTION

Vitamin D plays an essential role in maintaining bone health through regulating calcium concentrations in the body. The development of vitamin D deficiency is associated with deteriorating bone health and in severe cases, hypocalcemia, rickets, and osteomalacia in children and adults.[1] Those at greatest risk of vitamin D deficiency include patients with chronic illnesses (e.g., chronic kidney disease [CKD], cystic fibrosis [CF], asthma, and sickle cell disease), dark-pigmented skin, poor nutrition, and infants who are exclusively breastfed.[2,3] The primary source of vitamin D is sunlight exposure, which has been limited or blocked extensively for many children over the past 20 years due to the association of skin cancer and ultraviolet rays. Chronic use of certain medications (e.g., glucocorticoids, cytochrome P450 3A4 inducers, anticonvulsants, and antiretroviral agents) has also been associated with compromised vitamin D concentrations. Given the high rate of bone development early in life, adequate serum concentrations of vitamin D are crucial for the developing child. There has also been a piquing interest in vitamin D in pediatric patients due to the recent epidemiologic reports suggesting that vitamin D may protect against autoimmune disease and play a role in innate immunity.[2]

VITAMIN D DEFICIENCY

The serum concentration that constitutes vitamin D deficiency is controversial and not well supported by clinical trials, especially in the pediatric population. Deficiency is generally measured by the calcidiol concentration because of its long half-life of 2 to 3 weeks, relatively robust circulating concentration, and resilience to fluctuations in PTH concentrations.[4] Table 1 summarizes normal and abnormal serum vitamin D concentrations as classified by the American Academy of Pediatrics (AAP).[1,2,5,6] The AAP and the Institute of Medicine (IOM) both define vitamin D insufficiency as calcidiol (25-OH-D) concentrations < 20 ng/mL in the pediatric population.[1,7] In contrast, the Endocrine Society and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines both classify insufficiency as calcidiol concentrations < 30 ng/mL. The Endo-

Table 1. Vitamin D Status Based on Calcidiol Concentrations[1,7-9]

Vitamin D Status	Calcidiol (ng/mL)			
	AAP 2008, IOM	Endocrine Society	KDOQI	Adult – NEJM 2007
Severe deficiency	< 5	—	< 5	—
Mild to moderate deficiency	5-15	< 20	5-15	< 20
Insufficiency	16-20	21-30	16-30	20-30
Sufficiency	21-100	31-60	> 30	31-60
Excess	101-149	—	—	—
Intoxication	> 150	—	—	> 150

AAP, American Academy of Pediatrics; IOM, Institute of Medicine; KDOQI, Kidney Disease Outcomes Quality Initiative; NEJM, New England Journal of Medicine

crine Society defines deficiency as < 20 ng/mL, and KDOQI defines deficiency as < 15 ng/mL.[8,9] The definitions in these last 2 groups are more consistent with the classification system used in adults based on evidence of compromised bone health and elevations in parathyroid hormone (PTH) at calcidiol concentrations up to 32 ng/mL (80 nmol/L) (Table 1).[2,10]

In a vitamin D deficient patient, the intestinal absorption of calcium and phosphorus is decreased. The parathyroid gland recognizes the low serum calcium concentrations and releases PTH to increase the serum calcium back into an adequate range. PTH increases the calcium reabsorption in the kidneys and the excretion of phosphorus, therefore decreasing the risk of complication from an elevated calcium phosphate product (e.g., kidney stones). While this reduction is protecting the body, it is also decreasing bone mineralization at the same time. Over weeks to months, osteomalacia, stunted growth, and rickets may develop.[1] Studies have shown that over half of infants, children, and adolescents may be inadequately supplemented.[11,12] In 2008, the AAP published a review article with recommended target vitamin D concentrations for healthy infants, children, and adolescents (Table 1).[1,9,13]

In efforts to achieve and maintain the target vitamin concentrations, the AAP recommends all infants, children, and adolescents should receive a minimum daily intake of 400 international units of vitamin D to prevent rickets and to maintain vitamin D concentrations at > 20 ng/mL (50 nmol/L).[1] Term infants should be supplemented with 400 to 800 units daily to account for the insufficient transfer of maternal vitamin D stores and ensure calcidiol concentrations of > 20 ng/mL (50 nmol/L).[1] Preterm infants are more likely to be vitamin D deficient since their transplacental transfer from the mother was a shorter duration, hospitalization leading to a negligible amount of UV-mediated vitamin D formation, and possibly lower vitamin D stores due to a lower fat mass.[14] To address this population, the AAP published an expert opinion report in 2013 on the calcium and vitamin D requirements of enterally fed preterm infants.[14] Although there are no clinical outcome studies in this population, the AAP recommends 200 to 400 units per day of vitamin D supplementation in very low birth weight infants (<1500 g) and 400 units per day of vitamin D supplementation in infants weighing > 1500 g.[14] It is reasonable to consider increasing this dose to 1000 units per day in > 1500 g infants, as this is the established upper tolerable intake for healthy full-term infants. The calcidiol concentration goal in the preterm population remains the same as full-term infants (>20 ng/mL).[14] In 2010, the IOM issued guidelines that increased the recommended dietary allowance of vitamin D to 600 units daily for healthy children 1 to 18 years of age, which has been echoed by the Endocrine Society.[7,9]

PHARMACOLOGY

Our bodies obtain vitamin D in 2 different ways. The primary source of vitamin D_3 (cholecalciferol) comes from direct synthesis in our skin (>90%). Upon exposure to ultraviolet radiation, 7-dehydrocholesterol in our epidermal cells synthesizes vitamin D_3. The remainder of our need is typically obtained from dietary sources in either form, vitamin D_3 or vitamin D_2 (ergocalciferol). Both forms undergo hydroxylation in the liver to create the storage form of vitamin D, 25-hydroxy vitamin D (25[OH]-D, calcidiol, or calcifediol). Furthermore, in the kidneys, hydroxylation of calcidiol synthesizes the active

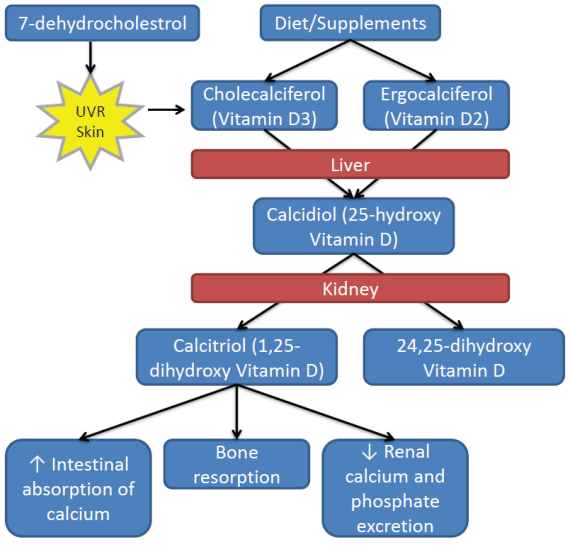

Figure. Vitamin D metabolism.[87]

metabolite, 1,25-dihydroxyvitamin D (1,25[OH]-D) (calcitriol). This pathway is visually depicted in Figure. Calcitriol is responsible for increasing calcium absorption, bone resorption, and decreasing renal calcium and phosphate excretion to maintain bone health.[15] The synthesis of calcitriol is mediated by PTH, serum phosphate concentration, and growth hormone, and may occur in non-renal sites, such as alveolar macrophages and osteoblasts.[2,16] Additionally, vitamin D has extraskeletal responsibilities, with vitamin D receptors in the small intestine, colon, osteoblasts, activated T and B lymphocytes, beta islet cells, and major organs (brain, heart, skin, gonads, prostate, breast, and mononuclear cells).[2,16] The immunologic effects of vitamin D have stimulated great interest, but studies in these areas are currently limited in pediatric patients.

MEDICATION INDUCED VITAMIN D DEFICIENCY

Metabolism of dietary vitamin D to calcidiol occurs in the liver through the cytochrome P450 enzyme system. Certain classes of medications act on this enzyme system to increase the metabolism of vitamin D and therefore reduce the body's systemic exposure to active vitamin D concentrations. Some anti-epileptic drugs (AEDs) are inducers of the cytochrome P450 system (phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone). Aside from the detrimental bone effects of vitamin D deficiency, rapid decreases in calcium may precipitate a seizure, further complicating the clinical picture (e.g., etiology of seizures). Valproic acid, though it is an inhibitor of the enzyme system, increases bone turnover through increasing osteoclast activity and therefore tilting the balance of bone formation and bone resorption.[17,18]

Recommendations have been made for all patients on an AED to receive a preventative dose of vitamin D 400 to 2000 units per day.[17] Patient characteristics such as baseline calcidiol concentration, polypharmacy, and sun exposure should help guide vitamin D therapy as well. Patients diagnosed with AED-induced osteoporosis may need larger doses of vitamin D replacement therapy to correct biochemical abnormalities (PTH, calcium, and phosphorus).[18] Calcidiol concentrations should be monitored (prior to or at the start of AED initiation) and then yearly thereafter. If diagnosed with vitamin D deficiency, initiating therapy with the standard dosing recommendation for children with vitamin D deficiency is acceptable; however, the doses may need to be increased according to the calcidiol concentrations, which should be measured monthly during treatment. Doses of 5000 to 15,000 units per day have been used for AED-induced osteomalacia.[17]

Rates of vitamin D insufficiency are high in pediatric patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome due to the disease itself and the life-saving highly active antiretroviral therapy (HAART). Rutstein and colleagues[19] compared the rates of vitamin D deficiency/insufficiency in children and young adults with HIV to a healthy group. Vitamin D deficiency/insufficiency was present in 36% and 89% of those with HIV (84% on HAART therapy) compared to 15% and 84% of the comparison group, respectively. Protease inhibitors inhibit the cytochrome P450 enzyme system and decrease the production of active vitamin D (calcitriol). Nucleoside reverse transcriptase inhibitors have also been linked to vitamin D deficiency through increased lactate concentrations and not due to cytochrome P450 inhibition. Due to the presence of multiple risk factors for osteoporosis and the high prevalence of deficiency, all patients on HAART should be screened annually for vitamin D deficiency and encouraged to maintain sufficient calcium and vitamin D intake.[20]

Other drug classes that may affect the absorp-

Table 2. Vitamin D Content of Foods[88]

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

IU, international unit
**Infants consuming ≥ 1 L of formula daily do not require additional supplementation*

tion, metabolism, or activation of vitamin D include corticosteroids, azole antifungals, and cytochrome P450 3A4 inducers. Although there is no formal recommendation for monitoring, annual monitoring of calcidiol concentrations may be warranted in pediatrics receiving these medications.[21]

SOURCES OF VITAMIN D

UV Radiation and Cutaneous Cholecalciferol Synthesis

Cutaneous synthesis of vitamin D is a significant source of vitamin D replenishment. The amount of vitamin D synthesized by our skin depends on a number of factors: the age of the individual, the amount of skin exposed, the duration of exposure, geographic-related factors (i.e., latitude, season, time of day, shade, and air pollution), sun block use, and the skin pigment of the individual.[1,2] Holick[2] estimates exposure of the body in a bathing suit to 1 minimal erythemal dose (MED or the dose of radiation that causes a slight pinkness to the skin 24 hours after exposure) equals about 20,000 units. Thus, exposure of arms and legs to 0.5 MED approximates ingesting 3000 units of vitamin D_3. Studies have shown that children, especially infants, may require less sun exposure than adults to produce adequate vitamin D concentrations because of greater surface area to volume ratio and enhanced ability to produce vitamin D than older people.[22] A study in 1985 found that 30 minutes of sun exposure for infants in diapers or 2 hours for fully clothed infants without a hat maintained weekly calcidiol concentrations of 11 ng/mL (27.5 nmol/L).[23] The AAP recommends that children younger than 6 months be kept out of direct sunlight to reduce the risks of skin cancer.[24] Currently, there are no recommendations available to validate the appropriate duration of sun exposure in the pediatric population, and the variability of vitamin D synthesis between individuals would make such a recommendation difficult. The lack of data and the risks associated with prolonged sun exposure suggest food and supplementation as the preferred mode of repleting vitamin D stores.

Dietary Sources of Vitamin D

There are many natural food sources of vitamin D_2 and vitamin D_3, including oily fish (e.g., salmon, mackerel), cod liver oil, organ meats, and egg yolks (Table 2). However, these products are not particularly kid-friendly and routine adequate intake may be difficult. In the United States (US), there are fortified food options, including infant

Table 3. Available Formulations of Vitamin D[89]

Dosage Form	Strength	Trade Names
Vitamin D2 (ergocalciferol)		
Oral solution	8000-IU/mL (may contain propylene glycol)	Calcidiol, Calciferol, Drisdol,
Capsule	50,000-IU	Drisdol
Tablet	400-IU	Various
Vitamin D3 (cholecalciferol)		
Oral drops	400-, 1000-, 2000-IU/drop	Baby D drops, D drops
Oral solution	400-IU/mL	D-Vi-Sol, Just D
Capsule	400-, 1000-, 2000-, 5000-, 25,000-IU	Dialyvite, Decara (25,000-IU)
Tablet	400-, 1000-, 2000-, 5000-IU	Thera-D
Chewable tablet	400-, 1000-, 2000-, 5000-IU	Various
Dispersible tablet	2000-IU	Various
1,25-Dihydroxy Vitamin D (calcitriol)*		
Oral solution	1-mcg/mL	Rocaltrol
Capsule	0.25-, 0.5-mcg	Rocaltrol
Solution for injection	1-mcg/mL (may contain EDTA)	Calcijex

EDTA, ethylenediaminetetraacetic acid; IU, international unit
**1 mg = 40,000 IU of vitamin D activity*

formula, milk, and orange juice, to help meet needs. Also, all infant formulas sold in the US contain at least 400 units/L of vitamin D.[25]

Vitamin D in Breast Milk

Breast milk contains very little vitamin D, an average of 22 units/L (range 15 to 50 units/L) in a vitamin D-sufficient mother.[26] Recent studies suggest that maternal intake of higher than recommended doses of vitamin D (4000 to 6400 units daily) may achieve vitamin D concentrations in breast milk to provide sufficient vitamin D supplementation for breastfeeding infants. However, this approach is not recommended.[27,28] Due to the low vitamin D concentrations found in breast milk, the newest recommendation for exclusively breastfed infants is to provide a supplement of 400 units per day (increased from 200 units per day).[1]

Vitamin D Formulations

Vitamin D is available commercially as ergocalciferol, cholecalciferol, and calcitriol. Ergocalciferol and cholecalciferol, once thought to be equipotent, may increase vitamin D stores to varying degrees. Recent evidence suggests that cholecalciferol increases calcidiol concentrations two- to threefold more than ergocalciferol.[29,30] The formulations available in the US are summarized in Table 3 and the vitamin D content of commonly used pediatric multivitamins in Table 4. Despite the evidence suggesting the pharmacodynamic differences between cholecalciferol and ergocalciferol, most guidelines do not have a preference between the 2 products.[1,7,9] However, the KDOQI and Cystic Fibrosis Foundation (CFF) guidelines prefer vitamin D_2 due to safety data in animals.[8,31,32] There are no direct comparisons of the 2 formulations and in general, calcitriol does not have a role in repleting vitamin D stores.

VITAMIN D SUPPLEMENTATION IN CHRONIC DISEASE

Vitamin D Deficiency Rickets

Severe vitamin D deficiency can lead to symptomatic hypocalcemia, which can result in seizures, osteomalacia, or rickets. Rickets involves bone demineralization that occurs in areas adjacent to the growth plate.[1] The exact prevalence of rickets is unknown. However, case reports and case series of documented rickets suggest this problem still exists today.[1] Rickets may be caused by reasons other than nutritional vitamin D deficiency (e.g., calcium and phosphorus deficiency, inherited forms of hypophosphatemic rickets, and vitamin D receptor mutations); however, these etiologies will not be discussed in this review.

Dosing

For the treatment of vitamin D deficiency rickets, the AAP recommends an initial 2- to 3-month regimen of "high-dose" vitamin D

Table 4. Vitamin D, Calcium, and Phosphorous Content of Common Multivitamins[90]

	Vitamin D2 or D3 (IU)	Calcium (mg)	Phosphorous (mg)
Infant multivitamin drops (per mL)*			
AquADEKs†	400	—	—
D-Vi-Sol	400	—	—
Enfamil Poly-Vi-Sol	400	—	—
SourceCF	500	—	—
Tri-Vi-Sol	400	—	—
Vitamax†‡	400	—	—
Multivitamin Tablet (per tablet)			
ADEK (chewable)	400	—	—
AquADEKs (soft gel)	800	—	—
Centrum	400	200	20
Centrum Kids Complete	400	100	100
Flintstones Complete	400	108	50
Flintstones Sour Gummies	100	—	—
Phlexy-Vits (7-g packet)	400	1000	775
Source CF (chewable, soft gel)	1000	—	—
Vitamax (chewable)	400	—	—

IU, international unit
**Standard dose = 1 mL*
†Recommended for use in infant with fat malabsorption (e.g., cystic fibrosis, liver disease)
‡Sold exclusively via Cystic Fibrosis Services Pharmacy

therapy of 1000 units daily in neonates, 1000 to 5000 units daily in infants 1 to 12 months old, and 5000 units daily in patients over 12 months old.[1] These recommendations are summarized in Table 5. Although radiologic evidence of healing occurs within 2 to 4 weeks of treatment, large dose treatment (of either vitamin D_3 or D_2) should be continued for 2 to 3 months.[1] After sufficient calcidiol concentrations are achieved, a maintenance dose of 400 units of vitamin D daily is recommended in all age groups.[1] Larger maintenance doses (800 units per day) may be considered in the following at-risk populations: premature infants, dark-skinned infants and children, children who reside in areas of limited sun exposure (>37.5° latitude), obese patients (due to fat sequestration of vitamin D), and those on medications known to compromise vitamin D concentrations discussed in this review.[1,9,33]

In patients where daily compliance is a concern, an alternative dosing strategy can be utilized for the treatment of vitamin D deficiency, known as "stoss therapy," from the German word *stossen*, meaning "to push." For patients over 1 month of age, 100,000 to 600,000 units of vitamin D can be given orally as a single dose, followed by maintenance doses.[34,35] When instituting this approach, liquid formulations (e.g., Drisdol) should be avoided to prevent potential propylene glycol toxicity.[35] Calcitriol is also not preferred for stoss therapy as it has a short half-life and does not build up vitamin D body stores. Strategies to safely institute stoss therapy include crushing 25,000 units or 50,000 units tablets or softening 50,000 units gel capsules in water and blending in foods, such as applesauce.[35] Stoss therapy has been successfully implemented using intramuscular formulations as well; however, this option will not be explored since this product is no longer available in the US.

Evidence

Evidence in infants, children, and adolescents are sparse concerning what dose corrects vitamin D deficiency rickets. Current recommendations have been made based on expert opinion.[1,22] There is, however, published evidence on the safety and efficacy of stoss therapy in children with clinical and biochemical evidence of vitamin D deficiency.[34-37] Shah et al[35] administered 300,000 or 600,000 units of vitamin D_2 orally (100,000 units every 2 weeks) to 42 patients with vitamin D deficiency rickets between 5 and 109 months of age. At 14 days postadministration, radiographic evaluations confirmed the efficacy of this regimen. However, routine use of stoss therapy has

Table 5. Vitamin D Dosing for Prevention and Treatment of Nutritional Vitamin D Deficiency in Children[1]

	Vitamin D Supplementation (Cholecalciferol)
Prevention	400 IU/day
Treatment	< 1 month: 1000 IU/day orally for × 2-3 months
	1–12 months: 1000–5000 IU/day orally for × 2-3 months
	> 12 months: 5000 IU/day orally for × 2-3 months

IU, international unit

overwhelming risk of hypercalcemia; 34% of infants who received 600,000 units of vitamin D every 3 to 5 months during the first one and a half years of life reported hypercalcemia.[38] A study involving Turkish children and adolescents 12 to 17 years old showed intake of < 100 units of vitamin D was inadequate, resulting in calcidiol concentrations < 11 ng/mL.[39] The 2003 AAP guideline recommendations were based on the premise that 200 units daily of vitamin D would achieve calcidiol concentrations > 11 ng/mL to prevent rickets. Since then, more studies have shown rickets can manifest in patients with calcidiol concentrations up to 20 ng/mL.[40,41] In the past, doses of cod liver oil equal to 400 units of vitamin D daily achieved calcidiol concentrations > 20 ng/mL without concerning adverse effects.[42,43] Based on this evidence, most guidelines recommend at least 400 units of vitamin D daily.[1,7,9] Clinical trials are still needed to exactly determine the dose of vitamin D to achieve optimal calcidiol concentrations as well as the calcidiol concentration required to prevent bone demineralization and rickets in the pediatric population.

Vitamin D Deficiency in CKD

Epidemiologic studies suggest that patients with CKD are at an increased risk for vitamin D deficiency due to reduced sun exposure, lower intake of foods rich in vitamin D, and increased melanin content of the skin observed in this population.[8,44,45] In a cohort of children with CKD from 2005 to 2006, the prevalence of vitamin D deficiency was 39% (n=88) with the mean 25(OH) D concentration of 21.8 ng/mL.[46] Additionally, these patients exhibit physiologic challenges that increase risks for deficiency, including decreased endogenous production, decreased intestinal absorption, decreased enzyme activity to form functional vitamin D in the kidneys, and in those with proteinuria, increased urinary loss of calcidiol, and vitamin D-binding protein.[32,47-50] In patients with CKD, vitamin D supplementation appears to have benefit in preventing or reducing hyperparathyroidism that occurs as a part of renal osteodystrophy to repair bone and mineral disturbances.[32] The recommendations we will explore concerning vitamin D supplementation in pediatric patients with CKD were developed based on data observed in the adult population. However, since the publication of the KDOQI guidelines, more information is available in the literature about vitamin D deficiency in pediatric patients with CKD.

Dosing

Table 6 summarizes the recommendations in the pediatric KDOQI guidelines for patients with vitamin D insufficiency or deficiency.[8] Patients with calcidiol concentrations > 30 ng/mL are indicated for larger initial doses of vitamin D than those with adequate calcidiol concentrations. Of note, the guidelines prefer vitamin D_2 as the supplement of choice over vitamin D_3 due to safety data in animals.[8,31,51] However, vitamin D_3 is noted as an acceptable alternative. Calcidiol concentrations should be measured at 3 months of therapy, to assess the need for further treatment, and annually, once concentrations are adequate.[8] Additionally, serum corrected calcium concentrations and phosphorous concentrations should be assessed at 1 month and every 3 months.[8] If total serum corrected calcium exceeds 10.2 mg/dL or if serum phosphate exceeds the upper limit for age and calcidiol concentrations are normal, vitamin D may be discontinued. Otherwise, once calcidiol concentrations are deemed adequate, maintenance doses of vitamin D_2 (400 units daily) should be resumed.[7,8] For non-compliant patients, vitamin D can be administered as a single oral dose of 50,000 units monthly.[35,52]

Evidence

The prevalence of vitamin D insufficiency or deficiency in the pediatric population with CKD varies in recent literature from 39% to 77%.[46,53] Risk factors for more advanced deficiency include advanced CKD, non-Caucasian ethnicity,

Table 6. Recommendations for Vitamin D Supplementation in Children with CKD Stages 2 to 4[8]

Vitamin D Status*	Calcidiol (ng/mL)	Vitamin D2 Dose
Severe deficiency	< 5	Initial dose: 8000 IU/day orally or 50,000 IU/week orally × 4 weeks; then 4000 IU/day orally or 50,000 IU twice monthly orally × 2 months
Mild deficiency	5 to 15	4000 IU/day orally or 50,000 IU every other week orally × 3 months
Insufficiency	16 to 30	2000 IU/day orally or 50,000 IU every 4 weeks orally × 3 months

IU, international unit
**Hold vitamin D if calcium ≥ 10.2 mg/dL or if phosphorus exceeds the upper limit for age and calcidiol is normal. If phosphorus exceeds the upper limit for age and calcidiol is < 30 ng/mL, initiate oral phosphate binder therapy*

overweight or obesity, and lack of sun exposure.[46,53] In a retrospective, single center study of 57 children (mean age 11 years) with CKD (stages 2 through 4), vitamin D_2 was used for 12 weeks at doses recommended in the KDOQI guidelines to successfully replete vitamin D stores.[54] Of note in this study, PTH concentrations decreased from 122 to 80 ng/mL after treatment. In a study involving adults with CKD, administration of vitamin D_2 increased calcidiol concentrations from 17 to 27 ng/mL ($p<0.05$) and decreased PTH concentrations from 231 to 192 pg/mL ($p<0.05$) after 6 months.[55] In Zisman et al,[56] 52 adult patients with CKD (stage 3 or 4), vitamin D deficiency, and hyperparathyroidism observed normalization of calcidiol concentrations ($p<0.05$) and decrease in PTH concentrations from 13.1% to 2.0% (non-significant p-value) with vitamin D_2 supplementation. A prospective trial in pediatric patients with moderate CKD showed increased mean growth velocity into the normal range after 1 year of vitamin D therapy, which continued in the subsequent 2 years of treatment.[57]

Calcitriol

In vitamin D deficiency, calcitriol is not recommended as initial therapy or for routine use because of its short half-life and inability to increase vitamin D stores. Doses are limited because of its rapid onset and risk of hypercalcemia. However, calcitriol has utility in children with CKD stages 2 to 5 for the treatment of secondary hyperparathyroidism.[58] Additionally, it can be used as an adjunct to calcium supplementation for patients with severe vitamin D deficiency with severe symptomatic hypocalcemia, including seizure and tetany.[58] As kidney function continues to decline, the enzyme activity of 1-alpha hydroxylase decreases and therefore, calcitriol preparations may be needed rather than vitamin D_2 or D_3 preparations.

Vitamin D Deficiency in CF

With the increase in life expectancy from 2 to 36 years in the last 40 years, bone disease has transpired as a common complication in patients with CF with low bone mineral density observed in 50% to 75% of patients.[59] There are a myriad of contributory risk factors including malnutrition, vitamin D deficiency due to malabsorption from pancreatic insufficiency, inadequate absorption of calcium, physical inactivity, altered sex hormone production, chronic lung infection with elevated level of bone-active cytokines, and glucocorticoid use in this population. Maintaining optimal vitamin D stores in this population is especially important because severe bone disease may exclude these individuals from being qualified for lung transplantation. Guidelines from the CFF's Consensus Conference on Bone Health recommend that vitamin D_2 supplementation be given to maintain calcidiol concentrations ≥ 30 ng/mL.[59] However, a more recent study published in 2011 suggests that 35 ng/mL is the more appropriate cut off, where PTH is < 50 pg/mL and bone resorption and fracture risk is decreased.[60]

Dosing

In CF patients with insufficient calcidiol concentrations, doses up to 50,000 units of vitamin D_2 daily for several months may be necessary for initial treatment.[61] For maintenance therapy, the CFF guidelines recommend at least 400 units and 800 units of vitamin D_2 daily for infants and patients over 1 year of age, respectively.[62] However, as supported by the literature, these doses have been found not to sustain calcidiol concentrations in this population and therefore, doses should be titrated to obtain calcidiol concentrations > 30 to 35 ng/mL. Dosing recommendations for children younger than 5 years old are vitamin D_2 12,000 units biweekly, and 50,000 units weekly or biweekly of vitamin D_2 for those 5 years and older.[59]

Very high dosing strategies such as 700,000 units of vitamin D_2 over 14 days have been safely administered to a pediatric CF population with successful adequate calcidiol concentration.[63] If high dose vitamin D_2 is inadequate, more polar vitamin D analogs, calcitriol, or phototherapy may be reasonable alternatives.[59] Of note, the treatment doses are recommended in addition to the daily recommended maintenance therapy these patients are receiving.[62]

Evidence

Given that the majority (60%) of the 60,000 patients with CF in North America and Europe are under the age of 18, studies concerning vitamin D status in patients with CF often involve pediatric patients.[59] In a retrospective chart review of 147 concentrations from 97 pediatric individuals with calcidiol concentrations < 30 ng/mL, 50,000 units of vitamin D_2 daily for 28 days resulted in approximately half achieving concentrations > 30 ng/mL.[61] This initial regimen was more successful than vitamin D 250,000 units 1, 2, or 3 times a week for 8 weeks in pediatric patients.[64] Long-term follow-up (6 to 18 months posttreatment) in 39 patients showed 48% of those who achieved sufficient calcidiol concentrations became insufficient on maintenance doses of 400 to 800 units of vitamin D_2.[61] In a 2011 trial of adult patients with CF, patients with calcidiol concentrations < 30 ng/mL were given 50,000 units of vitamin D_2 daily for 30 days followed by maintenance doses of vitamin D_3 800 to 1000 units daily. After 30 days of treatment, serum calcidiol increased from 15.1 to 48.7 ng/mL ($p<0.05$) without any concerning side effects. However, adequate concentrations were not sustained on maintenance doses. The mean serum calcidiol dropped to 18.9 ng/mL ($p<0.05$), and 50% of treated patients became vitamin D insufficient within 1 year.[60] In a study of 20 adolescent and adult patients with CF, administration of 800 units daily of vitamin D was inadequate for 40% of patients after 4 to 10 weeks of therapy.[65] In another study of exclusively adult CF patients, administration of vitamin D_3 (>400 units daily) increased calcidiol concentrations in 92% of patients; however, normalized calcidiol concentrations were achieved in only 17% of patients and no assessment on the most appropriate dose was made.[66] In a study conducted by Kelly et al,[67] 95% of adult CF patients required 1800 units of vitamin D_2 daily to achieve calcidiol concentrations above 25 ng/mL. Although supplementation with calcitriol does not replete vitamin D stores, it may be an option for CF patients unresponsive to vitamin D_2 and D_3 to manage consequences of vitamin D deficiency. Brown et al[68] reported that calcitriol (0.5 mcg daily for 14 days) increased the fractional absorption of calcium ($p<0.05$) and lowered PTH ($p<0.03$) in 10 adults with CF.

Vitamin D Deficiency in Sickle Cell Disease

Pain crisis is a hallmark of sickle cell disease. The symptoms of pain crisis are thought to be somewhat similar to the symptoms that one would experience with vitamin D deficiency. For example, in both conditions, pain is characterized by an aching and dull pain. The location of the pain can be limited to the extremities and lower spine. It can be exacerbated by increased activities and exertion.[2,69-71] Because of these similarities, studies have looked at the prevalence of vitamin D deficiency in the sickle cell population. In fact, in 1 recent study that was performed in Madrid, Spain, 56% of children with sickle cell had concentrations of vitamin D < 20 ng/mL and 18% of them had concentrations < 11 ng/mL.[72] The ranges of prevalence from other studies, however, were as high as 65% to 100%.[73-75] Supplement of vitamin D may help alleviate the pain experienced by patients with sickle cell disease and improve their overall bone health.

Evidence

Evidence of vitamin D supplementation in children and adolescents with sickle cell disease are limited. In 1 case report, a 16-year-old female with homozygous SS disease presented with chronic pain involving many parts of her body, which included the lower extremities, left shoulder, and neck.[76] Her pain was not alleviated by ibuprofen, pregabalin, amitriptyline, or various opioids (totaled about 40 mg equivalents of morphine daily). A detailed metabolic workup was performed, and she was found to have a vitamin D concentration of < 7.9 ng/mL. Because of this finding, she was started on cholecalciferol 50,000 units orally twice a week for 8 weeks. At the end of this course of therapy, her vitamin D concentration had jumped up to 47 ng/mL and was switched to cholecalciferol 50,000 units once weekly. By week 14, her concentration was at 30 ng/mL, and she had complete alleviation of all

her pain symptoms and her bone mass density increased by 11% in 2 years.

Because of the success found in the previous case report, the same investigator performed a randomized, double blind pilot study in 2012, in which subjects (n=46; 13.2 ± 3.1 years) with sickle cell disease were given either high dose cholecalciferol (40,000 to 100,000 units weekly) or placebo for 6 weeks.[77] Approximately 53% and 83% of the subjects were initially found to have vitamin D insufficiency and deficiency, respectively. The treatment group was found to have fewer pain days per week, higher quality-of-life scores, and higher serum 25-hydroxyvitamin D concentrations. The authors suggested that a larger study with longer duration will need to be performed to validate this result. In fact, at the hospital where one of the authors of this review article works, he also had successes in using cholecalciferol 50,000 units orally twice a week in 2 pediatric patients with sickle cell disease, and their pain scores were greatly reduced.

Even with theses success stories, numerous questions still remain about the use of vitamin D supplementation in sickle cell disease, such as 1) what is the optimal dose of cholecalciferol, 2) what is the duration of therapy, 3) what are the long-term side effects of such a large dose therapy in the pediatric population, 4) does it work for all forms of sickle cell disease, and 5) will this therapy work for patients without vitamin D deficiency?

Vitamin D Deficiency in Asthma

Asthma is a common diagnosis found in the pediatric population. Scientists hypothesize that the increased prevalence of asthma may be in part due to the rise of vitamin D deficiency in the pediatric population.[78] Maternal intake of vitamin D during pregnancy may also play a role in the children's risk of having wheezing symptoms.[79] In fact, some studies have described an association between vitamin D deficiency and asthma, while one has not.[80-82] We will look at the evidence on the association between vitamin D deficiency and asthma and the need of vitamin D supplementation in patients with this clinical condition.

Evidence

Limited data exist on vitamin D concentrations in children with asthma. A case control study was performed at a pediatric allergy and immunology clinic in Qatar.[81] The aim of the study was to describe the association between asthma and vitamin D in children and to look at the difference in vitamin D concentrations in asthmatic children (7.0 ± 3.8 years) and control (8.4 ± 3.6 years). In this study, vitamin D deficiency was found to be more prevalent in asthmatics than controls. The mean value of vitamin D was 17.5 ± 11 ng/mL in the group with asthma and 20.8 ± 10.0 ng/mL in the controlled group. Elevated serum immunoglobulin E was observed in patients with lower vitamin D concentrations.[13]

In another cross-sectional study, serum 25-hydroxyvitamin D3 concentrations were compared between the group with asthma (n=50) and the healthy group (n=50).[80] The age of the subjects ranged from 6 to 18 years. The results of this study showed that vitamin D concentrations had direct correlations with both the forced expiratory volume/forced vital capacity (FEV1/FVC) ratio and the predicted FEV1 (p=0.024 and p=0.026, respectively), meaning that the less the vitamin D concentrations, the more significantly increased odds of the subjects' asthmatic state. However, the state of vitamin D deficiency was not associated with the duration of disease, number of hospitalization, and the eosinophil counts.[80]

On the other hand, one retrospective, case-control study did not find an association between asthma severity and serum 25-hydroxyvitamin D concentrations.[82] In this study, 263 subjects with asthma were compared to 284 normal subjects (ages: 2 to 19 years). Their asthma symptoms were assessed and serum vitamin D concentrations were obtained. No significant difference in vitamin D concentrations was found between the asthmatic group and the controlled group, and the severity of asthma symptoms was not correlated with the vitamin D concentrations.[82]

Oral or intravenous corticosteroids are often used as a regimen for patients with asthma exacerbation. If the patients' asthma is not well-controlled, they may potentially be exposed to repeated courses of corticosteroids. Long-term or repeated course of corticosteroids is known to cause vitamin D deficiency.[83] One may wonder is the decrease in serum vitamin D concentrations in children with asthma due to the disease itself or the use of corticosteroids. To answer part of this question, a retrospective review was performed in 100 asthmatic children looking at the patients' characteristics and their vitamin D concentrations.[84] This study showed that the total ste-

roid dose, the use of oral steroids, and the use of inhaled steroids were associated with an inverse correlation with their vitamin D concentrations (p=0.001, p=0.02, and p=0.0475, respectively).[17] There may be a never ending cycle in which poor control of asthma will lead to the use of inhaled and oral corticosteroid, which in turn may cause a reduction in vitamin D concentrations, which in turn may worsen the patients' asthmatic state.

The next question that one would ask is: does vitamin D supplementation improve the clinical course of asthma? The addition of vitamin D supplementation was evaluated in a study of subjects with steroid-resistant asthma.[85] After exposing a small amount of vitamin D (5×10^{-7} M) to cultures of CD4+ regulatory T cells, the secretion of IL-10 was greatly increased in this steroid-resistant group and was comparable to the concentrations seen in the controlled group. Similarly, in an experimental model of asthmatic patients, the addition of vitamin D helped decrease the dose of dexamethasone by 10-fold.[86] The authors of this study postulated that vitamin D supplementation may increase the anti-inflammatory property of corticosteroid in asthmatic patients by enhancing the glucocorticoid-induced mitogen-activated protein kinase phosphatase-1 expression.[86]

Before starting every asthmatic patient on vitamin D supplementation, larger studies need to be performed to evaluate the efficacy of this regimen in improving the clinical course of asthma and reducing the need of steroid use in asthmatic patients. Also, studies need to look at the optimal dose and duration of use for this clinical condition.

CONCLUSION

Vitamin D insufficiency is a common problem in pediatrics, especially those who have chronic illness, and who are malnourished, limited geographically to the amount of sun exposure, as well as those with darker skin, and on chronic medications. The accelerated rate of bone development during a child's life suggests that adequate concentrations of vitamin D are an important issue in this population. Although more research is needed concerning the goals of vitamin D therapy and dosing in this population, there are helpful evidence-based guidelines to direct therapy for rickets, CKD, and CF. More research is needed to evaluate the efficacy of vitamin D supplementations for pediatric patients with asthma and sickle cell disease. In patients with growth delays or reasons to suspect deficiency, calcidiol concentrations should be evaluated to assess the need for supplementation.

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ABBREVIATIONS AAP, American Academy of Pediatrics; AEDs, anti-epileptic drugs; CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CKD, chronic kidney disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IOM, Institute of Medicine; IU, international units; KDOQI, Kidney Disease Outcomes Quality Initiative; NEJM, New England Journal of Medicine; PTH, parathyroid hormone; US, United States

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