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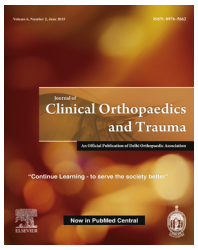

Review Article

Resurgence of vitamin D: Old wine in new bottle

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ABSTRACT

There are early references of it in ancient text and physicians have discussed its importance and features of its deficiency in the past. Vitamin D has again regained interest with recent dramatic rise in the incidence of deficiency in the developing as well as developing world. In this review article, we discuss the biochemical and role of vitamin D in the skeletal system. We also discuss the recommended dietary requirements and features of skeletal deficiency. Extra-skeletal roles of vitamin D deficiency have been a matter of debate lately and it has also been discussed in detail in this article. In conclusion, it would not be wrong to label vitamin D as one of the most important vitamin involved in the metabolism of the musculoskeletal system and any clinician, especially the orthopaedician, should be well versed with its overall mechanism and roles in the human body.

1. Introduction

Although Vitamin D Deficiency disorder (VDD), namely Rickets was known for centuries, but its causative factor was known only after the discovery of Vitamin D (VD) by E.V. McCollum and his associates in 1913. But it attained a new interest in recent years as VDD has been found to be pandemic worldwide and its association with others diseases.[1,2] **Vitamin D** is a group of fat-soluble secosteroids (a steroid with a "broken" ring) plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. Several forms (vitamers) of VD exist namely, VD_1 (ergocalciferol with lumisterol), VD_2 (ergocalciferol), VD_3 (cholecalciferol) VD_4 (dihydroergocalciferol), VD_5 (sitacalciferol). The most important compounds in this group are VD_3 and VD_2.[3–5] In this review article we discuss vitamin D metabolism and functions in the human body. The common causes of vitamin D deficiency along with daily requirements and prevalence of vitamin D deficiency in the world and India have been discussed along with the extra-skeletal manifestations of vitamin D.

2. Vitamin D metabolism and functions

Ultra Violet (UV)-B irradiation of skin triggers photolysis of 7-dehydrocholesterol ($proVD_3$) to $preVD_3$ in the plasma membrane of human skin keratinocytes.[6–8] Once formed in the skin, cell plasma membrane $preVD_3$ is rapidly converted to VD_3 by

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the skin's temperature VD_3 from the skin and VD from the diet undergo two sequential hydroxylations, first in the liver to 25 (OH)D and then in the kidney to its biologically active form, 1,25-dihydroxyVD (1,25[OH]2D) (Fig. 1).

3. Mechanism of action

VD acts in 2 ways:

I) *Genomic action of VD*: VD Receptor (VDR) is a member of the superfamily of nuclear receptors for steroid hormones, which can be categorized as a ligand activated transcription factor.[9] VDR is also thought to play an important role in engendering to rapid action of 1, 25 (OH)2D3.[10]

II) *Non genomic action of VD*: There exist rapid response non-genomic actions of VD, which are mediated through cell surface receptors, known as 1, 25 D3 MARRS (membrane associated rapid response steroid binding proteins).[11]

4. Bioactions of VD

On Intestine: 1, 25 (OH)2D3 enhances the efficacy of small intestine to absorb calcium and phosphorus, iron, magnesium, zinc.[10]

On Skeleton: VD is essential for the development and maintenance of mineralized skeleton.

Growth plate development requires coordinated calcium and 1, 25 (OH)2D3 actions and VDR, where as optimal osteoblastic bone formation and osteoclastic bone resorption demand both 1, 25(OH)2D3 and VDR.1, 25(OH)2D3 regulates osteoclastogenesis in reciprocal regulation of receptor

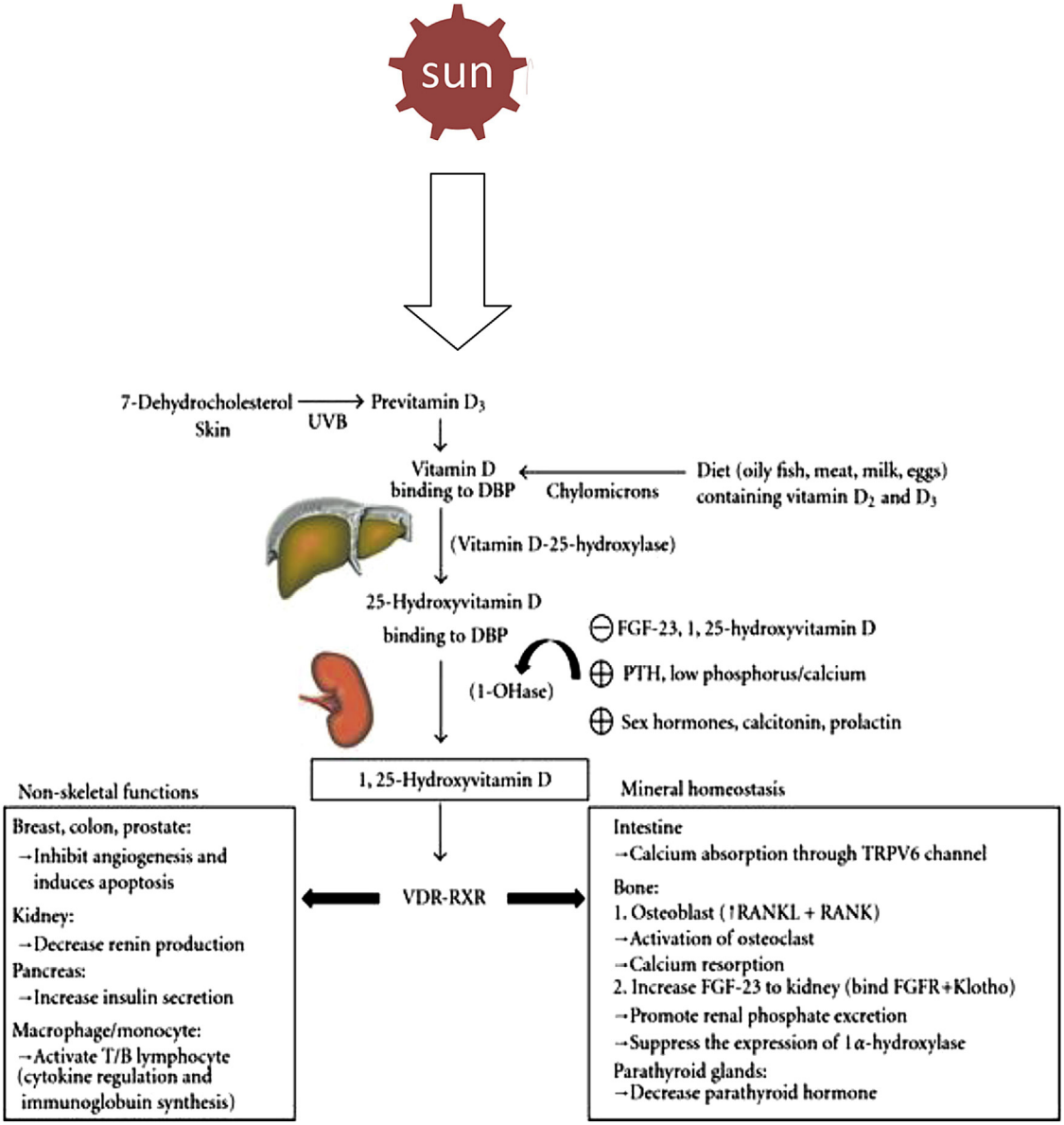

Fig. 1 – Biosynthesis and metabolism of vitamin D (*UVB* = Ultraviolet ray B, *DBP* = VD Binding Protein, *FGF* = Fibroblast Growth Factor, *PTH* = Parathormone, *VDR* = VD Receptor).

activation of NF-kB (RANK) ligand (RANKL) and osteoprotegerin (OPG).[12]Interactions between osteoblasts and osteoclasts integrate bone remodelling.

5. Requirement

There is difference in recommendation of daily requirement by different authority and the commonly accepted recommended dietary allowances (RDA) for VD are from Health Canada.[13]

6. Sources of VD

The main sources of VD_2 and D3 include[3,14–21]: A) Natural sources like Fish (Salmon, Sardines, Mackerel, Tuna etc), Cod Liver oil, mushrooms, egg yolk, sun light exposure etc; B) Fortified foods like butter, milk, yogurts, cheese, margarine, orange juice, breakfast cereals etc; C) Pharmaceutical supplements like VD_2, D3 and multivitamin.

7. Deficiency

VD deficiency is the most common and is the most underdiagnosed medical condition in children and adults. This is largely because patients do not typically present with overt clinical signs and symptoms until the deficiency is severe and prolonged. It is now accepted that the circulating level of 25-hydroxy VD should be used as an indicator of VD status due to its ease of measurement, long half-life in circulation (approximately 2 or 3 weeks), and the correlation of its level with clinical disease states.[22–24] Although no consensus on an optimal level of 25-hydroxyVD has been reached, however its level can determine various states of clinical conditions.[25–29]:

A) Deficiency: <20 ng/ml
B) Insufficiency: 20–29 ng/ml
C) Sufficiency: 30–100 ng/ml
D) Toxicity: >100 ng/ml

8. Deficiency disorder

Children with established VD deficiency present with features of ***rickets*** in the form of skeletal abnormalities like knee deformities (Fig. 2), developmental delay, failure to thrive etc., with characteristic biochemical and radiological features. The typical radiological features include widening and cupping of the metaphysis etc, whereas adults present with signs and symptoms of ***osteomalacia*** like bone pain and tenderness, proximal muscle weakness presenting as difficulty in rising from a sitting position with biochemical and radiological feature. The typical radiological features include insufficiency fractures or looser zones (Fig. 3), osteoporosis, biconcave discs, 'rugger jersey' spine (Fig. 4).

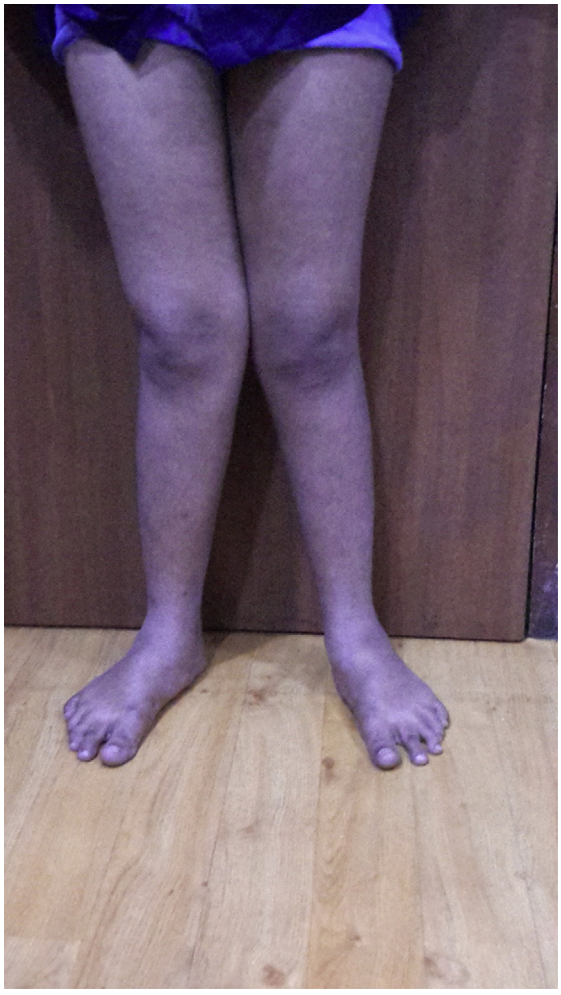

Fig. 2 – Bilateral genu valgum deformity due to vitamin D deficiency.

9. Causes of VD deficiency

A) UVB-related deficiency

The elderly due to decreased presence of skin 7-dehydrocholesterol, reduced mobility or institutionalization (that discourages sun exposure), reduced renal production of 1,25-dihydroxyVD as well as decreased intake of fortified foods.[30,31]

B) Dark skin

Melanin competes with 7-dehydrocholesterol for absorption of UVB photons. Dark skin requires 10–50times the exposure to sunlight to produce the same amount of VD as does a white person.[32]

C) Season, latitude, and the time of day

The thicker the ozone layer is, the fewer amounts of UVB photons can reach the earth, thus few preVD3 can be produced. Zenith angle, defined as the angle of the sunlight reaching the Earth's surface, decides the thickness of ozone

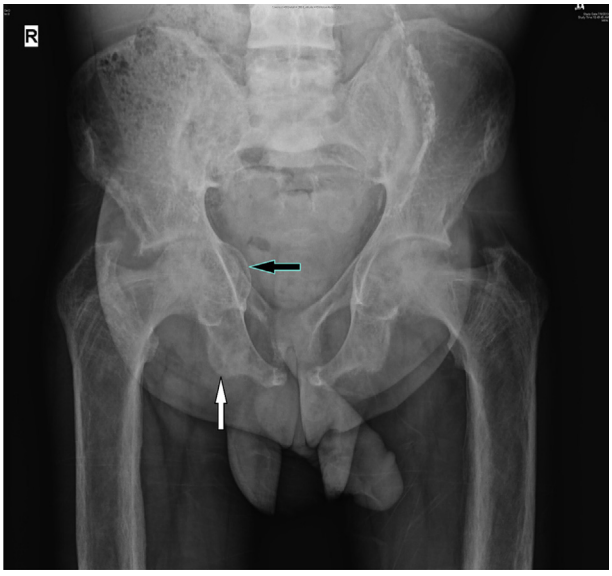

Fig. 3 – X-ray of the pelvis showing protrusio acetabuli (black arrow) and multiple insufficiency fractures (white arrow).

layer which sunlight needs to penetrate. Zenith angle is dependent on factors such as time of day, season of the year, and latitude.[33,34]

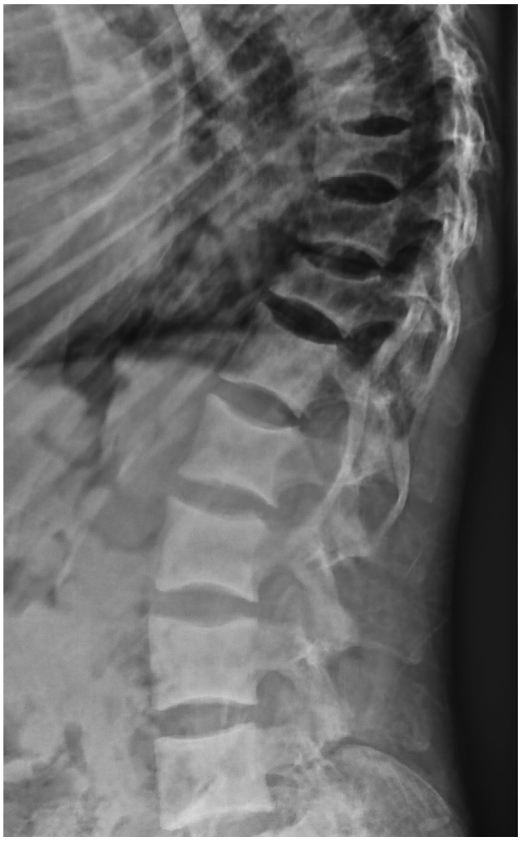

Fig. 4 – Lateral X-ray of the spine showing rugger jersey spine and multiple biconcave veretbra (cod fish mouth appearance).

D) Sunscreen users

Sunscreens can efficiently absorb UVB radiation. This dramatically prevents the interaction of UVB with 7-dehydrocholesterol, the process of preVD3 generation.[8,35]

E) Medical/physical condition-related deficiency, fat malabsorption

Crohn's disease, cystic fibrosis (CF), celiac disease, surgical removal of part of the stomach or intestines are associated with fat malabsorption and thus may lead to VD deficiency.[36]

F) Anticonvulsant use

Long-term use of some antiepileptic drugs, including phenobarbital, phenytoin, and carbamazepine and the antimicrobial agent rifampicin (RIF) can result in osteomalacia.[37–41] The induction of the catabolism of 1,25-dihydroxyVD by these drugs is thought to contribute to their deleterious side effects.[37–41]

G) Chronic kidney disease

Chronic kidney disease, as well as those requiring dialysis, leads to an inability to make sufficient 1,25-dihydroxyVD which has a direct effect in inhibiting parathyroid hormones expression.[42,43]

H) Liver diseases

Liver is the main site where hydroxylation of VD at position C-25 takes place. Thus, it is not surprising that the degree of liver dysfunction correlates with calcidiol levels[44] and that the prevalence of VD insufficiency is particularly high in patients with chronic liver disease.[45–48] The levels of 25-hydroxyVD can be low in severe liver diseases and liver diseases directly could lead to impaired absorption of VD.

I) Obesity

Obese people have lower 25-hydroxyVD levels. The subcutaneous fat, which is known to store VD, sequestered more of the cutaneous synthesized VD, which results in less release of VD from the skin into the circulation in the obese subject than non-obese subject.[49–54]

10. Prevalence of VD deficiency in the world and in India

VD deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world.[55–57] Several studies showed that 40–100% of U.S. and European elderly men and women still living in the community (not nursing homes) are deficient in VD.[25–27] It has already become a largely unrecognized global epidemic. VD inadequacy can be seen in young adults as well as healthy children. For example, 48% of white preadolescent girls in a study in Maine[58] and 52% of Hispanic and black adolescents in a study in Boston are VD

deficient.[59] In Europe, where very few foods are fortified with VD, children and adults would appear to be at especially highrisk.[60–62] A study of middle aged British adults showed that 60% are VD insufficient, and the number rose to 90% during winter and spring.[63]

VD deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%–100% in the general population. In India, widely consumed food items such as dairy products are rarely fortified with VD. Indian socio religious and cultural practices do not facilitate adequate sun exposure, thereby negating potential benefits of plentiful sunshine. Consequently, subclinical VD deficiency is highly prevalent in both urban and rural settings, and across all socioeconomic and geographic strata. Countrywide studies have reported VD deficiency in as high as 70%–100% of ostensibly healthy individuals. High prevalence of VD deficiency was reported from northern to southern and western to eastern India, in ostensibly healthy children, adolescents, young adults and those ≥50 years old. All over India, VD deficiency was highly prevalent in pregnant women and lactating mothers. VD status of these mothers correlated well with their neonates and their exclusively breastfed infants. Subjects from rural and urban areas presented a similar picture. Relatively, fish are a rich source of VD. The residents of Bengal (eastern India) eat more fish compared to the rest of the Indians. Surprisingly, their VD status appears to be just as poor as in the rest of the country.[64] Similarly, even healthy young soldiers with sufficient intake of calcium, adequate sun exposure and regular exercise regimen were found to be VDdeficient,[65,66] as were young sportswomen.[67] Among resident doctors from Mumbai (western India)[68] and also doctors from eastern India,[64] most were VD deficient. VD deficiency was also observed in most of 2119 healthcare professionals studied from all over India.[69] Evidently, countrywide prevalence of VD deficiency is undeniable.

11. Treatment of disease and supplementation

11.1. *VD DOSING, supplementation, and UV irradiation and/or sensible sun exposure*

Supplementation with VD has been estimated to prevent VD deficiency in approximately 98% of the general population.[70–72] VD supplementation and exposure to sunlight or simulated sunlight have been shown to increase serum 25 (OH)D levels in elderly patients.[36,73–84] The Institute of Medicine's adequate intake for the United States and Canada is 200 IU/d for all children and adults younger than 51 years, 400 IU/d for people aged 51–70 years, and 600 IU/d for those older than 70 years.[72,85] A report by the Scientific Committee for Food, established by the European Commission, indicated that adults 65 years and older should receive 400 IU/d of VD_3 and suggested that the requirements of all adults, including those with inadequate sunlight exposure, would be met by this dietary intake.[86] This recommendation is consistent with that of the US Food and Drug Administration's daily recommended value of 400 IU/d (10 μg/d) of VD_3regardless of age.[87] Because it has been suggested that amounts up to 1000 IU/d of VD_3 may be needed to maintain a healthy 25(OH)D level of more than 30 ng/mL (75 nmol/L),[88–91] an intake of 400 IU/d may represent a minimum. This is especially true in the winter or for children and adults not exposed to sunlight.

11.2. *Treatment of severe VD deficiency*

Although severe VD deficiency (25[OH] levels <10 ng/mL [25 nmol/L]) is much less common than inadequacy, it does occur, especially in elderly house-bound people. The best method for treating VD deficiency is an oral dose of 50,000 IU/wk of VD_2 for 8 weeks, then checking 25(OH)D levels.[70,73] In some cases, another once-weekly 8-week course of 50,000 IU of VD_2 may be necessary to boost 25(OH)D levels into the desired range of more than 30–50 ng/mL (75–125 nmol/L). For patients prone to developing VD deficiency, after correcting the deficiency, giving patients 50,000 IU every 2 weeks will sustain them in a VD-sufficient state. Alternatively, 1000 IU of VD_3 intake should be maintained. Cutaneous exposure to sunlight or artificial UV-B such as a tanning bed is also helpful, especially if the patient is prone to VD deficiency.[82–84,92–95] Exposure to direct sunlight typically of no more than 5–10 min on the arms and legs between the hours of 10 AM and 3 PM during the spring, summer, and fall will prevent VD inadequacy.[33,70,71]

11.3. *Hypervitaminosis*

VD intoxication is extremely rare. Studies showed that doses of more than 50,000 IU per day, which raises 25-hydroxyVD to more than 150 ng/ml, is associated with hypercalcemia and hyperphosphatemia.[96–98] VD toxicity is not caused by sunlight exposure, but can be caused by supplementing with high doses of VD presenting with hypercalcemia as anorexia, nausea, and vomiting, frequently followed by polyuria, polydipsia, weakness, insomnia, nervousness, pruritus, and, ultimately, renal failure. Proteinuria, urinary casts, azotemia, and metastatic calcification (especially in the kidneys) may also develop. Other symptoms of VD toxicity include mental retardation in young children, abnormal bone growth and formation, diarrhea, irritability, weight loss, and severe depression.[16,99] Hence, abuse and misuse of VD supplementation by the physician and general public must be stopped and sufficient awareness about it must be created.

12. Extra skeletal effects of VD

The small intestine, kidneys, and bones are the primary organs and tissues responsive to VD that are involved in mineral metabolism that affects skeletal health. However, the effects of VD are not limited to mineral homeostasis and the maintenance of skeletal health. The presence of the VDR in other tissues and organs suggests that VD may also be important in extra skeletal biological processes.[100–102] Additionally, the enzyme responsible for conversion of 25(OH)D to the biologically active form of VD (1,25[OH]2D) has been identified in tissues other than kidney,[103–106] and evidence is growing that extrarenal synthesis of 1,25(OH)2D may be

important for regulating cell growth and cellular differentiation[70,99,100,107] via paracrine or autocrine regulatory mechanisms. The VDR is a steroid hormone nuclear receptor that binds 1,25(OH)2D with high affinity and mediates transcriptional gene regulation.[70,100,102,107–109] Mounting biochemical and epidemiological evidence suggests that the VDR is also involved in mediating the noncalcemic effects of VD and its analogues and may play a vital role in disease prevention and maintenance of extraskeletalhealth.[70,110,111] The VDR has been isolated from many cell types, tissues, and organs, including those not typically associated with calcium homeostasis and bone metabolism. Some of these include the heart, stomach, pancreas, brain, skin, gonads, and various cells of the immune system.[70,99,100,107] Genetic variants of the gene encoding the VDR have also been associated with differential risk of developing variouscancers[112,113] and immune disorders, including type 1 diabetesmellitus.[114,115] In addition, 1,25(OH)2D is involved in non-genomic mediated intracellular signaling pathways.[116–119] Both1,25(OH)2D and its synthetic analogues (collectively, VDR ligands) have demonstrated anti proliferative, pro differentiative, and immune modulatory activities (which may be mediated by both the genomic and the nongenomic mechanisms)in several clinical and experimental settings,[116] and are being investigated for the potential treatment of many pathologic conditions, including psoriasis, type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Crohn's disease, hypertension, cardiovascular heart disease, and many common cancers.[70,110,120–122] Since the primary function of VD is to modulate calcium homeostasis, the use of analogues for the treatment of conditions other than osteoporosis or osteomalacia could trigger hypercalcemia or other unwanted adverse effects.

12.1. *VD and cancer*

VD is one of the most potent hormones for regulating cell growth; 1,25(OH)2D inhibits proliferation and induces differentiation into normally functioning cells.[70,99,102,107,123] Some evidence suggests that 1,25(OH)2D helps to regulate cell growth and prevent cancer progression[70,99,100,124] by reducingangiogenesis,[125] increasing cell differentiation and apoptosis of cancer cells, and reducing cell proliferation[126–128] and metastases.[70,99,100,106,107,120,126,129]

12.2. *VD and cardiovascular disease*

Adding to the evidence of the effect of VD on extraskeletal tissues are data that suggest that inadequate VD and calcium and living at higher latitudes may being dependent contributing factors in the pathogenesis and progression of hypertension and cardiovascular disease.[70,110,130,131]

12.3. *VD and multiple sclerosis*

As with previous epidemiological data reporting a latitudinal risk gradient for cancer and cardiovascular disease[110,132–137] a similar risk gradient exists for developing multiple sclerosis.[138–141] One double-blinded RCT involving patients with multiples clerosis who were randomized to receive either VD supplementation or placebo showed that patients who received supplementation had increased serum transforming growth factor β1 levels vs those who did not receive supplementation.[142] Elevated transforming growth factor β1 levels have been associated with the stable phase of multiple sclerosis, whereas reduced levels have been associated with relapsing-remitting multiple sclerosis.[143,144]

12.4. *VD and type I diabetes mellitus*

1,25(OH)2D acts as an immune modulator, reducing cytokine production and lymphocyte proliferation, which have been implicated in the destruction of insulin-secreting β cells in the pancreas and the development of type 1diabetes mellitus.[87] In addition, β-islet cells express the VDR and respond to 1,25(OH)2D by increasing insulinproduction.[70,87,145,146]

12.5. *VD and psoriasis*

One of the great successes of VD therapy for treating an extraskeletal disorder is in the treatment of psoriasis.[122,147] Smith et al.[148] showed that 1,25(OH)2D3 inhibited the proliferation of human keratinocytes that express the VDR in vitro and accelerated their differentiation. This suggested that hyper proliferative skin disorders such as psoriasis might be responsive to treatment with 1,25(OH)2D3.[149] Initial treatments with topical 1,25(OH)2D3 showed great improvements in reducing the severity and area of psoriatic lesions, with little or no adverse effects.[122,150–152] Today, three VD analogues including calcipotriene, 1,24(OH)2D3, and 22-oxo-1,25(OH)2D3, are among the first-line treatments used for psoriasis.[122,147,151,152]

12.6. *VD in OA and degenerative disc disease*

There is a small but statistically significant clinical benefit to VD treatment in patients with Knee OA.[153] VD deficiency is greatly associated with early stage of OA, suggesting VD supplementation before cartilage damage occur.[154] Several clinical trial have ensued and are ongoing. These studies are in the initial stage, and to date no strong evidence has been available establish the role of vitamin D in OA. There is also some evidence of association with degenerative disc disease with VD deficiency.[155,156]

12.7. *VD in other diseases*

A possible role of VD has also been implicated in several other diseases, including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, osteoarthritis, and periodontal disease.

13. Conclusion

VD inadequacy is a global problem and widespread prevalence of its deficiency in India is undeniable. Although recommendations of daily VD intake have been provided, higher levels are required in order to have real preventive or treatment effects as numerous studies have proved. UVB radiation plays

an alternative in improving VD content other than oral supplementation. Its advantage is that it wills not cause VD intoxication since excessive VD will be broken down by UVB. However, a number of factors of the UVB such as wavelength, duration of exposure are needed to be carefully controlled so as to avoid erythema. Factually, sun exposure is an untenable solution, for most individuals in India, towards attaining VD sufficiency. Low calcium intake in conjunction with VD deficiency makes matters worse. The need for improvement in vitamin status of the Indian population is both important and urgent. The Indian government needs to take substantive measures in this direction. Revision of recommended daily allowance of calcium and VD is required. Despite the close link of VD with human health, VD inadequacy is not widely recognized as a problem by physicians and patients. Not only VD deficiency produces skeletal changes but may also be responsible for causation and or progression of many other non musculoskeletal diseases. Hence, greater awareness of this problem is required among researchers, clinician, and patients about VD inadequacy and its consequences. On the contrary, the misuse and abuse of VD supplementation must also be highlighted as it can cause life threatening hypercalcemia is some patients. The value of extra skeletal use of VD, at present, is doubtful in various chronic diseases as its use in these conditions had been based on observational data and mixed quality evidence from predominately small trials. Appropriate interpretation of the data is further muddied by seemingly endless media reports suggesting vitamin D as a panacea for chronic disease.[157]

Conflicts of interest

All authors have none to declare.

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