Vitamin D: Important for Prevention of Osteoporosis, Cardiovascular Heart Disease, Type 1 Diabetes, Autoimmune Diseases, and Some Cancers

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Abstract: Vitamin D is very important for overall health and well-being. A major source of vitamin D comes from exposure to sunlight. Measurement of 25-hydroxyvitamin D in the blood and not 1,25-dihydroxyvitamin D is used to determine vitamin D status. A blood level of 25-hydroxyvitamin D of at least 20 ng/mL is considered to be vitamin D sufficient. Vitamin D deficiency increases the risk of many common cancers, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and type 1 diabetes.

Key Words: cardiovascular heart disease, disease prevention, type I diabetes, vitamin D

Vitamin D is recognized as the sunshine vitamin for good reason. During exposure to sunlight, the ultraviolet B portion of the solar spectrum, with energies between 290 to 315 nm, penetrates into the epidermis. This ultraviolet radiation is absorbed by 7-dehydrocholesterol in the skin, which results in its transformation into previtamin D₃ (see Fig. 1).¹ Previtamin D₃ is rapidly transformed into vitamin D₃ by a temperature-dependent process. Vitamin D₃ enters the circulation and is metabolized sequentially first in the liver to 25-hydroxyvitamin D [25(OH)D] and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Once formed, 1,25(OH)₂D interacts with its specific nuclear vitamin D receptor (VDR) in the small intestine to enhance the efficiency of intestinal calcium absorption.¹ It also maintains serum calcium within the normal range by interacting with its VDR in the osteoblast, which results in the expression of receptor activator of NF-κB ligand (RANKL).¹² This plasma membrane ligand is recognized by its corresponding receptor RANK on the preosteoclast. The intimate interaction between the RANKL on the osteoblast with the preosteoclast's RANK results in signal transduction inducing the preosteoclast to become a mature osteoclast (Fig. 2). The mature osteoclast releases both proteolytic and hydrolytic enzymes and hydrochloric acid to destroy the bone's protein matrix—releasing calcium and other minerals as well as hydrolytic collagen fragments, including N-terminal telopeptide (NTX) and C-terminal peptides (CTX) into the circulation.³

Consequences for the Skeleton of Vitamin D Deficiency

Vitamin D deficiency during the first 2 years of life results in rickets. In adults, vitamin D deficiency can cause or exacerbate osteoporosis and induce osteomalacia. Vitamin D deficiency results in a decrease in the efficiency of intestinal calcium absorption, which results in a decrease in ionized blood calcium. The calcium sensor in the parathyroid gland responds by increasing the production of parathyroid hormone (PTH).⁴ PTH interacts with its receptor on the osteoblasts to increase the RANKL. This signal induces preosteoclasts to become mature osteoclasts. The action of osteoclasts dissolving bone matrix and releasing calcium into the extracellular

Key Points
• Ninety percent or more of our vitamin D requirement comes from exposure to sunlight. Without sun exposure, 1,000 IU of vitamin D per day is required.
• 25-hydroxyvitamin D is the major circulating form that is used to determine vitamin D status.
• 1,25-dihydroxyvitamin controls cell growth, regulates renin production, and modulates immune function.
• Season, latitude, sunscreen use, skin pigmentation, and aging can markedly affect vitamin D synthesis in the skin.
Review Article

**ProD$_3$ ^ preD$_3$, ^ Vitamin D**

**SKIN**

**Liver**

**Diet**

**Vitamin D$_2$**

**Vitamin D$_3$**

**Major circulating form**

**25(OH)D**

**Kidney**

**1,25(OH)$_2$D**

**Intestine**

**Bone**

**Increase Calcium & Phosphorus Absorption**

**Maintain Serum Calcium & Phosphorus**

Fig. 1 Schematic representation for cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth. During exposure to sunlight, 7-dehydrolcholesterol (7-DHC) in the skin absorbs solar ultraviolet (UVB) radiation and is converted to previtamin D$_3$ (preD$_3$). Once formed, D$_3$ undergoes thermally induced transformation to vitamin D$_3$. Further exposure to sunlight converts preD$_3$ and vitamin D$_3$ to biologically inert photoproducts. Vitamin D coming from the diet or from the skin enters the circulation and is metabolized in the liver by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D$_3$ ($25$(OH)$_3$D$_3$). 25(OH)D$_3$ reenters the circulation and is converted in the kidney by the 25-hydroxyvitamin D$_3$-1a-hydroxylase (1-OHase) to 1,25-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$]. A variety of factors, including serum phosphorus ($P_s$) and parathyroid hormone (PTH), regulate the renal production of 1,25(OH)$_2$D$_3$. 1,25(OH)$_2$D$_3$ regulates calcium metabolism through its interaction with its major target tissues, bone and the intestine. 1,25(OH)$_2$D$_3$ also induces its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). 25(OH)D is metabolized in other tissues for the purpose of regulation of cellular growth (copyright Michael F. Holick, 2004, used with permission).

Fig. 2 Both 1,25(OH)$_2$D and PTH stimulate the mobilization of calcium from the skeleton by interacting with their respective receptors on osteoblasts, which induces expression of receptor activator of NF$_{κB}$ (RANK) ligand (RANKL). RANK on the immature osteoclast binds to RANKL, which causes it to mature and coalesce with other osteoclast precursors to become mature multinuclear osteoclasts. Osteoclasts digest bone-releasing calcium (Ca) and other minerals as well as hydrolyzed collagen fragments including C-telopeptide (CTX) and N-telopeptide (NTX) (copyright Michael F. Holick, 2004, used with permission).

Osteoporosis does not cause bone pain. However, poorly mineralized bone, that is, osteomalacia, can cause isolated or generalized aching in the bones as well as muscle pain and muscle weakness. Recently, Plotnikoff and Quigley reported that 163 patients 10 to 65 years of age who presented to Minnesota Hospital with nonspecific muscle aches and bone pain more than 90% had severe vitamin D deficiency. Similarly, Gluer et al. reported that 88% of Arab women living in Denmark with muscle weakness and bone pain were severely vitamin D deficient. Vitamin D deficiency also causes muscle weakness and therefore increases risk of the elderly to fall and thereby fracture.

Typically patients with nonspecific muscle aches and pain and bone discomfort are given the diagnosis of fibromyalgia, myositis, or chronic fatigue syndrome. Malabanab et al. reported in a black woman with severe bone discomfort and muscle aches that correction of her vitamin D deficiency not only increased her bone mineral density by almost 25% within 2 years but also gave her complete relief of her muscle aches and bone discomfort.

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Other Consequences of Chronic Vitamin D Deficiency

Essentially every tissue and cell in the body has a VDR, including brain, heart, stomach, pancreas, skin and gonads, and immune cells.\(^1,5,13\) 1,25(OH)\(_2\)D\(_3\) is one of the most potent inhibitors of both normal and cancer cell growth.\(^14,15\) 1,25(OH)\(_2\)D also regulates both activated T- and B-cell function.\(^1,5,16,17\) The pancreas responds to 1,25(OH)\(_2\)D by enhancing insulin production.\(^1,5\) The kidney is not only the organ for the synthesis of 1,25(OH)\(_2\)D but also responds to it by decreasing the production of renin.\(^18\)

The wide-ranging actions of 1,25(OH)\(_2\)D help explain why vitamin D deficiency has been associated with several chronic diseases. It is known that vitamin D deficiency and living at higher latitudes increases the risk of development of colon, breast, prostate, ovarian, and esophageal cancer.\(^11^-21\) Children in Finland who received 2,000 IU of vitamin D per day from 1 year of age and followed as adults had a reduced risk of developing type 1 diabetes by 80%.\(^22\) Children who had rickets and were followed had a fourfold increased risk of development of type 1 diabetes. It is also known that people living at higher latitudes are at higher risk of hypertension.\(^23\) A study of hypertensive patients who received ultraviolet B irradiation from a tanning bed for 3 months not only increased their blood level of 25(OH)D by more than 100% but also completely resolved their hypertension.\(^24\) There is evidence that there is increased risk of development of congestive heart failure with vitamin D deficiency.\(^25\) It is also known that people living at higher latitudes are at higher risk of development of schizophrenia and multiple sclerosis later in life.\(^26,27\) These diseases as well as rheumatoid arthritis have also been related to vitamin D deficiency.

Evaluation and Treatment of Vitamin D Deficiency

Measurement of 25(OH)D is the only means to determine whether a patient is vitamin D deficient or sufficient. The measurement of 1,25(OH)\(_2\)D is not only useless, but can mislead the physician because it is often either normal or even elevated when a patient is vitamin D deficient and has secondary hyperparathyroidism. Most commercial laboratories report that a 25(OH)D less than 10 ng/mL is synonymous with vitamin D deficiency. Most experts recommend that less than 20 ng/mL should be designated as vitamin D deficiency.\(^28^-30\) To maintain a healthy level of 25(OH)D, the recommendation is that it should be above 30 ng/mL.

The easiest way to correct vitamin D deficiency is to fill up the empty vitamin D tank by giving the patient an oral dose of 50,000 IU of vitamin D once per week for 8 weeks. To maintain vitamin D sufficiency, the patient should receive either 50,000 IU of vitamin D once or twice per month thereafter. There is an intramuscular form of vitamin D that is usually not very bioavailable and can cause significant discomfort; therefore it is not recommended. However, in Europe, intramuscular injection of 500,000 IU of vitamin D twice per year has appeared to be effective in preventing vitamin D deficiency.

A multivitamin containing 400 IU of vitamin D is insufficient to satisfy the body's requirement.\(^32\) It is estimated that at least 1,000 IU of vitamin D per day is needed to satisfy the body's requirement.\(^31,33\)

Conclusion

Vitamin D deficiency is common in all age groups. Even young children and young and middle-aged adults are at significantly increased risk of vitamin D deficiency.\(^28,31^-36\) This is in part due to the fact that there is very little vitamin D in the diet, and increased use of sunscreens and diminished outdoor activity also contribute to this problem. More than 90% of the human vitamin D requirement comes from casual exposure to sunlight.\(^1\) Wearing a sunscreen with an SPF of 8 reduces the ability of the skin to produce vitamin D by 95%.\(^37\) Thus, judicious exposure to sunlight typically no more than 5 to 15 minutes per day (depending on latitude, time of day and degree of skin pigmentation) of arms and legs or hands, face, and arms two to three times per week during the spring, summer, and fall in latitudes above 37° and throughout the year below 37° is all that is required to satisfy the body's requirement.\(^38\) A yearly measurement of 25(OH)D during the annual physical examination is prudent not only to maximize bone health but also to prevent many chronic diseases that are linked with vitamin D deficiency (Fig. 3).

**Fig. 3** Photoproduction and sources of vitamin D. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], which is responsible for maintaining calcium homeostasis. 25(OH)D is also converted to 1,25(OH)\(_2\)D in a variety of other cells and tissues for the purpose of regulating cell growth, immune function, as well as a variety of other physiologic processes that are important for the prevention of many chronic diseases (copyright Michael F. Holick, 2004, used with permission).

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