

Vitamin D Supplementation: Optimal Dose, Real Benefits and Potential Side Effects (A Review)

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Abstract: Vitamin D, is a lipid- soluble vitamin obtained from both exogenous and endogenous sources. Vitamin D₃ is found naturally contains vitamin D, but other dietary sources of Vitamin D are from the fortified foods, like milk and cereals, or from nutritional supplements. In recent years, rickets and Osteomalacia are reappearing, not only in temperate zones with limited sunshine but also in sunnier climates such as Australia, the USA, Ethiopia, Lebanon and Saudi Arabia. Research results strongly suggested that 1,25-(OH)₂D₃ may have a direct action through its receptor in the parathyroid glands, The presence of receptor has led to a study of the possible function of vitamin D in these organs. A good example of a new function described for 1,25-dihydroxyvitamin D₃ is that found in the parathyroid gland, this is also true for the role of vitamin D hormone in skin, the immune system, a possible role in the pancreas, i.e., in the islet cells, and a possible role in female reproduction. Many studies have examined the relationship between Vitamin D levels and cardiovascular disease, metabolic, immune system and cancer risk. With the reemergence of hypovitaminosis D among adults and elderly age group, questions regarding the most appropriate treatment regimen require clarifications. Multiple treatment regimens have been proposed to treat hypo-vitaminosis D in young children and adults, including the daily or weekly, yearly orally and parental routes. New megadoses therapies have been used recently. We would like to highlight the recent evidence regarding their uses and safety.

Keywords: Vitamin D, Hypovitaminosis, Megadose, Stosstherapy

Vitamin D: An overview

Vitamin-D, which has also been referred to as the “sunshine vitamin” is a lipid-soluble vitamin obtained from both exogenous and endogenous sources. Vitamin D (calciferol), which comprises a group of fat-soluble secosterols found naturally in very few foods, is photosynthesized in human skin. When

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humans are exposed to sunlight, 7-dehydrocholesterol in the skin absorbs UVB radiation (290 to 315 nm), resulting in the production of vitamin D₃.^(1,2) Vitamin D comes in many forms, but the two major physiologically relevant ones are Vitamin D₂ (ergocalciferol) and Vitamin D₃ (cholecalciferol).⁽³⁾ Vitamin D₂ originates from ergosterol, a yeast and plant sterol; Vitamin D₃ originates from 7-dehydrocholesterol, a precursor of cholesterol that is synthesized when the skin is exposed to sunlight. The major metabolic steps involved in D₂ metabolism are similar to those in D₃ metabolism. Vitamin D represents either D₂ or D₃ or both and is biologically inert, requiring two obligate hydroxylations to form its biologically active hormone, 1,25-dihydroxyvitamin D (1,25(OH)₂D).⁽⁴⁾ This last step occurs predominantly, if not exclusively, in the proximal convoluted

tubule cells of the kidney and produces the metabolically active form of vitamin D, 1,25(OH)₂D₃.⁽⁵⁾

Vitamin D₃ is found naturally in some foods, such as eggs, fatty fish, and liver. Other dietary sources of Vitamin D are fortified foods, such as milk and cereals, or nutritional supplements. Vitamin D's main function is to promote calcium absorption in the gut and maintain adequate blood levels of calcium and phosphorus.⁽¹⁾

Research results strongly suggest that 1,25(OH)₂D₃ may have a direct action through its receptor in the parathyroid glands. The presence of a receptor in previously unrecognized target organs has led to an interest in the possible function of Vitamin D in these organs. A good example of a new function for 1,25-dihydroxyvitamin D₃ found in the parathyroid gland. Vitamin-D

hormone also plays a role in the skin and the immune system, and may have a role in pancreatic function (i.e., in the islet cells) in female reproduction.⁽⁵⁾ Vitamin D is also known to increase postural stability. Bischoff et al. reported a 22% reduction in fall incidence in elderly subjects; however, about 15 people must take Vitamin D to prevent one person from falling (NNT 15:1).⁽⁶⁾

Prevalence of Vitamin D deficiency

Vitamin D deficiency has been identified as the leading cause of rickets among breast-fed infants, as breast milk contains inadequate amounts of Vitamin D to support skeletal health in this age group.^(7,8)

In recent years, despite better understanding and a wide choice of preventive and therapeutic strategies, rickets and osteomalacia have reappeared, not only in temperate zones

with limited sunshine (e.g., Canada, Finland, and the United Kingdom).⁽⁹⁻¹¹⁾ but also in sunnier climates such as Australia.⁽¹²⁾ the United States.⁽¹³⁻¹⁷⁾ Ethiopia.⁽¹⁸⁾, Qatar.⁽¹⁹⁾ and Saudi Arabia.⁽²⁰⁻²²⁾

Low levels of serum 25(OH) Vitamin D (Vitamin D deficiency) were reported in a few brief Saudi reports. Sedrani (1984) reported that 58% of Saudi subjects had low Vitamin D levels, despite abundant year-round sunlight.⁽²⁰⁾ A recent study found Vitamin D deficiency in 30% of healthy Saudi women aged 25 to 35 years and 55% in women older than 50 years.⁽²¹⁾ The prevalence of vitamin D deficiency among healthy young and middle-aged Saudi Arabian men was between 28% and 37%.⁽²²⁾

Vitamin D and cardiometabolic effect

Many studies have examined the relationship between Vitamin D levels

and cardiovascular disease^(23,24) These studies have demonstrated significant associations between 25(OH) Vitamin D concentrations and cardiovascular events, but they did not confirm a direct causal relationship. Consideration should be given to whether vitamin D deficiency is cause or an effect of cardiovascular disease. Until further studies are available, the role of Vitamin D and its metabolites in the management of heart disease will remain unclear.⁽²⁴⁾

Two recent systematic reviews.⁽²⁵⁻²⁶⁾ summarized the role of Vitamin D in cardiovascular disease and provided insight into the evidence necessary to fully understand its effects. Wang and colleagues.⁽²⁵⁾ reviewed 17 prospective (observational) studies and randomized trials that examined whether Vitamin D and calcium supplements reduced the risk of cardiovascular events in adults.

They concluded that vitamin D supplementation at moderate to high doses (800-1000 IU) may reduce the risk of CVD, whereas calcium supplementation seems to have no effect on CVD risk. Pittas and colleagues.⁽²⁶⁾ reviewed the available prospective observational studies of the association between Vitamin D status and cardio metabolic outcomes. As a whole, the trials showed no statistically significant effect of Vitamin D supplementation on cardiometabolic outcomes.

It has been hypothesized that Vitamin D deficiency is associated with hypertension, a well documented risk factor for CVD, possibly through activation of the renin-angiotensin system. This hypothesis arises from the finding that 1,25(OH)₂D is a negative endocrine regulator of the renin-angiotensin system.⁽²⁷⁾ A study

describing data from the third National Health and Nutrition Examination Survey (NHANES, 1988-1992), including 16,135 participants older than 19 years of age, found that systolic blood pressure (SBP) was inversely associated with serum vitamin D concentrations in non-hypertensive white persons in the United States.⁽²⁸⁾

Vitamin D in the treatment and prevention of fractures in postmenopausal women

A recent meta-analysis concluded that oral vitamin D supplementation of 700 to 800 IU per day could reduce the risk of hip or other non vertebral fracture by approximately 25%. The role of calcium supplementation in addition to Vitamin D could not be clearly defined.⁽²⁹⁾ A Japanese study of an institutionalized elderly population.⁽³⁰⁾ Showed that daily supplementation with 800 IU of oral

vitamin D₃ for 30 days markedly increased circulating 25(OH) concentrations from 9.7 ± 2.8 to 19.3 ± 4.1 ng/ml.

A recent meta-analysis.⁽³¹⁾ Examining the efficacy of oral supplemental Vitamin D in preventing non vertebral and hip fractures among older individuals (more than 65 years) concluded that daily oral vitamin D doses as high as 770 IU/d could reduce non vertebral fractures by at least 20% and hip fractures by at least 18%. A more recent study, "The DIPART Group",⁽³²⁾ conducted a meta-analysis of individual patient data using the pooled data from randomized trials. When they assessed the patient characteristics that might influence the anti fracture efficacy of Vitamin D or Vitamin D plus calcium, they found that Vitamin D alone was not effective for fracture prevention.

However, when daily calcium (1,000 mg./day) was combined with Vitamin D supplementation, even at doses as low as 10 mg. daily, the risk of fractures was significantly reduced.

Vitamin D and diabetes

A recent systematic review and meta-analysis by Parker and colleagues.⁽³³⁾ critically evaluated the current evidence regarding the association between Vitamin D levels and the presence of cardio metabolic disorders, including cardiovascular disease, diabetes and metabolic syndrome. Their conclusions suggest that high levels of vitamin D among adult populations are associated with a substantial decrease in cardiovascular disease, type-2 diabetes and metabolic syndrome. Interventions targeting Vitamin D deficiency in adult and elderly populations could substantially contribute

to halting the current epidemic of cardiometabolic disorders. Further controlled trials are required to evaluate the causal association between Vitamin D levels and diabetes and the benefits of Vitamin D supplementation for insulin resistant or frank diabetes. Another study.⁽³⁴⁾ suggests that the reported association between Vitamin D and glucose metabolism may depend on body size and body mass index (BMI). There is a need for future prospective, randomized, controlled studies to evaluate the effect of Vitamin D supplementation on glucose metabolism.

Vitamin D: Cancer risk and the immune system

A comprehensive study, based on a western European population has shown that pre diagnostic circulating 25(OH) concentrations below 50 nmol/l are associated with an increased risk of

colon cancer, whereas concentrations above 75.0 nmol/l are associated with a non-significant reduced risk. However, no statistically significant interaction was observed between circulating 25(OH) D concentrations and dietary calcium intake.⁽³⁵⁾

A systematic review by Rhee and colleagues of epidemiological studies.⁽³⁶⁾ found that chronic sun exposure, whether or not (partially) mediated by vitamin D, decreased the risk of some cancers, particularly colon, breast and prostate cancer and non-Hodgkin's lymphoma. There is also evidence that relatively high personal sun exposure may improve the outcomes of colon, breast and prostate cancer, lung carcinoma, melanoma and Hodgkin's lymphoma. It might, therefore, be more appropriate to speak of the "sunlight hypothesis" instead of the "vitamin D

hypothesis".⁽³⁶⁾

A recent study by Berhm and colleagues from Costa Rica reported that Vitamin D levels were inversely associated with markers for asthma and allergy severity. Low Vitamin D levels were associated with elevated total IgE and eosinophil counts and an increased Likelihood of methacholine airway responsiveness and anti-inflammatory medication use.⁽³⁷⁾ Early Vitamin D repletion through supervised supplementation may have a positive impact on later neurological health.⁽³⁸⁾ immune function.^(39,40) and chronic disease risk.^(41,42)

Defining Vitamin D deficiency

Most, but not all, experts agree that a serum 25(OH) D level of 30 ng/ml is desirable (sufficient) in adults.^(43,44)

- Vitamin D deficiency is defined as a serum 25(OH)D level of less than 20

ng/ml (50 nmol/l).

- Insufficiency is defined as a serum 25(OH) D level of 20 to 30 ng/ml (50 to 75 nmol/l).⁽⁴⁵⁾

Determining serum 25(OH)D level

Clinicians increasingly use 25(OH)D measurement to diagnose low Vitamin D levels and prescribe Vitamin D supplementation based upon these values; however, 25(OH)D measurement is challenging because circulating 25(OH)D is highly lipophilic, bound strongly to protein, present in low (nanomolar) concentrations, and exists in two structurally similar forms, 25(OH)D₃ and 25(OH)D₂.⁽⁴⁶⁾ Blood is usually obtained by routine venipuncture, allowed to clot for 30 min at room temperature and then centrifuged. The serum is then sent as frozen clinical specimens. Serum aliquots are then prepared and frozen at -80 °C until

shipped in a routine clinical manner for analysis.

Several published methods exist for determining 25(OH) D concentrations, including competitive protein-binding assays, radioimmunoassay (RIA), high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC-MS), and the more recent automated immunoassays. In 1989, the International External Quality Assessment Scheme for Vitamin D metabolites (DEQAS, Northwest Thames, United Kingdom) was established to monitor the analytical reliability of 25(OH) D assays.⁽⁴³⁾

However, several reports have demonstrated considerable inconsistency and variability in 25(OH) D measurements among methods and laboratories.⁽⁴⁸⁻⁵⁰⁾ As a result, some groups have emphasized a need for

appropriate reference materials and standardization of 25(OH) D assays.^(48,49)

Interpretation of studies dealing with Vitamin D stores must be based on precise and correct analytical procedures. However, limited information exist on the influence of other Vitamin D metabolites and conjugates on the concentration of immune-analytically measured serum 25(OH) D or $1\alpha,25(\text{OH})_2\text{D}$.⁽⁵¹⁾

Recommended Vitamin D supplementation values

Vitamin D is a fat-soluble vitamin with the potential for toxicity if it is chronically consumed at very high doses. Therefore, in Canada and the United States, the addition of vitamin D to foods is very carefully regulated. In developing regulations concerning the lawful addition of Vitamin D and calcium to foods, both countries used the same dietary

guidelines for adequate intakes (AIs) of Vitamin D and calcium for all sex and age groups and the upper limits of safe intakes of Vitamin D and calcium.⁽⁵²⁾

Since 1997, the Institute of Medicine has recommended AIs of 5 μg (200 IU)/ day for individuals aged 6 months through 50 years and AIs of 10 μg (400 IU/day) for adults aged 51 to 70 years of age. The corresponding value for adults older than 70 years was 15 μg (600 IU/d). The AI was used instead of the more-familiar recommended dietary allowance derived from estimated average requirements because of uncertainties about study participants' sun exposure and body stores of and potential errors in food composition values. The American Academy of Pediatrics (AAP).⁽⁵³⁾ revised its guidelines regarding Vitamin D intake in 2008. Vitamin D recommendations now include all infants, including those

who are exclusively breastfed, along with older children and adolescents. It is now recommended that all infants and children, including adolescents, have a minimum daily Vitamin D intake of 400 IU beginning soon after birth. This replaces the previous recommendation of a minimum daily Vitamin D intake of 200 IU/day.⁽⁵³⁾

With the reemergence of hypovitaminosis D among adults and the elderly, questions about the most appropriate treatment regimen have arisen.

Vitamin D therapeutic regimens

Multiple treatment regimens have been proposed to treat hypovitaminosis D in young children and adults, including daily or weekly dosing for varying periods of time.

*A Finnish study concluded that a dose of 15 µg: 600 IU (54) raised and

maintained serum levels of 25(OH)D of 40 to 55 nmol/l among ambulatory elderly people.

*A Lebanese study (55) of healthy children aged 10 to 17 years found that an oral dose of 2000 IU=50 µg Vitamin D well tolerated and led to desirable 25(OH)D levels with no evidence of Vitamin D toxicity.

*An American.⁽⁵⁶⁾ randomized clinical trial in infants and toddlers administered oral doses of either 2,000 IU=50 µg Vitamin D₂ daily, 50,000 IU Vitamin D₂ once weekly, or 2,000 IU Vitamin D₃ daily. Infants and toddlers aged 8 to 24 months who were seen at the Children's Hospital Boston Primary Care Center over a 6-week period were enrolled consecutively. Study data demonstrated that all 3 doses yielded equivalent outcomes in the short-term treatment of hypovitaminosis D among otherwise

healthy infants and toddlers.

*A Romanian study.⁽⁵⁷⁾ examined the effects of an oral dose of 5000 IU=125 µg of Vitamin D₃ administered to nursing home residents aged 58 to 89 years through bread fortification. The researchers concluded that fortifying bread with Vitamin D₃ and calcium effectively suppressed PTH and bone-turnover markers while improving BMD at the hip and spine. They suggest that their results provide a plausible rationale for conducting clinical trials of Vitamin D₃ at intakes of 800 IU/day.

Vitamin D₂ and D₃: Do they differ?

A recent randomized, placebo-controlled, double-blinded study (58) of healthy adults ages 18 to 84 years who received either 1000 IU of Vitamin D₃ or 1000 IU of Vitamin D₂ showed that Vitamin D₂ was as effective as Vitamin D₃ in maintaining 25 (OH)D levels above a

mean of 20 ng/ml and improving bone health. These findings are consistent with those of Rapuri et al.⁽⁵⁹⁾, who observed that Vitamin D₂ and Vitamin D₃ contributed equally to serum 25(OH)D levels in elderly women.

Sun exposure: How much do we need?

We should push toward moderation in sun exposure and Vitamin D supplementation. In populations that have moved from their traditional habitats, problems of both excess sun exposure and Vitamin D insufficiency are clearly evident.^(60,61) Studies from Australia show that for a person with moderately fair skin, exposure of hands, face and arms for 6 to 7 minutes at 10:00 a.m. or 2:00 p.m. in the summer or 9 to 12 minutes in the winter in North Australia (latitude 17° south) should produce 1000 IU of vitamin D, an amount

Sufficient to maintain vitamin D concentrations within the normal range⁽⁶¹⁾.

Megadose therapy for Vitamin D deficiency (Stoss therapy)

The argument for using large-dose oral and depot therapies for correcting hypovitaminosis D has been reported in many studies.

*A Turkish study.⁽⁶²⁾ examined 3 to 36-month old infants with rickets who randomly divided into 3 groups who received vitamin D as follows: group one received 150,000 IU orally, group two 300,000 IU and group three received 600,000 IU orally once. The researchers found no differences among treatment approaches (150,000 IU, 300,000 IU and 600,000 IU Vitamin D p.o.) in the improvement of rickets. However, hypercalcemia developed in 25% of the infants who were given 300,000 IU and

600,000 IU vitamins D. Zeghoud et al.⁽⁶³⁾ and Markestad et al.⁽⁶⁴⁾ also found that infants who received 600,000 IU vitamin D prophylaxis developed symptomatic hypercalcemia and nephrocalcinosis.

*An Italian study.⁽⁶⁵⁾ of elderly female nursing home residents aged 66 to 97 years compared the results of a single intramuscular dose of 300,000 IU of vitamin D₂ with 300,000 IU vitamin D₃ given orally. The researchers concluded that cholecalciferol is almost twice as potent as ergocalciferol in increasing and maintaining serum 25(OH)D. Importantly, patients who took intramuscular ergocalciferol (Vitamin D₂) never reached the threshold level of 32 ng/ml.

*A Finnish study.⁽⁶⁶⁾ examined the effects of Vitamin D supplementation in preventing bone fractures in elderly people. An annual intramuscular injection

of ergocalciferol (150,000 to 300,000 IU) was given for 4 years. Data indicated that lower limb fractures occurred almost as frequently among the vitamin D recipients as among the controls. No documented fracture reduction was attributed to the annual injection of vitamin D.

*An Australian prospective study.⁽⁶⁷⁾ used 600,000 IU=15 mg of cholecalciferol (Vitamin D₃) as an annual intramuscular injection for the treatment of hypovitaminosis. This study showed an effective normalization of vitamin D serum levels to above 50 nmol/l at 12 months. The researchers also found a progressive increase in urine calcium excretion indices and possible hypercalciuria in 20% of patients. They recommend 24-hour urine calcium excretion measurements for patients receiving high doses of Vitamin D.

These studies indicate that intramuscular Vitamin D megadoses are not able to adequately increase 25(OH)D serum levels, probably because this is not the physiological route of administration.⁽⁵⁶⁾ Therefore, a more conservative regimen of daily or weekly oral Vitamin D may provide the necessary benefit without the increased risk of hypercalcemia commonly associated with single large-dose therapies. The argument favoring large-dose depot therapies for correcting hypovitaminosis D must be reevaluated because more conservative lower-dose therapies maybe safer, especially in the outpatient setting.

CONCLUSIONS

- Despite the possibilities for of disease prevention suggested by available studies, researchers believe that the evidence supporting widespread high-

dose Vitamin D supplementation in the general population remains insufficient.

- We must better define the optimal dose, the real benefits and the potential harmful effects of Vitamin D supplementation.
- Additional studies of Vitamin D are needed, especially trials of Vitamin D given daily at higher doses without calcium.
- Adequate randomized trials conducted in well-defined populations are needed to test the potential role of Vitamin D in primary prevention or therapy.
- Local food and drug authorities should enforce regulations related to Vitamin D fortification in foods, especially milk, dairy products and cereals.

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