

A Review on Vitamin D Deficiency

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ABSTRACT

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. In addition, recent epidemiologic studies have observed relationships between low vitamin D levels and multiple disease states. Low vitamin D levels are associated with increased overall and cardiovascular mortality, cancer incidence and mortality, and autoimmune diseases such as multiple sclerosis. Although it is well known that the combination of vitamin D and calcium is necessary to maintain bone density as people age, vitamin D may also be an independent risk factor for falls among the elderly.

Vitamin D had been linked to skeletal disease including calcium, phosphorus, and bone metabolism, osteoporosis, fractures, muscle strength, and falls. In the 2000s, growing scientific attention turned to non-skeletal chronic diseases as vitamin D deficiency was linked to cancer, cardiovascular diseases, metabolic disorders, infectious diseases, and autoimmune diseases, as well as mortality.

Keywords- Vitamin D, bone metabolism, skeletal disease, immune-modulating, autoimmune.

I. INTRODUCTION

Vitamin D is a vitamin. Vitamin D consists of 2 bioequivalent forms. Vitamin D₂ also known as ergocalciferol is obtained from dietary vegetable sources and oral supplements [1]. Vitamin D₃, also known as cholecalciferol, is obtained primarily from skin exposure to ultraviolet B (UVB) radiation, including fatty fish such as herring, mackerel, sardines and tuna. To make vitamin D more available, it is added to dairy products, juices, and cereals that are then said to be “fortified with vitamin D [2].” But most vitamin D – 80% to 90% of what the body gets – is obtained through exposure to sunlight. Vitamin D can also be made in the laboratory as medicine.

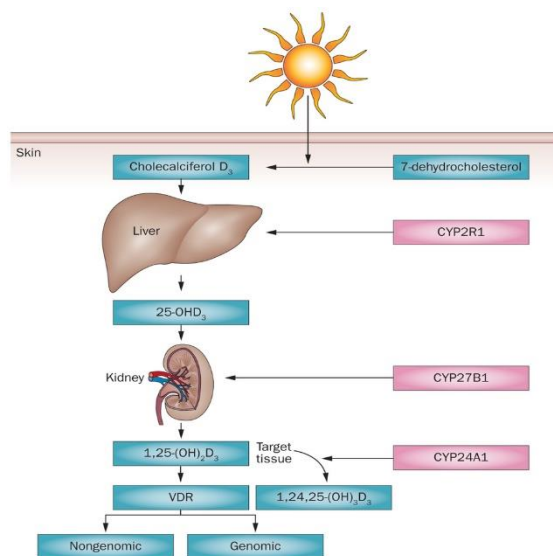


Figure 1: Mood of action of sun rays on our skin

Etiology of Vitamin D Deficiency

The prevalence of vitamin D deficiency is 50-90 % in the Indian subcontinent and is attributed to low dietary calcium along with skin color and changing lifestyle [3]. Some postulate that a deficiency of dietary calcium rather than vitamin D deficiency is responsible for rickets after infancy, supported by the fact that they have a better response to treatment with calcium alone or in combination with vitamin D rather than vitamin D alone [4]. Vitamin D deficiency is observed among breastfed infants at one end with dietary calcium deficiency in older children at the other end. Between

these two extremes, it is likely that vitamin D insufficiency and decreased calcium intake or high phytate intake combine to induce vitamin D deficiency and rickets, which may be the most frequent cause of rickets globally [5].

Vitamin D deficiency is common in infancy due to several factors such as – decreased dietary intake, decreased coetaneous synthesis (because of cultural and religious practices, seasonal variation, fear of cancer, and practice of not taking the child out, increase in pigmentation), increasing rate of exclusive breast feeding, and low maternal vitamin D[6].

Table 1: Etiology of Vitamin D Deficiency

Decreased vitamin D synthesis	Skin pigmentation, physical agents blocking UVR exposure, clothing, latitude, season, air pollution, cloud cover, altitude
Decreased nutritional intake of vitamin	Strict vegan diet
Age and physiology	Related Elderly, obese and institutionalized
Decreased maternal vitamin D stores	Exclusive breast feeding
Malabsorption	Celiac disease, pancreatic insufficiency (cystic fibrosis), biliary obstruction (biliary atresia)
Decreased synthesis	Chronic liver disease
Increased degradation of 25 (OH) D	Drugs such as rifampicin, isoniazid, anticonvulsants, glucocorticoids

Vitamin D Deficiency

Vitamin D is essential for healthy bones. We get some of it from food, but most comes from sunlight [7].

Most people should be able to get all the vitamin D they need from summer sun and a healthy balanced diet. However, up to a quarter of the population has low levels of vitamin D in their blood [8].

Not getting enough sunlight is one reason some people suffer from vitamin D deficiency, putting them at

risk of bone problems, including rickets in children and osteomalacia in adults. Some research suggests that not getting enough vitamin D may also be linked to heart conditions, diabetes, asthma and cognitive impairment in older adults [9].

Vitamin D is also found in oily fish, such as salmon, mackerel and sardines, eggs, fortified fat spreads, fortified breakfast cereals and powdered milk. However, it is hard to get enough vitamin D just from food [10].

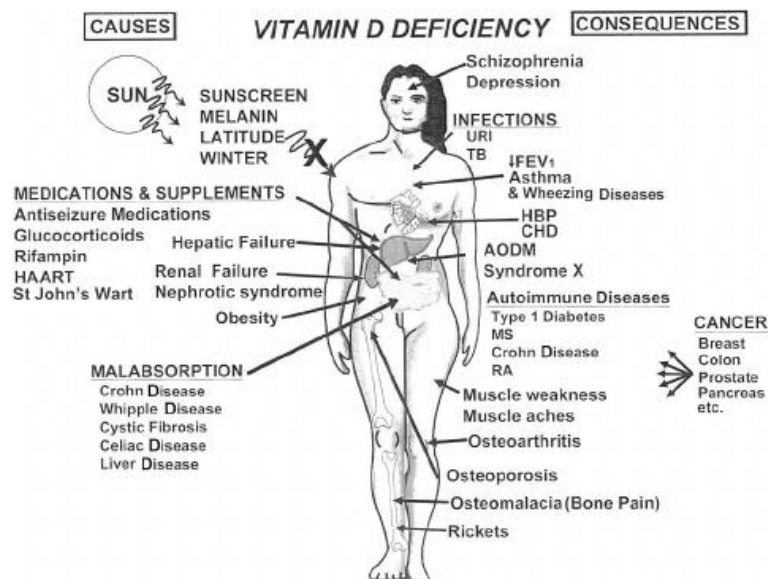


Figure 2: Vit D deficiency

Vitamin D metabolism and physiology

Perhaps because the term vitamin D contains the word ‘vitamin’, most people wrongly assume it is like other vitamins, that is, they can obtain adequate amounts by eating a good diet [11]. However, the natural diets most humans consume contain little vitamin D, unless those diets are rich in wild-caught, fatty fish. Small amounts of vitamin D are contained in fortified foods, such as fortified milk, orange juice and cereals in the US, and margarines in Europe, but such sources are usually minor contributors to vitamin D stores. Traditionally, the human vitamin D system began in the skin, not in the mouth [12]. The manufacture of vitamin D by skin is extraordinarily rapid and remarkably robust; production after only a few minutes of sunlight easily exceeds dietary sources by an order of magnitude [13].

Incidental sun exposure, not dietary intake, is the principal source of circulating vitamin D stores and to a degree that is a function of skin surface area exposed [14]. For example, when fair-skinned people sunbathe in the summer (one, full-body, minimal erythema dose of ultraviolet B radiation [UVB]), they produce ~ 20,000 IU of vitamin D in < 30 min [15]. One would have to drink 200 glasses of American milk (100 IU/8-oz glass) or take 50 standard multivitamins (400 IU/tablet) in one sitting to obtain this amount orally [16].

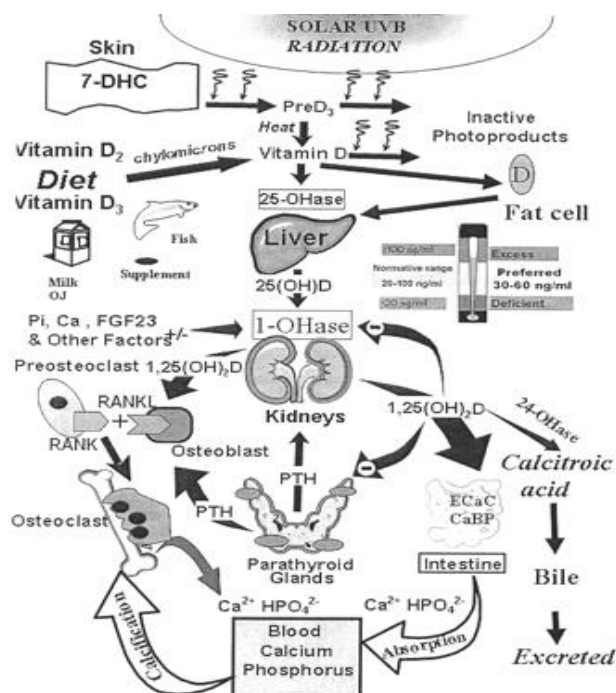


Figure 3: Vit D synthesis

Vitamin D deficiency at-risk groups

The Chief Medical Officers of the UK say these groups are at particular risk of vitamin D deficiency: Pregnant and breastfeeding women, especially teenagers and young women. Infants and children under 5 years of age. 65 year olds and over [17].

People who have little or no exposure to the sun. This includes covering-up for cultural reasons, people who are housebound or who stay indoors for long periods of time. People with darker skin, such as African, African-Caribbean and South Asian origin. These groups are not able to make as much vitamin D as those with paler skin [18].

Function of Vit-D

Vitamin D is required for the regulation of the minerals calcium and phosphorus found in the body. It also plays an important role in maintaining proper bone structure.

Sun exposure is an easy, reliable way for most people to get vitamin D. Exposure of the hands, face, arms, and legs to sunlight two to three times a week for about one-fourth of the time it would take to develop mild sunburn will cause the skin to produce enough vitamin D. The necessary exposure time varies with age, skin type, season, time of day, etc [19].

It’s amazing how quickly adequate levels of vitamin D can be restored by sunlight. Just 6 days of casual sunlight exposure without sunscreen can make up for 49 days of no sunlight exposure. Body fat acts like a kind of storage battery for vitamin D [20]. During periods of sunlight, vitamin D is stored in fatty fat and then released when sunlight is gone.

Nevertheless, vitamin D deficiency is more common than you might expect. People who don’t get enough sun, especially people living in Canada and the northern half of the US, are especially at risk.

Vitamin D deficiency also occurs even in sunny climates, possibly because people are staying indoors more, covering up when outside, or using sunscreens consistently these days to reduce skin cancer risk.

Older people are also at risk for vitamin D deficiency. They are less likely to spend time in the sun, have fewer “receptors” in their skin that convert sunlight to vitamin D, may not get vitamin D in their diet, may have trouble absorbing vitamin D even if they do get it in their diet, and may have more trouble converting dietary vitamin D to a useful form due to aging kidneys [21]. In fact, the risk for vitamin D deficiency in people over 65 years of age is very high. Surprisingly, as many as 40% of older people even in sunny climates such as South Florida don’t have enough vitamin D in their systems.

II. MANIFESTATION

Symptoms of bone pain and muscle weakness can mean you have a vitamin D deficiency. Low blood levels of the vitamin have been associated with the following[22].

- Increased risk of death from cardiovascular disease.
- Cognitive impairment in older adults.
- Severe asthma in children.
- Cancer
- Darker skin.

- A big-time head sweater.
- Gut trouble.
- Overweight or obese.
- Got the blues.
- Bones ache.

How do I know if I need testing?

People who have or are at higher risk of the following health concerns should seriously consider getting their vitamin D levels tested:

- Family history or personal history of cancer
- Hypertension (high blood pressure)
- Schizophrenia
- Depression
- Migraines
- Epilepsy
- Osteoarthritis

Autoimmune conditions (such as lupus, ankylosing spondylitis, multiple sclerosis, rheumatoid arthritis) [23].

- PCOS (polycystic ovarian syndrome)
- Diabetes mellitus (both types 1 and 2)
- Fibromyalgia
- Osteoporosis/osteopenia

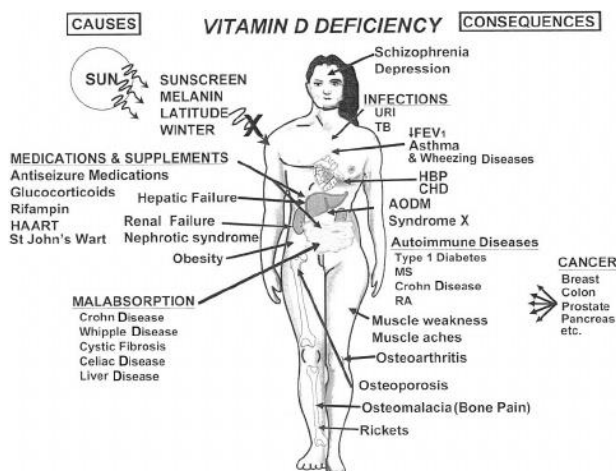


Figure 4: Vit D Deficiency

III. TEST FOR VITAMIN D DEFICIENCY

Blood test for vitamin D deficiency

The most accurate way to measure how much vitamin D is in your body is the 25-hydroxy vitamin D test. In the kidney, 25-hydroxy vitamin D changes into an active form of the vitamin. The active form of the vitamin can be measured through a blood test. The active form of vitamin D helps control calcium and phosphate levels in the body. The normal range is 80 to 120 nanomols per liter (nmol/L)[24].

Safe sun exposure

Around 10 to 15 minutes a day in the summer sun without sunscreen is enough to top up vitamin D

levels for most people. Health officials don't give firm recommendations on the duration because the ideal amount of sun depends on people's skin type and how quickly they get sun burn. People with darker skin need longer in the sun than those with lighter skin.

The best time of day for making vitamin D from sunlight is 11am to 3pm, April to October.

It doesn't require putting on a bikini or trunks, but the bigger the area of the body uncovered, the more vitamin D the body makes.

After the daily vitamin D top-up, the usual sun protection measures should be taken, including using sun protection factor or at least SPF 15 [25].

Laboratory tests

Serum parathyroid measurements were performed using an electro chemiluminescence-based method on an E 170 Modular Analytic System (Roche, USA) device. 25-OHD levels were measured using a 25OH-Vitamin D3-Ria-CT Kit (Biosource Europe, Belgium). Reference ranges for 25-OHD were 10 ng/mL to 50 ng/mL for the winter season and 20 ng/mL to 120 ng/mL for the summer season [26]. Hepatitis markers were determined using commercially available kits based on chemiluminescence assays. HBV DNA was quantified using the PCR Cobas Taqman 48 system (Roche, USA [27].

Statistical analysis

Statistical analyses were performed using SPSS version 13 (IBM Corporation, USA) and Epi Info (Centers for Disease Control and Prevention, USA). Numerical variables are presented as median ± SD and categorical variables are presented as percentages. The normality of the data was tested using the Shapiro-Wilk test. Because the data were not normally distributed, the Mann-Whitney U test, a nonparametric statistical test, was used to compare the mean values among the groups. Categorical variables were compared using the χ^2 test or Fisher's exact χ^2 test. For all statistical studies, $P < 0.05$ was considered to be statistically significant.

Vitamin D toxicity

The adverse effects of high vitamin D intakes – hypercalciuria and hypocalcaemia – do not occur at these new recommended intake levels. In fact, it is worth noting that the recommended intakes for all age groups are still well below the lowest observed adverse effect level of 50 $\mu\text{g/day}$ and have not yet even reached the no observed adverse effect level of 20 $\mu\text{g/day}$ [28].

Outbreaks of idiopathic infantile hypocalcaemia in the United Kingdom in the post-World War II era led to the withdrawal of vitamin D fortification from all foods in that country because of concerns that they were due to hypovitaminosis D[29]. Hypocalcaemia may have been multifactorial with genetic and dietary components and were not just due to technical problems with over-fortification as was assumed. In retrospect, the termination of the vitamin D fortification may have been counterproductive because it exposed segments of the UK community to vitamin deficiency and may have

discouraged other nations from starting vitamin D fortification programmes. This is all the more cause for concern because hypovitaminosis D is still a problem worldwide, particularly in developing countries at high latitudes and in countries where skin exposure to sunlight is discouraged [31-35].

Factors affecting vitamin D levels

Factors that affect cutaneous production of vitamin D include latitude, season, time of day, air pollution, cloud cover, melanin content of the skin, use of sunblock, age and the extent of clothing covering the body. When the sun is low on the horizon, atmospheric ozone, clouds and particulate air pollution deflect UVB radiation away from the surface of the Earth. Therefore, cutaneous vitamin D production is effectively absent early and late in the day and for the entire day during several wintertime months at latitudes $> 35^\circ$. For that reason, vitamin D deficiency is more common the further poleward the population. For example, Boston, Massachusetts (latitude 42°) has a 4-month 'vitamin D winter' centred around the winter solstice when no UVB penetrates the atmosphere and an even longer period in the fall and late winter when UVB only penetrates around solar noon. In northern Europe or Canada, the 'vitamin D winter' can extend for 6 months. Furthermore, properly applied sunblock, common window glass in homes or cars, and clothing, all effectively block UVB radiation – even in the summer. Those who avoid sunlight – at any latitude – are at risk any time of the year. For example, a surprisingly high incidence of vitamin D deficiency exists in Miami, Florida despite its sunny weather and subtropical latitude. African-Americans, the elderly and the obese face added risk. As melanin in the skin acts as an effective and ever-present sunscreen, dark-skinned patients need much longer UVB exposure times to generate the same 25(OH)D stores compared with fair-skinned patients. The elderly makes much less vitamin D than 20-year-olds after exposure to the same amount of sunlight. Obesity is also major risk factor for vitamin D deficiency with obese African-Americans at an even higher risk. Therefore, those who work indoors, live at higher latitudes, wear extensive clothing, regularly use sunblock, are dark-skinned, obese, aged or consciously avoid the sun, are at high-risk for vitamin D deficiency [40-45].

IV. PREVENTION AND TREATMENT OF VITAMIN D DEFICIENCY

The Institute of Medicine recommended that all children (also endorsed by the American Academy of Pediatrics) and adults up to the age of 50 y require 200 IU vitamin D/d and adults aged 51–70 and ≥ 71 y need 400 and 600 IU vitamin D/d. The National Osteoporosis Foundation recently recommended that all postmenopausal women take 800–1000 IU vitamin D/d (84). Cheng et al reported an association of low

25(OH)D concentrations with elevated serum PTH concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. This confirmed the earlier observations of Outila et al, who noted elevated PTH concentrations and lower forearm bone density and vitamin D deficiency in the winter in adolescent females, and Guillemant et al, who observed seasonal variation in PTH concentrations in growing male adolescents. When 171 prepubertal girls were given 400 IU vitamin D₂/d from October to February and 500 mg Ca supplementation, their serum 25(OH)D concentrations did not change. When these girls received 800 IU vitamin D₂/d, their blood concentrations rose during the winter but did not reach concentrations observed during the summer. Thus, on the basis of these and other observations, many experts now agree that in the absence of adequate sun exposure, 800–1000 IU vitamin D/d is needed for children of all ages and adults of all ages, although this is not the current recommendation of pediatric or governmental organizations. Higher doses may be required if fat malabsorption, obesity, or other causes exist that would enhance vitamin D catabolism and its destruction [46-50].

V. SUMMARY

Vitamin D deficiency is endemic and associated with numerous serious diseases. Understanding the physiology of vitamin D and having a high index of suspicion are keys to suspecting the diagnosis. Serum 25(OH)D levels < 40 ng/ml are seldom found in humans living naturally in a sun-rich environment. Treatment with sunlight or artificial UVB radiation is simple, but increases the risk of non-melanoma skin cancers and ages the skin. Sunburns increase the risk of malignant melanoma. Adequate oral supplementation will require doses that make many physicians uncomfortable [51-55].

VI. DISCUSSION

Recent studies have revealed functions of vitamin D in addition to those in bone metabolism. It has been found to be involved in autoimmune disorders such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, psoriasis, diabetes, certain cancer types, hypertension, heart failure, atherosclerosis, peripheral artery disease and several infectious diseases. Vitamin D directly leads to the expression of vitamin D receptor and CYP27B1 in vascular smooth muscle cells and in endothelial cells. Recently, it has been recognized that vitamin D has other functions in addition to its role in bone metabolism. It has been demonstrated that vitamin D deficiency may play a role in the development of autoimmune diseases, inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, diabetes, certain cancer types, cardiac failure, stroke and infectious diseases such as tuberculosis and

pneumonia, and that vitamin D supplementation is efficacious in these patients. There is evidence that vitamin D may have a protective role in influenza and other viral diseases and may decrease the risk of developing AIDS in HIV-positive patients, hepatitis and other viral infections, demonstrated that maintenance of a vitamin D serum concentration of 38 ng/mL or higher could significantly reduce the incidence of acute viral respiratory tract infections, including influenza, at least during the fall and winter in temperate zones. The most important limitation of our study was the small number of patients [56-60].

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DECLARATIONS

Conflict of Interest

The authors declare no potential conflicts of interest.

Ethical Approval

In this study there was no need of human and animal participants.

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