Critical Reviews in Food Science and Nutrition, 50:24–25 (2010)
ISSN: 1040-8398 print / 1549-7852 online
DOI: 10.1080/10408398.2010.526858

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Vitamin D Status and Health

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Vitamin D is a unique nutrient in that it is actually a prohormone obtained by endogenous synthesis from sun exposure on 7-dehydrocholesterol in skin and from certain foods and dietary supplements. Endogenous synthesis produces cholecalciferol (vitamin D_3) and is transported to the liver bound to the vitamin D-binding protein (DBP). In foods and dietary supplements, vitamin D exists either as cholecalciferol or plant-derived ergocalciferol (vitamin D_2). Both forms of the ingested vitamin are absorbed via the lymphatic system and transported to the liver. Vitamin D occurs naturally in a limited number of foods, and fish are found to have the highest amounts of the vitamin. Fortified foods provide the major dietary food sources of vitamin D (e.g., milk and milk products, margarines, and breakfast cereals) in the United States (Whiting and Calvo, 2006).

In the liver, vitamin D is converted to 25(OH)D by the enzyme 25-hydroxylase. Conversion to the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], is achieved in renal tissue by the enzyme 1α-hydroxylase (1α-OHase). The 1,25$(OH)_2$D form of vitamin D can depress the activity of 1α-OHase, and the parathyroid hormone (PTH) can stimulate its activity. As such, 1,25$(OH)_2$D exerts its effects by binding to a specific nuclear receptor (vitamin D receptor [VDR]), a ligand-dependent transcription factor that recognizes specific DNA sequences known as vitamin D response elements (DeLuca, 2004).

The main circulating vitamin D metabolite is 25(OH)D, which is used as an indicator of vitamin D nutrition status. The appearance in the circulation of native vitamin D is brief because it is rapidly metabolized in the liver or stored in adipose tissue (Holick, 2007). DBP binds approximately 99% of circulating vitamin D and its metabolites and has a higher affinity for 25(OH)D than 1,25$(OH)_2$D or native vitamin D.

Vitamin D deficiency results in diseases such as rickets in infants and children, and osteomalacia in adults (Prentice et al., 2008). Investigations into possible non-bone-related functions of vitamin D are increasing because of the recognition that (1) expression of 1α-OHase occurs in many extrarenal tissues and (2) the VDR appears not only in the target cells of enterocytes, osteoblasts, and distal renal tubule cells, but also in parathyroid gland cells, skin keratinocytes, promyelocytes, lymphocytes, colon cells, pituitary gland cells, and ovarian cells (Jones et al., 1998). Areas of promising research include osteoporosis, type-1 diabetes, some cancers, autoimmune diseases, and infectious diseases such as tuberculosis (Brannon et al., 2008).

The most commonly used method for assessing Vitamin D status is the measurement of circulating 25(OH)D. There are major limitations of using 25(OH)D as a status biomarker, including the unknown extent of storage of vitamin D, potential dangers of its accumulation in adipose tissue, regulation of its mobilization from these stores, and the consequences of the saturation of this storage. Different methods are used to measure serum or plasma 25(OH)D concentration and comparisons have been complicated by a lack of a standardized reference material. Different laboratories and different methods yield different results using the same sample. The international Vitamin D Quality Assessment Scheme (DEQAS), established in 1989, monitors the performance of 25(OH)D assays and currently has over 100 registered participants from 18 countries (Carter et al., 2004). The DEQAS has shown that samples analyzed by most commercially available methods are capable of providing results close to the target value for 25(OH)D3, but that results are highly dependent on the laboratory of analysis and the skill of the operator. The DEQAS has also shown that not all assay methods are capable of detecting 25(OH)D2 with the same efficiency as 25(OH)D3. The National Institute of Standards and Technology released standard reference materials (SRMS) for 25(OH)D2 and D3 in July 2009 (NIST, 2009). The availability of these SRMs should permit greater accuracy and precision for measuring 25(OH) D2 and D3 and enable meaningful comparison across laboratories.

Vitamin D insufficiency or hypovitaminosis D is likely to be evident in individuals with 25(OH)D values less than 11 ng/mL or 27.5 nmol/L. However, there is no agreement for levels corresponding to sufficiency or "optimal" vitamin D status. From associations between 25(OH) D concentrations with PTH concentrations and fractional calcium absorption rates, researchers have proposed that plasma 25(OH)D values greater than 50 and 75 nmol/L should define vitamin D sufficiency and "optimal" concentrations (Dawson-Hughes, 2008; Heaney, 2008).

Assessment of Vitamin D status in nationally representative samples from the National Health and Nutrition Examination Surveys (NHANES) 2000–2004 were compared with NHANES III 1988–1994 data (Looker et al., 2008). Mean serum 25(OH)D concentrations were significantly lower in 2000 to 2004 than in 1988 to 1994 in all of the groups examined. Adjustment for assay changes noticeably reduced the difference between surveys. This remaining difference likely represents a real decline in vitamin D status. Changes in body mass index, milk intake, and sun protection seemed to contribute to this decline.

Ingested vitamin D is potentially toxic if taken in high amounts over long periods of time. Unfortunately, the available evidence on the quantitative aspects of the safety of vitamin D is very limited. Most of the available information is from studies of short duration. In the Women's Health Initiative, postmenopausal women supplemented with 10 μg (400 IU) of vitamin D per day in combination with 1000 mg Ca/d exhibited a 17% increase in kidney stones (Jackson et al., 2006).

Despite the considerable progress made in recent years, the available evidence on the relationship between vitamin D and health is far from complete. Investigations are needed that focus on understudied key population subgroups, such as dark-skinned individuals; reproductive-age, pregnant, and lactating women; infants; and adolescents.

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