



Review

Vitamin D: Health panacea or false prophet?

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ABSTRACT

Vitamin D deficiency, diagnosed when the serum 25-hydroxyvitamin D (25-OHD₃) concentration is less than 20 ng/mL, has joined vitamin A deficiency as two of the most common nutrition-responsive medical conditions worldwide. There have been more scientific articles published about vitamin D in the 21st century than about any other vitamin, reflecting the massive expansion of the field of vitamin D research. Adequate vitamin D status has been linked to decreased risks of developing specific cancers, including cancers of the esophagus, stomach, colon, rectum, gallbladder, pancreas, lung, breast, uterus, ovary, prostate, urinary bladder, kidney, skin, thyroid, and hematopoietic system (e.g., Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma); bacterial infections; rheumatoid arthritis; Crohn's disease; periodontal disease; multiple sclerosis; asthma; type 2 diabetes; cardiovascular disease; stroke; peripheral artery disease; hypertension; chronic kidney disease; muscle weakness; cognitive impairment; Alzheimer's disease; clinical depression; and premature death. On the other hand, inadequate vitamin D status during human pregnancy may be associated with increased risk for the development of type 1 diabetes in the offspring. However, this point of view may be excessively optimistic. There also is evidence that despite the current heavy reliance on serum 25-OHD₃ concentration for the diagnosis of an individual's vitamin D status, local tissue vitamin D intoxication may be present in individuals with much lower serum 25-OHD₃ concentrations than are currently appreciated. Only rarely are the symptoms of local tissue vitamin D intoxication associated with vitamin D status or intake. An individual's serum 25-OHD₃ concentration may appear to be "low" for reasons totally independent of sunlight exposure or vitamin D intake. Serum 25-OHD₃ concentration is only poorly responsive to increases in vitamin D intake, and the prolonged routine consumption of thousands of international units of vitamin D may interfere with the regulation of phosphate homeostasis by fibroblast growth factor-23 (FGF23) and the Klotho gene product, with consequences that are detrimental to human health. In light of these counterbalancing observations, curbing excessive enthusiasm for universally increasing vitamin D intake recommendations may be in order.

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Introduction

There have been more scientific articles published about vitamin D in the 21st century than about any other vitamin (25 724 listed in MedLine between January 1, 2000 and April 30, 2012), reflecting the massive expansion of the field of vitamin D research. A recognized leader in this field, Michael F. Holick, Ph.D., M.D., has published innovative studies that have inspired hundreds of researchers around the globe to join the quest to identify and understand the roles of vitamin D in subcellular, cellular, tissue, and organ physiology, and human nutrition and nutritional therapeutics. This storm of scientific activity has been collated

and summarized in the second edition of Dr. Holick's comprehensive textbook, *Vitamin D: Physiology, Molecular Biology, and Clinical Applications* (Humana Press, 2010). As Dr. Holick explains, vitamin D deficiency, diagnosed when blood 25-hydroxyvitamin D (25-OHD₃) concentration is less than 20 ng/mL, has joined vitamin A deficiency as two of the most common nutrition-responsive medical conditions worldwide.

With classical clinical expression as poor skeletal development and bone and joint deterioration, vitamin D deficiency often begins with inadequate exposure to sunlight and is compounded by insufficient consumption of naturally occurring vitamin D and its precursors [1,2]. According to D. Holick, the biochemistry of vitamin D within the human body drives its physiology and ensures a wide margin of safety. He and his colleagues cite evidence that supports the argument that the chronic daily intake of 10 000 IU of

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vitamin D by adults in the absence of significant exposure to sunlight approximates the daily production of vitamin D in response to full-body exposure to sunlight and does not alter whole-body calcium metabolism or produce kidney stones and therefore is safe. In practice, Dr. Holick recommends adult daily vitamin D intakes of 1000 IU to 2000 IU, although he considers 10 000 IU to be completely safe for long-term daily consumption. Dr. Holick also recommends the therapeutic use of much larger amounts of vitamin D in the adjunctive treatment of several diseases that impair vitamin D absorption or utilization, including the nephritic syndrome, chronic renal disease, hyperparathyroidism, and granulomatous disorders in which the conversion of 25-OHD₃ to 1,25-dihydroxyvitamin D (1,25-(OH)₂D₃) by CYP27B1 (formerly 1 α -hydroxylase) is accelerated within macrophages.

The diversity of vitamin D target genes is almost universal and the effects of vitamin D-induced gene activation affect nearly every cell in the body [3–5]. As explained by Carsten Carlberg of the University of Kuopio (Kuopio, Finland), the vitamin D receptor is a ligand-inducible transcription factor with target genes that are involved in cellular metabolism, bone formation, cellular development, and inflammation [6]. The ability to convert 25-OHD₃ to 1,25-(OH)₂D₃ is not a strict prerequisite for vitamin D responsiveness; for example, human adipocytes lack CYP27B1 activity yet express the vitamin D receptor (VDR), with vitamin D response element (VDRE)-responsive genes suppressing the expression of uncoupling protein-2 and the induction of futile energy cycling [7,8]. In contrast to the many beneficial cellular responses to vitamin D, many of the genes containing VDRE are involved in dysregulated pathways that can produce cancer, osteoporosis, or the metabolic syndrome [6].

According to Dr. Holick and his colleagues, the extrarenal activation of vitamin D links vitamin D status to many aspects of human health. The discovery of extrarenal conversion of 25-OHD₃ to 1,25-(OH)₂D₃ by CYP27B1 in many tissues and of tissue-specific regulation of CYP27B1 expression is receiving increasing emphasis in current medical research [9]. For example, the roles played by extrarenal CYP27B1 activity and vitamin D in the differentiation and regulation of the immune system and in human defense mechanisms against tuberculosis have been examined in detail [10]. In another example of the critical roles played by tissue-specific regulation of local vitamin D activation, the human colonocyte expression of CYP27B1 activity suggests that the induction of this activity by dietary factors, coupled with concurrent suppression of vitamin D-deactivating CYP24A1 (formerly 25-OHD₃-24-hydroxylase), may be truly chemopreventive by inhibiting the uncontrolled proliferation of human colonic epithelial cells while promoting their differentiation and normal apoptotic death [11]. In contrast, overexpression of CYP24A1 and of several VDR corepressors along with the cosuppression of CYP27B1 and the VDR may explain the resistance to vitamin D exhibited by human colon cancer cells [12].

The interactions between exposure to sunlight, vitamin D status, and cancer have been receiving serious examination in the post melanoma-panic era. It is now established that adequate vitamin D status is linked to decreased risks of developing specific cancers, including cancers of the esophagus, stomach, colon, rectum, gallbladder, pancreas, lung, breast, uterus, ovary, prostate, urinary bladder, kidney, skin, thyroid and hematopoietic system (e.g., Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma) [3–5,13–34]. Similar data associate adequate vitamin D status with reduced risks for bacterial infections, rheumatoid arthritis, Crohn's disease, periodontal disease, multiple sclerosis, asthma, type 2 diabetes, cardiovascular disease, stroke, peripheral artery disease, hypertension, chronic kidney disease, muscle

weakness, cognitive impairment, Alzheimer's disease, clinical depression, and premature death [3–5,13–16,18–21,35–75]. Emerging data also link inadequate vitamin D status during human pregnancy with increased risk for the development of type 1 diabetes in the offspring [76].

Many of these putative benefits have been deduced from observed relationships between vitamin D intake, sunlight exposure, and the serum 25-OHD₃ concentration. However, according to a series of lectures presented by H.L. Sam Queen, M.S., of the Institute for Health Realities, Colorado Springs, CO, USA (available from <http://www.healthrealities.com>), although a direct correspondence between vitamin D exposure and serum 25-OHD₃ concentration does appear to characterize healthy individuals, an individual's serum 25-OHD₃ concentration may be low for reasons other than a lack of exposure to vitamin D. According to Queen, the existing data contain a perplexing anomaly: as many as 40% of men and women over the age of 85 y exhibit a serum 25-OHD₃ concentration consistent with a diagnosis of long-standing vitamin D deficiency (serum 25-OHD₃ concentration <20 ng/mL) [77]. Queen suggests that, taken together, these reports indicate that there may be an age at which vitamin D deficiency (as currently defined) may be life-sustaining, not life-threatening.

The explanation for this apparent paradox may be found in the emerging data regarding the interactions between the Klotho gene product and osteocyte-secreted FGF23 [78–82]. The Klotho gene product, a transmembrane protein with local glucosidase and hypocalciuric activities synthesized locally within renal tissue [79,83–86], is a required coactivator of FGF23 [82,87,88]. The rate of FGF23 secretion is correlated with the serum 1,25-(OH)₂D₃ concentration (and, therefore, with the serum 25-OHD₃ concentration) [89,90]. Klotho gene product binding to the renal tubule FGF receptor (FGF receptor-1; FGFR1) increases the affinity of the receptor for FGF23 [83,85,91,92]. Coactivation of renal tubule FGFR1 by the Klotho gene product and FGF23 produces inhibition of renal reabsorption of phosphate via suppression of the activity of sodium-phosphate cotransporter type IIa on the apical brush-border membrane of renal tubules [82,86,88,93,94]. FGFR1 activation also produces concurrent down-regulation of renal CYP27B1 [95] and up-regulation of the expression of CYP24A1 [88], reducing the renal content of active 1,25-(OH)₂D₃ and reducing further the efficiency of renal phosphate reabsorption [78,79, 82–84,88–90].

Klotho-deficient mice develop hypervitaminosis D at an early age and exhibit increased incidence of hyperphosphatemia, osteoporosis, ectopic calcifications, arteriosclerosis, hair loss, dermal thinning, emphysema, pituitary atrophy, infertility, and premature death [79,80]. In contrast, genetically altered mice that overexpress the Klotho gene exhibit increased resistance to oxidative stress and prolonged lifespan [79,81]. FGF23-deficient animals also develop hypervitaminosis D, hyperphosphatemia, and ectopic calcifications [96–98], while in humans early kidney disease is associated with decreased expression of the Klotho gene product, abnormally elevated serum FGF23 concentrations (that further down-regulate the Klotho gene) and hypovitaminosis D [99], hypophosphatemia [100,101], secondary hyperparathyroidism [99], cardiac dysfunction [102,103], and premature death [103,104].

Interestingly, when an across-species comparison of average longevity and average serum phosphate concentration was conducted, it was found that the average longevity per species (in years) was significantly inversely correlated with the average within-species serum phosphate concentration [78], suggesting (according to Queen) that excessive 1,25-(OH)₂D₃-induced stimulation of FGF23 secretion may not be consistent with maximum longevity.

In humans, the only known influences on Klotho expression are age and 1,25-(OH)₂D₃. Among the elderly, Klotho gene expression appears to become increasingly sensitive to negative feedback suppression by 1,25-(OH)₂D₃ [79]. In addition, genetic polymorphisms, toxic insults, autoimmune disease, gradually accumulating oxidative damage, or chronic mineral imbalances may result in dysfunctional vitamin D receptors with reduced affinity for 1,25-(OH)₂D₃ and reduced ability of 1,25-(OH)₂D₃ to induce the activity of renal CYP24A1, allowing 1,25-(OH)₂D₃ concentration to rise while relieving some of the negative feedback inhibition of the conversion of 25-OHD₃ to 1,25-(OH)₂D₃ [105,106]. When an excess of dietary vitamin D is present, elevated systemic and local concentrations of 1,25-(OH)₂D₃ can occur. When an excess of 1,25-(OH)₂D₃ is present within a tissue, local hypervitaminosis D can be produced. In the mildly compromised kidney, local hypervitaminosis D can produce hyperphosphatemia, triggering increased FGF23 secretion, whereas elevated 1,25-(OH)₂D₃ concentration can inhibit hepatic 25-hydroxylation of ingested vitamin D, resulting in concurrent renal hypervitaminosis D and low serum 25-OHD₃ concentration [100]. A desire to establish a higher serum 25-OHD₃ concentration may encourage undue clinical reliance on potentially counterproductive dietary supplementation with increasing amounts of vitamin D.

In such a scenario, local vitamin D toxicosis can occur and produce renal atrophy and calcification that may go unrecognized until clinical signs of “idiopathic” renal disease appear [107]. Although Queen acknowledges that vitamin D plays important preventive and therapeutic roles in supporting human health, he cautions that renal and cardiovascular toxicity and increased mortality can be caused by covert physiologic vitamin D toxicosis [107]. For example, in the presence of age-associated reduction in Klotho expression, prolonged supplementation with large Klotho-suppressing amounts of vitamin D may produce 1,25-(OH)₂D₃ excess and low serum 25-OHD₃ concentration while increasing the risk of the expression of an aberrant FGF23 gene product that fails to regulate renal phosphate reabsorption, resulting in hyperphosphatemic tumoral calcinosis with carotid artery calcification [108,109].

Queen also expresses concerns that the current interpretation of vitamin D requirements and contributions to human health results from an excessive reliance on epidemiologic evidence (the science of association) that has become dissociated from the basic science of vitamin D and mineral homeostasis. He suggests that rather than reflecting inadequate exposure to vitamin D, a low serum 25-OHD₃ concentration may reflect, in some individuals, a set of internal homeostatic attempts to correct an excess of free calcium ions and therefore, viewed from a basic science perspective, a strong argument can be made for the conclusion that in some individuals, a low serum 25-OHD₃ concentration *results* from disease rather than *produces* disease.

In cautioning against excessive enthusiasm for increasing vitamin D intake recommendations, Queen emphasizes the following key points:

- Despite the current heavy reliance on serum 25-OHD₃ concentration for the diagnosis of an individual's vitamin D status, local tissue vitamin D intoxication may be present in individuals with much lower serum 25-OHD₃ concentrations than are currently appreciated.
- Only rarely are the symptoms of local tissue vitamin D associated with vitamin D status or intake.
- A serum 25-OHD₃ concentration may appear to be “low” for reasons totally independent of sunlight exposure or vitamin D intake.

- Serum 25-OHD₃ concentration is only poorly responsive to increases in vitamin D intake.
- The prolonged routine consumption of megadoses of vitamin D may interfere with Klotho and FGF23 regulation of phosphate homeostasis with consequences that are detrimental to health.

The recent rush to elevate serum 25-OHD₃ concentrations universally may benefit from a brief pause to reflect on the actual merits (and potential pitfalls) of doing so. Despite the detailed and persuasive data presented by Holick and his colleagues, reconsideration of the paradigm that a single or even a few biochemical markers can provide meaningful insight into the health status of an individual may be appropriate. This may be an area in which the modern reductionist approach to medical nutrition can benefit from an organismal reassessment.

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