

Effects of Vitamin D Deficiency - An Update

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Summary

Vitamin D deficiency is a world-wide problem and it is defined as 25(OH)D₃ level below 20 ng/ml. It contributes skeletal and non-skeletal health effects. Musculo-skeletal abnormalities along with non-skeletal health effects such as microbial infection, cardiovascular disorders, cancers, autoimmune diseases, asthma and allergy, endocrine and metabolic diseases, mental health etc are seen in Vitamin D deficiency. Vitamin D deficiency or insufficiency is mostly under diagnosed or under attention topics or unaware matter to general population. It is mostly preventable and treatable condition that needs due attention to life-style modification, medication, self-awareness and campaign and further research.

Introduction

Vitamin D, also known as sunshine vitamin or a potential magic bullet^{1,2} is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, phosphate, and multiple other biological effects³. Vitamin D has been appreciated for its role in calcium homeostasis and bone health since its identification⁴ in 1921. Activated Vitamin D is actually a hormone. Recent studies have proved that vitamin D has got anti-cancer, anti-inflammatory, anti-microbial, immunomodulatory, anti-depressant and other functions⁵.

Common forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol); structurally these two forms are different but bioequivalent.³ Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements^{6,7,8}. Daily requirement of vitamin D from diet is 400 I.U in children under one year, 600 I.U in children, teens and adult upto age 70 and 800 I.U in adults over the age of 70 years.

If underexposed to sunlight, this requirement increases to 1000 I.U. Most authority agree that a 25(OH)D concentration <50 nmol/L or 20ng/ml is an indication of vitamin D deficiency; 51-74 nmol or 21-29 ng/ml is considered as insufficiency and concentration of ≥75nmol/L or ≥30 ng/ml is considered as

sufficient⁹. Vitamin D deficiency is now recognized as a pandemic¹⁰. It is a global health problem caused mainly by insufficient exposure to sunlight. It is estimated that one million people have vitamin D deficiency or insufficiency worldwide¹¹.

Sources of vitamin D

Vitamin D is one of the four fat-soluble vitamins (A, D, E, and K). Vitamin D2 is obtained from dietary plants, mushrooms, fungi, yeast and algae. Vitamin D3 is obtained primarily from skin exposure to ultraviolet B (UVB) radiation in sunlight. Other sources are oily fish, sea fish (tuna, salmon, mackerel, oysters), fish liver oil, beef liver, egg yolk, milk, swiss cheese, fortified bread, oatmeal, cereals, orange juice, yoghurt, cow milk, soy milk, almond milk. It can also be obtained from oral supplements¹².

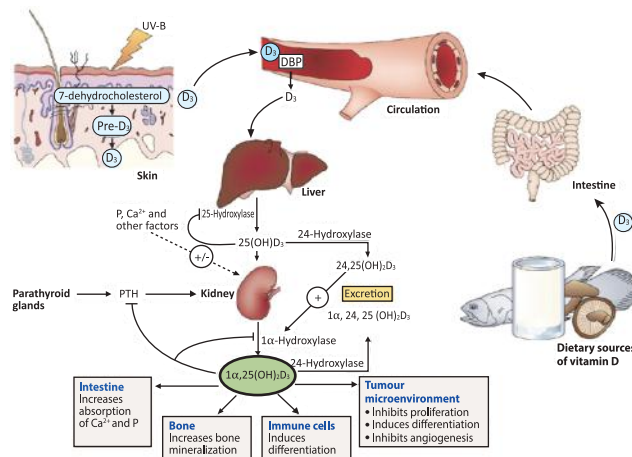


Fig 1: Sources and activation pathway¹³ of vitamin D2 and D3

Causes of vitamin D deficiency

Vitamin D deficiency is now recognized as a world-wide problem. No one is immune from vitamin D deficiency. This includes both children and adults living in the United States, Europe, Middle East, India, Australia, and Asia including

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Bangladesh. Studies suggest that upwards of 30–50% of children and adults are at risk of vitamin D deficiency¹⁴. Vitamin D deficiency can occur for a number of reasons, such as limited exposure to sunlight, inadequate consumption of the vitamin D (strict vegan diet) over time, dark skin complexion, renal insufficiency, intestinal disease like cystic fibrosis, crohn's disease and celiac disease causing inadequate absorption of vitamin D. Because vitamin D is fat soluble, it is readily taken up by fat cells. Obesity is also associated with vitamin D deficiency, and it is believed to be due to the sequestration of vitamin D by the large body fat pool¹⁵. Aging is also associated with decreased concentrations of 7-dehydrocholesterol in skin. A 70-year-old has ≈25% of the 7-dehydrocholesterol that a young adult does and thus has a 75% reduced capacity to make vitamin D₃ in the skin¹⁶. Medications including antiseizure medications, glucocorticoids and fat malabsorption are also common causes of vitamin D deficiency¹⁷. A recent study revealed that occupation can also play a big role in vitamin D levels. It is demonstrated that shift-workers, healthcare workers and indoor workers are at high risk to develop vitamin D deficiency due to reduced outdoor time and sunlight exposure¹⁸. It is demonstrated that more than 90 percent of people with darker skin pigments (Blacks, Hispanics and Asians) living in the United States now suffer from vitamin D insufficiency, while 75 percent of the white population is deficient. Muslim women wearing burka, veil, purdah, hijab and niqab are vulnerable to vitamin D deficiency¹⁹.

Calcium, phosphate and bone metabolism

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed. The interaction of 1, 25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80%²⁰.

In one study, serum levels of 25-hydroxyvitamin D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more. When the level was 30 ng per milliliter or less, there was a significant decrease in intestinal calcium absorption that was associated with increased parathyroid hormone. Parathyroid hormone enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D. Parathyroid hormone also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts²¹.

Osteoporosis and fracture

Osteoclasts dissolve the mineralized collagen matrix in bone, causing osteopenia and osteoporosis and increasing the risk of fracture²¹. Approximately 33% of women 60 to 70 years of

age and 66% of those 80 years of age or older have osteoporosis. It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime. Chapuy et al²². reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D₃ daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%. A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D₃ and 500 mg of calcium per day²³.

Rickets and osteomalacia

Maternal vitamin D deficiency may cause overt bone disease from before birth and impairment of bone quality after birth^{24,25}. Nutritional rickets exists in countries with intense year-round sunlight such as Nigeria and can occur without vitamin D deficiency. Vitamin D deficiency in children will cause growth retardation and classic signs and symptoms of rickets. In adult vitamin D deficiency produces osteomalacia due to defective bone mineralization and metabolism^{26,27}.



Fig 2: Classic features of rickets in a Bangladeshi child

Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate sun exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh, where rickets occurs among older toddlers and children, it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products²⁸.

Autoimmune diseases

Vitamin D is an extrinsic factor capable of affecting the prevalence of autoimmune diseases.²⁹ Association between vitamin D deficiency and autoimmune diseases has been supported by epidemiological studies, demonstrating higher prevalence of vitamin D deficiency among autoimmune patients, in comparison to the general population. As a rule, the effects of vitamin D in the immune system translate into an enhancement of innate immunity associated with a multifaceted regulation of

acquired immunity.³⁰ Vitamin D deficiency is associated with increased prevalence of various autoimmune diseases like insulin dependent diabetes mellitus (IDDM), multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel disease (IBD). It has been suggested that vitamin D and its analogues not only prevent the development of autoimmune diseases, but they could also be used in their treatment^{31,32}.

Systemic lupus erythematosus

Many studies have shown that there is a link between vitamin D and lupus. People who have lupus are more likely to have low levels of vitamin D³³. In addition, the disease severity has been linked to low vitamin D levels. This may be because people with lupus are sensitive to the sun, so they often wear veil/burkha, use sunscreen or avoid being outdoors. There are vitamin D receptors found on cells in the immune system, and vitamin D can bind to these receptors³⁴. This can cause the auto-antibodies to decrease and stop attacking the healthy cells in the body. Therefore, it is believed that vitamin D can help prevent lupus flares by reducing inflammation in the body³⁵. However, researchers have not been able to show conclusively yet that low vitamin D levels cause lupus. Researchers have found however, that in winter months with low sunlight, people with lupus are more likely to have active symptoms, as well as more likely to have low levels of vitamin D. People with lupus are also more likely to have more flares during low sunlight months compared to high sunlight months³⁶.

Rheumatoid arthritis

Reduced vitamin D intake has been linked to increased susceptibility to the development of rheumatoid arthritis (RA) and vitamin D deficiency has been found to be associated with disease activity in patients with RA. Vitamin D deficiency is highly prevalent in patients with RA, and that vitamin D deficiency may be linked to disease severity in RA. As vitamin D deficiency has been linked to diffuse musculoskeletal pain, these results have therapeutic implications. Vitamin D supplementation may be needed for pain relief in patients with RA³⁷.

Osteoarthritis

Low levels of vitamin D have been shown to associate with an increase in radiographic progression of knee osteoarthritis, osteoblastic activity matrix ossification and bone density³⁸.

Other musculoskeletal problems

Vitamin D deficiency also has been linked to ankylosing spondylitis, osteoarthritis, backache, chronic muscle pain like fibromyalgia, proximal muscle weakness, fatigue, increased chance of fall and fracture³⁸.

Non-musculoskeletal consequences of vitamin D deficiency

Nearly every cell in the body has receptor for vitamin D. The widespread systemic effects of vitamin D have been attributed to the ubiquitous expression of vitamin D receptors in various organ systems. Therefore deficiency of vitamin D produces varieties of clinical manifestations.

Brain, prostate, breast, and colon tissues as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D. In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1 α -hydroxylase. Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis. Active form of vitamin D is also a potent immunomodulator³⁸.

Microbial diseases

Vitamin D deficiency may cause increased microbial infection. Monocytes and macrophages exposed to a lipopolysaccharide of or to *Mycobacterium tuberculosis* up-regulate the vitamin D receptor gene and the 25-hydroxyvitamin D-1 α -hydroxylase gene. Increased production of 1,25-dihydroxyvitamin D₃ result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25-hydroxyvitamin D fall below 20 ng per milliliter, the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D deficient, are more prone to contracting tuberculosis than are whites, and tend to have a more aggressive form of the disease³⁹.

Diabetes mellitus and other metabolic disorders

Vitamin D deficiency is associated with increased risk of developing diabetes mellitus and other metabolic disorders. It is associated with increased insulin resistance, decreased insulin production, and is associated with the metabolic syndrome⁴⁰. Very recently published study data showed, vitamin D deficiency in postmenopausal women was associated with a higher prevalence of metabolic syndrome. Women with vitamin D deficiency had a higher risk of metabolic syndrome, hypertriglyceridemia and low high density lipoprotein (HDL) than those with adequate levels⁴¹. It is observed that Vitamin D deficiency causes increased risk of developing type 1 diabetes; whereas supplementation of vitamin D reduces the risk. It is also observed that increasing vitamin D intake during pregnancy reduces the development of islet auto-antibodies in offspring⁴².

Cardiovascular disease

Vitamin D deficiency is associated with a number of cardiovascular morbidity and mortality. Low 25(OH)D levels are an

independent risk factor for prevalence and incidence of hypertension⁴³. It is associated with congestive heart failure and increased blood levels of inflammatory factors, including C-reactive protein and interleukin-10⁴⁴. Hypertension is considered as the fundamental reason for mortality on the planet, the most well-known reason for going to doctor, and the least complex treatable and cognizable risk factor for diseases like cerebrovascular accident (CVA), myocardial infarction (MI), congestive heart failure (CHF), sudden cardiac death (SCD), peripheral arterial disease (PAD) and atrial fibrillation (AF). Living at higher latitudes increases the risk of hypertension and cardiovascular diseases due to low vitamin D production in high altitude. The prevalence of coronary artery disease, heart failure, and peripheral artery disease is significantly increased in a stepwise fashion as the serum 25(OH)D3 level drops to less than 30 and then 20 ng/ml⁴⁵. Because of the opposing consequences of different reviews on the role of vitamin D in preventing hypertension development or its treatment, it appears that vitamin D level in the body modulate blood pressure indirectly⁴⁶.

Lung function and wheezing illnesses

The epidemic rise in asthma and related allergic disease is a major public health problem worldwide⁴⁷. Several studies have reported that Vitamin D deficiency is associated with an increased incidence of asthma and allergy symptoms⁴⁸. Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses⁴⁹. Recent observational study showed lower serum 25(OH) D levels in children with asthma, allergic rhinitis and wheezing than healthy children. It was also observed that vitamin D insufficiency was common in the study population whereas severe Vitamin D deficiency was significantly higher in children with asthma and allergic diseases than in healthy children⁵⁰.

Cancer

Calcitriol stimulates apoptosis and differentiation and inhibits angiogenesis and proliferation in tumor cells⁵¹. Association studies suggest that serum vitamin D levels are inversely associated with the risk of many types of cancer. People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes⁵². But currently there is little evidence for linear causal association between genetic determinants of circulating vitamin D concentration and risk of colorectal, breast, prostate, ovarian, lung, and pancreatic cancer, and neuroblastoma⁵³.

Psychiatric health

Vitamin D deficiency has been linked to a wide range of major psychiatric illnesses. The link between vitamin D

deficiency and the development of schizophrenia has been researched among patients of all ages around the globe and found a strong association between vitamin D deficiency and schizophrenia⁵⁴. Most recently, laboratory tests of individuals with schizophrenia, psychosis, elective mutism, and bipolar disorders revealed consistent serum vitamin D levels below 20 ng/ml and symptoms improved when vitamin D levels become normalized. While the mechanism is unclear, recent research suggests that vitamin D's action on the regulation of inflammatory and immunological processes likely affects the manifestation of clinical symptoms and treatment response in schizophrenic patients⁵⁵.

Neurological disorders

Dementia, Alzheimer's disease, cognitive impairment, multiple sclerosis etc are associated with vitamin D deficiency⁵⁵.

Vitamin D and belly fat

The strong relationship between increasing amounts of abdominal fat and lower levels of vitamin D suggests that individuals with larger waistlines are at a greater risk of developing deficiency and should consider having their vitamin D levels checked¹.

Miscellaneous effects

Vitamin D deficiency has been associated with alopecia, eczema, tooth decay, gum disease and tooth loss, erectile dysfunction, female incontinence premature birth, childhood language impairment, perimenopausal syndrome, UTI and poor wound healing⁵⁶.

Conclusion

Vitamin D deficiency is incredibly common and most people are unaware of it especially non-skeletal effects. The global prevalence of vitamin D deficiency has reached an alarming proportion. This trend has elicited a significant amount of research interest to elucidate the potential causes of vitamin D deficiency and insufficiency in order to advance interventional strategies to ameliorate the associated risks. Although population-wide vitamin D deficiency is a global phenomenon, some workers in some occupational categories such as shifting workers, indoor workers, health workers etc and home bound elderly people are at a greater risk for vitamin D deficiency than others. Regular screening for vitamin D levels in shift workers and other specific groups of people should be considered for future clinical practice guidelines and population health initiatives, while existing workplace wellness programs should incorporate education about the importance of adequate vitamin D levels, sunlight exposure and adequate nutritional intake of vitamin D rich foods to prevent adverse health outcomes, both skeletal and non-skeletal related to vitamin D deficiency.

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