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NEED OF VITAMIN D BEYOND BONE: A CONSISE REVIEW.

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Abstract

Vitamin D is also known as calciferol because of its role in calcium metabolism and antirachitic factor because it prevents rickets. It is a modified steroid, synthesised in the skin under the influence of sunlight and is necessary for metabolism of calcium and phosphorus. Its RDA is 400 IU or 10 mg, it binds to the receptor of target cells and regulate through gene expression. Vitamin D undergoes hydroxylation in the liver to form 25 hydroxy vitamin D [25(OH) vitamin D]. The two main forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The main source of vitamin D in humans is in the form of vitamin D3, which is derived from synthesis in the skin via exposure of 7-dehydrocholesterol, concentrated in the stratum basale and stratum spinosum, to ultraviolet B (UV-B) radiation. Vitamin D2 is obtained from the diet, and is derived from ultraviolet irradiation of ergosterol, found in fungi. Both metabolites are transported in the blood bound to vitamin D binding protein (DBP). These inactive vitamin D metabolites must undergo a two-step hydroxylation process to become biologically active. Initially, vitamin D2 and D3 undergo hydroxylation in the maternal liver, via the action of vitamin D 25-hydroxylase enzyme (CYP27A1), to form the inactive steroid precursor 25-hydroxy-vitamin D (25[OH]D). 25[OH]D is the major circulating and stored form of vitamin D. In this present review we have focused on need of vitamin D beyond bone.

Keywords

Vitamin D, Vitiligo, Cognitive function, Cancer, Mental health, Obesity

Introduction

Nearly 30 percent to 50 percent of people are estimated to have deficiency of vitamin D, and insufficiency and vitamin D deficiency are recognized as global health issues in the world.[1] Vitamin D is produced endogenously through exposure of skin to sunlight and it is absorbed from foods containing or supplemented with Vitamin D.[2,3] Its RDA is 400 IU or 10 mg, it binds to the receptor of target cells and regulate through gene expression.[4] Pro-vitamin D3 or 7-dehydrocholestrol, which is primarily found in the basal and spinous cell layers of the epidermis, undergoes a photochemical reaction to form pre-vitamin D3. The UV light blocking function of melanin leads to a requirement of greater UV light exposure in order to produce equivalent amounts of Vitamin D3 in dark skinned populations. In addition to its action on the kidneys, calcitriol bound to vitamin D binding protein acts by both genomic and non-genomic mechanisms on certain other target tissues like bone, intestine, and parathyroid gland that express the vitamin D receptors.[5] Vitamin D is metabolized to its biologically active form, 1,25-dihydroxyvitamin D, a hormone that regulates calcium and phosphate metabolism. Deficiency of vitamin D results in impaired bone formation and produces rickets in children and osteomalacia in adults. [2] Poor diet, lack of sun exposure, decreased synthesis of Vitamin D and decreased renal hydroxylation of 25(OH) D due to old age are the main cause of Vitamin D deficiency.[6]

Table 1: Vitamin D and its Metabolites in Plasma[2]

Vitamin D and its Metabolites in Plasma[1]			
Compound	Concentration	Free,%	Half-life
Vitamin D	<0.2-20ng/mL	-	1-2 days
	<0.5-52nmol/L		
25-Hydroxyvitamin D	10-65ng/mL	0.03	2-3 weeks
	25-162pg/mL		
1,25-Dihydroxyvitamin D	15-60pg/mL	0.4	4-6 hours
	36-144pmol/L		

Table 2: Abnormal Circulating Concentration of 25(OH)D[2]

Decreased 25(OH)D
• Inadequate exposure to sunlight
• Inadequate dietary Vitamin D
• Vitamin D Malabsorption
• Severe hepatocellular disease
• Increased catabolism (e.g. drugs such as anticonvulsants)
• Increased loss (Nephrotic syndrome)
Increased 25(OH)D(Hypercalcemia)
• Vitamin D or 25(OH)D intoxication

Table 3:Abnormal Circulating Concentration of $1,25(OH)_2D$[2]

Decreased $1,25(OH)_2D$
• Hypercalcemia of malignancy

• Vitamin D –dependent rickets, type I
• Pseudohypoparathyroidism
• Hypoparathyroidism
• Hypomagnesemia
• Renal failure
• Hyperphosphatemia
Increased $1,25(OH)_2D$
• Vitamin D –dependent rickets, type II
• $1,25(OH)_2D$ intoxication
• Lymphoma
• Primary hyperparathyroidism
• Granulomatous disease

Role of Vitamin D beyond bone:

Vitamin D and vitiligo

In the pathogenesis of vitiligo, autoimmunity plays an important part, which is also evident by the coexistence of different autoimmune disorders with vitiligo.[7] In turn, vitamin D levels have been found to be decreased in various autoimmune disorders,[8] suggesting a possible connexion between vitiligo and vitamin D levels. The exact process by which autoimmunity induces vitamin D, however, remains an enigma. Some studies have examined the relationship between the levels of vitiligo and 25(OH)D. Prasad et al. documented first the use of vitamin D analog in conjunction with PUVA sol in the therapy of vitiligo.[9] Then topical vitamin D analog was successfully used in both monotherapy and other modalities such as corticosteroids and UV therapy. Vitiligo has been treated effectively. Studies have shown that melanocytes and immune systems are the targets of this therapeutic intervention. Through its anti-apoptotic effect, vitamin D regulates the activation, proliferation and migration of melanocytes by increasing melanogenesis and the content of tyrosinase in cultured human melanocytes.[10] By modulating T-cell activation, vitamin D also reduces the autoimmune harm of melanocytes.[11] A pilot study was performed to test the effectiveness and safety of extended treatment with high-dose vitamin D3 in patients with psoriasis and vitiligo. This study was focused on the fact that autoimmunity and vitamin D deficiency are related, and the frequent existence of gene polymorphisms is correlated with vitamin D metabolism in affected patients. Therefore, the administration of high doses of vitamin D3 to patients with autoimmune disorders will offset genetic susceptibility to its biological impact. In combination with a low calcium diet and hydration, Finamor et al. treated 16 patients with vitiligo with 35,000 IU of vitamin D3 once daily for 6 months. Fourteen of the 16 patients had 25-75% repigmentation without any substantial improvement in metabolic parameters, suggesting that for vitiligo patients, high-dose vitamin D3 therapy could be successful and safe.[12]

Vitamin D and chronic kidney disease

Vitamin D plays a non-classical role in chronic kidney disease through the regulation of the renin-angiotensin system and the nuclear factor (NF) kB pathway, both of which are involved

in a wide variety of pathological processes. As the kidney is a major organ for the action of vitamin D (both classical and non-classical) and plays an important role in morbidity and mortality in CKD patients. In CKD patients Vitamin D regulates the Renin-Angiotensin system (RAS) leading to angiotensin II activation in CKD patients who have deleterious effects on vasculature and blood pressure and contribute to renal parenchymal injury. Vitamin D deficiency appears to be a strong activator of the RAS intra-renal portion. NF-kB pathway is regulated by the non-classical autocrine role of vitamin D, NF-kB is the transcription factor group involved in the immune response as well as inflammation and fibrosis and underscores the pathogenesis of CKD and results in tissue injury. In CKD ability to produce renal hydroxylated 1,25 Vitamin D gets diminishes and 1,25 Vitamin D Deficiency ensures. As vitamin D does not occur naturally, ample exposure to the sun and supplementation are now widely essential to resolve the deep deficits.[13]

Vitamin D and CVD

The vitamin D receptor is found in cells in the vascular system. Many types of cells, including vascular smooth muscle cells, endothelial cells, and cardiomyocytes, produce 1 alpha-hydroxylase, a natural vitamin D receptor ligand that transforms 25-hydroxyvitamin D into calcitriol. It has been shown that calcitriol prevents the proliferation of vascular smooth muscle cells, controls the renin-angiotensin system, reduces coagulation, and has anti-inflammatory properties.[14]

Vitamin D and Leprosy

Vitamin D3 acts along with its receptor, VDR, which gets activated and controls the transcription of various gene groups, including those involved in immune reactions, after binding to vitamin D3. Thus, levels of VDR expression are essential for controlling disease progression in these cell types. VDR binds to the response element of VDR and regulates the expression of genes.[15] Analysis of ChIP-seq showed that major changes in the number of genes occurred during the stimulation of vitamin D3 and were coupled with enriched VDR binding.[16] Autoimmune disorders and cancer-related genes reported from genome-wide related studies, VDR binding sites are substantially enriched. IRF8, associated with multiple sclerosis, and PTPN2, associated with Crohn's disease and type 1 diabetes, were among the prominent genes with VDR binding.[17] VDR is considered to play an important role in regulating miRNA and therefore may be involved indirectly in the primary regulation of other genes. The MCM7 gene, which encodes MIR 106b and is known to control the expression of MIR181a and MIR-22,[18,19]is also controlled by VDR. Several diseases are associated with MicroRNA control, and their existence is often used as a marker for them. Previous studies have shown that leprosy complexity is associated with some mutations in the VDR gene.[20,21] Many results showed that people with complex leprosy reactions in combination with low vitamin D3 have very low VDR expression. Such people had very high BI, and all had ENL. Interestingly, two people with average levels of vitamin D3 but with very low levels of VDR had high BI and manifested neuritis and/or ENL type 2 reactions. This indicates not only that it is important to have a certain level of vitamin D3-VDR interaction, but also that the level of VDR expression is the deciding factor in leprosy reaction regulation. We do not yet understand how the expression of VDR affects the

outcome of the leprosy response. It is of interest to consider the exact mechanism, and it remains to be explained. Detailed information can be generated by ChIP-seq analysis of the genes of leprosy reaction patients.

Vitamin D and cognitive function

An elevated level of Hcy as a neurotoxin was also shown to affect the redox signalling pathways in neurons through the generation of reactive oxygen species (ROS) and a decrease in endogenous antioxidants.[22] Insufficiency of vitamin D is associated with cognitive impairment and dementia. A number of neuroprotective mechanisms have been identified (an increase of amyloid beta-peptide phagocytosis, control of neurotrophins and calcium homeostasis, anti-inflammatory and antioxidant action), indicating that vitamin D may play a significant role in dementia prevention. Since vitamin D has a neuroprotective function, vitamin D insufficiency contributes to diminished memory and cognitive function. Vitamin D receptors are found in the human cortex and hippocampus, which are essential places for cognitive control, and neurodegenerative dementia such as Alzheimer's disease has been correlated with absence or malfunction. [23]

Vitamin D and Lung diseases

Asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease and cystic fibrosis are associated with severity and low vitamin D status, as the frequency of pulmonary infections and lung cancer.[24] The circulating precursor 25-dihydroxy vitamin D3 (25(OH)D3) can be converted to local active 1,25(OH)D3 by the bronchial epithelium and immune cells. In response to various stimuli, including cytokines, and toll-like receptors (TLR) ligands such as mycobacterial lipopeptides (TLR1/2L) and viral dsRNA (TLR3L), and other parameters within the vitamin D axis (eg, cytochrome P450 27 (CYP27), CYP24) is modulated. By modulating the nuclear factor axis, 1,25(OH)D3 decreases the development of inflammatory cytokines (such as interleukin-8 (IL-8)) and chemokines (such as CXCL10-leucocyte attracting) from activated epithelial cells. Although a decrease in inflammatory cytokines could be expected to lead to an impaired antimicrobial response, in the presence of vitamin D, cell culture experiments actually show a preserved or reinforced antimicrobial response (see below). Cell proliferation and differentiation involve other pathways in vitamin D-regulated parenchymal cells. Vitamin D, for example, can inhibit airway smooth muscle proliferation and several pathways involved in airway remodeling, such as matrix metalloproteases.[25] Vitamin D control of cell proliferation appears to be significant in cancer prevention and treatment.

Vitamin D and Cancer

Vitamin D deficiency accounts for breast, colon, prostate and ovarian cancer. Normal colon, breast and prostate epithelial cells have vitamin D receptor that is highly sensitive to 1,25 (OH)2D which provides anticarcinogenic mechanism of action. Individual with circulating levels below 30ng/ml had twice the risk of developing colon cancer and had higher incidence of colonic adenomas. Vitamin D and its metabolites reduces the incidence of many types of cancer by inhibiting tumour angiogenesis stimulating mutual adherence of cells and enhancing intercellular communication through gap junction there by strengthening the

inhibition of proliferation that results from physical contact with adjacent cells within a tissue. Many studies indicate that adequate intake of Vitamin D is associated with reduced incidence and death rates of colon, breast, prostate and ovary cancer.[26]

Vitamin D and Mental Health

In India, one among every seven people suffering from mental disorder, ranging from mild to severe.[27] Mental disorders were associated with a wide range of chronic illnesses, disability, and even mortality, particularly among elderly people.[28] In mental wellbeing and cognitive functions, Vitamin D plays a major role.[29,30] In different parts of the brain, Vitamin D receptors are active, including the amygdala, which is correlated with the control of emotions and actions.[31] Vitamin D controls the concentration of intracellular and extracellular calcium in neurons.[32] Researchers found that mood disorders affect patients with low levels of vitamin D.[33,34] Vitamin D deficiency has also been associated with neuropsychiatric conditions such as Parkinson's disease, schizophrenic disorder, multiple sclerosis (MS), Alzheimer's disease, and disorders on the autism spectrum.[35-37] Significant associations between vitamin D deficiency and depressive symptoms or cognitive dysfunction have been observed in other studies.[38,39]Low sunlight sensitivity and inadequate diet[40] are the key factors for vitamin D deficiency in patients with mental disorders. Therapy with anticonvulsants can also play a role.[41] While screening psychiatric patients for vitamin D deficiency is not standard practice, evidence indicates that routine screening should include Vitamin D levels. In a UK study, for example, 100 percent of psychiatric male hospitalized patients were vitamin D deficient during hospital care.[42] Researchers found in another study conducted in the same country that 83 percent of hospitalized patients were vitamin D deficient.[43]

Vitamin D and Obesity

Obesity is a health and dietary problem in both developed and developing countries.[44] Nowadays, the most plausible reason for the inverse association between vitamin D serum levels and BMI in volumetric dilution of VD. Although obese and lean subjects have equivalent amounts of VD, in overweight individuals, VD is split into a higher amount, decreasing serum concentrations. In other words, 25(OH)D is primarily divided into compartments of serum, muscle, fat, and liver that increase obesity. [45] The explanation for this can be found in the fact that seasonal variation has a major impact on the difference in the serum 25(OH)D concentration between normal weight and obese classes. The disparity is greater in summer, according to Bolland et al.[46] ,since the increase in serum 25(OH)D due to sunlight exposure is lower in obese people compared to normal weight groups due to distribution to compartments other than serum. In addition, in response to VD supplementation, another study showed a lower 25(OH)D rise in serum in obesity than in normal body weight.[47]Drincic et al.[48], therefore, indicate that VD supplementation needs to be tailored for body size in order to eliminate the rise in serum disparity between obese and lean subjects. Moreover, in the obese population in their analysis, the 25(OH)D response to VD supplementation was approximately 30 percent lower. In both obese individuals and in the control group, Carelli et al.[49] measured the concentration of VD in plasma and omental and subcutaneous tissue and found that the relationship between plasma VD and VD concentrations in the subcutaneous and omental fat compartments was similar between the

two groups and that the distribution pattern of VD between these two fat tissues was similar. However, if the main cause of low 25(OH)D in obese people is volumetric dilution, this means that weight loss would further increase serum VD levels. Weight-loss experiments, however, produce inconsistent findings. Some studies have increased serum levels to 25OHD [50,51], while others have shown negligible serum level changes. Weight-loss research was carried out by Mason et al.[52] on a large number of obese postmenopausal participants (N = 398) who underwent a 12-month long weight loss plan involving calorie restriction and exercise and found that serum levels of 25(OH)D increased significantly in weight loss. However, in the group of women who lost more than 15 percent of their body weight, 25(OH)D increased significantly (7.7 ng / mL), suggesting that there may be a weight loss threshold that can positively affect the concentration of VD serum. On the other hand, Wortsman et al.[53] proposed the hypothesis of VD sequestration in adipose tissue (AT), which showed that while VD dermal synthesis does not differ between two groups, obese subjects have lower plasma increases of 25(OH)D compared to normal-weight subjects after exposure to sunlight and oral VD supplementation. They indicated that VD is processed and retained in AT as a fat-soluble vitamin, which leads to lower plasma levels of VD in individuals with high levels of AT. This hypothesis of sequestration was the basis for the previously mentioned volumetric dilution hypothesis. However, compared with volumetric dilution, ergocalciferol (VD2) and cholecalciferol (VD3) prohormone sequestration relate not only to their hydrophobic nature and tendency to dissolve in AT but also to their inability to return to circulation as a 25-hydroxylase substrate in the liver, which transforms these prohormones once stored into 25(OH)D. Impaired hepatic 25-hydroxylation is a further mechanism for lower 25(OH)D. Targher et al.[54] reported that in non-alcoholic fatty liver disease (NAFLD) patients, 25-hydroxylation is impaired, a condition that is very common in obesity. Furthermore, decreased serum 25(OH)D levels were found to be closely related to the severity of histologically reported liver steatosis, inflammation, and necrosis.

Vitamin D and Polycystic ovarian syndrome

Vitamin D plays a physiological function in reproduction, including ovarian follicular growth and luteinisation by altering anti-muller hormone (AMH) signalling, follicle-stimulating hormone sensitivity and progesterone formation in human granulosa cells. It also affects glucose homeostasis across multiple functions. Potential effects of vitamin D on glucose homeostasis include the existence of specific vitamin D receptors (VDRs) in pancreatic β-cells and skeletal muscles, the expression of 1-α-hydroxylase enzyme that can catalyze the conversion of 25-hydroxy vitamin D [25(OH)D] to 1,25-dihydroxyvitamin D, and the existence of a vitamin D response factor in the human insulin promoter. Polycystic ovarian syndrome (PCOS) is a general cause of ovarian dysfunction in women with anovulation. The key signs are persistent anovulation, hyperandrogenism and/or the presence of polycystic ovarian morphology from ultrasound testing. The phenotypic presentation of this condition is associated with varying degrees of gonadotropic and metabolic disorders determined by the combination of various genetic and environmental factors. The prevalence of vitamin D deficiency in women with PCOS is approximately 67-85 percent, with serum concentrations of 25(OH)D < 20 ng / ml. While there is no substantial difference in 25(OH)D levels between PCOS and normal control women, a high prevalence of vitamin D deficiency has been found

to be associated with metabolic syndrome, which could have a substantial effect on public health. Low 25(OH)D levels can exacerbate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity, and increase the risk of cardiovascular disease. Many observational studies indicate a possible role of vitamin D in the inverse association between vitamin D status and metabolic disturbances in PCOS, but it is still difficult to draw a definite conclusion in the causal relationship due to contradictory results from numerous individual studies and a recent meta-analysis study of a systematic review of vitamin D supplementation. In particular, in addition to metformin therapy, vitamin D and calcium supplementation in women with PCOS may have beneficial effects on menstrual regularity and ovulation. Further study with high-quality randomized controlled trials is therefore warranted to assess the effect of vitamin D supplementation on the management of PCOS. Low 25(OH)D levels have been shown to be significantly associated with insulin resistance in women with PCOS.[55]

Vitamin D and Pre-eclampsia

Preeclampsia is a multifactorial pregnancy-specific disorder which is symbolized by the development of hypertension and proteinuria after 20 weeks of gestation.[56] Preeclampsia is a complication of pregnancy with significant implications. The condition is diagnosed with gestational hypertension and proteinuria. Preeclampsia is proposed to occur in two stages.[57] Placental perfusion is decreased in stage 1. This could happen after irregular implantation. Bad blood flow through the placenta is proposed to produce substances that initiate multisystem abnormalities in a favourable maternal environment (stage 2). Endothelial dysfunction is part of a systemic intravascular inflammatory response involving leukocytes and clotting and complementing processes. Bad placental blood flow does not appear to be the main cause of preeclampsia but is a strong predisposing factor.[58] The active form of vitamin D, 1,25-dihydroxyvitamin D3, has been shown to change the transcription and function of genes associated with normal implantation, placental invasion, and angiogenesis.[59] The immunomodulatory properties of 1,25-dihydroxy vitamin D are important. Abnormal implantation is hypothesized to be mediated at least in part by abnormal immune responses between pregnant mothers and infants.[60] Maternal vitamin D deficiency can increase inflammatory reactions.[61] Deficiency in vitamin D can also increase the risk of hypertension.[62] Finally, the endothelial growth factor (VEGF) of the renal vascular tends to be associated with proteinuria. 1,25-dihydroxyvitamin D3 could control angiogenic processes by affecting the transcription of the VEGF gene.[63] Vitamin D deficiency, as calculated by 25-hydroxyvitamin D [25(OH)D] serum levels, is normal in pregnant women. A strong association between vitamin D and adverse pregnancy outcomes, such as preeclampsia, preterm birth and gestational diabetes mellitus, has been shown in several observational studies.[64] Many studies have shown that the risk of preeclampsia is increased when vitamin D serum levels are low.[65] Normal dihydroxyvitamin D level 1,25 may prevent preeclampsia by having an effect on immune modulation and vascular function. Numerous clinical studies have been sponsored by the National Institutes of Health with the goal of evaluating the impact of vitamin D supplementation during pregnancy and preventing adverse pregnancy outcomes.[66]

Vitamin D and Psoriasis

Inflammatory disorders with an inherited predisposition affecting the skin, joints and immune system are psoriasis and psoriatic arthritis (PA). It is not well known about the pathogenesis of psoriasis. Records of psoriasis being treated with Vitamin D oral intake are available. On the basis of the beneficial effects of UVR on the condition, the role of oral administration of vitamin D supplements in the treatment of psoriatic skin was first described 60 years ago.[67] The possibility of calcemic side effects, however, loses the advantage of oral administration of vitamin D. Topical calcipotriol, a vitamin D analog, is now used successfully in the treatment of psoriasis. It is healthy and good without systemic side effects for the treatment of psoriasis. Several studies have shown that vitamin D suppresses IL 2, IL 6, and interferon-gamma growth, which are potent inflammation mediators. Surveys also reported the existence in psoriatic patients of an interplay between T helper cells (Th 17) and vitamin D. Furthermore, vitamin D activates the activity of T-cell suppressors and prevents cytotoxic and natural killer cells from developing. It has been suggested that the therapeutic effects of topical vitamin D and its analogs on psoriatic lesions may be explained by a combination of mechanisms for decreased cell proliferation, increased cell differentiation, and immunomodulation. However, for all patients with psoriasis, treatment with Vitamin D is not effective. As a result, the exact mechanism of action of vitamin D in psoriasis and the etiology of the disease should be explained. The precise action of vitamin D in psoriasis, which is also the aim of this research, needs to be determined. To this end, a literature review was conducted to assess if there is a link between serum vitamin D deficiency and psoriasis incidence.[68,69]

Vitamin D and Diabetes

Diabetes mellitus is a group of metabolic disorder characterized by insulin resistance initially, impaired insulin secretion, insulin deficiency, increase glucose production and decreased glucose utilization and the complications arising from this disease is the major cause of death worldwide. The cells of the body cannot metabolize carbohydrate due to relative or complete lack of insulin and body breaks its own protein, fat, glycogen resulting in hyperglycemia. Deficiency of vitamin D was linked to DM induction and progression. While the relationship between vitamin D and insulin secretion, insulin tolerance, and β-cell dysfunction is highlighted in patients with DM, evidence of vitamin D and DM levels is inconsistent, and well-controlled studies are required. [70-72]

Conclusion

Vitamin D deficiency is not very common since it can be synthesised in the body in adequate amounts by simple exposure to sunlight even for 10 minutes every day. It may be seen in people who are bedridden for long periods, strict vegetarians, chronic alcoholics and person suffering from severe liver and kidney diseases or fat Malabsorption syndromes. Women who cover their entire body are susceptible to vitamin D deficiency, if the requirement is not met through the diet. Vitamin D is also involved in some function in addition to calcium homeostasis and bone metabolism. Receptors for calcitriol occur in many other tissues such as the parathyroid gland, islet of pancreas, myeloid stem cells in bone marrow and keratinocytes of skin. Vitamin D seems to be involved in cell differentiation, both in normal

and malignant tissues. It also stimulates the production of cytokines thus playing a role in immunomodulation. Adequate intake of vitamin D is beneficial in reducing the risk of certain autoimmune disease. The supplementation of Vitamin D3 is said to decrease the overall mortality and thus has a positive effect on the lifespan. So adequate amount of Vitamin D should be taken as Vitamin D plays role beyond calcium homeostasis and bone formation.

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