

Vitamin Excess and Deficiency

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Education Gap

Vitamins are organic compounds that humans cannot synthesize but need in small amounts to sustain life.

Pediatricians' knowledge about vitamins is challenged daily. Pediatricians are faced not only with parents requesting supplements but also with parents refusing them when they are clinically indicated.

In addition, pediatricians need to be familiar with the effect of maternal health and diet on human milk to counsel their patients on how to prevent potentially devastating health consequences for the breastfed infant.

Tables 1 and 2 provide the reader with a quick reference to who is at risk and when to consider a vitamin or mineral deficiency (minerals will be covered in the second part of this review). Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D and Table 4 provides a quick reference for diagnostic tests and treatment doses for vitamin deficiencies.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
CT	computed tomography
DRIs	Dietary Reference Intakes
FDA	Food and Drug Administration
ICH	intracranial hemorrhage
IF	intrinsic factor
IM	intramuscular
IOM	Institute of Medicine
MMA	methylmalonic acid
NASH	nonalcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NTD	neural tube defect
PIVKA	proteins induced by vitamin K absence
PTH	parathyroid hormone
RAE	retinol activity equivalent
RDA	Recommended Dietary Allowance
UL	Tolerable Upper Intake Level
VKDB	vitamin K deficiency bleeding
1,25(OH) ₂ D	1,25 dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

Objectives After completing this article, readers should be able to:

1. Discuss the risk factors for developing selected vitamin deficiencies.
2. Identify the role of natural foods, fortified foods, and supplements in meeting the Dietary Reference Intakes of various vitamins.
3. Discuss the biological functions of various vitamins and their role in disease prevention.
4. Describe the clinical symptoms of various vitamin deficiencies and the role of laboratory data in making the diagnosis.
5. Explain treatment and prevention strategies for various vitamin deficiencies.

Abstract

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. Pediatricians today are faced with questions from parents and patients about the benefits, safety, efficacy, and correct dose of vitamins and minerals. In this article, we review 7 vitamins with the most clinical relevance as judged by abundance in food, risks and symptoms of deficiency, and potential for

toxicity. Specifically, we focus on possible clinical scenarios that can be indicative of nutritional deficiency. We synthesize and summarize guidelines from nutrition experts, various medical societies, the World Health Organization, and the American Academy of Pediatrics.

PREVALENCE OF SUPPLEMENT USE IN THE UNITED STATES

The published literature supports the high prevalence of supplement use in children and adolescents in the United States. According to the National Health and Nutrition Examination Survey (NHANES), 34% of US children and adolescents used supplements in the past month, and almost half of those took a supplement daily. Supplement use was high in underweight patients. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to health care. (2)

THE DIETARY REFERENCE INTAKES

According to the Institute of Medicine (IOM), the Dietary Reference Intakes (DRIs) include 4 nutrient-based reference values that are used to assess and plan the diet of healthy people:

- Estimated Average Requirement: the average daily nutrient intake level that is sufficient to meet the requirements of half of the healthy population of a particular age and sex
- Recommended Dietary Allowance (RDA): the average daily nutrient intake level that is sufficient to meet the requirements of nearly all (97%–98%) of the healthy individual of a particular age and sex
- Adequate intake: the recommended average daily intake level based on estimated intake of apparently healthy people; adequate intake is used when RDA cannot be determined
- Tolerable Upper Intake Level (UL): the highest average daily nutrient intake level that is unlikely to pose a risk of adverse effects to almost the whole general population (3)

VITAMIN A (RETINOL)

Introduction

Until the 1980s, the focus on vitamin A deficiency was limited to its ocular manifestations as the leading cause of

blindness in developing countries. However, in the past 3 decades, international studies indicate that subclinical vitamin A deficiency has broader consequences regarding childhood morbidity and mortality in the developing world. Vitamin A deficiency accounts for 1.7% of all deaths in children younger than 5 years in developing countries. (4)

Case

J.H. is a 14-year-old with autism who presented to the emergency department for evaluation because he fell off the school bus. J.H.'s mother reports that recently he has been keeping his eye closed and he has been walking with his arms outstretched. J.H. was born full-term and has no other health conditions except for autism. J.H.'s diet consisted of crackers and chips only, and he was not taking any vitamins or supplements. On physical examination, J.H. looked underweight (body mass index, 13 [<5 th percentile for age and sex]) and was agitated. Results of a head computed tomographic (CT) scan and a lumbar puncture were negative, so J.H. was discharged. On follow-up with his primary care doctor, bilateral corneal lesions were noted, so J.H. was referred for an urgent ophthalmology evaluation. J.H. was diagnosed as having xerophthalmia and corneal ulcers secondary to vitamin A deficiency. J.H. was treated with high-dose vitamin A. Two years later, on ophthalmology follow-up he was noted to be able to see objects and ambulate without assistance, but he had complete opacification of his left cornea and a corneal scar in his right eye.

Sources and DRIs

Vitamin A is the collective name for a family of fat-soluble compounds referred to as retinoic acids. There are 2 forms of dietary vitamin A. Preformed vitamin A is found in supplements and food from animal sources, such as fortified dairy products and liver. Provitamin A carotenoids are dietary precursors of retinol. The most important provitamin A carotenoid is β -carotene, which is found in carrots, broccoli, squash, peas, spinach, and cantaloupe. (3)

The RDAs for vitamin A are given as micrograms of retinol activity equivalents (RAEs) to recognize the different bioactivities of retinol and β -carotene. However, food and supplement labels state vitamin A levels in International Units. (3)

TABLE 1. Clinical and Laboratory Indicators of Selected Nutritional Deficiency States

FINDING	SUSPECTED MICRONUTRIENT DEFICIENCY
Skin	
• Dry skin (xerosis)	Vitamin A
• Petechiae, purpura	Vitamin C or vitamin K
• Ecchymosis, mucosal bleeding	Vitamin C or vitamin K
• Perioral and perianal rash	(Zinc)
• Poor wound healing	Vitamin C, (zinc)
Eyes	
• Bitot spots	Vitamin A
• Keratomalacia, conjunctival xerosis	Vitamin A
Mouth	
• Stomatitis and/or glossitis	Vitamin B ₁₂ , folate
• Bleeding and swollen gums	Vitamin C
Skeletal	
• Genu varum or valgum	Vitamin D
• Epiphyseal widening (especially wrists)	Vitamin D
• Costochondral beading	Vitamin D
• Bone pain	Vitamin C, (vitamin A toxicity)
• Refusal to walk, joint swelling	Vitamin C
Neurologic	
• Sensory loss	Vitamin B ₁₂ , vitamin E
• Ataxia	Vitamin B ₁₂ , vitamin E
• Loss of deep tendon reflexes	Vitamin B ₁₂ , vitamin E
Anemia	
• Microcytic	(Iron)
• Macrocytic	Vitamin B ₁₂ , folate
• Hemolytic	Vitamin E

Micronutrients in parentheses are not covered in this article.

When reading supplement labels it is important to note that 1 μg RAE = 1 μg retinol = 2 μg β -carotene (supplement) = 12 μg β -carotene (dietary) = 3.3 IU. (3)

Infants aged 0 to 1 year require 400 to 500 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 1 to 3 years require 300 μg RAE/d of vitamin A, with a UL of 600 μg RAE. Children aged 3 to 8 years require 400 μg RAE/d of vitamin A, with a UL of 900 μg RAE. Children

aged 9 to 18 years require 600 to 900 μg RAE/d of vitamin A, with a UL of 1,700 to 2,800 μg RAE. (3)

Functions

Vitamin A plays a critical role in vision, immunity, and cell differentiation and growth. In the vitamin A–dependent vision cycle, 11-cis-retinal, a derivative of vitamin A, combines with a membrane protein in the retina called opsin to form rhodopsin. Rhodopsin absorbs light and enables the transmission of its stimuli to the brain. Vitamin A is essential to the integrity of the cornea and conjunctiva as well as many other organs because of its importance for cell differentiation. (5)

Factors and Consequences of Vitamin A Deficiency

Xerophthalmia is the term used to describe the ocular manifestations of vitamin A deficiency. Night blindness is the earliest symptom and it is normally a sensitive and specific indicator for vitamin A deficiency. Patients with night blindness cannot see well at night or in dim light, and this can be difficult to recognize, especially among toddlers. Mild cases of night blindness can become apparent only after exposure to a bright light that depletes the limited stores of 11-cis-retinal in the affected patient. Night blindness responds to vitamin A therapy within 24 to 48 hours. If untreated, it leads to keratinization of the surface of the conjunctivae and, thus, is the histopathologic picture of conjunctival xerosis and Bitot spots that are characteristic for vitamin A deficiency. Bitot spots are generally whitish, foamy-appearing ovoid areas on the conjunctiva that result from a buildup of keratin. (6) Corneal xerosis and ulceration can develop in advanced eye disease and can subsequently lead to blindness. (7)

Before xerophthalmia is apparent, other serious consequences, including increased mortality, result from subclinical vitamin A deficiency. The protective effect of vitamin A against infant morbidity and mortality is due to its vital role in enhancing the host immune functions at different levels. Its protective effect against diarrheal diseases is due to its vital role in sustaining the integrity of the intestinal mucosa. The positive effect of vitamin A in human immunodeficiency virus–infected children is due to increased T-cell lymphopoiesis. The therapeutic effects of vitamin A against measles are well validated and are attributed to enhanced antibody production. (8)

Without supplementation, measles can induce a decompensation of vitamin A status and is known to precipitate 25% to 50% of blinding xerophthalmia in Asia. In many parts of Africa, measles is considered the leading cause of childhood blindness. (7)

TABLE 2. Examples of Micronutrient Deficiencies that Are Associated with Selected Clinical Conditions

CLINICAL SCENARIO	NUTRITIONAL DEFICIENCY
Vegetarian diet	Vitamin B ₁₂
Obesity	Vitamin D (iron)
Cystic fibrosis	Vitamins A, D, E, K, B ₁₂
Inflammatory bowel disease, short gut syndrome	Folate, vitamin B ₁₂ , fat soluble vitamins (iron)
Celiac disease	Folate, vitamin B ₁₂ , fat soluble vitamins (iron, zinc)
Prolonged diarrhea	(Zinc)
Medications	
• Antacids	Vitamin D, (iron)
• Seizure medications	Vitamin D
• Corticosteroids	Vitamin D
• Methotrexate	Folate
• Sulfasalazine	Folate
• Trimethoprim	Folate
The breastfed toddler with limited complementary food	(Iron, zinc)
Predominantly breastfed infant or toddler, refusing to walk, growth plateau	Vitamin D
Exclusively breastfed newborn, symptoms of bleeding or altered mental status	Vitamin K
The use of unfortified goat milk in infants with limited complementary food.	Folate
Highly restrictive diet (autism, developmental delay, food allergies)	Depends on the diet Vitamin A is vulnerable as in the case in the vignette; vitamin C
Highly restrictive diet and refusal to walk	Vitamin C
Measles	Vitamin A
Severe protein-energy malnutrition	Vitamin A, vitamin D, (zinc, iron)

Micronutrients in parentheses are not covered in this article.

The American Academy of Pediatrics (AAP) recommends vitamin A supplementation for children 6 months to 2 years old who are hospitalized for measles. The recommended oral supplement dose is 100,000 IU (30,000 µg) for children 6 to 12 months old and 200,000 IU (60,000 µg) for children older than 1 year. (9)

Measles is one example of how seemingly unrelated disease states can alter an individual's vitamin A balance and lead to deficiency.

The role of vitamin A for maintenance of normal epithelial cell integrity in the lungs has been examined in relation to chronic lung disease of preterm infants. A recent systematic review concluded that vitamin A supplementation had a modest benefit on risk of death, oxygen requirement, and development of chronic lung disease. No benefit was found

on neurodevelopment in the second year of life. Definitive recommendations were not supported by the data. (10)

In patients with protein energy malnutrition, vitamin A deficiency can develop not only secondary to low dietary intake but also due to the effect of malnutrition on the transport and storage of vitamin A. (7)

Young children in developing countries are especially vulnerable to and at risk for vitamin A deficiency due to their dependence on human milk, which can be deficient if the mother is deficient. Intestinal infections that impair vitamin A absorption and respiratory infections, such as tuberculosis, that increase metabolic demands make affected children the most vulnerable victims of xerophthalmia. The same factors can affect older individuals, such as refugees who experience unsanitary conditions and nutritional deprivation. (7)

Risk of Toxicity

Preformed vitamin A toxicity can be acute (a single or short-term doses of retinol $\geq 150,000 \mu\text{g}$ for adults and proportionally lower doses for children) or chronic (long-term exposure to daily doses $\geq 600 \mu\text{g}$). The toxic effects are transient and are due to increased intracranial pressure (pseudotumor cerebri). Symptoms include headache, blurred vision, vertigo, and a bulging fontanelle in infants. (5) This has led the IOM to apply a large safety margin in recommending the ULs for vitamin A. This is specifically important for women of childbearing age whose intake of retinol should not exceed 2,800 to 3,000 $\mu\text{g}/\text{d}$ due to the risk of teratogenicity. (3)

Isotretinoin (13-*cis*-retinoic acid), a medication used to treat severe acne, is a teratogen that is associated with common birth defects. Since 2006, the Food and Drug Administration (FDA) established the iPLEDGE program by which the prescribing and dispensing of isotretinoin is more tightly controlled in an effort to reduce inappropriate drug use and exposure to women of childbearing age.

VITAMIN B₁₂ (CYANOCOBALAMIN)

Case

C.S. is a 7-month-old infant who presented with failure to thrive, progressive loss of milestones, and shaking movements (Fig 1). On physical examination on the day of



Figure 1. C.S. at 7 months of age presenting with marked hypotonia and loss of milestones.

admission she looked pale but was alert and had normal vital signs. Her length and weight were below the 5th percentile, and she appeared malnourished. She showed generalized hypotonia with constant tremors of her tongue and extremities. The remainder of her physical examination was normal, with no anomalies or organomegalies.

C.S. was exclusively breastfed. The mother was on a well-balanced diet with oral multivitamins, and she has previously breastfed C.S.'s 2 siblings, who were reportedly healthy. The mother's medical history was significant for Graves disease.

Results of a CT scan of her head were normal. Laboratory evaluation was notable for macrocytic anemia. The findings of macrocytosis triggered further evaluation of vitamin B₁₂ and folate levels, and her level of vitamin B₁₂ was found to be significantly low. The mother's level of vitamin B₁₂ was undetectable. The mother was found to have intrinsic factor (IF) antibodies secondary to an autoimmune process triggered by Graves disease.

C.S. was treated with vitamin B₁₂ and was reported to have a nearly normal developmental outcome at 2 years of age.

Sources and Homeostasis of Vitamin B₁₂

Animal source foods such as milk, eggs, and meat are the only natural sources of vitamin B₁₂. (11) Absorption of the vitamin is distinctively complex, especially compared with other water-soluble vitamins. In the stomach, hydrochloric acid and pepsin release vitamin B₁₂ from dietary protein, and cyanocobalamin is then bound to IF secreted by the gastric parietal cells. The complex B₁₂-IF remains intact until its uptake is facilitated by a specific receptor in the distal ileum. (12) Vitamin B₁₂ deficiency can result from low dietary intake of animal source food due to cost, low availability, or religious and cultural beliefs. Dysfunction in any part of the sophisticated gastrointestinal pathway of cyanocobalamin absorption—from stomach to ileum—can lead to non-dietary-induced vitamin B₁₂ deficiency.

The DRIs

The RDA for vitamin B₁₂ is 0.9 $\mu\text{g}/\text{d}$ for infants and toddlers, 1.2 to 1.8 $\mu\text{g}/\text{d}$ for 4- to 13-year-olds, and 2.4 $\mu\text{g}/\text{d}$ thereafter.

No adverse effects have been reported with excess vitamin B₁₂ intake, and the risk of toxicity is very low; therefore, a UL is not established (3)

Maternal and Infant Vitamin B₁₂ Deficiency

Most adults can tolerate a low vitamin B₁₂ intake status for years without any clinical symptoms. Mothers of infants

with vitamin B₁₂ deficiency often have unrecognized pernicious anemia due to impaired vitamin B₁₂ absorption, but other etiologies were reported, including gastric bypass surgery, short gut syndrome, or long-term vegetarian or vegan diet. (13) Newborn infants have limited endogenous stores and are at risk for vitamin B₁₂ deficiency if they are predominantly breastfed, with a poor maternal vitamin B₁₂ status and intake. (14) Typical manifestations usually start between 4 and 10 months of age and include growth faltering, developmental regression, tremors, hypotonia, lethargy, irritability, and feeding difficulties. (14) Megaloblastic anemia is not always present. (13)

Vitamin B₁₂ replacement (1 mg intramuscular for 2 to 7 days [15]) leads to rapid recovery, with documented reversal of apathy, hypotonia, anorexia, and tremors within days of initiating treatment. Brain atrophy and growth failure reversed within several months. Unfortunately, despite the dramatic rapid improvement, many infants with vitamin B₁₂ deficiency experience long-term cognitive and developmental delay. (14)

Similar symptoms are seen in infants with inborn errors of vitamin B₁₂ absorption and utilization. A full discussion of these conditions is beyond the scope of this article.

Vitamin B₁₂ Deficiency in Children and Adolescents

A study of serum B₁₂ levels in 3,766 US children (4–19 years old) identified 3 children with levels less than 100 pg/mL (<74 pmol/L) (1 of 1,255) and 18 with levels less than 200 pg/mL (<148 pmol/L) (1 of 200). The highest incidence of children with levels less than 200 pg/mL (<148 pmol/L) was reported in the 12- to 19-year-old category, with a rate of 1 in 112. (15) Because the cutoff value suggested to define vitamin B₁₂ deficiency is a level less than 203 pg/mL (<150 pmol/L), (11) these data indicate that B₁₂ deficiency in children and adolescents is more common than previously suggested.

Of note, a vitamin B₁₂ level greater than 300 pg/mL (>221 pmol/L) is tentatively considered as the cutoff value for B₁₂ repletion. (16)

The estimated vitamin B₁₂ intake in the United States is higher than the RDA, but dietary B₁₂ deficiency is increasing due to atypical diets, such as extreme vegetarianism. (17) Patients who undergo gastric bypass or other bariatric surgeries are at risk for vitamin B₁₂ deficiency due to the loss of gastric production of IF. (13) Pathologic disorders that disrupt the ileal length or surface, such as short gut syndrome, Crohn disease, and celiac disease, can affect B₁₂ absorption. (15) It is especially important to note that previous and current use of gastric acid inhibitors for 2

or more years was significantly associated with the occurrence of vitamin B₁₂ deficiency in adults. (18)

Neurologic changes secondary to B₁₂ deficiency can occur without hematologic abnormality, including loss of deep tendon reflexes, developmental regression, hypotonia, and neuropsychiatric changes (eg, depression). (15)

Laboratory Evaluation

Several feasible indicators to assess vitamin B₁₂ status are available, and the least expensive is a serum vitamin B₁₂ level. (11) However, serum B₁₂ level is not always reflective of tissue levels that can be depleted with a low normal or borderline serum cobalamin level. (15) Methylmalonic acid (MMA) and homocysteine are 2 precursors in the metabolic pathway and are affected by B₁₂ deficiency. Homocysteine is elevated in both B₁₂ and folate deficiencies, but an elevated MMA level is reasonably specific for B₁₂ deficiency; MMA levels can be measured in both serum and urine. (13)

Studies are needed to determine the optimum strategy for the diagnosis of vitamin B₁₂ deficiency in children. Several experts recommend B₁₂, MMA, and homocysteine levels when B₁₂ deficiency is suspected. (13)(15) Once B₁₂ deficiency is confirmed, subspecialty consultation, eg, a physician nutrition specialist, gastroenterologist, or hematologist, is recommended to guide further evaluation and treatment.

VITAMIN C (ASCORBIC ACID)

Introduction

In 1747, Dr James Lind, a surgeon in the British Navy, demonstrated that scurvy can be cured by consuming oranges and lemons. Since then, scurvy, or vitamin C deficiency, which used to debilitate sailors, has become a rare disease that warrants a case report. A recent one was published in the *New York Times* in July 2015. Although a clue to a disrupted eating pattern was clear on the initial presentation (the child has developmental delay and will eat only macaroni and cheese), a nutritional deficiency was not suspected. The patient had an extensive evaluation that included bone marrow biopsy and many subspecialist consults. This case is a testimony to the importance of physician knowledge about certain clues that should prompt a more detailed nutritional history.

Functions

Vitamin C is a water-soluble vitamin that acts as an antioxidant and free radical scavenger. Vitamin C is a cofactor for many enzymes and hormones and plays a major role in the

biosynthesis of many components of connective tissue, such as collagen. It also modulates the absorption, transport, and storage of iron. (3)

The DRIs

The DRIs for vitamin C are based on estimates of tissue levels that are deemed adequate to provide antioxidant protection with minimal urinary loss. Tobacco smoking or environmental exposure to nicotine increases the vitamin C requirement by 35% to 40% due to increased oxidative stress. Vitamin C absorption in the small intestine is dose dependent, and the kidney also regulates its body content. As a result, excessive intake of vitamin C is unlikely to cause adverse effects other than gastrointestinal upset and osmotic diarrhea occasionally reported with large doses.

The RDA for vitamin C is 15 to 45 mg/d for children aged 1 to 13 years and 65 to 75 mg/d for those aged 14 to 18 years. (3)

Sources

Fruits and vegetables provide 90% of the vitamin C found in the typical diet. The major contributors are potatoes and citrus fruits and juices. (3) A diet that is persistently limited to meat, bread and/or dairy presents a high risk for inadequate vitamin C intake and development of deficiency.

Deficiency

Scurvy is rare in the current era but should not be forgotten. According to NHANES, children aged 6 to 11 years old had the highest mean serum concentration of ascorbic acid but showed a linear decrease thereafter. (19) In the pediatric population there are many case reports of scurvy in patients with autism due to their severely restrictive diet. Adults at risk for vitamin C deficiency include smokers, alcoholics, and those on a very restricted diet due to social isolation. (20)(21)

Clinical symptoms can develop only after 30- to 40 days of consuming a diet that is void of vitamin C. (22) The earliest symptoms of vitamin C deficiency are fatigue and refusal to walk. (20) Dermatologic findings include petechiae centered on hair follicles with hyperkeratosis and coiled hair. Hematomas, ecchymosis, poor wound healing, and edema may also be noted. Oral manifestations occur only in patients with teeth and include bleeding and hypertrophic gums. Musculoskeletal findings include joint pain, hemarthrosis, and muscle pain. Anemia is a common finding in vitamin C deficiency, and it can be attributed to the hemorrhagic symptoms and the role of ascorbic

acid in iron absorption. (23) Infantile scurvy is rarely seen because human milk (if the maternal diet is sufficient) and formula provide an adequate supply of vitamin C. Infantile scurvy presents with bone abnormalities, bleeding, and anemia. (3)

High-Dose Vitamin C for the Treatment of Upper Respiratory Tract Infections

Supplementation trials have shown that vitamin C reduces the duration of colds, but this effect was not replicated in therapeutic trials. Further randomized controlled trials are warranted to investigate the role of vitamin C in the treatment of upper respiratory tract infections. However, given its low cost and excellent safety profile, it may be worthwhile for patients with common cold to try a therapeutic dose of vitamin C. (24)

VITAMIN D (CHOLECALCIFEROL)

Introduction

Rickets has plagued children, especially in the northeastern United States, since the 1800s. However, the beneficial effect of sunlight was not elucidated until 1921 when Hess and Unger reported a dramatic improvement in rachitic children who were exposed to the sun. (25) Contemporaneously, investigators observed that ultraviolet irradiation of milk and various foods imparted antirachitic activity. With this discovery it was thought that rickets was conquered. (25) However, in the 19th century it became clear that vitamin D deficiency is a common problem in children and adults worldwide. In fact, the discovery that various cells and tissues express the vitamin D receptor has highlighted its many other nonskeletal functions. Now experts believe that rickets is simply only the “tip of the iceberg” of the consequences of vitamin D deficiency. (26)

Case

J.L. is a 15-month-old white boy who fell off his bed and refused to walk afterward. He had been walking for about a month before this episode. His dietary history showed that he was breastfed until 6 months of age and then was placed on a mostly liquid diet consisting of water, juice, and some milk. Solids in his diet consisted of some baby food without dairy products. No supplemental vitamins were given.

Physical examination was significant for underweight status (weight-for-length <5th percentile), length age of 9 months (his length was 70.6 cm), a prominent forehead, and swelling at the wrists. Radiographs of his leg revealed a distal left femur fracture, and wrist radiographs showed osteopenia with metaphyseal flaring.

Laboratory studies showed a low-normal serum calcium level of 8.2 mg/dL (2.05 mmol/L), a low serum phosphorus level of 3.4 mg/dL (1.1 mmol/L), but elevated alkaline phosphatase and parathyroid hormone (PTH) levels. The serum 25-hydroxyvitamin D (25[OH]D) level was low at 11 ng/mL (27 nmol/L).

J.L. was given stoss therapy with a high dose of vitamin D (100,000–600,000 IU given over 1–5 days). The appearance of his wrist at 1 and 5 months of age showed gradual healing of his rickets (Fig 2).

Definition of Vitamin D Deficiency

There continues to be much debate regarding what constitutes vitamin D deficiency, insufficiency, and sufficiency. Vitamin D status is defined by the level of serum circulating 25(OH)D. (27)(28)

The Endocrine Society proposed the following cutoff points (27):

- Vitamin D deficiency: 25(OH)D level ≤ 20 ng/mL (< 50 nmol/L)
- Vitamin D insufficiency: 25(OH)D level of 21 to 29 ng/mL (52–72 nmol/L)
- Vitamin D sufficiency: 25(OH)D level of 30 to 100 ng/mL (75–250 nmol/L)

The Endocrine Society determined these cutoff points using many criteria that affect bone metabolism, such as PTH, bone mineralization, and intestinal calcium absorption.

However, to establish vitamin D requirements through the life cycle at a population level, the IOM prioritizes specific end points associated with health outcomes. Accordingly, the IOM has questioned the premise that a serum

level of 25(OH)D greater than 30 ng/mL (> 75 nmol/L) provides additional health benefits. (29) At present, the IOM, the AAP, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition also suggest 20 ng/mL (50 nmol/L) as the cutoff value for deficiency, (30) but the controversy continues regarding the level of serum 25(OH)D that defines sufficiency.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency is widespread around the world. (27) The NHANES studies examined thousands of American children and adolescents, which provides a reliable report of their vitamin D status. According to NHANES 2001–2004, 9% of US children and adolescents had vitamin D deficiency (25[OH]D levels < 15 ng/mL [< 37 nmol/L]), and 61% had vitamin D insufficiency (25[OH]D levels of 15–29 ng/mL [37–72 nmol/L]). (31)

Causes and Risk Factors for Vitamin D Deficiency

Limited Sunlight Exposure. When absorbed by the skin, UV-B converts 7-dehydrocholesterol to previtamin D₃, which is isomerized to vitamin D₃.

There are many factors, such as skin pigment and use of sun screen, that influence the cutaneous production of vitamin D₃. Increased skin pigmentation causes the melanin to absorb most of the UV-B, resulting in much lower vitamin D₃ production in African American individuals compared with white individuals for the same UV-B exposure. Sunscreen with a sun-protecting factor of 30 can reduce the skin's ability to produce vitamin D by 95% to 99%. The influence of these factors is exacerbated by the season, latitude, and time of day. When the zenith angle of

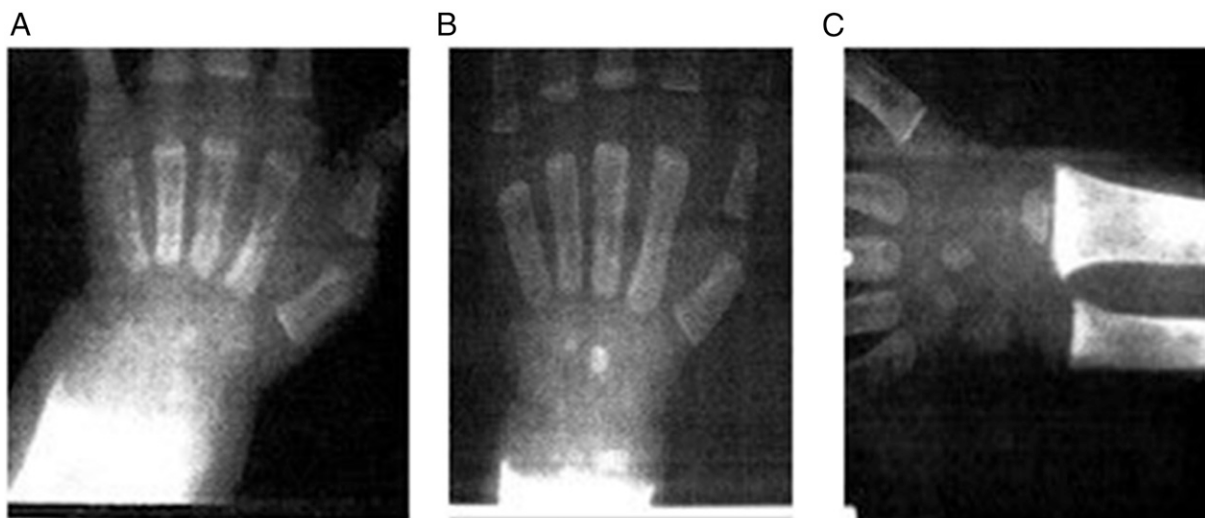


Figure 2. J.L. wrist radiographs from left to right: at presentation and 1 and 5 months after treatment. Notice the swelling at the wrist.

the sun is more oblique during the winter season (especially far north and south) and for the daylight hours before 10 AM and after 3 PM, more UV-B radiation is absorbed by the ozone layer. Passage through glass or plastic and air pollution also dramatically reduces UV-B. (32)

Limited Nutritional Intake in Infancy and Beyond. Breastfed infants and toddlers are at risk for vitamin D deficiency. The content of vitamin D in human milk is greatly influenced by all the factors that affect maternal vitamin D status, such as sun exposure, skin pigmentation, season, latitude, and maternal vitamin D intake. The optimal vitamin D supplement dose for nursing mothers is not yet established. However, studies have shown that maternal supplementation of vitamin D at 4,000 IU/d was not enough to consistently yield at least 400 IU of vitamin D per liter of human milk. It is hypothesized that a supplemental dose of 6,000 IU/d may be needed to achieve this effect. This should not undermine the value of human milk as a vital source of nutrition for infants but highlights the basis for the recommendation to supplement all infants who are breastfeeding or taking less than 1 L of formula per day with 400 IU of vitamin D daily. (33)(34)

Beyond the first year of life, an intake of 32 oz of vitamin D–fortified milk provides 400 IU of vitamin D. Fatty fish and other vitamin D–rich foods tend to be absent in most infant and adolescent diets, and the content of vitamin D in fortified foods may be overestimated. For example, fortified cereal provides only 40 IU per serving. Thus, for children and adolescents who do not receive regular sunlight exposure, they may be at increased risk for nutritional vitamin D deficiency and insufficiency. (35)

The Effect of Obesity. The association between obesity and lower 25(OH)D serum concentration is well established. Possible mechanisms include lower dietary intake, sedentary behavior that tends to limit sunlight exposure, and sequestration of 25(OH)D in the adipose tissue. (36)

Medications. Antiepileptic drugs and systemic glucocorticoids have been shown to reduce 25(OH)D concentrations when dietary sources of vitamin D and sunlight exposure are limited. Of note, there is no evidence that inhaled corticosteroids at a conventional dose given for 2 to 3 years have a negative effect on bone mineral density and bone turnover biomarkers, including 25(OH)D. (37)

Orlistat and cholestyramine cause fat malabsorption and, thus, impair vitamin D absorption. (38)

Diseases that Interfere with Vitamin D Absorption and Metabolism. Vitamin D absorption is chylomicron dependent; thus, children with fat malabsorption are at increased risk for deficiency. Cystic fibrosis, Crohn disease, and celiac disease are known risk factors for nutritional rickets.

(38) Food allergies and small-bowel resection can also lead to fat malabsorption and vitamin D deficiency. (35)

Genetic Factors. In a study published in the *New England Journal of Medicine*, Powe et al report that more than 90% of African American individuals have a genotype that is associated with a lower level of vitamin D–binding protein compared with white individuals. (39) The authors speculate that variation in vitamin D–binding protein levels may be responsible for observed racial differences in 25(OH)D levels and the clinical manifestations of vitamin D deficiency. (39) More research is needed to elucidate if genetic polymorphism plays a role in determining vitamin D requirements in different ethnic groups.

Skeletal Consequences of Vitamin D Deficiency

A vitamin D–deficient state is associated with reduction in intestinal calcium absorption from approximately 30% to 40% to 10% to 15%. The body responds to the reduction in serum calcium with hyperparathyroidism. (35)

Parathyroid hormone enhances calcium absorption in the renal tubules. It also causes phosphaturia, leading to a low serum phosphorus level that causes a maturation defect in the chondrocytes with cellular ballooning and disruption of the growth plate, leading to the widening at the end of the long bones that is characteristic of rickets. (35)

Rickets can be divided into 3 stages (Fig 3). The first stage is characterized by osteopenia and subclinical hypocalcemia. Bone pain and rachitic changes start in the second stage and become progressively worse in the third stage. (35)

Clinically, rickets in children ranges from an asymptomatic disease to varying degrees of poor growth, bone pain, irritability, and gross motor delay.

The signs of rickets include, but are not limited to, genu varum (bowing of the legs) or genu valgum (knock-knees), due to the lack of structural support as the child learns to walk. The widening at the end of the long bones is most commonly manifested in the wrist. The *rachitic rosary* is a term used to describe the beading along the anterior chest wall and is a result of the hypertrophy of the costochondral joints. (25)(35)

In rare cases of severe maternal vitamin D deficiency, rickets can develop in utero. (33)(34)

Nonskeletal Consequences of Vitamin D Deficiency

Every cell and tissue in the body has a vitamin D receptor. Therefore, vitamin D deficiency has been associated with a plethora of negative health consequences. (25)(40) Maternal vitamin D deficiency is associated with low birthweight (33) and is linked to increased risk of preeclampsia. (25)(40)

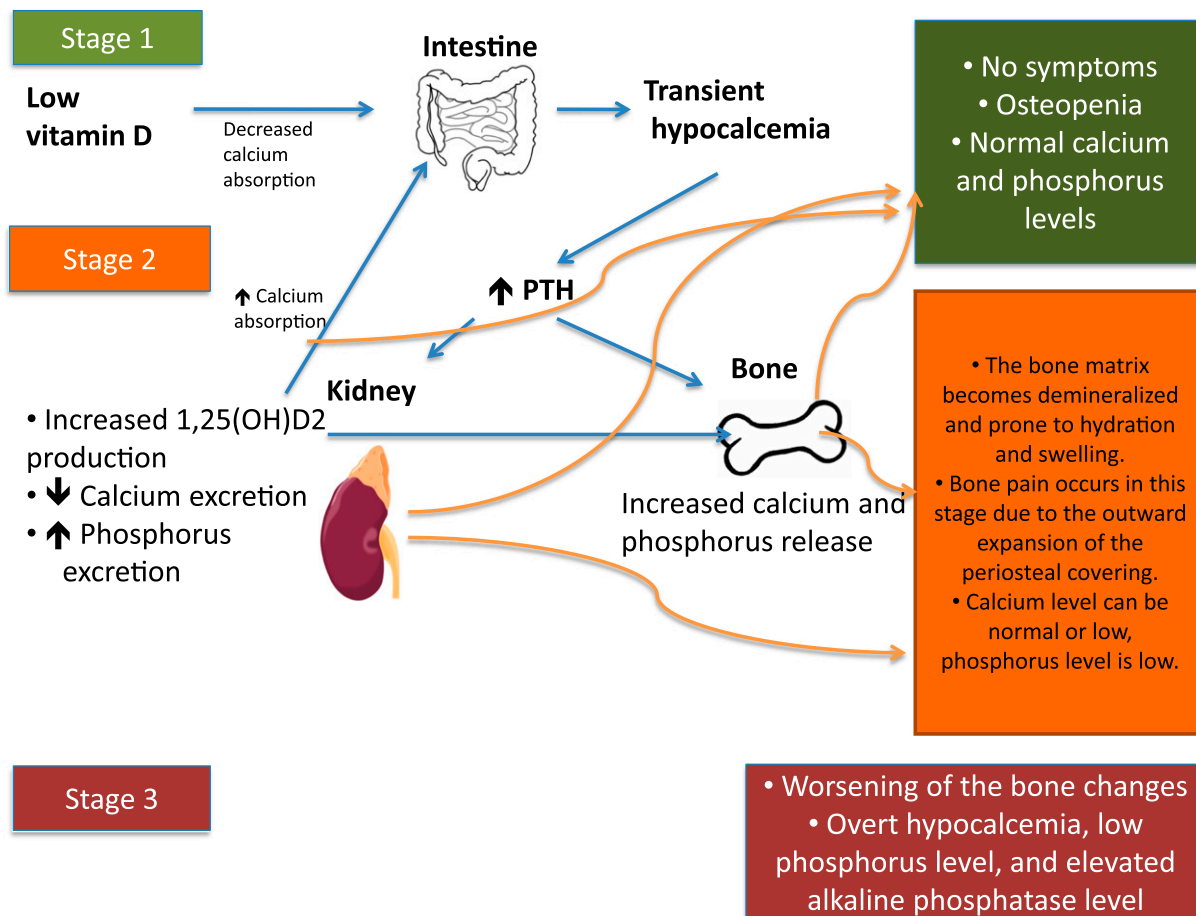


Figure 3. Stages and skeletal consequences of vitamin D deficiency. PTH=parathyroid hormone; 1,25(OH)2D=1,25 dihydroxyvitamin D.

Vitamin D deficiency has also been linked to increased risk of infectious disease, types 1 and 2 diabetes, multiple sclerosis, cardiovascular disease, dementia, and cancer, (40)(41) but controlled trials to determine causality are not available.

Laboratory Evaluation of Vitamin D Status

Circulating 25(OH)D level measured by a reliable assay is the best indicator of vitamin D status and stores. Measurement of serum 1,25 dihydroxyvitamin D (1,25[OH]2D) is not recommended because 1,25(OH)2D does not reflect vitamin D reserves and can be normal or elevated in patients with vitamin D deficiency due to secondary hyperparathyroidism. Measurement of the 1,25(OH)2D level is useful in conjunction with the PTH level in disorders of 25(OH)D and phosphate metabolism, such as chronic kidney disorders and vitamin D-resistant rickets. (27) In nutritional rickets, the classic biochemical profile includes the triad of hypocalcemia, hypophosphatemia, and elevated alkaline phosphatase levels.

Some experts recommend incorporating the measurement of vitamin D-binding protein for better assessment of vitamin D status in African American individuals and in diverse populations, (39) but more research is needed.

Screening

Universal screening of all patients for vitamin D deficiency is not recommended (27) and should be reserved and considered only for high-risk patients, including but not limited to:

- Patients with nonspecific symptoms, such as poor growth, irritability, and gross motor delay (35)
- Dark-skinned patients, especially those who live in higher latitudes (27)(35)
- Children taking long-term glucocorticoids or seizure medications (27)(35)
- Children with chronic diseases that are associated with fat malabsorption, such as cystic fibrosis, inflammatory bowel disease, (35) and post-bariatric surgery (27)

- Patients with frequent fractures and low bone density (35)
- Patients with chronic kidney disease (27)
- Obese patients (27)

Screening can also be considered for patients with low dietary intake and very limited sun exposure.

Sources and Forms of Vitamin D

There are 2 sources of vitamin D. Cholecalciferol (D₃) is synthesized in the skin and found in oily fish. Ergocalciferol (D₂) is synthesized by plants and produced from the irradiation of yeast. Both forms are used to fortify milk and are found in dietary supplements, but vitamin D₂ is the only prescription form available in the United States. (33)(42) Table 3 summarizes the pharmaceutical and supplemental sources of vitamin D.

Calcidiol (25[OH]D), the form that defines vitamin D status, is formed in the liver from vitamins D₂ and D₃ by the action of 25-hydroxylase. Calcitriol (1,25[OH]₂D), the active form of vitamin D, is created when a second hydroxylation occurs in the kidney and many other tissues in the body. (33)(42)

Treatment of Vitamin D Deficiency

There are many strategies to treat vitamin D deficiency. Based on studies that examine the effect of D₂ and D₃ administered in different doses on 25(OH)D serum level, experts estimate that 100 IU of vitamin D₂ or D₃ daily will raise the blood level of 25(OH)D by 1 ng/mL (2.5 nmol/L). (25)(26) Short-term administration of 2,000 IU of vitamin D₂ or D₃ daily yields an equivalent outcome to weekly 50,000 IU of vitamin D₂. (27)(43) Thus, pediatricians can individualize their treatment of vitamin D to meet the patients' and families' preferences and probability of compliance. When compliance is a major concern, stoss

therapy (*stoss* in German means to push), with doses of 100,000 to 600,000 IU given over 1 to 5 days, can be administered to infants older than 1 month of age. (35) However, the recommendations of the stoss therapy, especially in outpatient settings, have been met with controversy due to the risk of hypercalcemia. (43)

In July 2011, the Endocrine Society published the following guidelines for the evaluation, treatment, and prevention of vitamin D deficiency (27):

- Infants 0 to 1 year old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the 25(OH)D blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (400–1,000 IU/d)
- Children 1 to 18 years old: 2,000 IU orally once daily or 50,000 IU orally once weekly for 6 weeks until the blood level is greater than 30 ng/mL (>75 nmol/L), followed by maintenance therapy (600–1,000 IU/d)
- Use of a high dose (double or triple the 2 previously mentioned doses) is recommended for obese patients or patients taking medications or having conditions that affect vitamin D metabolism and/or absorption

Prevention of Vitamin D Deficiency: The DRIs and Other Recommendations

The AAP recommendations on vitamin D supplementation are in agreement with the IOM recommendations released in 2011. The IOM proposed that healthy infants younger than 1 year of age consume 400 IU/d of vitamin D, and older children (1–18 years old) consume 600 IU/d. (35)(44)

Dietary Sources of Vitamin D. Many children and adolescents in the United States do not consume most of the natural food sources of vitamin D in sufficient quantities. Furthermore, meeting the RDA of vitamin D would require an impractically large intake of fortified food. For example,

TABLE 3. **Summary of Supplemental and Pharmaceutical Sources of Vitamin D (26)**

VITAMIN D SUPPLEMENT	DOSE	NOTES
Prescription		
<ul style="list-style-type: none"> • Vitamin D₂ (ergocalciferol, labeled calciferol) 	Capsule: 50,000 IU Liquid: 8,000 IU/mL	For small children, the capsule can be soaked in water to soften it, then given intact with blended food such as apple sauce (35)
Over the counter		
<ul style="list-style-type: none"> • Pediatric multivitamin (liquid or chewable) • Vitamin D₃ (labeled cholecalciferol) 	300, 400, 600 IU D ₂ or D ₃ 400, 800, 1,000, and 2,000 IU	D ₃ 400 IU/mL is the standard to use (1 mL/d) for prevention of vitamin D deficiency in newborns and toddlers who are breastfeeding or taking <1,000 mL/d of formula/whole milk. It is available over the counter under many brand names.

TABLE 4. Diagnostic Tests and Treatment Doses for Selected Vitamin Deficiencies

VITAMIN	DIAGNOSTIC LABORATORY TEST	TREATMENT
Vitamin A	Serum retinol <20 $\mu\text{g/dL}$ Molar ratio of retinol to retinol binding protein <0.8 (calculated in $\mu\text{mol/L}$) (75)	<ul style="list-style-type: none"> ■ Infants <6 mo old: 50,000 IU orally \times 1 ■ Infants 6–12 mo old: 100,000 IU orally \times 1 ■ Children >12 mo old: 200,000 IU orally \times 1 (76) Additional doses can be given, as needed, every 4 weeks based on clinical response.
Vitamin B ₁₂	Use serum B ₁₂ as the initial test; if the level is <271 pg/mL (<200 pmol/L), check for elevated methylmalonic acid level (>0.37 μmol) (16)	<ul style="list-style-type: none"> • Dietary deficiency: Infants (breastfed by vitamin B₁₂-deficient mothers): IM 250–1,000 μg once daily for 1–2 wk, then weekly until recovery • Malabsorption: Infants, children, and adolescents: IM 250–1,000 $\mu\text{g/d}$ or every other day for 1 wk, then weekly for up to 8 wk, and then every 4 wk; oral administration of a high dose of 2,000 $\mu\text{g/d}$ can also be considered (16)
Vitamin C	Plasma and leukocyte vitamin C level (77)	Scurvy: Oral, IM, IV, SC: Initial: 100 mg per dose 3 times daily for 1 wk (300 mg/d) followed by 100 mg once daily for 1–3 mo (47)
Vitamin E	Serum α -tocopherol and serum α -tocopherol to lipid ratio (47)	Fat malabsorption: Supplement with 25 IU/kg per day to prevent deficiency (47)
Folate	Serum homocysteine level elevated (also elevated in B ₁₂ and B ₆ deficiencies) (47)	Oral daily administration of 0.1 mg in infants and 1 mg in children followed by oral daily maintenance of 0.1–0.5 mg (47) Note that treatment for folate deficiency without assessment of vitamin B ₁₂ status can mask B ₁₂ deficiency
Vitamin K	Prothrombin time is elevated (4 times normal) and the presence of protein induced by vitamin K deficiency (73)	<ul style="list-style-type: none"> • Prevention: A single 1-mg IM dose for the full-term infant and 0.3–0.5 mg for the preterm infant • Fat malabsorption: 2.5–7 mg/d 2–7 times per week (47)

IM=intramuscular, IV=intravenous, SC=subcutaneous.

a 15-year-old must consume a pound of cheese or 6 glasses of milk per day to obtain the recommended 600 IU of vitamin D daily.

Good natural food sources of vitamin D include salmon (100–1,000 IU of vitamin D per 3.5 oz) and cod liver oil (400–1,000 IU of vitamin D per 1 tsp). (26)

Preventive Use of Supplemental Vitamin D. Taking into consideration the IOM and AAP recommendations for the general population and the Endocrine Society focus on high-risk patients, the following key points are proposed in guidelines and experts' statements:

- Vitamin D supplementation is recommended for all young infants regardless of the type of feeding because it takes 1 L of formula to provide 400 IU of vitamin D (33)
- Vitamin D supplementation should be started within the first days after birth (33)
- Recommended vitamin D supplement intake for children and adolescents without risk factors for vitamin D deficiency are 400 IU/d during the first year and 600 IU/d for children 1 to 18 years old (33)(44)
- Recommended vitamin D intakes for infants, children, and adolescents with risk factors for deficiency

are 400 to 1,000 IU/d during the first year and 600 to 1,000 IU/d for children 1 to 18 years old (30)

- For preterm infants the recommended vitamin D intake is 400 to 800 IU/d (30)
- The optimal duration of vitamin D supplementation has not yet been established; it is reasonable to consider supplementing while the growth velocity is high, until age 2 years (30)
- In children older than 2 years of age, vitamin D supplementation should be based on risk factors, dietary intake, and sun exposure; a supplemental dose of 400 IU/d is recommended for children and adolescents who do not obtain such a dose from fortified milk (33)
- Children with limited summer sun exposure may be supplemented in the late fall and winter (30)
- Obese children or patients taking anticonvulsants or glucocorticoids should receive at least 2 to 3 times more vitamin D than children without such risk factors (27)(30)
- Pregnant and lactating women require 600 IU/d of vitamin D; a dose of 1,500 to 2,000 IU/d may be needed

to maintain the 25(OH)D serum level greater than 30 ng/mL (>75 nmol/L) (27)

Sensible Sunlight Exposure. Human skin has a wonderful capacity to produce vitamin D₃, which is stored in the fat tissue and released during the winter months. Sensible sun exposure, defined by the exposure of the arms and legs without sunscreen for 5 to 30 minutes between 10 AM and 3 PM twice a week, is often adequate. (26)(45)

Toxicity

Excessive intake of vitamin D can cause hypervitaminosis D and results in hypercalcemia and hypercalciuria. (28) However, vitamin D intoxication is rare, and the cases reported were the result of inadvertent ingestion of extremely high doses of vitamin D for prolonged periods. (32) Sunlight exposure never causes vitamin D intoxication. (32) The UL of vitamin D intake should not exceed 1,000 IU for infants 0 to 12 months old and 2,000 IU for older children (28) unless deficiency has been documented and therapy is being monitored.

VITAMIN E (TOCOPHEROL)

Vitamin E is a fat-soluble antioxidant that protects the cells from the damaging effects of free radicals. Cell damage due to free radicals has been linked to the development of cardiovascular disease and cancer.

Structure, Sources, and the DRIs

Vitamin E is abundant in many food sources, such as fruits, vegetables, meats, grains, and vegetable oils. Vitamin E is also available as a dietary supplement. Naturally occurring vitamin E exists in 8 forms (α -, β -, γ -, and δ -tocopherols and tocotrienols). α -Tocopherol is the only form recognized to meet human requirements and is the form referred to in the DRIs as set by the IOM. (3)

Adequate intake of vitamin E in the first year of life is 4 to 5 mg/d of α -tocopherol. The RDA of vitamin E for children aged 1 to 8 years is 6 to 7 mg/d of α -tocopherol, with a UL of 200 to 300 mg. The RDA of vitamin E for children aged 9 to 13 years is 11 mg/d of α -tocopherol, with a UL of 600 mg. The RDA for age 14 years through adulthood is 15 mg/d of α -tocopherol, with a UL of 800 to 1,000 mg. (3)

Vitamin E Deficiency

Because of its abundance in natural sources, vitamin E deficiency is rare and generally occurs as a result of fat malabsorption syndromes or in the setting of protein energy malnutrition. The main clinical symptom of vitamin E deficiency is peripheral neuropathy with ataxia and

hyporeflexia. (3)(46) Patients with malabsorption (cystic fibrosis, pancreatic insufficiency) and biliary tract disorders are at risk for vitamin E deficiency. Failure to supplement high-risk patients leads to a progressive neurologic disorder, including ataxia, peripheral neuropathy, proximal muscle weakness, and ophthalmoplegia. These effects may be irreversible if the deficiency is longstanding. (47)

Risk of Toxicity

Supplements of vitamin E provide α -tocopherol with amounts that are more than or equal to 100 IU. These amounts are significantly higher than the RDAs. The possible effects of a high supplemental level of α -tocopherol remain uncertain. However, some adult studies suggest that the use of high doses of vitamin E may increase all-cause mortality. (48)

Vitamin E supplement use is high in the US population. The most frequently reported motivation for use was to improve overall health. (49) The 1986 National Health Interview Survey reports that supplements containing vitamin E are used by 37% of young children in the United States. (3) Excess vitamin E intake in individuals who are deficient in vitamin K or receiving anticoagulant therapy can lead to hemorrhagic toxicity. (3)

There is no evidence of adverse effects from exposure to high levels of the vitamin E naturally occurring in foods. (3)

Therapeutic and Preventive Use of Vitamin E

Using pharmacologic doses of vitamin E as an antioxidant has been proposed for the treatment or prevention of many diseases. Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage (ICH), and in the very low-birthweight infant it also reduced the risk of severe retinopathy. (50) However, the current evidence does not support the routine use of vitamin E supplementation intravenously in high doses due to the increased risk of sepsis. (51)

Several studies investigated the role of vitamin E and the reduction of oxidative stress in the treatment of non-alcoholic steatohepatitis (NASH) and have led to variable results. (52)(53)(54)

One of the largest studies in adults (247 patients) concluded that vitamin E at a dose of 800 IU/d was superior to placebo in the treatment of NASH in nondiabetic adults. (55) The same dose is proved to offer histologic benefits to children with biopsy-proven NASH, but more studies are needed before its use can be recommended in pediatric clinical practice. (56)

Vitamin E may have functions that are not related to its role as a free radical scavenger. Vitamin E has a positive

effect on the immune system and a possible protective effect against upper respiratory tract infection. Vitamin E also has anti-DNA mutagenic damage properties that may explain its protective effects against cardiovascular diseases, Alzheimer disease, and cancer. (5)

FOLATE (PTEROYLPOLYGLUTAMATE)

Introduction

In 1931, Dr Lucy Willis demonstrated that a factor in yeast, subsequently shown to be folate, cured megaloblastic anemia of pregnancy. (57) In the 87 years since that original discovery, the roles of folate in the pathogenesis of neural tube defects (NTDs), vascular disease, and certain types of cancer have been established.

Sources and the DRIs

The term *dietary folate* is used to denote folate that occurs naturally in food sources and the more active synthetic form of folic acid used in fortified food. *Total folate* is an umbrella term used to encompass all dietary and supplemental exposure to folate and folic acid. (58)

Rich food sources of folate include dark green vegetables, beans, and legumes. (3) However, the food retention of folate is highly dependent on the type of food and the method of cooking. Folate from animal sources is more stable than folate in green vegetables, and steaming is superior to boiling for folate retention. (59) This has led to public health efforts to increase folic acid intake on a population level, especially since the finding that folic acid supplementation in the preconception period unequivocally decreases the incidence of NTDs. (60) The FDA authorized the addition of folic acid to enriched grain products in March 1996, with compliance mandatory by January 1998. (61) This resulted in a dramatic decrease in folate deficiency and NTDs. (61)(62)

The RDA of folate is 150 $\mu\text{g}/\text{d}$ for the first 3 years after birth, then 200 to 300 $\mu\text{g}/\text{d}$ for 4 to 13 years old and 400 $\mu\text{g}/\text{d}$ thereafter. The RDA for pregnant women is 600 $\mu\text{g}/\text{d}$. The UL applies to folic acid from fortified food and supplements and ranges from 300 to 1,000 $\mu\text{g}/\text{d}$. (3)

Causes and Metabolic Indicators of Folate Deficiency

Isolated folate deficiency is rare; it is often associated with conditions that affect other nutrients. Small-bowel disorders associated with malabsorption, such as inflammatory bowel disease and celiac disease, can cause folate deficiency. Pregnancy, lactation, and chronic hemolytic anemia increase folate requirements. Other populations at risk for folate deficiency include premature infants and

alcoholics. (46) Infants consuming unfortified goat milk have classically been found to develop folate deficiency, manifesting as macrocytic anemia.

Several medications, such as methotrexate and trimethoprim, act as folate antagonists and produce a deficiency by inhibiting dihydrofolate reductase. Other medications that can lead to folate deficiency include anticonvulsants, anti-tuberculosis drugs, and oral contraceptives, but the mechanism is unclear. (46)

Serum or erythrocyte concentrations of folate are reasonable indicators of this vitamin status. Serum levels reflect relatively recent intake and can respond quickly; erythrocyte levels may be preferred as an indicator of chronic intake. Both MMA and homocysteine assays obtained in the setting of megaloblastic anemia help differentiate between B₁₂ and folate deficiency. Both are elevated in B₁₂ deficiency, but only homocysteine is increased in folate deficiency. (11)

Correction of macrocytic anemia with folate can mask an underlying B₁₂ deficiency and will allow progression of neurologic damage due to the latter. It is, thus, critical to distinguish folate vs B₁₂ deficiency before initiating treatment.

Health Consequences of Folate Deficiency

A decline in serum folate level occurs in approximately 2 weeks of consumption of a folate-deficient diet, and megaloblastic anemia occurs within weeks if the deficiency continues. (11)

The effect of maternal folate status on pregnancy outcome is indisputable. There is a strong association between low maternal folate status and increased risk of NTDs. However, the association between folate status and the risk of other birth defects, such as cleft palate, is not as strongly established. (11)

There is also strong evidence of an inverse association between blood folate concentration and the risk of low birthweight. (11)

In adults, there is moderate evidence that low folate concentration is associated with a higher prevalence of depression, cognitive impairment, and dementia. The association between folate status and cognitive function is weaker in children. (11)

Folate and Chronic Disease Prevention

Folate plays an important role in DNA synthesis and repair, but the research about its effect on carcinogenesis and cancer prevention has been contradictory, and this has led to its being called a double-edged sword. Earlier studies suggested that the use of folate in adults can reduce the risk

of colon cancer in women and men. (63)(64) However, randomized controlled trials did not confirm this effect and raised the possibility of a cancer-promoting effect. (65) More research is needed from a public health perspective on the effect of folate on cancer risk and prognosis.

Folate was also postulated to play a protective role against cardiovascular disease because of its role in lowering the homocysteine level, (66) but randomized controlled trials did not provide any evidence to support this role. (67)

Risk of Toxicity

No adverse effects have been attributed to excessive consumption of folate from food. Excessive intake from supplemental folate may obscure and potentially delay the diagnosis and treatment of vitamin B₁₂ deficiency, which can lead to neurologic damage. (3)

VITAMIN K (PHYTONADIONE)

In 1943, Dam and Doisy received the Nobel Prize in Medicine for elucidating the chemical structure of vitamin K. They named this fat-soluble compound K due to its role in “Koagulation.”

Structure and Sources

Vitamin K belongs to a family of molecules that share a 2-methyl-1, 4-naphthoquinone ring but differ in the identity of the side chain at the 3-position. Vitamin K is present in plants as phyloquinone and is produced by bacteria in human and animal large intestine as menaquinone. The significance of the gut microbial production of vitamin K is not clear because most of the absorption occurs in the small intestine. The small intestinal absorption of this liposoluble vitamin is enhanced by dietary fat but also depends on the flow of bile and pancreatic enzymes. Vitamin K is stored in the liver. (3)(5)

Dietary sources of vitamin K include green leafy vegetables such as spinach and collard greens, soy and canola oils, and margarine.

The DRIs

The data were insufficient to recommend an Estimated Average Requirement and an RDA for vitamin K. Adequate intake of vitamin K intake is 2 to 2.5 $\mu\text{g}/\text{d}$ for infants and 30 to 75 $\mu\text{g}/\text{d}$ for 1- to 18-year-olds. Others have recommended 1 $\mu\text{g}/\text{kg}$ per day. (68) No adverse effects were reported from high vitamin K intake from food or supplements in healthy individuals who are not receiving anticoagulant drug therapy. The data were insufficient to establish a UL. (3)

Functions and Consequences of Vitamin K Deficiency

Vitamin K is a cofactor for γ -glutamyl carboxylase, the enzyme responsible for the modification of the side chain of some proteins from glutamate to γ -carboxyglutamate. Most γ -carboxylated proteins are clotting factors such as factors II (prothrombin) VII, IX, and X. This underlies the essential role of vitamin K in the coagulation cascade.

Other carboxylated proteins play an important role in calcium homeostasis and, thus, are important for bone and cardiovascular health. There is also emerging evidence about the protective effects of vitamin K against oxidative stress, age-related decline in motor and cognitive functions, cancer, and hepatitis C. (5)

Clinically relevant vitamin K deficiency is rare and is usually limited to patients with lipid malabsorption syndromes or those who take certain medications (such as antibiotics, vitamin A, and vitamin E) that interfere with vitamin K metabolism. (3) In this review, we focus on the importance of recognizing the recrudescence of vitamin K deficiency bleeding (VKDB), formerly known as hemorrhagic disease of the newborn.

Cases

A 6-week-old infant presented to a tertiary care center emergency department with a 1-day history of poor breastfeeding, increased crying, pallor, and a “full and hard” anterior fontanelle. The medical history was relevant for exclusive breastfeeding and no vitamin K prophylaxis at birth. A full sepsis evaluation was initiated, and due to the bloody cerebrospinal fluid and the altered mental status, a head CT was obtained, which demonstrated a large ICH. The infant was treated with neurosurgical evacuation of the hematoma and administration of anticonvulsant agents. He remained seizure free with therapy but had a right hemiparesis and significant developmental deficit 3 months after ICH.

This infant was 1 of 5 cases of late VKDB presenting to a tertiary care center in Tennessee between February and September 2013, raising concerns about an increased occurrence of late VKDB due to parental refusal of vitamin K prophylaxis at birth. All 5 infants were exclusively breastfed and did not receive vitamin K prophylaxis at birth. Their age range was 6 weeks to 5 months, and 2 of the infants were born at home. One of the infants presented with a gastrointestinal bleed, and the other 4 had ICH. Of those who presented with ICH, 3 had varying degrees of developmental delay on follow-up. (69)

Symptoms and Risk Factors for VKDB

Recognition of VKDB is critical for prompt diagnosis and urgent therapy. Vitamin K deficiency bleeding can be classified as early (<24 hours after birth), classic (2–14 days), and late (2–12 weeks but can be seen in infants up to 6 months old). Symptoms of VKDB range from mild “warning bleeds” (umbilical cord, gastrointestinal, or circumcision bleeding) to severe (ICH). (5)(69) It is important to note that warning bleeds precede ICH by days to weeks. (70)

Newborn infants are at increased risk for VKDB for several reasons. First, the placental transfer of vitamin K is poor, and its half-life in the liver stores is short. Second, the newborn gut flora is immature and unable to produce vitamin K, rendering the newborn infant dependent on dietary intake as the main source of vitamin K. The exclusively breastfed infant is especially at risk for late VKDB because the human milk content of vitamin K is low; standard fortification of infant formulas provides adequate intake. (5)(69)

Incidence

Early VKDB is rare and is almost exclusively related to maternal medications, especially antiepileptic drugs, that increase the degradation of vitamin K (ICH occurs in 20%–25% of such infants) (71).

Classic VKDB often presents with mild symptoms such as gastrointestinal and umbilical blood loss and rarely ICH; however, VKDB incidence without vitamin K prophylaxis is estimated to be 0.25% to 1.7%. (72)

Late VKDB incidence in exclusively breastfed infants with no vitamin K prophylaxis is 4.4 of 100,000 to 7.2 of 100,000. Infants with fat malabsorption syndromes (cystic fibrosis, cholestatic jaundice, etc) are especially at risk, and sometimes VKDB is the presenting symptom. (72) Late VKDB often presents with ICH. (73)

Diagnosis

In vitamin K–deficient individuals, uncarboxylated vitamin K–dependent proteins, normally called “proteins induced by vitamin K absence” (PIVKA), are present in the blood and can be measured. PIVKA II, or uncarboxylated prothrombin, is a marker of subclinical vitamin K deficiency and is usually present before the development of abnormal coagulation test results. (68)(73)

A confirmed case of VKDB should fulfill the diagnostic criteria of prothrombin time that is 4 times the control value, and at least 1 of the following:

- Normal or elevated platelet count, normal fibrinogen level, and absent fibrin degradation products

- Normalization of prothrombin time after vitamin K administration
- PIVKA (usually PIVKA II) level greater than that of healthy controls

The prompt diagnosis of late VKDB can have important legal consequences in cases of suspected nonaccidental brain injury. Retinal hemorrhage, a signature of nonaccidental brain injury, was recently documented in 2 confirmed cases of VKDB. PIVKA II has a long half-life and can be of major value in retrospective diagnosis of VKDB even weeks after the event. (73)

Vitamin K Prophylaxis

The AAP recommends that vitamin K be given to all newborns as a single intramuscular (IM) dose of 0.5 to 1 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72)

Oral administration of vitamin K for the prevention of VKDB was promoted due to concerns regarding a possible causal association between parenteral vitamin K and childhood cancer, a claim that was subsequently and definitively debunked. Orally administered vitamin K prophylaxis, even with multiple-dose regimens, is associated with a resurgence of late VKDB in several countries. (68)(72)

Some oral regimens have proven efficacy in the prevention of late VKDB and are used in Europe, such as the weekly administration of 1 mg of vitamin K for 12 weeks or 2 mg at weeks 1 and 4. However, oral vitamin K is not effective in the prevention of late VKDB in patients with liver disease or malabsorption. (68) Currently, the Canadian Paediatric Society suggests that oral vitamin K should be given to newborns whose parents decline IM vitamin K as a 2-mg dose at birth and at weeks 1 and 6. (74)

Talking Points for the Clinician when Parents Decline Vitamin K Prophylaxis

After the recent increase of infants presenting with late VKDB, the Centers for Disease Control and Prevention (CDC) conducted an investigation and determined that 28% of the parents for children born at local private birthing centers in Tennessee declined vitamin K prophylaxis. Some reasons for parental refusal include concern about an increased risk of leukemia, concern about the use of a synthetic medication, and the impression that giving medications at birth is neither natural nor necessary for healthy term infants. There was a remarkable lack of awareness among the Tennessee families about the potentially life-threatening nature of late VKDB. (69)

When faced with vitamin K refusal, the clinician should respectfully elicit the parents' concerns and attempt to educate and correct any misinformation. The clinician can discuss the recent cases of late VKDB in Nashville, Tennessee, and point out that in all cases the parents had refused the vitamin K prophylaxis at birth.

There is no expert consensus on whether circumcision should be refused or deferred in infants whose parents refuse vitamin K prophylaxis. When confronted with this request there are many considerations. First, there is no available data on the optimal timing of the procedure. Second, the medical provider and the nursing staff comfort with this decision must be taken into analysis because they have to practically manage the bleeding should it occur.

In contemplating the idea of suggesting oral vitamin K to parents who refused the IM injection, it is important to note that oral vitamin K preparations used in Europe with proven efficacy are not available in the United States. The phytonadione 5-mg tablet is the only oral formulation of vitamin K currently approved by the FDA. However, because giving a tablet to a newborn can be challenging and requires crushing or compounding, the injectable phytonadine (1 mg/0.5 mL) is sometimes given orally. Unlike the European vitamin K preparations, US formulations have not been studied for efficacy. (74)

One can argue that delivery of some vitamin K is better than none, but when parents are offered oral vitamin K they seem to perceive it as equally effective as the IM injection. Some parents may consider the IM route if the oral form is not an option. There is also the ethical aspect of prescribing an unproven formulation for the prevention of a potentially life-threatening disease when a treatment of proven efficacy exists. (74)

Summary

- Thirty-four percent of US children and adolescents used vitamin supplements in the past month, and almost half of those children took a supplement daily. (1) Supplement users were more likely to be Asian, white, or non-Hispanic; to belong to families with higher income and education; to be in good or excellent health; and to have access to health care. (2) (Evidence Quality B)
- Vitamin A deficiency is prevalent, especially in the developing world. In fact, vitamin A deficiency accounts for 1.7% of child mortality. (4) (Evidence Quality B)
- The American Academy of Pediatrics recommends a vitamin A supplement for children 6 months to 2 years old who are hospitalized for measles. (9) (Evidence Quality D)

- The recognition and treatment of vitamin B₁₂ deficiency is critical, especially in infants, because with early diagnosis it is a reversible cause of developmental regression and cognitive delay. (13)(14) (Evidence Quality D)
- In the exclusively breastfed infant, the most common cause of B₁₂ deficiency is undiagnosed maternal pernicious anemia. Other etiologies include maternal gastric bypass surgery and vegetarian diet. (13) (Evidence Quality D)
- Neurologic symptoms secondary to B₁₂ deficiency can occur without hematologic abnormalities. (13) (Evidence Quality D)
- It is reasonable to suspect B₁₂ deficiency in any infant with failure to thrive and developmental regression. (14) (Evidence Quality D)
- Symptoms of vitamin C deficiency can develop after 30 to 40 days of consuming a diet that is void of vitamin C. (22) Scurvy should be considered in the differential diagnosis of an at-risk child (especially in the setting of a developmental disorder and a restrictive diet) who presents with refusal to walk. (21)(22) (Evidence Quality D)
- Infants and children aged 0 to 1 year need at least 400 IU/d of vitamin D. Children 1 year and older need at least 600 IU/d of vitamin D. (27) (Evidence Quality A)
- Infants and children aged 0 to 18 years who are vitamin D deficient can be treated with 2,000 IU/d of vitamin D₂ or D₃, or with 50,000 IU of vitamin D₂ or D₃ once a week for 6 weeks to achieve a blood level of 25(OH)D greater than 30 ng/mL (>75 nmol/L). (27) (Evidence Quality B)
- Universal screening of all patients for vitamin D deficiency is not recommended and should be reserved and considered only for high-risk patients. (27) (Evidence Quality D)
- Vitamin E at a dose of 800 IU/d is beneficial for the treatment of nonalcoholic steatohepatitis in adults. More studies are needed before its use can be recommended in children. (55)(56) (Evidence Quality D)
- Since the Food and Drug Administration authorized the addition of folic acid to enriched grain products in 1996 there has been a dramatic decrease in folate deficiency and neural tube defects. (61) (Evidence Quality C)
- Recognition of vitamin K deficiency bleeding (VKDB) is critical for prompt diagnosis and urgent therapy. Warning bleeds (umbilical cord, gastrointestinal, or circumcision bleeding) precede ICH by days to weeks. (70) (Evidence Quality C)
- The American Academy of Pediatrics (AAP) recommends that vitamin K be given to all newborns as a single intramuscular dose of 0.5 to 1.0 mg. The AAP concludes that additional research is needed regarding the oral administration of vitamin K to prevent late VKDB. (72) (Evidence Quality C)

References for this article are at <http://pedsinreview.aappublications.org/content/39/4/161>.

PIR Quiz

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1. A 20-month-old boy is brought to the pediatrician's office for a well-child checkup. He has recently immigrated to the United States from East Africa. The mother reports that he has trouble seeing at night and stumbles repeatedly. On physical examination, his cornea is normal. You diagnose the patient as having night blindness. Deficiency of which of the following vitamins is most likely responsible for this condition in this patient?
 - A. Vitamin A.
 - B. Vitamin B₁₂.
 - C. Vitamin C.
 - D. Vitamin D.
 - E. Vitamin E.
2. You are part of the Global Health Brigade and are taking care of a hospitalized infant with measles in rural Uganda. According to the American Academy of Pediatrics, which of the following is the recommended dose of vitamin A supplementation in this patient?
 - A. 10,000 IU.
 - B. 50,000 IU.
 - C. 100,000 IU.
 - D. 200,000 IU.
 - E. 300,000 IU.
3. In your office you are seeing a 4-month-old girl for failure to thrive. The child was born at term, and the mother had an uneventful pregnancy. You notice that since the last time you saw her, she has been having some trembling movements and has lost her deep tendon reflexes. The child is exclusively breastfed, and the mother is strictly vegan. You decide to send the patient to the hospital for direct admission. In addition to a complete blood cell count, which of the following vitamin serum levels will you most likely order in this patient?
 - A. Vitamin A.
 - B. Vitamin B₁₂.
 - C. Vitamin C.
 - D. Vitamin D.
 - E. Vitamin E.
4. You practice in a small clinic in the Northeastern United States and are seeing an African American toddler who does not play outside because of the cold weather. He was exclusively breastfed until 6 months of age. He mostly eats pureed foods and does not like eating any dairy foods. You notice that he walks with bowed legs and has widening of wrists on physical examination. Based on the history and physical examination findings, which of the following is the most likely diagnosis in this patient?
 - A. Langerhans cell histiocytosis.
 - B. Megaloblastic anemia.
 - C. Osteogenesis imperfecta.
 - D. Rickets.
 - E. Scurvy.

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5. You are a pediatrician practicing in rural Tennessee and are seeing a 6-week-old girl who was born at home. Per the parents, there were no problems at birth, and she has been exclusively breastfed. She has not been previously seen by a medical provider. She now presents with poor feeding, irritability, and a bulging fontanelle. Which of the following is the most likely underlying vitamin deficiency to explain the presumed diagnosis of intracranial hemorrhage?
- A. Hypervitaminosis A.
 - B. Hypervitaminosis D.
 - C. Vitamin B₆ deficiency.
 - D. Vitamin K deficiency.
 - E. Vitamin E deficiency.