Vitamin D[1]

Vitamin D, a seco-sterol, is unique among nutrients, because it can be obtained either from the diet or by endogenous synthesis. In the skin, UVB (290–320 nm) exposure converts 7-dehydrocholesterol to pre-vitamin D_3, which isomerizes to vitamin D_3 (cholecalciferol), the form that is transported to the liver bound to vitamin D binding protein (DBP)[2] (1). Several factors limit the skin production of vitamin D, including high latitudes, darker skin pigmentation, winter, and avoidance of the sun (including use of clothes or sunblocks). From the diet, vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) is absorbed, packaged into chylomicrons, released into the peripheral circulation, and then transported to the liver in the remnant particle. Another unique aspect of vitamin D is that it must be metabolically activated, after which it functions classically as a hormone in calcium and phosphorous homeostasis. There are 2 hydroxylations needed to produce the hormonally active form of vitamin D. The first occurs in the liver to form 25-hydroxyvitamin D (25OHD; calcidiol) through the action of 25-hydroxylase (most likely CYP2R1). Upon its release into the blood, 25OHD binds to DBP and is delivered to the kidney where it is hydroxylated again to form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D; calcitriol] by 1-α-hydroxylase (CYP27B1). Parathyroid hormone that is produced in response to low-serum Ca positively regulates this second hydroxylation, whereas fibroblast growth factor 23 released from bone in response to high-serum phosphate levels negatively regulates it. 1,25$(OH)_2$D bound to DBP is delivered to target tissues where it acts as an endocrine hormone to regulate the function of intestine (increasing absorption), bone (promoting resorption), and kidney (increasing retention) to modulate calcium and phosphorous metabolism and maintain normal serum Ca and phosphate levels (2). Both 1,25$(OH)_2$D and 25OHD are catabolized by 24-hydroxylase (CYP24A1) to inactive calcitroic acid and 24,25dihydroxyvitamin D, respectively; 1,25$(OH)_2$D and fibroblast growth factor 23 enhance this catabolism. Of its metabolites, serum 25OHD level is the best biomarker of total "exposure" to vitamin D, because it reflects both dietary and endogenous sources and because 25OHD has a relatively long half-life.

Within cells, 1,25$(OH)_2$D regulates the transcription of a large and diverse number of genes by binding to its nuclear receptor, the vitamin D receptor (VDR). The VDR forms a heterodimer with the Retinoid X Receptor (RXR, another member of the steroid nuclear receptor family) and interacts with its consensus regulatory sequence on DNA (3). Through this mechanism, 1,25$(OH)_2$D not only maintains calcium and phosphate homeostasis and bone mineralization but also regulates cellular growth, differentiation, and immune function. Local production of 1,25$(OH)_2$D may also occur extra-renally in many tissues that express 1α-hydroxylase, leading to autocrine/paracrine/intracrine action. However, the production of 1,25$(OH)_2$D by nonrenal cells has only been demonstrated in vitro.

Deficiencies: Frank deficiency of vitamin D results in impaired bone mineralization. In children, this presents clinically as rickets, a condition of soft bones and skeletal malformation. In adults, this presents clinically as osteomalacia, which leads to skeletal malformations and an increased risk of fracture. However, calcium deficiency can also cause rickets and osteomalacia. The interdependence of vitamin D and calcium for normal bone mineralization may explain the difficulty in identifying a threshold of serum 25OHD level for rickets or osteomalacia (1). Individuals with very low serum 25OHD levels may not exhibit rickets or osteomalacia if their calcium intakes are sufficient to support bone mineralization. Nonetheless, the risk of rickets increases when serum 25OHD levels are $<$30 nmol/L (12.5 μg/L) (1).

Diet recommendations: The 2011 DRI were set based on bone health outcomes and assuming minimal sun exposure and endogenous synthesis and adequate calcium intakes. Thus, the DRI meets the needs of the healthy population irrespective of latitude, season, skin pigmentation, cultural behaviors, etc. Of the $>$25 health outcomes critically reviewed by the DRI committee, the consistency and causality of effect and availability of dose-response data were sufficient only for bone health outcomes in terms of establishing a DRI (1). For all other health outcomes considered (cancer, cardiovascular disease, diabetes, autoimmune disorders, infectious diseases, falls, etc.), the evidence was contradictory, and thus inconclusive, from relatively few randomized clinical trials (primarily for cancer and infectious disease) and

more numerous observational studies, which were lacking in causality.

The Estimated Average Requirement to meet the needs of 50% of the healthy population ages 1–71 y and older was linked to a serum 25OHD level of 40 nmol/L (16 μg/L) and was established at 400 IU/d. The RDA to meet the needs of 97.5% of the population from 1 to 70 y and those $\geq$71 y was linked to a serum 25OHD level of 50 nmol/L (20 μg/L) or greater and established at 600 IU/d and 800 IU/d, respectively. Current evidence suggests that neither pregnancy nor lactation alters the requirements for vitamin D relative to bone health (1). In the most recent NHANES surveys, 81% of Americans have serum 25OHD levels $>$40 nmol/L, indicating adequacy of exposure even though intakes are well below the EAR. These data suggest that incidental sun exposure significantly contributes to meeting the needs for vitamin D. Although on average only 18.8% of all Americans from 1 to $\geq$71 y have serum levels $<$40 nmol/L, the prevalence of inadequate levels are higher in African Americans (53.6%) and Hispanic Americans (27.2%).

Food sources: Few foods naturally contain cholecalciferol. These foods include the richest sources (cod liver oil and fatty fish such as salmon, tuna or mackerel) and more modest sources (beef liver, eggs, and sardines). Mushrooms contain variable amounts of vitamin D_2 depending on their UVB exposure during production. In the US and Canada, fortified foods are the primary dietary sources of vitamin D as either vitamin D_2 or cholecalciferol. Foods fortified with vitamin D include milk and selected dairy products, orange juice, margarine, and grains, primarily ready-to-eat cereals. Controversy exists over the bioequivalency of vitamin D_2 and cholecalciferol despite the fact that both are equally potent in curing rickets. Each one achieves and sustains similar serum 25OHD levels when given daily as a low-dose regimen, but when given as a single high dose, cholecalciferol sustains these levels longer (1).

Clinical uses: Vitamin D is used in a high-dose and short-duration treatment to correct deficiency based on low serum 25OHD levels, i.e. typically 50,0000 IU/wk for 4–8 wk with careful monitoring of serum 25OHD levels. Currently, however, there are no evidence-based consensus guidelines for the interpretation of serum 25OHD levels (1), nor are there uniformly accepted cutpoints for diagnosing vitamin D deficiency and sufficiency. For example, a range of cutpoints has been suggested and are in use for defining deficiency ranging from $<$30 nmol/L (12 μg/L) to as high as $<$75–80 nmol/L (30–32 μg/L) and sufficiency ranging from $\geq$50 nmol/L (20 μg/L) to $\geq$75–80 nmol/L (30–32 μg/L). Application of the 2011 DRI suggests that serum 25OH D levels $<$ 30 nmol/L (12 μg/L) are deficient, $<$40 nmol/L (16 μg/L) are inadequate, and $\geq$50 nmol/l (20 μg/L) are adequate/sufficient. Further, sustained high levels of $>$125 nmol/L (50 μg/L) may increase the risk of adverse outcomes. Combined supplementation of postmenopausal women and men older than 70 y of age with both vitamin D (800–1000 IU/d) and calcium (1000 mg/d) is also used to reduce the risk of fractures and enhance bone mineral density. Patients with chronic kidney disease, in which the production of $1,25(OH)_2D$ is impaired, are treated with calcitriol or its analogs.

Toxicity and adverse outcomes: Case studies of acute toxicity resulting in hypercalcemia and hypercalciuria have been reported to occur with ingestion of 10,000 IU/d or more of vitamin D (1). The current Tolerable Upper Intake Level was set lower at 4000 IU/d in adults because of the emerging evidence of other adverse outcomes at exposures lower than those that are acutely toxic. Elevated serum 25OHD levels $>$125–150 nmol/L have been associated with increased risk for all-cause mortality, cardiovascular disease, selected cancers (pancreatic, prostate, and breast), fractures, and falls (1).

Recent research: Rapidly emerging research has explored the role of vitamin D in nonskeletal health outcomes. These studies are cell-based mechanistic studies using $1,25(OH)_2D$ and animal models using severe vitamin D deficiency or deletion of VDR or CYP27B1 genes to disrupt vitamin D metabolism and action. They demonstrate the biological plausibility of a role for $1,25(OH)_2D$ signaling through the VDR in cancer (3), autoimmune disorders, immune function, cardiovascular disease, and other diseases. In addition, an increased risk for many nonskeletal health outcomes is based on associations with low serum 25OHD levels (e.g. diabetes, various cancers, autoimmune diseases, etc.). However, other association studies show an increased risk of some diseases with higher serum 25OHD levels (e.g. all-cause mortality, pancreatic and prostate cancer, cardiovascular disease, falls, etc.), suggesting a U-shaped or J-shaped risk relationship between vitamin D status

and disease risk. Recent studies have also investigated the possible role that in utero vitamin D exposure may have on fetal programming of adult disease risk. There is inconclusive evidence that polymorphisms in several genes may alter the relationship between vitamin D and health outcomes.

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[2]Abbreviations used: DBP, vitamin D binding protein; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; VDR, vitamin D receptor.

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