Vitamin D

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Hypertension
Hypocalcemia

Cholecalciferol (vitamin D_3) is the mammalian form of vitamin D and is produced by ultraviolet irradiation of inactive precursors in the skin. Ergocalciferol (vitamin D_2) is derived from plants. Vitamin D_2 and vitamin D_3 require further metabolism to become active. They are of equivalent potency. Clothing, lack of sunlight exposure, and skin pigmentation decrease generation of vitamin D in the epidermis and dermis.

Vitamin D (D_2 and D_3) is metabolized in the liver to calcidiol, or 25-hydroxyvitamin D (25-[OH]-D); this metabolite, which has little intrinsic activity, is transported by a plasma-binding globulin to the kidney, where it is converted to the most active metabolite calcitriol, or 1,25-dihydroxyvitamin D (1,25-$[OH]_2$-D). The action of 1,25-$(OH)_2$-D results in a decrease in the concentration of messenger RNA (mRNA) for collagen in bone and an increase in the concentration of mRNA for vitamin D–dependent calcium-binding protein in the intestine (directly mediating increased intestinal calcium transport). The antirachitic action of vitamin D probably is mediated by provision of appropriate concentrations of calcium and phosphate in the extracellular space of bone and by enhanced intestinal absorption of these minerals. Vitamin D also may have a direct anabolic effect on bone. 1,25-$(OH)_2$-D has direct feedback to the parathyroid gland and inhibits secretion of parathyroid hormone.

Vitamin D deficiency appears as **rickets** in children and as **osteomalacia** in postpubertal adolescents. Inadequate direct sun exposure and vitamin D intake are sufficient causes, but other factors, such as various drugs (phenobarbital, phenytoin) and malabsorption, may increase the risk of development of vitamin-deficiency rickets. Breastfed infants, especially those with dark-pigmented skin, are at risk for vitamin D deficiency.

The pathophysiology of rickets results from defective bone growth, especially at the epiphyseal cartilage matrix, which fails to mineralize. The uncalcified osteoid results in a wide, irregular zone of poorly supported tissue, the rachitic metaphysis. This soft, rather than hardened, zone produces many of the skeletal deformities through compression and lateral bulging or flaring of the ends of bones.

The **clinical manifestations** of rickets are most common during the first 2 years of life and may become evident only after several months of a vitamin D–deficient diet. **Craniotabes** is caused by thinning of the outer table of the skull, which when compressed feels like a Ping-Pong ball to the touch. Enlargement of the costochondral junction **(rachitic rosary)** and thickening of the wrists and ankles may be palpated. The anterior fontanelle is enlarged, and its closure may be delayed. In advanced rickets, scoliosis and exaggerated lordosis may be present. Bowlegs or knock-knees may be evident in older infants, and greenstick fractures may be observed in long bones.

The **diagnosis** of rickets is based on a history of poor vitamin D intake and little exposure to direct ultraviolet sunlight. The serum calcium usually is normal but may be low; the serum phosphorus level usually is reduced, and serum alkaline phosphatase activity is elevated. When serum calcium levels decline to less than 7.5 mg/dL, tetany may occur. Levels of 24,25-$(OH)_2$-D are undetectable, and serum 1,25-(OH)2-D levels are commonly less than 7 ng/mL, although 1,25-$(OH)_2$-D levels also may be normal. The best measure of vitamin D status is the level of 25-(OH)-D. Characteristic **radiographic** changes of the distal ulna and radius include widening; concave cupping; and frayed, poorly demarcated ends. The increased space seen between the distal ends of the radius and ulna and the metacarpal bones is the enlarged, nonossified metaphysis.

Breastfed infants born of mothers with adequate vitamin D stores usually maintain adequate serum vitamin D levels for at least 2 months, but rickets may develop subsequently if these infants are not exposed to the sun or do not receive supplementary vitamin D. The American Academy of Pediatrics recommends vitamin D supplementation of all breastfed infants in the amount of 400 IU/day, started soon after birth and given until the infant is taking more than 1000 mL/day of formula or vitamin D–fortified milk (for age >1 year). Toxic effects of excessive chronic vitamin D may include hypercalcemia, muscle weakness, polyuria, and nephrocalcinosis.

Vitamin K

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Bleeding

The plant form of vitamin K is phylloquinone, or vitamin K_1. Another form is menaquinone, or vitamin K_2, one of a series of compounds with unsaturated side chains synthesized by intestinal bacteria. Plasma factors II (prothrombin), VII, IX, and X in the cascade of blood coagulation factors depend on vitamin K for synthesis and for post-translational conversion of their precursor proteins. The post-translational conversion of glutamyl residues to carboxyglutamic acid residues of a prothrombin molecule creates effective calcium-binding sites, making the protein active.

Other vitamin K–dependent proteins include proteins C, S, and Z in plasma and γ-carboxyglutamic acid–containing proteins in several tissues. Bone contains a major vitamin K–dependent protein, osteocalcin, and lesser amounts of other glutamic acid–containing proteins.

Phylloquinone is absorbed from the intestine and transported by chylomicrons. The rarity of dietary vitamin K deficiency in humans with normal intestinal function suggests that the absorption of menaquinones is possible. Vitamin K deficiency has been observed in subjects with impaired fat absorption caused by obstructive jaundice, pancreatic insufficiency, and celiac disease; often these problems are combined with the use of antibiotics that change intestinal flora.

Hemorrhagic disease of the newborn, a disease more common among breastfed infants, occurs in the first few weeks of life. It is rare in infants who receive prophylactic intramuscular vitamin K on the first day of life. Hemorrhagic disease of the newborn usually is marked by generalized ecchymoses, gastrointestinal hemorrhage, or bleeding from a circumcision or umbilical stump; intracranial hemorrhage can occur, but