

Role of Vitamin D in Various Illnesses: A Review

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Abstract

Vitamin D, a fat-soluble vitamin, concentrations need to be maintained for functioning of the metabolic, immune, reproductive, muscular, skeletal, respiratory and cutaneous systems of men and women of all ages. A rough estimate indicates that about 1 billion people globally are vitamin D deficient. The physiological functions of active vitamin D (calcitriol) are related to calcium homeostasis and osteoporosis, with possible roles in diabetes, cancer, ischemic heart disease, and autoimmune and infectious diseases. Vitamin D deficit increases the risk of malignancies, particularly of colon, breast and prostate gland, of chronic inflammatory and autoimmune diseases (e.g. insulin-dependent diabetes mellitus, inflammatory bowel disease, multiple sclerosis), as well as of metabolic disorders (metabolic syndrome, hypertension). The eight disorders discussed in this review are heart disease, bone disorder, colorectal cancer and other malignancies, infectious, inflammatory and autoimmune diseases, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and type-I diabetes mellitus. There is a strong evidence for association between heart diseases, bone disorders, colorectal cancers, infectious, inflammatory and autoimmune diseases, inflammatory bowel diseases, multiple sclerosis, diabetes mellitus type-I and vitamin D. the extent of vitamin D deficiency's contribution in the development of osteoporosis, breast cancer, rheumatoid arthritis is unclear.

Keywords: Vitamin D; Global deficiency; Heart disease; Bone disorder; Colorectal cancer; Infectious

Introduction

Vitamin D, a fat-soluble vitamin, is now recognized as a prohormone because the body can synthesize vitamin D from its precursor (7-dehydrocholesterol) when exposed to ultraviolet light at a wavelength between 290-315 nm. Adequate circulating 25-hydroxy vitamin D concentrations need to be maintained for functioning of the metabolic, immune, reproductive, muscular, skeletal, respiratory and cutaneous systems of men and women of all ages.

Lately, the scientific evidence is piling up to demonstrate the insufficiency of vitamin D globally. Factors, which play a crucial role in the worldwide prevalence of vitamin D insufficiency, vary among countries; but in all cases involve limitations in either or both cutaneous synthesis and dietary sources of vitamin D [1-3].

A rough estimate indicates that about 1 billion people globally are vitamin D deficient which is defined as the concentration of 25-hydroxy vitamin D less than 50 nmol/L or vitamin D insufficient which is defined as the concentration of 25-hydroxy vitamin D less than 75 nmol/L. Vitamin D deficiency is quite common in regions and countries including North America, Northern Europe, Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon [4]. A number of studies have shown that vitamin D deficiency and insufficiency is associated with a rise of serum Parathyroid Hormone (PTH) indicative of secondary hyperparathyroidism [5].

Since geographical location of India provides plenty of sunlight throughout the year, vitamin D deficiency was never a concern among Indians. Contrary to this assumption, high prevalence of vitamin D deficiency has been reported throughout the country for all age groups including neonates, infants, school going children, adolescents, adults, pregnancy, lactating women, and senior citizens. This is probably a result of poor sun exposure, dark skin complexion, atmospheric pollution, vegetarian foods habits, absence of food fortification with vitamin D, and poor intake of vitamin D supplements.

However, there is no governmental regulation mandating vitamin D fortification of food products in India, despite widespread vitamin

D deficiency till date. Though there are a few studies where vitamin D has been supplemented to high-risk population in India, but there are no studies that have evaluated the beneficial effects of food fortified with vitamin D in Indian population. Moreover there is neither an official recommendation for adequate dietary vitamin D intake nor a national food fortification program. Therefore, absence of Vitamin D fortification, low dietary intake and modernization of India collectively caused vitamin D insufficiency [6].

Vitamin D Deficiency and Association with Different Disorders

To understand the role of deficiency of Vitamin D in various health disorders, it is appropriate to capture its role in human physiology. The physiological functions of active vitamin D (calcitriol) are related to calcium homeostasis and osteoporosis, with possible roles in diabetes, cancer, ischemic heart disease, and autoimmune and infectious diseases. In addition to skeletal disorders, calcium and vitamin D deficits increase the risk of malignancies, particularly of colon, breast and prostate gland, of chronic inflammatory and autoimmune diseases (e.g. insulin-dependent diabetes mellitus, inflammatory bowel disease, multiple sclerosis), as well as of metabolic disorders (metabolic syndrome, hypertension) [7].

The eight disorders discussed in this review are heart disease, bone disorder, colorectal cancer and other malignancies, infectious, inflammatory and autoimmune diseases, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and type-I diabetes mellitus.

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Heart disease

Mounting evidence suggests that vitamin D deficiency is associated with increased cardiovascular risk and myocardial diseases, but the underlying mechanisms still remaining to be explored in detail [8]. Some observational studies have shown that vitamin D deficiency is associated with greater risk of cardiovascular diseases (e.g., stroke, sudden cardiac death) and their risk factors (e.g., hypertension, diabetes). However, a few randomized, controlled trials are available, and the evidence from observational studies is not conclusive [9].

Drechsler et al. investigated the impact of vitamin D status on cardiovascular outcomes and fatal infections in haemodialysis patients and reported that severe vitamin D deficiency was strongly associated with sudden cardiac death, cardiac vascular event, and mortality, and there were borderline associations with stroke and fatal infection [10]. Findings from RCTs among patients free of advanced CKD have to be very cautiously extrapolated to haemodialysis patients. Drechsler et al. believe that these results need to be supported by a meta-analysis. In this context, it should be mentioned that results of the study are limited due to the observational nature of study. This design precludes any conclusion regarding cause and effect relationship. Despite the extensive adjustments, the investigators were unable to exclude residual confounding. A yet one more limitation of this study is that due to lack of data, the authors unable to study interactions and confounding by levels of 1,25-dihydroxy vitamin D or fibroblast growth factor-23, which suppresses 1,25-dihydroxy vitamin D synthesis. Another drawback of work is missing data on left ventricular ejection fraction and severity of CAD.

Evidence suggests that higher plasma concentrations of 25-hydroxy vitamin D may reduce the risk of hypertension [11]. Some meta-analyses have suggested a blood pressure lowering effect of vitamin D supplementation, while other meta-analyses, in 2015, could not confirm these findings and showed no effect of vitamin D supplementation on blood pressure [12]. Further, in a recent randomized controlled trial of 200 hypertensive patients, no significant effect of vitamin D supplementation on 24 h blood pressure could be observed [13]. This study was limited by the reduced sample size, short intervention period and the single-blinded approach. In addition, recommended dietary intake of vitamin D is 10-20 µg/day and the participant's average dietary intake was 1.87 ± 0.41 µg/day. Since plasma levels of 25-hydroxy vitamin D were not measured, it can be safely assumed that participants were vitamin D-deficient. In effect, the vitamin D supplementation may have only restored the body's vitamin D levels and full biological effects were not observed. Higher number of females in this study could be one of the confounding factors, as blood pressure is linked with the gender.

1,25-dihydroxy vitamin D was shown to exert antihypertrophic effects on cardiomyocytes and reduced the expression of several genes which are upregulated in myocardial hypertrophy [14]. Suppression of the cardiac Renin-Angiotensin System (RAS) and of natriuretic peptides may partially mediate these antihypertrophic effects of vitamin D. Apart from this; vitamin D exerts various effects on the growth and differentiation of cardiomyocytes. One beneficial key mechanism of vitamin D is to inhibit excessive proliferation of cardiomyocytes [15].

Pilz et al. elucidated whether insufficient vitamin D status is associated with heart failure and Sudden Cardiac Death (SCD). Major finding of the study was that low levels of 25-hydroxy vitamin D and 1,25-dihydroxyvitamin D were associated with prevalent myocardial dysfunction, deaths due to heart failure, and SCD [15].

The low prevalence of patients with severe vitamin D deficiency and the relatively short treatment period appear to be the limitations of this study as authors were unable to exclude significant effects of vitamin D in populations with low vitamin D levels and with longer treatment or different doses of vitamin D. It should be noted that when supplementing vitamin D, it usually takes nearly 3 months to reach a steady state in circulating 25-hydroxy vitamin D concentrations; but in this study treatment period was relatively short, which increases the bias in results.

Pilz et al. performed another study with the aim to provide an overview of the pathophysiological mechanisms and the epidemiological data concerning vitamin D deficiency and myocardial diseases [16]. Several case reports highlight pediatric cardiomyopathies, which are associated with vitamin D deficiency or rickets [17,18]. More importantly, children with vitamin D deficiency associated heart failure showed in most cases a significant clinical improvement after vitamin D and calcium supplementation [11]. A post mortem examination of a child, who died due to vitamin D deficiency associated cardiomyopathy showed a large pericardial effusion and an enlarged heart with a dilated and concentric hypertrophic left ventricle. There was a mild increase in interstitial fibrous tissue, particularly in the subendocardial regions and the cardiomyocytes were thin and elongated in keeping with dilated cardiomyopathy [14].

Zittermann et al. found significantly reduced 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D levels in 54 heart failure patients when compared with 34 age, sex, and BMI-matched controls [18]. In a study among 102 African Americans, vitamin D deficiency was observed in 84-96% of heart failure patients, whereas only one-third of the healthy controls were vitamin D deficient [14]. Two more studies among African Americans also showed a high prevalence of vitamin D deficiency in patients with heart failure. Interestingly, not all heart failure patients with vitamin D deficiency show elevations in PTH levels, but those with secondary hyperparathyroidism have more severe forms of heart failure [10].

In the National Health and Nutrition Examination Survey (NHANES), a population-based study in the US including 8351 persons, 25-hydroxy vitamin D levels were significantly reduced in patients with self-reported heart failure with the highest prevalence of vitamin D deficiency in patients suffering from both, coronary heart disease and heart failure. In this study, low 25-hydroxy vitamin D levels were associated with more severe congestive heart failure and with impaired exercise capacity. In a cohort of over 3,000 patients referred for coronary angiography, 25-hydroxy vitamin D as well as 1,25-hydroxy vitamin D were inversely correlated with left ventricular dysfunction [16].

Results from a study among 150 patients with congestive heart failure and 150 age, sex, and race-matched controls showed that life-style factors associated with low 25-hydroxy vitamin D levels in earlier life (childhood, adolescence, and adulthood) including residence in large towns, low physical activity, and low frequency of summer holidays were significantly more common in heart failure patients than in controls [14].

A prospective study in which 3299 patients referred for coronary angiography found that low 25-hydroxy vitamin D as well as 1,25-hydroxy vitamin D levels were prospectively and independent of cardiovascular risk factors associated with an increased risk of death due to heart failure and of sudden cardiac death [19,20]. Furthermore, low 1,25-dihydroxy vitamin D concentrations were associated with

increased mortality in 510 patients from a specialized heart center and were an independent predictor of death and the need for cardiac transplantation in 383 end-stage congestive heart failure patients [14].

Bone disorders

There is growing evidence for the critical role of vitamin D in the prevention of serious chronic diseases beyond osteoporosis, osteomalacia, and rickets [21]. A huge national survey conducted by Teotia and Teotia and a case control study from villages in the Indian state of Bihar showed increased bone deformities. Although dietary calcium was low, serum calcium was within normal range, suggesting that calcium homeostasis was maintained, but it does not preclude the possibility that poor vitamin D status may also be a contributing factor to the observed bone deformities [22].

Teotia and Teotia described the widespread vitamin D deficiency associated bone disorders that are observed in the Indian population. This large population survey conducted between 1963 and 2005, involved 338 million people residing in 390,000 villages in 22 of the 28 states of India. The findings show that greater than 400,000 survey participants experienced bone disorders. Among these were 75,600 cases of vitamin-D-deficiency-related osteomalacia and 16,300 cases of frank rickets [22,23].

The extent of vitamin D deficiency's contribution in the development of osteoporosis is unclear [24]. Hypovitaminosis D could be associated with osteoporosis because a fall in circulating 25-hydroxy vitamin D levels into the 25-50 nM range induces secondary hyperparathyroidism that consequently increases osteoclastic bone resorption [25].

Colorectal cancer and other malignancies

According to the National Cancer Institute breast and prostate cancer cohort consortium (2009), vitamin D is hypothesized to reduce the risk of breast cancer by inhibiting cell proliferation via the nuclear Vitamin D Receptor (VDR). Nucleotide polymorphisms (SNP) in the VDR gene have been inconsistently associated with breast cancer risks. The VDR gene polymorphisms are also suspected in type 2 diabetes mellitus [26]. Garland and Garland postulated that vitamin D as a protective factor against colon cancer development [27].

A recent systematic review found that the relationship between 25-hydroxy vitamin D and cancer mortality was mixed. However, cancer patients with higher 25-hydroxy vitamin D tended to have lower risk of mortality, especially patients with colorectal cancer. There was no significant association between vitamin D supplementation and breast cancer incidence in a randomized, controlled trial [28]. The relatively small size of the study limited authors ability to detect statistically significant trends of vitamin D deficiency with respect to histopathological characteristics of the breast cancer. The authors apprehend that the results of mammography may not always be reliable. Not all breast cancers will be detected by a mammogram, and some breast cancers that are screen-detected still have a poor prognosis. Sometimes, mammography results in false-positive results as well as over diagnosis and overtreatment of some breast cancers. In spite of these limitations, numerous studies have shown that early detection with mammography saves lives and increases treatment options.

Human colon adenocarcinoma cells express CYP27B1 and are thus able to convert 25-hydroxy vitamin D into 1,25-dihydroxy vitamin D, which is a potent antimetabolic factor for human colon carcinoma cells. In fact, there are several reports that a compromised vitamin D status is associated with an increased risk for colorectal cancer [29]. There is

evidence from both observational studies and clinical trials that calcium malnutrition and hypovitaminosis D are predisposing conditions for various common chronic diseases.

Considering the importance of extra renal CYP27B1-mediated production of 1,25-dihydroxy vitamin D for control of cell proliferation, e.g. in breast, ovary, uterus, prostate and pancreas, vitamin D insufficiency can increase the risk of malignancies other than colorectal cancer [30]. Studies on cancer mortality rates in the US and Europe found a highly significant association with the incidence of breast, esophagus, stomach, pancreas, bladder, ovary, uterus, prostate and non-melanoma skin cancer as well as non-Hodgkin lymphoma [31].

Infectious, inflammatory and autoimmune diseases

1,25-hydroxy vitamin D has also been identified as a potent modulator of macrophage functions as well as of B- and T-lymphocyte mediated immune responses. Of paramount importance for the activating effect of 1,25-hydroxy vitamin D on various monocyte/macrophage functions is the fact that macrophages not only express the VDR, but are also endowed with CYP27B1 activity [32]. Therefore, under conditions of low serum 25-hydroxy vitamin D levels, only limited 1,25-hydroxy vitamin D can be produced by macrophages from the precursor. The ensuing impairment of macrophage activation and function explains the well-known fact that the prevalence of infectious diseases is high in children with rickets [33]. This assumption is consistent with findings from epidemiological studies that a compromised vitamin D status in humans increases the risk for cytokine-mediated autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis as well as type I diabetes mellitus [34].

Inflammatory bowel disease

Although Crohn's disease and Ulcerative Colitis (UC) are two clinically distinct forms of Inflammatory Bowel Disease (IBD); they have some basic pathogenetic features in common such as an aberrant local immune reaction i.e., an excessive Th/Tc1 response to luminal, mainly bacterial antigens in genetically predisposed individuals. In addition, evidence is accumulating that links a number of environmental factors to the pathogenesis of IBD, particularly of UC [35]. Vitamin D deficiency might be one of those factors. Due to hypovitaminosis D, local production of 1,25-(OH)₂D₃ by mucosal epithelial cells as well as by macrophages within inflammatory lesions falls below a level that is critical for suppression of enhanced Th-1-cell responses, which are typically associated with chronic enterocolitis [34].

Multiple sclerosis

Multiple sclerosis is an autoimmune disease in which overreaction of the Th-1 lymphocyte system to an as yet unidentified antigenic stimulus leads to an immune attack on the central nervous system. An association between hypovitaminosis D owing to low sunlight exposure and incidence of multiple sclerosis was first recognized by Goldberg 30 years ago [36]. Since then, this notion has been supported by data from additional epidemiological as well as experimental animal studies.

Rheumatoid arthritis

There is substantial evidence from studies with animal models of rheumatoid arthritis that the beneficial effect of vitamin D on the development of the disease results from its specific immunomodulatory effects [37]. Hypovitaminosis D is involved in the pathogenesis of rheumatoid arthritis recently gained support from an 11-year prospective study of a cohort of nearly 30,000 women aged 55 years and

older, which revealed an inverse association between vitamin D intake and rheumatoid arthritis [38]. In this respect, it is important to note that CYP27B1 activity is present in synovial tissue, so that in cases of low serum 25-hydroxy vitamin D local production of 1,25-dihydroxy vitamin D is too low to sufficiently suppress the activity of Th-1 cytokines, particularly that of TNF- α , which plays a central role in the development of chronic inflammatory symptoms and bone destruction.

Type I diabetes mellitus

Recently, the results of a large birth-cohort study highlighted the importance of vitamin D supplementation for the prevention of diabetes mellitus type I in children. There is substantial evidence from studies with non-obese diabetic mice that vitamin D deficiency in early life accelerates the appearance of the symptoms of autoimmune diabetes mellitus and that conversely 1,25-dihydroxy vitamin D can prevent the development of the disease. Recently, Hyppönen et al. reported the results of a large birth-cohort study highlighting the importance of vitamin D supplementation for the prevention of diabetes mellitus type I in children [37]. Their data clearly showed that regular vitamin D intake compared with no supplementation during the first year of life was associated with an 88% risk reduction of type I diabetes mellitus in later life [39]. There is substantial evidence from studies with non-obese diabetic mice that vitamin D deficiency in early life accelerates the appearance of the symptoms of autoimmune diabetes mellitus and that conversely 1,25-hydroxy vitamin D can prevent the development of the disease [7,40]. Even children who received vitamin D irregularly had an 84% lower risk than those with no supplementation. It has been known for a long time that 1,25-hydroxy vitamin D is a positive regulator of insulin secretion by pancreatic β cells. These cells are endowed with CYP27B1 activity and thus low 25-hydroxy vitamin D levels are associated with impaired β -cell function [7].

Conclusion

In summary, there is a strong evidence for association between heart diseases, bone disorders, colorectal cancers and other malignancies, infectious, inflammatory and autoimmune diseases, inflammatory bowel diseases, multiple sclerosis, rheumatoid arthritis, diabetes mellitus type-I and vitamin D. The authors are of the strong opinion that collation of epidemiological data shall help to consolidate the role of vitamin D in various illnesses.

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