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Should everyone be taking vitamin D?: Narrative review on vitamin D in health and diseases

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Abstract
Insufficiency of vitamin D affects about 50 per cent of the world's population. An estimated 1 billion people worldwide have a vitamin D deficiency from all ethnicities and age groups. This disease outbreak of hypovitaminosis D can mainly be due to lifestyle (e.g. decreased physical activity) and environmental (e.g. air pollution) factors that reduce access to sunlight needed for the production of ultraviolet-B (UVB)-induced vitamin D in the skin. New research indicates we may need more vitamin D to avoid chronic disease than is currently recommended. As the number of people with VDD keeps increasing, the importance of this hormone is at the forefront of research in overall health and the prevention of chronic illness. In this review, we will outline the processes presumed to underlie the vitamin D relationship and acknowledge its biological and clinical implications.

Keywords: Research, ethics, knowledge, attitude, postgraduates, dental

Introduction
Vitamins are essential nutrients that are required for various biochemical and physiological processes in the body. It is well known that most of the vitamins cannot be synthesized in the body and hence their supplementation in diet is essential. Vitamins are classified on the basis of their solubility as water soluble (C and B complexes) and fat soluble vitamins (A, D, E, K). Vitamin D is a fat soluble secosteroid (steroid with broken rings) which was first discovered in 1919–1924 as an antirachitic agent [1]. It enters in the circulation of human body through diet or synthesized in skin from 7-dehydrocholestrol, by the means of ultraviolet (UV) light of the sun [2, 3]. Vitamin D helps in maintaining the homeostasis of all the diverse biological systems including the neuromuscular, skeletal, cutaneous, cardiovascular, and immune systems (Fig.1).Vitamin D also has tumour suppressing, anti-inflammatory and antibacterial properties.

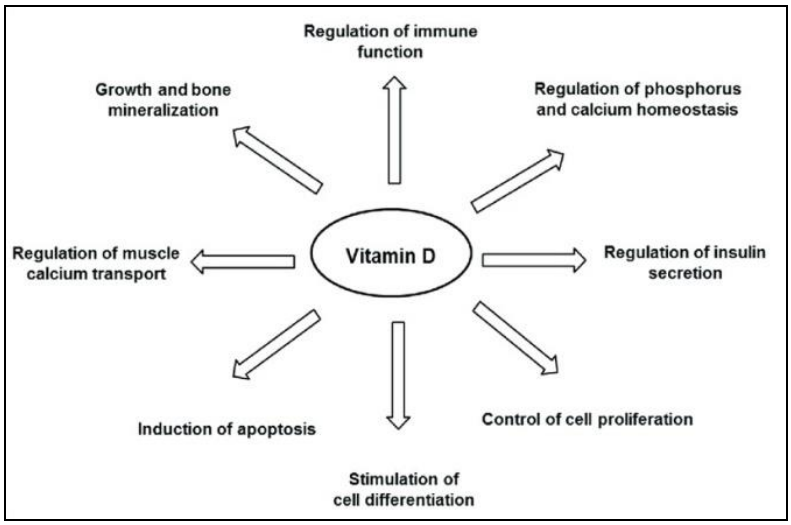


Fig 1: Functions of Vit D.

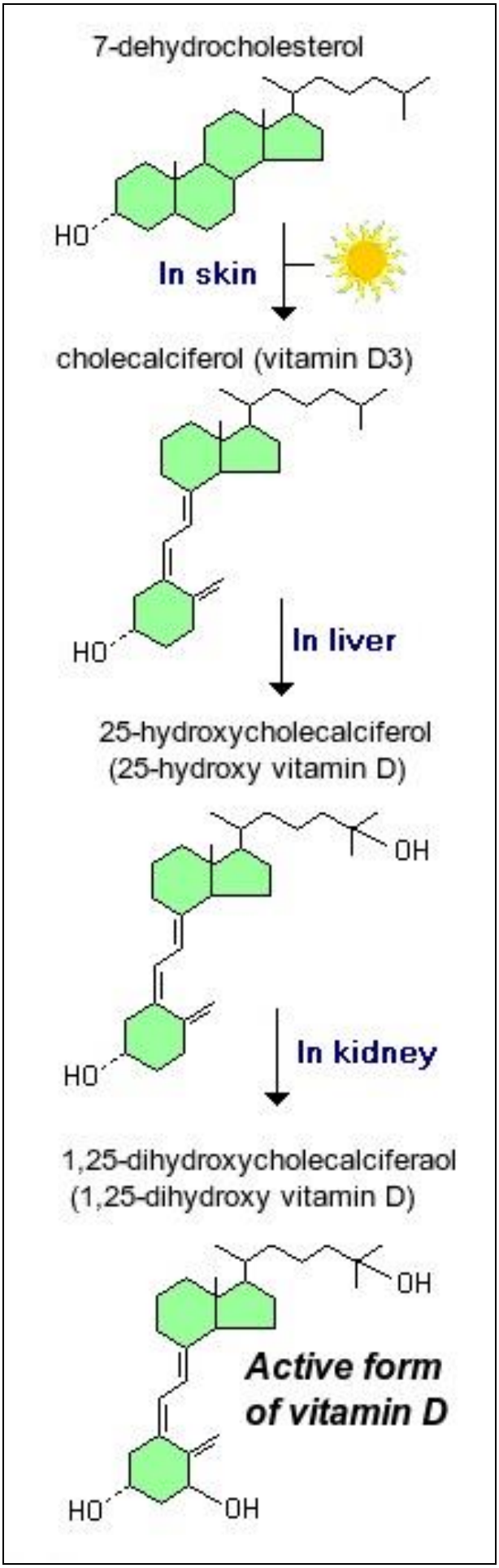


Fig 2: Active Form of Vit D

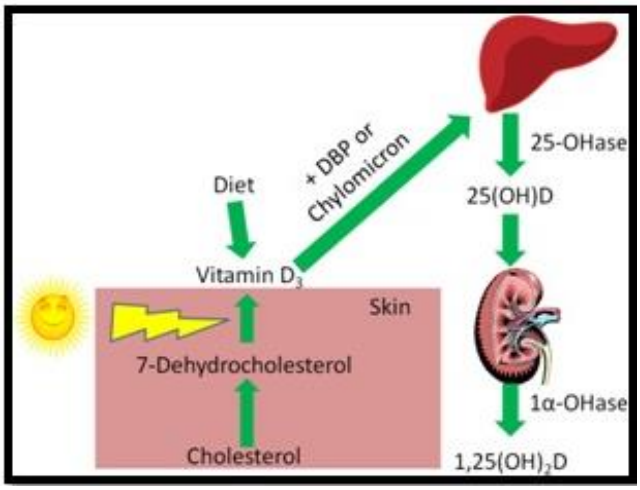


Fig 3: Metabolism of Vit D.

Physiology and Metabolism

Vitamin D (calciferol) exists in two forms: Vit D2 (Ergocalciferol) and Vit D3 (Cholecalciferol) [4]. Both of these forms are biologically inactive. They are first hydroxylated into 25(OH) D in the liver, then 25(OH) D undergoes hydroxylation again in the kidney into the biologically active 1, 25(OH)$_2$D (Fig2,3). This biologically active form plays an important role in bone and muscle health .Formation of vitamin D is under the influence of various hormones i.e. parathormone and calcium (Fig.4) [5].

Vitamin D is considered as a hormone because it is secreted by kidney and it circulates in the body to perform its functions.

The biologically active molecule binds to vitamin D nuclear receptors (VDR) to perform its actions (FIG. 5). VDRs are present in cells of immune system, bone, kidney and cells of intestine which are ultimately involved in calcium, phosphate and bone metabolism. A bound vitamin D molecule then joins with retinoic acid X receptor (RXR) and forms a heterodimer – VDR/RXR. This heterodimer serves as a nuclear transcription factor which regulates gene expression (which influence calcium and phosphorus metabolism) [4].

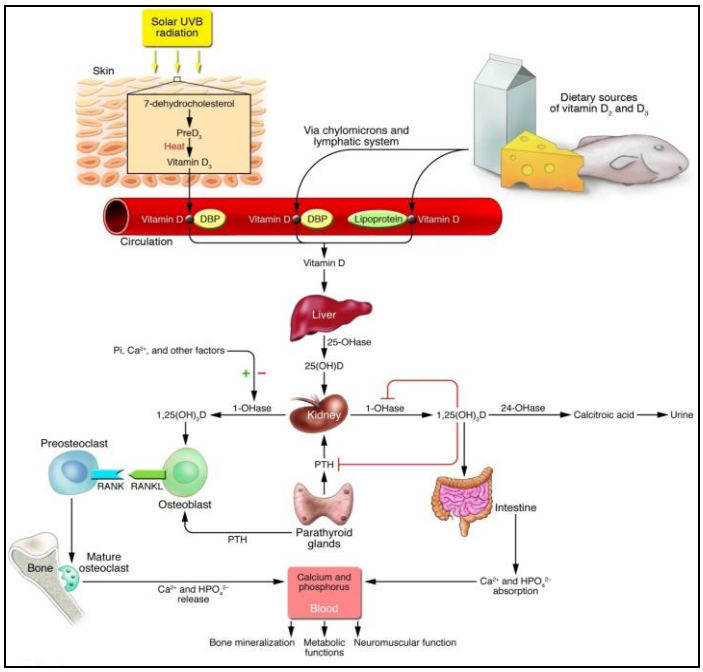
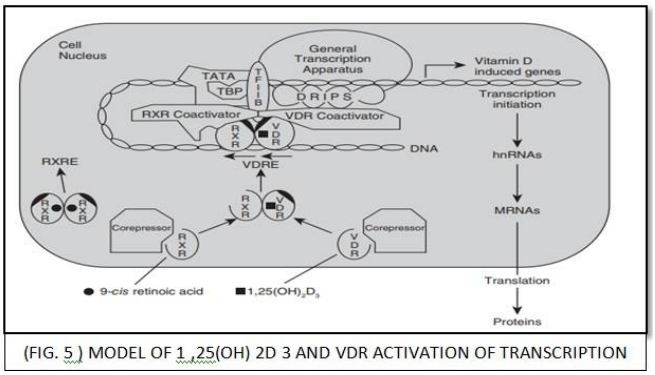


Fig 4: Formation of Vit D

Vitamin D and Bone Metabolism



(FIG. 5) MODEL OF 1 ,25(OH) 2D 3 AND VDR ACTIVATION OF TRANSCRIPTION

Fig 5: VDR Activation.

VITAMIN D plays an important role in maintaining the skeletal integrity by regulating calcium and bone metabolism. It has osteoprotective role, thus reduces the alveolar bone resorption. Along with vitamin D, several other molecules also control bone remodeling i.e. RANK (receptor activated nuclear kappa-B), OPG (osteoprotegrin), RANKL (nuclear factor-kappa beta ligand). RANKL and OPG (RANKL antagonist) are produced by osteoblasts and RANK is expressed on the surface of osteoclast progenitor cells. RANKL to RANK binding leads to differentiation of osteoclast progenitor cells into mature osteoclasts. OPG is a decoy receptor of RANKL and antagonizes RANK-RANKL interaction. RANKL gene promoter region is found to have VDRE (Vitamin D response elements) (Fig. 5). It has been found that vit D –VDR interaction stimulates RANKL expression in bone marrow derived stromal cells and osteoblasts [6]. Vit D also decreases the levels of OPG. Thus, vitamin D helps in up regulation of RANKL along with down regulation of OPG; ultimately favoring osteoclastic activity and bone resorption [7]According to KITAZAW *et al.* the catabolic effect of vitamin D is transient because level of OPG increased on continuous intake of vitamin D. [7] Vitamin D stimulates osteopontin and alkaline phosphatase; increasing the osteoblastic activity. Therefore Vitamin D has a significant effect on bone remodeling.

Vitamin D in Periodontal Health, Disease and Treatment

A significant association is seen between periodontal health and intake of vitamin D (FIG. 6). Evidence gathered from studies indicates that vitamin D supplementation improve periodontal health, periodontal stability, bone mineral density and inhibit alveolar bone resorption [8, 9]. Based on the US National Health and Nutrition Examination Survey[10-11], Dietrich *et al*. reported that Vitamin D concentrations were inversely and significantly associated with clinical attachment loss in participants ≥50 years. The observed correlation between vitamin D levels and attachment loss was independent on bone mineral density. They compared the level of gingival inflammation in relation to plasma concentration of vitamin D. He reported that subjects with higher concentrations of Vitamin D were 20% less likely to show bleeding on probing than people who had lower levels of Vitamin D.

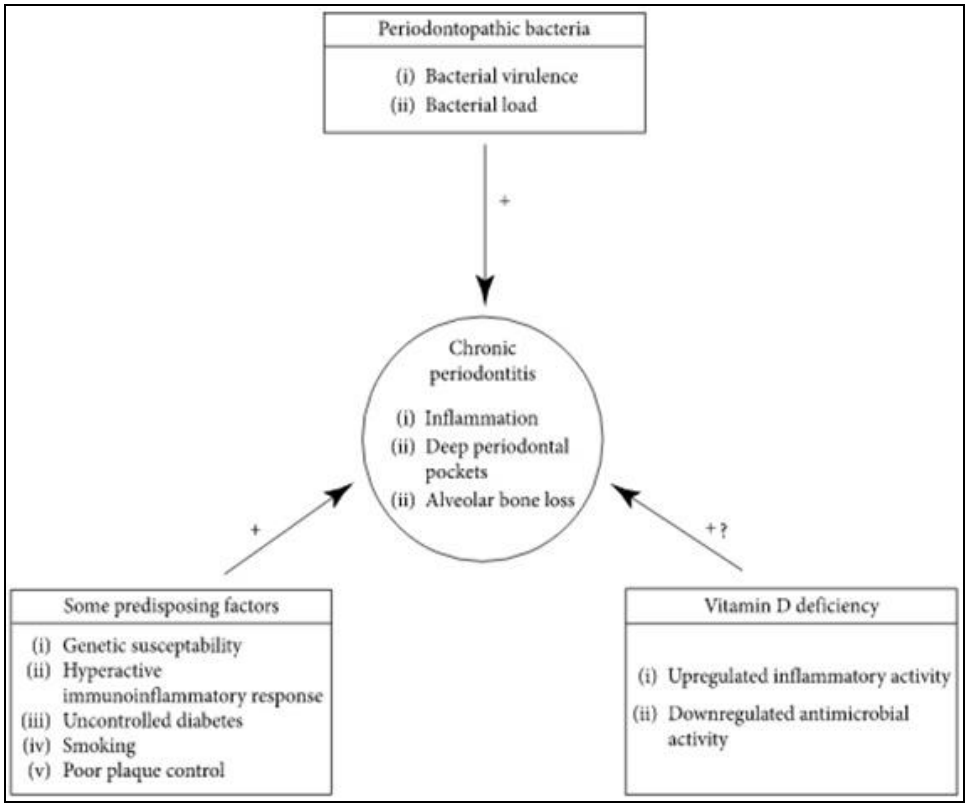


Fig 6: Association between Periodontal Health and Vitamin D

According to *Garcia et al.* [12] Calcium and vitamin D supplementation at higher doses (>800-1000 IU daily) diminished the severity of periodontal disease. He reported that vitamin D also has anti inflammatory action as it represses the cytokine expression and leads to secretion of molecules which have strong antibiotic effects from macrophages / monocytes. Vitamin D deficiency has also been found to be associated with increased risk of infectious diseases. This suggests that vitamin D may be used in treatment of periodontitis as it has direct effect on bone

metabolism along with antibacterial action on periodontopathogens and also inhibits proinflammatory mediators.

Krall EA *et al.* [13] in 2001 studied the effects of vitamin D supplementation on tooth loss and reported that vitamin D supplementation for 3 years daily reduced tooth loss by 60%. But the drawback of the study was that calcium supplementation was given along with vitamin D; therefore the effects of vitamin D alone could not be studied.

Bashutski JD *et al* [14] studied the impact of vitamin D status on periodontal surgery outcomes. He reported that patients who had less vitamin D levels and who underwent flap surgery had less probing depth reduction and attachment gain compared to the patients with adequate vitamin D levels.

Vitamin D Receptor Polymorphism and Periodontal Disease

Various studies have reported that vitamin D expresses its activities by activation of VDR [15]. VDR gene polymorphism is found to affect alveolar bone remodeling and host response to periopathogenic bacteria. Gene polymorphism is usually detected by restriction enzyme digestion and polymerase chain reaction. [16] Many VDR polymorphisms have been found to be associated with periodontal disease. Further studies needs to be conducted to understand functional relevance of VDR polymorphism**.**

Immunomodulatory Role of Vitamin D

Oral epithelium separates a microorganism ridden environment from underlying connective tissue. Epithelium acts as a barrier protecting the deeper tissue from microorganisms, their associated antigens, toxins and from minor mechanical damage. [17] VDR is expressed by keratinocytes of basal and spinous layerous of epithelium. Vit D/VDR signaling influences proliferation, differentiation and apoptosis of keratinocytes along with local immune responses[18]. This signaling mediates antiproliferative and pro differentiation effects. Moreover, MARTIN HEWISON stated the major effect of Vitamin D is its ability to act as a potent modulator of human immune responses on. He made the following observations:

- Numerous cells from both innate and adative immune system communicates the VDR.
- Also, antigen presenting cells i.e. macrophages and dendritic cells also express alpha 1 hydroxylase enzyme which converts biologically inactive molecule of vitamin D to biologically active form that can incite reactions in the cells by binding to their VDRs and advancing transcriptional guidelines. [19] Vitamin D inhibits innate immune system by inhibiting antigen presentation and innate antibacterial activity.

In innate immune response, Toll Like Receptors sense pathogen associated molecular patterns followed by increased synthesis of 1,25(OH)2D3 in macrophages ultimately leading to the generation of antibacterial substances such as cathelicidin and beta-defensins. Wang *et al.*[20], reported that the expression of cathelicidins and defensins is dependent on plasma concentration of Vitamin D. Vitamin D can promote expression of cathelicidins in diverse cell types such as macrophages, keratinocytes, neutrophils, and T lymphocytes [21].

Deficiency of Vitamin D may weaken innate immune reactions and make individuals prone to infections and low serum centralization of 25(OH) D3 have been connected to irresistible maladies such as tuberculosis.

Vitamin D also influences the adaptive immune response. The activation of CD4 + T-cells increases the VDR expression to five folds, enabling calcitriol to regulate at least 102 identified genes [22]. This regulatory effect decreases the levels of chemokines and cytokines. Vitamin D has a strong suppressive effects on IL-2 and IFNγ in a VDR-regulated mechanism. T helper cells(Th1) release (IFNγ), IL-2, IL-12, and tumor necrosis factor alpha Th2 cells express IL-4, IL-5, and IL-13, which further propagate the Th2 response. These Th2-derived cytokines modulate the immune response. The suppression of IL-2 production, in turn, inhibits T-cell proliferation. In general, vitamin D diminishes cell mediated immune response of body. This suppression is enhanced by action of Vitamin D on antigen presenting cells where vitamin D inhibits the production of IL-12 (which enhance Th1 response). Vitamin D acts as a physiological brake on adaptive immunity.

Role of Vitamin D in Cardiovascular System

The cardiovascular system has recently been recognized as potential target of Vitamin D action. It has been discovered that Activated VDR plays a crucial role in regulation of cardiovascular activities [23]. VDR and Vitamin D have been discovered in cardiac mycocytes, cardiac fibroblasts, vascular muscles and endothelial cells. Deficiency of vitamin D in rodents have been identified to cause increased blood pressure and cardiac hypertrophy. It has been recognized that the presence of 1,25(OH)2D3 and its analogs can reverse agonist –induced mytocyte hypertrophy. Decreased levels of 25 (OH)D3 can be connected to numerous cardiovascular disorders such as congestive heart failure, coronary artery disease etc. Examination of a mouse with complete deletion of the VDR gene demonstrated both cardiac hypertrophy and hyperreninemic hypertension [24].

To understand the role of VDR inmycocardium, Gardener And Colleagues ran several tests on the rats by selectively eliminating the fourth exon of the murine VDR gene in cardiac myocytes of a mouse and observes increase in the size of myocyte. Experiments of Gardener and group showed that if we give isoproterenol treatment to neonatal cardiac myocytes of a rat in vitro it will result in myocyte hypertrophy and increased MCIP1 expression. A reduction in MCIP1 expression can be observed by coadministration of 1,25(OH)2 D3 [25]

Gardener and group also stated that Endothelial dysfunction can be connected to the deficiency of VDR.

Vitamin D during Pregnancy and Lactation

During Pregnancy, the production of 1,25(OH)2D3 is 2.5 times above that at nonpregnant levels. Vitamin D effects stretch out calcium metabolism and homeostasis as preprohormone are experienced in their most vivid stage. During Pregnancy, the metabolism of vitamin D is way too different from its usual metabolism. *Carol l. Wagner* shared her two recent studies which indicated that the concentration of vitamin D required to optimize the production of 1,25(OH)D3 is 4000 IU/day. Prenatally this amount is 400IU which is inadequate as the optimization can be achieved only when the total circulating Vitamin D level is at least 40 ng/ml. [26] Moreover ,When two groups were given different concentration levels it was observed that the group taking 4000IU/day attained optimal 1,25(OH)2D3 concentration throughout pregnancy than the other taking lower. Both studies have proven that 4000IU/day Vitamin D isnotonly

adequate but it also results in lesser adverse effects (comorbidities) of pregnancy as compared to the lower dose groups.

Vitamin D and Obesity

Igor N. sergeev (South Dakota state University) discussed Vitamin D supplements as strategies to treat obesity. He introduced the use of apoptosis to induce the adipocyte death as one of the strategies. He stated that Hypertrophy and Hyperplasia are the causes of Increased mass of adipose tissue. Once maximum size is obtained by these adipocytes, the number of adipocytes increase with any increase in the adipose tissue mass. This provides a way to prevent excessive accumulation of adipose tissue as any decrease in the number of adipocytes will cause weight loss and even a small increase in the amount of adipose apoptosis will be enough to loose adipose tissue mass also. Various studies have suggested Vitamin D induced cellular calcium signal is an apoptotic initiator. [27, 28] It has been found that Vitamin D and calcium intake decreases diet induced obesity. This might be due to activation of calcium mediated apototic pathways in adipocytes.

Thus vitamin D supplementation is plausible and reasonable methodology in prevention and treatment of obesity.

Vitamin D and Diabetes

The role of Vitamin D has been redefined by Anastassios G. Pittas (Tufts Medical Center) as helpful in numerous non skeletal medical conditions such as Diabetes Type 2. He evaluated the first Bradford Hill rules, which have been adjusted to incorporate three general classes that are Mechanistic studies, Direct Evidence and Parallel Evidence. [29] The theory that Vitamin D might be a determinant of diabetesis conceivable , as both impaired insulin secretion and action have been associated with Vitamin D insufficiency. Role of Vitamin D may be direct or indirect in diabetes. Direct action is due to the expression of VDR and local production of Vitamin D in pancreatic beta cells. And the indirect role is due to the role of vitamin D in Calcium metabolism and calcium influx through plasma membranes.

Numerous cross sectional studies have proven that there exists an inverse relationship between Vitamin D status and hyperglycemia. [30] *Song et al*. found that the risk of diabetes was 38% less in individual with higher concentrations of Vitamin D. Dose response analysis showed that for every 4ng/ml increment of 25(OH)D3, risk of diabetes ws decreases by 4%.

Although, Pittas said that observational studies should not be used to make inferences as confounding factors are always present. Interventional studies are must for drawing any conclusions. He concluded that observational studies are strongly suggesting vitamin D as a risk factor for type2 diabetes but there is paucity of interventional studies to support relevance of Vitamin D in treatment of Type 2 diabetes.

Thus, unproven hypothesis that vitamin D is direct contributor in pathogenesis of type 2 diabetes needs specially designed studies to confirm it.

Vitamin D Deficiency

Because of limited dietary sources of vitamin D and deficient uptake of food, the main source of vitamin D is sunlight. The amount of sunlight received by a person depends on various elements i.e. time, weather, pigmentation etc. Regardless of standard presentation to sunlight, older individuals produce 75% less cutaneous D3 than younger age group. Thus vitamin D deficiency is a more typical issue nowadays than beforehand thought. As per different investigations, it has been estimated that worldwide approximately 1 billion population endure vitamin D deficiency [31].

$T_{1/2}$ of 1, $25(OH)_2D$ is anly 4 hours, however, $t_{1/2}$ of 25(OH)D is long i.e. about 3 weeks. Therefore for assessing vitamin D levels in body, levels of 25(oh)D is assessed. Normally vitamin D levels fluctuate between 25 to 138nmol/L. however, there is no clear agreement on the ideal levels of 25(OH)D. according to European society clinical practice guidelines vitamin D deficiency is defined as plasma 25(OH)D level <50nmol/L.[32] Values less than 37.5 nmol/L shows vitamin D deficiency and concentrations higher than 200 nmol/L show hypervitaminosis.

Management

U.S. government's present proposal for oral nutrient D is 200 IU day by day for person's age ≤50 years, 400 IU day by day for people between age 50 years and 70 years, and 600 IU for those more age than 70 years. Generally, for every 100IU vitamin D ingested increase the level of 25(OH)D by 1ng/ml. D2 and D3 forms of Vitamin D are available as dietary supplements containing 300–400 IU/capsule. The treatment of Vitamin D-inadequate people should begin by 50,000 IU of Vitamin D for 8–12 weeks. Once the initial repletion phase is complete, maintenance therapy can be continued in 1 of 3 ways: (1) 50,000 IU vitamin D2 or D3 every 2 weeks; (2) 1,000-2,000 IU vitamin D3 daily; and (3) sunlight exposure for 5-10 min for Caucasians (longer times required for people with increased skin pigmentation) between the hours of 10 AM to 3 PM (spring, summer, and fall) [33].

Conclusion

Beside the role of vitamin d in prevention of rickets and osteomalacia, vitamin d also influences the periodontal status of individuals. This function of Vitamin D is because of anti inflammatory and immune modulatory role. Different studies have concluded that its deficiency associated with gene polymorphism triggers periodontitis. Along these lines, Vitamin D supplementation may cause decline in the bone destruction and inflammation, decreasing the rate of tooth loss. Although, further clinical trials need to be conducted to understand the overall role of Vitamin D and extra skeletal health.

Conflict of interest: The authors have declared that no competing interests exist.

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