

## Vitamin D: Nutrition Information Brief

### Vitamin D

**V**itamin D is a generic term for the parent compounds, vitamin D-3 (cholecalciferol) and vitamin D-2 (ergocalciferol) and their metabolites. Vitamin D is a hormone synthesized in the skin when adequate sunlight exposure as UVB radiation converts 7-dehydrocholesterol to cholecalciferol. In the absence of UVB rays there is a need for dietary sources, and thus the name “vitamin” reflects a need for vitamin D-3 and/or vitamin D-2. Vitamin D-3 enters the circulation from the skin or if ingested, both vitamins D-2 and D-3 in the gut are absorbed as chylomicrons, which enter the lymph via the thoracic duct. Circulating vitamin D released from skin is bound to vitamin D-binding protein. Protein-bound vitamin D is transported to adipose, where it is deposited, or to the liver. In the liver it is hydroxylated by 25-hydroxylases [cytochrome P450 (CYP) enzymes CYP2R1 and CYP27A1] to 25-hydroxyvitamin D [25(OH)D, also called calcidiol], which is the longer-lasting circulating metabolite. This circulating plasma 25(OH)D has several fates: 1) when there is a need for calcium reflected by an increase in parathyroid hormone (PTH) or a need for phosphate, 25(OH)D is activated in the kidney by 1- $\alpha$ -hydroxylase (CYP27B1) to produce the biologically active metabolite 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D, also called calcitriol], which circulates in plasma; 2) 25(OH)D can be taken up by tissues and subsequently converted to 1,25(OH)<sub>2</sub>D inside cells, if the 1-hydroxylase enzyme has been locally activated; and 3) 25(OH)D can be converted to 24,25-dihydroxyvitamin D by 24-hydroxylase (CYP24A1) in the pathway toward its excretion in bile. In a similar pathway, the enzyme 24-hydroxylase inactivates calcitriol (1).

Vitamin D in its active form functions to maintain calcium and phosphate homeostasis by regulating their intestinal absorption and deposition in bone, but it has other nonskeletal roles that involve extrarenal activation in specific cells with 1- $\alpha$ -hydroxylase activity and vitamin D receptors (1). Calcitriol plays a critical autocrine function in these cells when transported to the nucleus, where it functions in the regulation of the synthesis of specific proteins operative in modulating both innate and cellular immune responses, regulating cell differentiation, proliferation, and apoptosis, or a paracrine role when it is transported locally within a tissue.

With respect to skeletal homeostatic functions, the renal activation of vitamin D to calcitriol is regulated by PTH in response to hypocalcemia, and renal inactivation is regulated by the secretion of fibroblast growth factor-23 by bone osteocytes in response to elevated serum phosphate. Thus, circulating calcitriol is not a good indicator of vitamin D status,

but lower concentrations can be indicative of insufficient supply of 25(OH)D as its precursor, and insufficient 25(OH)D is often indicated by elevated PTH. The concentration of the circulating or transport form of vitamin D, 25(OH)D, is considered the best biomarker of vitamin D status and is used widely in surveys and intervention studies examining efficacy of supplementation and food fortification (1).

### Deficiencies

Plasma total 25(OH)D concentration reflects the sum of vitamin D from dietary intake and sunlight exposure. Severe deficiency occurs when concentrations are <30 nmol/L (12 ng/mL), whereas optimal concentrations are >75 nmol/L (30 ng/mL) (2, 3). It is more appropriate as a status indicator rather than the parent compound, given circulating 25(OH)D has a half-life of 14 d, in contrast to cholecalciferol (1–2 d) (1). It is not clear whether total, which includes protein-bound, or free 25(OH)D is the best measure of vitamin D nutritional status, but at this time dietary recommendations, survey data, and intervention studies only report total 25(OH)D concentrations (2). Significant variability in outcomes occurs when different assay platforms, research and clinical laboratories, and various reference standards are used in measuring circulating 25(OH)D. Strict adherence to proper assay platform standardization, retroactive validation of earlier assay results, and use of certified reference standards have become a necessity for accurate comparisons in population-based surveys and are now increasingly required for publication (3).

Nutritional rickets occurs with vitamin D deficiency in both infants and children who otherwise have sufficient calcium and other nutrient intakes, such as breastfed infants of vitamin D-deficient mothers (2). Abnormal softening of the skull accompanied by enlargement of the epiphyses of long bones and at the costochondral junction (rachitic rosary) occurs in infantile rickets. In Canada and the United States, as well as other countries, 10  $\mu$ g/d is recommended for all infants, birth to 12 mo, independent of their mode of feeding (2, 4). Rickets can also be caused by calcium deficiency so both nutrients should be monitored in infants, as well as in older children and adolescents (2, 4, 5). Vitamin D-resistant rickets (familial hypophosphatemia) is a defect in proximal renal tubular reabsorption of phosphate (renal phosphate wasting), and vitamin D-dependent rickets (VDDR type 1A) stems from a defect in the 1- $\alpha$ -hydroxylase enzyme due to mutations in CYP27B1 genes (1). Severe deficiency in adults results in osteomalacia, characterized by a failure to mineralize the organic matrix of bone, resulting in weak and painful bone, frailty fractures, and muscle fatigue and weakness. Osteomalacia often remains

undiagnosed, requiring radiographic confirmation and bone biopsy with histomorphological assessment (5). When calcium intake is low, vitamin D deficiency has been associated with increased risk of osteoporosis; however, a systematic review by the US Preventative Services Task Force has concluded that vitamin D supplementation alone or with calcium was not associated with reduced fracture incidence in community-dwelling adults without known vitamin D deficiency, osteoporosis, or prior fracture, and that vitamin D with calcium was associated with an increase in the incidence of kidney stones (6). This recommendation relates only to bone health and not to the critical role of vitamin D in immune responses (7, 8).

Other human chronic diseases associated with low vitamin D status in cross-sectional or cohort studies include those related to cancer development, immune system regulation, brain and neural function and cognition, and risk modification of other metabolic diseases such as diabetes (1). Poor vitamin D status is also associated with risk of infectious disease like acute respiratory tract infections (7), and is the basis for current efforts to optimize vitamin D status in the coronavirus disease 2019 (Covid-19) pandemic (7, 8).

### Diet Recommendations

In 2011, the Institute of Medicine (now the National Academy of Medicine) provided DRIs that for the first time included Estimated Average Requirement (EAR) values for vitamin D intake (9). For ages  $\geq 1$  y, the EAR was set as 10  $\mu\text{g}/\text{d}$  based on achieving 40 nmol/L serum 25(OH)D concentrations determined using dose–response data for maintenance of bone health in each age group. The RDA was set for ages 1 to 70 y at 15  $\mu\text{g}/\text{d}$ , wherein all ages would achieve a serum 25(OH)D concentration of 50 nmol/L. For adults  $>70$  y, the RDA was set higher, at 20  $\mu\text{g}/\text{d}$ , due to age-related absorption and other inefficiencies in vitamin D metabolism. The infant recommended intake is set as an Adequate Intake of 10  $\mu\text{g}$ . Since 2011, many other countries have set vitamin D intake recommendations at levels needed to achieve the same 25(OH)D cutoff threshold of 50 nmol/L in their population (10).

### Food Sources

There are few natural food sources rich in vitamin D: oily fish, seal, liver of lean fish, and UV-exposed mushrooms. In the United States, Canada, and Finland fluid milk is fortified with vitamin D, but this is mandated only in Canada and Finland. There is widespread acknowledgment that culturally appropriate fortification with vitamin D is needed to address global vitamin D inadequacy (11). National nutrition surveys show low ( $<3.0$   $\mu\text{g}/\text{d}$ ) intakes in countries where there is little to no vitamin D fortification, such as the United Kingdom (12). In contrast, indigenous people living around the Arctic circle still consuming a traditional fish- and seal-based diet have intakes ranging from 10 to 20  $\mu\text{g}/\text{d}$  (13). Only foods in the kingdom Fungi such as sun-exposed mushrooms naturally provide vitamin D-2, and both UV-exposed yeast and mushrooms can be added to the food supply to enhance the vitamin D content of foods. Unlike vitamin D-enhanced edible mushrooms, despite US FDA approved use of D-2-producing yeasts in baked products, there was poor bioavailability of vitamin D-2 compared with added vitamin

D-2 supplements when the yeast was used in making bread (14).

### Clinical Considerations

It has been proposed by the Endocrine Society and others (10) that high-risk patients with osteoporosis, obesity, malabsorption, required use of interfering medications, or liver or kidney disease aim for a higher threshold concentration of 25(OH)D at  $>75$  nmol/L. Obesity is a significant factor in many populations worldwide that is associated with vitamin D insufficiency and deficiency (1). Disease conditions affecting fat absorption impair vitamin D status, which can also occur with hepatic disorders and chronic renal failure and medications that impair liver or kidney cytochrome enzymes needed in vitamin D metabolism and activation (1).

### Toxicity

Vitamin D intoxication does not arise from the consumption of conventional foods, including fortified foods, nor does it occur with excessive exposure to sunlight (i.e., UVB). An isolated case resulted from the accidental overfortification of milk with vitamin D-3, and other cases have occurred with uncontrolled individual use of vitamin D megadoses and the inappropriate use of vitamin D metabolites (1). Evidence concerning efficacy of vitamin D-2 compared with vitamin D-3 suggests that whereas vitamin D-3 stimulates greater gene activation, vitamin D-2 demonstrates less toxicity at higher intakes that are often required in treating severe deficiency. Clinical signs of vitamin D toxicity, likely to occur when circulating 25(OH)D exceeds 250 nmol/L (1), include hypertension, hypercalcemia, hypercalciuria, and extraosseous calcification (1, 15). The Tolerable Upper Intake Level (UL) for vitamin D set for infants aged 0–6 mo is 25  $\mu\text{g}/\text{d}$ , and there is an increase in the UL with age through childhood to 100  $\mu\text{g}/\text{d}$  by age  $\geq 9$  y. For those under a physician's care for disorders impairing vitamin D status, a higher UL of 250  $\mu\text{g}/\text{d}$  could be warranted. In rare conditions, for example, sarcoidosis, tuberculosis, and some genetic disorders of vitamin D metabolism (idiopathic infantile hypercalcemia), there is increased risk of vitamin D toxicity with supplementation (15).

### Recent Research

Considerable controversy exists concerning how vitamin D status measurements [25(OH)D concentration] and dietary recommendations are interpreted, and how the amount gained from sun exposure, which can vary between 1000 IU/d and 10,000 IU/d, impacts dietary recommendations (2). Data from East Africa, where adults engaged in pastoral activities requiring them to work outdoors everyday, showed circulating 25(OH)D concentrations between 25 and 150 nmol/L (16). Determination of contributions to plasma 25(OH)D from safe sun exposure is fraught with too many confounding factors such as latitude, altitude, season, time of day, skin color, and use of sunscreens and traditional concealing clothing (2). Much remains to be determined regarding vitamin D-regulated genes responsible for the protective effects of vitamin D on disease risk (1).

Vitamin D research related to the Covid-19 pandemic has attracted a great deal of attention (8, 17). Preliminary studies provide strong associations of reduced risk of respiratory tract infection incidence and severity caused by the severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with optimal vitamin D status (18, 19). A recent meta-analysis found a 2.6-fold increased risk of severity in vitamin D deficiency (20) but cautioned that the evidence to date for reducing infection and mortality is insufficient.

Because randomized trials show inconsistent effects of vitamin D on health and disease, researchers are calling for recognition of vitamin D as a threshold nutrient and the need to recruit study participants with vitamin D insufficiency or deficiency. If participants are enrolled with adequate levels at study baseline in intervention studies, then the likelihood of observing beneficial effects of vitamin D supplementation are reduced (2).

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Abbreviations used: Covid-19, coronavirus disease 2019; CYP, cytochrome P450; EAR, Estimated Average Requirement; PTH, parathyroid hormone; UL, tolerable upper intake level; 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D (calcitriol); 25(OH)D, 25-hydroxyvitamin D (calcidiol).

## References

1. Fleet JC, Shapses S. Vitamin D. In: Marriot B, Birt B, Stallings V, Yates A, editors. *Present knowledge in nutrition*, 11th ed. Academic Press; 2020. p. 93–114.
2. Giustina A, Bouillon R, Binkley N, Sempos C, Adler RA, Bollerslev J, Dawson-Hughes B, Ebeling PR, Feldman D, Heijboer A, et al. Controversies in vitamin D: a statement from the Third International Conference. *JBM Plus* 2020;4(12):e10417.
3. Sempos CT, Binkley N. 25-Hydroxyvitamin D assay standardization and vitamin D guidelines paralysis. *Public Health Nutr* 2020;23(7):1153–64.
4. Munns CF, Shaw N, Kiely M, Specker B, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughai MZ, Makitie O, et al. Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* 2016;101:394–415.
5. Uday S, Hogler W. Spot the silent sufferers: a call for clinical diagnostic criteria for solar and nutritional osteomalacia. *J Steroid Biochem Mol Biol* 2019;188:141–6.
6. Kahwati LC, Weber RP, Pan H, Gourlay M, LeBlanc E, Coker-Schwimmer M, Viswanathan M. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: evidence report and systematic review for the us preventive services task force. *JAMA* 2018;319(15):1600–12.
7. Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess (Rockv)*. 2019;23(2):1–44.
8. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020;12(4):988.
9. Institute of Medicine. *Dietary reference intakes for calcium and vitamin D*. Washington (DC): The National Academies Press; 2011.
10. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol* 2017;13(8):466–79.
11. Roth D, Abrams S, Aloia J, Bourassa M, Calvo MS, Cashman KD, Jeffers ME, Jones KS, Kappner H, Martineau AR, et al. *Ann N Y Acad Sci* 2018;1430(1):44–79.
12. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, Stepan J, El-Hajj Fuleihan G, Bouillon R. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* 2019;180(4):P23–54.
13. Berti PR, Soueida R, Kuhnlein HV. Dietary assessment of Indigenous Canadian Arctic women with a focus on pregnancy and lactation. *Int J Circumpolar Health* 2008;67:349–62.
14. Itkonen ST, Skaffari E, Saaristo P, Saarnio EM, Erkkola M, Jakobsen J, Cashman KD, Lamberg-Allardt C. Effects of vitamin D<sub>2</sub>-fortified bread v. supplementation with vitamin D<sub>2</sub> or D<sub>3</sub> on serum 25-hydroxyvitamin D metabolites: an 8-week randomised-controlled trial in young adult Finnish women. *Br J Nutr* 2016;115:1232–9.
15. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiwicz J, Pludowski P, Jones G. Vitamin D toxicity—a clinical perspective. *Front Endocrinol (Lausanne)* 2018;9:550.
16. Luxwolda MF, Kuipers RS, Kema IP, Dijk-Brouwer DA, Muskiet FA. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L. *Br J Nutr* 2012;108(9):1557–61.
17. Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, Subramanian S, Thickett D. Preventing vitamin D deficiency during the COVID-19 pandemic: UK definitions of vitamin D sufficiency and recommended supplement dose are set too low. *Clin Med (Lond)* 2021;21(1):e48–51.
18. Ma H, Zhou T, Heianza Y, Qi L. Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. *Am J Clin Nutr* 2021;113(5):1275–81.
19. Entrenas Castillo M, Entrenas Cost LM, Vaquero Barrios JM, Alcalá Diaz JF, Lopez Miranda J, Bouillon R, Quesada Gomez J. Effect of calcifediol treatments and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for Covid-19: a pilot randomized clinical study. *J Steroid Biochem Mol Biol* 2020;203:105751.
20. Kazemi A, Mohammadi V, Aghababae SK, Golzarand M, Clark CCT, Babajafari S. Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. *Adv Nutr* 2021;12(5):1636–58.