Vitamin D in Health and Disease – An Update

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ABSTRACT

The importance of vitamin D in health and disease is being increasingly recognized nowadays and lots of research is being carried out in this area. Thus, it is essential to understand about this vitamin and this narrative review is one such initiative. The main aim of this review is to provide a comprehensive and in-depth knowledge of the role of vitamin D in health and disease. A comprehensive literature search was carried out in the search portals of PubMed, Google Scholar and Indmed to identify the role of vitamin D in health and disease. Vitamin D is a fat soluble prohormone, synthesized in our epidermal cells following exposure to sunlight. The synthesized precursors of vitamin D are metabolically activated by 25-hydroxylation in the liver and 1-α hydroxylation in the kidney. The biologically active form of vitamin D is 1, 25-dihydroxycholecalciferol which binds to the vitamin D receptor to mediate its effects. Vitamin D plays a key role in maintaining calcium and phosphate homeostasis in the body. However, vitamin D is also found to have various pleiotropic effects like anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulatory effects. The serum 25-hydroxyvitamin D levels are considered as indicator of body’s vitamin D stores. Deficiency of vitamin D is highly prevalent and is associated with various diseases like osteoporosis, hip fractures, myocardial infarction and malignancies of colon, breast and prostate.

Key words: Deficiency, Metabolism, Physiological role, Pleiotropic effects, Toxicity, Vitamin D.

INTRODUCTION

A comprehensive literature search was carried out in the search portals of PubMed, Google Scholar and Indmed without any time limitation, using the search terms “vitamin D in health” and “vitamin D in disease” in order to identify the role of vitamin D in health and disease. This is an indepth review of vitamin D which covers various topics like discovery, biosynthesis, metabolism, dietary sources, pharmacokinetics, mechanism of action, physiological role, pleiotropic actions and recommended dietary allowances of vitamin D. It also describes about the assessment of vitamin D status, sample processing for vitamin D analysis, classification of vitamin D status based on serum 25-hydroxyvitamin D levels, vitamin D toxicity and vitamin D deficiency.

Vitamin D is a fat soluble prohormone synthesized in our body. It is also derived from plant sources, fortified foods and dietary supplements. It is metabolically activated in the liver and kidney to form 1,25-dihydroxycholecalciferol, which has various physiological roles in the body, especially in maintaining the bone-mineral homeostasis. It has also been found to have various pleiotropic effects like anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulatory effects. This review describes in detail about the discovery of vitamin D, its biosynthesis, metabolism, physiological roles, pleiotropic actions, recommended dietary allowances, assessment of vitamin D levels, classification of vitamin D status, vitamin D toxicity and deficiency.

DISCOVERY OF VITAMIN D

Although rickets was prevalent from time immemorial, there was lack of knowledge regarding its etiology and treatment, until the discovery of vitamin D.1 In 1890, it was observed that prevalence of rickets was more in London compared to that in the tropical zones like India and China. This observation led to the speculation that exposure to sunlight was essential for prevention of rickets.2 Similarly experiments by Mellan by et al.4 in the year 1919, found that cod liver oil could cure rickets in dogs retained indoors without access to sunlight. The study concluded that probably vitamin A or a similar substance present in cod liver oil was responsible for the improvement in symptoms of rickets in the dogs and that rickets was produced due to deficiency of vitamin A in the diet. However, a subsequent study done by McCollum et al.5 in the year 1922, revealed that a new fat soluble vitamin (which they named as vitamin D) distinct from vitamin A, was responsible for the cure of rickets in dogs. This discovery was based on the finding that cod liver oil with vitamin A destroyed by oxidation, could not prevent the occurrence of xerophthalmia but still demonstrated the antirachitic effect in dogs. Following its discovery, various researchers like Windaus, Thiele, Schenck and Werder identified the structure and properties of vitamin D, which is derived from both plant and animal sources.5

VITAMIN D - A VITAMIN OR PROHORMONE?

Vitamin a micronutrient, essential for the survival of an organism is not synthesized in the body but is derived from dietary sources. Although vitamin D was initially classified as a vitamin, accumulating evidence indicated that it can be produced in our body with the help of ultraviolet radiation from sunlight, thus violating the definition of a vitamin. Thus, vitamin D is now thought to be a prohormone which on subsequent activation in the body gets converted to its active form 1,25-dihydroxyvitamin D which functions like a hormone (produced in one part of
body, transported through blood circulation to reach a distant site where it exerts its action) and mediates the endocrine effects of vitamin D.6

**VITAMIN D BIOSYNTHESIS, METABOLISM, AND INACTIVATION**

Vitamin D is a fat-soluble secosteroid synthesized primarily under our skin with the help of ultraviolet radiation (Figure 1). Sunlight (UVB of wavelength 290-320 nm), acts on 7-dehydrocholesterol (provitamin D$_3$) in the stratum basale and stratum spinosum layer of the epidermis and forms previtamin D$_3$, which undergoes thermal isomerization for 3 days to form cholecalciferol or vitamin D$_3$.7 The rate of vitamin D$_3$ production is influenced by the intensity of UVB radiation and melanin content of the skin. The lower intensity of UVB radiation and dark complexion limit the amount of vitamin D biosynthesis.2-4 It is estimated that on exposure of 20% of the total body surface area to ultraviolet radiation of 0.5 minimal erythemal dose (MED) produces vitamin D equal in amount to consumption of 1400 to 2000 IU of vitamin D$_3$.9 Minimal erythemal dose is a measure to quantify sunlight exposure. One minimal erythemal dose is the intensity of sunlight required to impart mild pink colour in the sun-exposed areas of skin after 24 hr.

Vitamin D$_3$ is transported in blood with the help of proteins synthesized in liver namely, vitamin D binding proteins (DBPs) to various target organs. In liver, vitamin D$_3$ undergoes 25-hydroxylation and gets converted to 25-hydroxycholecalciferol or calcidiol, which constitutes the primary circulating form of vitamin D. On reaching the proximal tubular epithelial cells of the kidney, calcidiol further undergoes 1-alfa hydroxylation by the enzyme 1-alfa hydroxylase (cytochrome P27B1 or CYP27B1) to form the active metabolite 1,25- dihydroxycholecalciferol or calcitriol.10 Calcitriol mediates all the physiological functions of vitamin D. The kidneys also contain 24-hydroxylase which can hydroxylate both 25-hydroxycholecalciferol and 1,25- dihydroxycholecalciferol to their inactive metabolites 24,25- dihydroxycholecalciferol and 1,24,25- trihydroxycholecalciferol respectively. Calcitroic acid (1 alpha-hydroxy-23 carboxy-24,25,26,27-tetranorvitamin D$_3$) is another inactive metabolite of calcitriol produced by the action of 24-hydroxylase enzyme. These inactive metabolites are excreted through the bile into faeces.10-11

**DIETARY SOURCES OF VITAMIN D**

Vitamin D is also derived from dietary sources, although the major contribution of the circulating vitamin D pool is derived from sunlight. Dietary sources can be in the form of natural foods, fortified food products or vitamin D supplements. Very few natural foods as summarized in Table 1 are rich in vitamin D and they serve to provide the body’s vitamin D requirement.12-15

**PHARMACOKINETICS OF VITAMIN D**

Various vitamin D supplements are available in the market, especially in the form of vitamin D$_3$ (ergocalciferol) and vitamin D$_2$ (cholecalciferol). According to a study by Lehmann et al.16 supplementation with vitamin D$_2$ was more effective in increasing the total serum 25-hydroxy vitamin D levels compared to vitamin D$_3$ supplementation. Vitamin D$_2$, being fat soluble is absorbed after incorporation into micelles with the help of bile salts. Its absorption occurs mainly in the proximal part of small intestine.11 It was found that absorption of vitamin D was increased when their supplements were taken along with a large meal, thus aiding in achieving a greater increase in serum 25-hydroxy vitamin D levels.17 The half-life of the metabolite 25-hydroxyvitamin D is 3 weeks, whereas that of the active metabolite 1,25-dihydroxyvitamin D is only 4 hr.18

**MECHANISM OF ACTION OF VITAMIN D**

The active form of vitamin D or cholecalciferol namely, 1,25- dihydroxycholecalciferol or calcitriol binds to vitamin D receptors (VDR) present in the nuclei of the target cells to mediate its genomic actions. VDRs belonging to the family of nuclear receptors contain a ligand binding domain and a DNA binding domain. On binding to their cognate ligand (calcitriol), the vitamin D receptor heterodimerizes with retinoid X receptor (RXR) and this VDR-RXR heterodimer binds specifically to the vitamin D response elements (VDRE) of the DNA to alter the transcription of vitamin D responsive genes, thus mediating the genomic actions of vitamin D.19

Vitamin D also mediates non-genomic effects by acting on vitamin D receptors located on the plasma membrane of the target cells.4 They also operate by various other mechanisms like the opening of ion channels and modulation of the levels of various enzymes like kinases and phosphatases which are involved in cell signaling. Unlike, genomic actions, the transcription independent actions of vitamin D are rapid.20

**PHYSIOLOGICAL ROLES OF VITAMIN D**

Vitamin D plays a key role in maintaining calcium and phosphate homeostasis in the body (Figure 2). It helps to maintain serum calcium levels within its normal limits by acting on various target organs like intestine, kidneys, bones and parathyroids. It increases serum calcium levels by the following mechanisms. Vitamin D increases intestinal calcium absorption by both transcellular and paracellular pathways. This is...
functions of vitamin D as a versatile signaling molecule. Thus, the role of vitamin D is further extended to a multitude of physiological roles beyond bone mineral homeostasis. Vitamin D is found to have anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulatory effects. It is also implicated in having anti-tumour action by inhibiting the growth and promoting the differentiation of cancer cells especially in colon cancer. It also protects against certain inflammatory diseases like inflammatory bowel disease, asthma, chronic kidney disease and nonalcoholic fatty liver disease. Vitamin D is involved in keratinocyte differentiation in the skin, and its deficiency is implicated in a variety of cutaneous diseases like skin cancer, psoriasis, vitiligo, pemphigus vulgaris and atopic dermatitis.

The evidence for pleiotropic actions of vitamin D was further substantiated by the discovery of extra-renal 1-alfa hydroxylase enzymes. Their presence came to limelight when cultured pulmonary alveolar macrophages from patients with chronic granulomatous diseases like sarcoidosis exhibited 1-alfa hydroxylase activity and could convert 25-hydroxyvitamin D3 to its active form 1,25-dihydroxyvitamin D3. Extra-renal 1-alfa hydroxylase (CYP27B1) enzymes were found in various tissues like placenta, lymph nodes, and skin. These enzymes aid in the local production of calcitriol which acts in an autocrine or paracrine manner on their cognate vitamin D receptors to modulate cell proliferation and differentiation. Other novel sites like adrenal medulla, brain, pancreas, and colon also demonstrated the presence of these enzymes. However, their precise physiological roles at extra-renal sites are yet to be demystified and warrant further studies. At present, studies have not yet been able to delineate the differences in the physiological roles played by calcitriol produced from kidney and extra renal tissues. However, studies have revealed that the extra-renal production and inactivation of calcitriol is under stringent control and is influenced by local production of various inflammatory mediators like interferon-γ.

RECOMMENDED DIETARY ALLOWANCES (RDA) OF VITAMIN D

According to the Institute of Medicine (IOM) committee’s 2011 report, adequate dietary vitamin D per day should be 400 IU in infants, 600 IU in the age group of 1 to 70 years, and 800 IU for individuals above 70 years of age (Table 2). This dietary recommendation is in addition to

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<tr>
<th>S. No.</th>
<th>Dietary source</th>
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<tr>
<td>1.</td>
<td>Animal sources (contain vitamin D3 or cholecalciferol)</td>
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<td></td>
<td>Fish (salmon, mackerel, tuna and sardines)</td>
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<td>Beef</td>
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<td>Egg yolk</td>
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<td>Milk and milk products (yogurt, butter, and cheese)</td>
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<td>2.</td>
<td>Plant sources (contain vitamin D2 or ergocalciferol)</td>
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<td>Mushrooms (when exposed to UVB radiation, ergosterol present in them gets converted to ergocalciferol)</td>
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<td>3.</td>
<td>Foods fortified with vitamin D</td>
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<td></td>
<td>Milk and milk products (cheese, yogurt)</td>
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<td>Bread</td>
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<td>4.</td>
<td>Vitamin D supplements</td>
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mineral sunlight exposure, and it aims to achieve a 25-hydroxyvitamin D concentration of 20 ng/ml, which is established to be sufficient for the optimal bone health of an individual.\textsuperscript{30}

As per the United States Endocrine Society Clinical Practice Guidelines, the recommended daily intake of vitamin D is much higher compared to the IOM recommendations. It estimated the RDA of vitamin D to be 1000 IU/day in children (age group of 1 to 18 years) and 1500–2000 IU/day in adults (≥ 19 years of age). This is required to increase the serum 25-hydroxyvitamin D levels above 30ng/ml, which is considered as appropriate vitamin D concentrations in the body to enjoy its skeletal and non-skeletal benefits.\textsuperscript{31}

However, the Indian Council of Medical Research (ICMR) recommends a lower daily intake of vitamin D compared to the international guidelines and stresses on the need for adequate exposure to sunlight for healthy bones. According to ICMR, diet cannot substitute sunlight exposure for ensuring adequate vitamin D stores in the body. Thus, ICMR recommends a daily intake of 400 IU (10 μg) of vitamin D with minimal exposure to sunlight. Unlike other guidelines, ICMR has not given any specific recommendations for vitamin D intake based on differences in age groups.\textsuperscript{32}

**ASSESSMENT OF VITAMIN D STATUS**

In spite of the fact that 1,25-dihydroxyvitamin D is the biologically active metabolite of vitamin D biosynthesis, estimation of its serum concentration is not routinely undertaken to determine the vitamin D status of an individual. This is attributed to its short half-life of 4 hr as serum concentrations will not reflect the vitamin D stores of the body, rather it would be influenced by the recent exposure to sunlight or dietary intake of vitamin D. Moreover, its serum concentration would be varying depending on the calcium requirements of the body.\textsuperscript{34} Therefore, measurement of serum 25-hydroxyvitamin D levels is considered as the single best indicator for estimation of the vitamin D status of a person.\textsuperscript{33} The main advantage of using 25-hydroxyvitamin D levels as a marker of vitamin D stores is that it has a longer half-life of 3 weeks, and thus its serum levels would be a better representation of body's vitamin D stores.\textsuperscript{34} Serum 25-hydroxyvitamin D levels reflect the amount of vitamin D synthesized from sunlight as well as that obtained from the dietary sources and supplements. There are two forms of 25-hydroxyvitamin D, namely 25-hydroxy vitamin D\textsubscript{3} and 25-hydroxy vitamin D\textsubscript{4}, obtained by 25-hydroxylation of ergocalciferol and cholecalciferol respectively. Majority of the methods measure both the metabolites of 25-hydroxyvitamin D, namely D\textsubscript{3} and D\textsubscript{4} as total 25-hydroxyvitamin D.\textsuperscript{35} The concentration of 25-hydroxyvitamin D in the blood is usually in nanomolar to micromolar range, thus requiring highly sensitive methods for its quantification.

The assay methods developed for measurement of serum or plasma 25-hydroxyvitamin D levels include high performance liquid chromatography (HPLC), radioimmunoassay (RIA), enzyme-linked immunoabsorbent assay (ELISA), chemiluminescent assay and liquid chromatography–tandem mass spectrometry (LCMS/MS).\textsuperscript{36} However, a lot of variation exists between the concentrations of 25-hydroxyvitamin D estimated by the various assay platforms in different laboratories due to a lack of proper standardization procedure.\textsuperscript{37} Among the various assay techniques, LCMS/MS is considered to be the gold standard method for estimating 25-hydroxyvitamin D levels to assess the vitamin D nutritional reserves of an individual.\textsuperscript{38}

Apart from 25-hydroxyvitamin D levels, other biomarkers like parathormone levels, bone mineral density, and intestinal calcium absorption are also being employed to assess the vitamin D nutritional status of an individual.\textsuperscript{39} Although 25-hydroxyvitamin D is the robust and reliable marker of vitamin D status, there are some cases where measurement of 1,25-dihydroxyvitamin D levels provide useful information. In certain conditions like chronic renal diseases (defects in 1-alfa hydroxylation), vitamin D-dependent rickets (absence of 1-alfa hydroxylase), vitamin D resistant rickets (genetic defects in vitamin D receptor and associated with high circulating levels of 1,25-dihydroxyvitamin D) and granulomatous diseases like sarcoidosis (extrarenal 1-alfa hydroxylation causes increase in 1,25-dihydroxyvitamin D levels), measurement of 1,25-dihydroxyvitamin D levels is indicated.\textsuperscript{40}

**SAMPLE PROCESSING FOR VITAMIN D ANALYSIS**

A study was undertaken by Colak et al.,\textsuperscript{41} to assess the influence of various parameters like sample type (serum or plasma), centrifugation temperature and storage conditions, on estimated 25-hydroxyvitamin D levels. It was found that neither sample type nor centrifugation temperature had an effect on the measured vitamin D concentration. Further, the authors observed that the stability of 25-hydroxyvitamin D was maintained over a duration of 4 hr when placed at room temperature and for 1 day when stored at 2-8°C. It was also noticed that preserving the samples at -20°C and -80°C increased the stability of the metabolite to be estimated for a period of 7 days and 3 months respectively.

In another study, done by Antoniucci et al.,\textsuperscript{42} the authors noticed that the metabolite 25-hydroxyvitamin D is highly stable, and its serum concentrations are not altered by multiple freeze-thaw cycles (up to four times). The effect of delayed centrifugation of collected blood samples (2, 24, 72 and 96 hr after blood sample collection), type of tubes for blood collection (serum tube, plasma tube with heparin as anticoagulant and plasma tube with EDTA as anticoagulant) and assay method (radioimmunoassay and chemiluminescence immunoassay) on the estimated 25-hydroxyvitamin D levels was analyzed in a study by Yu et al.,\textsuperscript{43} It was observed that there was no difference in 25-hydroxyvitamin D levels with respect to time of centrifugation or type of assay. However, it was found that the concentration of 25-hydroxyvitamin D in heparinized plasma was higher than that in serum especially when there was a substantial delay in centrifugation.

**CLASSIFICATION OF VITAMIN D STATUS BASED ON SERUM 25-Hydroxyvitamin D LEVELS**

There is no concurrence regarding the optimal serum vitamin D levels for better health. The cut-off value for serum 25-hydroxyvitamin D levels to determine vitamin D deficiency has been a matter of debate. Various biomarkers concerning calcium metabolism have been used to define the optimal 25-hydroxyvitamin D levels to maintain healthy bones. These biomarkers are serum parathormone levels and intestinal calcium absorption. It has been demonstrated that there is an inverse correlation between serum 25-hydroxyvitamin D levels and serum parathormone levels.\textsuperscript{44} When serum 25-hydroxyvitamin D levels are < 32 ng /ml, there is an elevation in the serum parathormone levels (secondary hyperparathyroidism) and once 25-hydroxyvitamin D levels reach this threshold concentration 32 ng /ml, serum parathormone levels normalize, and there is subsidence of secondary hyperparathyroidism.\textsuperscript{45}

Similarly, it was also found that there was an increase in intestinal calcium absorption with rise in serum 25-hydroxyvitamin D levels, and it reached a peak at serum 25-hydroxyvitamin D concentrations of 32 ng/ml and plateaued thereafter. This indicates that the maximum absorptive capacity for intestinal calcium has been achieved with serum 25-hydroxyvitamin D concentrations of 32 ng /ml.\textsuperscript{44} It was thus proposed that serum 25-hydroxyvitamin D level< 32 ng /ml to be used as the cut-off for classification of vitamin D deficiency.\textsuperscript{45,44}

Later, two professional organizations (US Endocrine Society and Institute of Medicine) have given their recommendations regarding the optimal
levels of 25-hydroxyvitamin D required for good bone health which is summarized in Table 3.31,45

Paul Lips has proposed a classification of vitamin D deficiency into mild, moderate and severe, based on serum 25-hydroxyvitamin D levels. He has classified serum 25-hydroxyvitamin D levels of 10-20 ng/ml as mild, 5-10 ng/ml as moderate and < 5 ng/ml as severe vitamin D deficiency.46 The conversion factors for various units used to quantify 25-hydroxy vitamin D levels are 1 ng/ml = 2.5 nmol/l, 1μg = 40 IU = 2.5 nmol.45

VITAMIN D TOXICITY
Vitamin D toxicity refers to serum 25-hydroxyvitamin D levels >150 ng/ml. Hypercalcemia, decrease in parathormone levels and elevated urine calcium levels are other biomarkers of vitamin D toxicity.47 Vitamin D toxicity occurs due to overconsumption of vitamin D supplements or fortified foods. Dietary intake of vitamin D containing natural foods contributes to only 10-20 % of circulating 25-hydroxyvitamin D levels and hence does not lead to vitamin D toxicity.45

Prolonged exposure to sunlight does not lead to vitamin D toxicity as it is a self-regulated process. During prolonged UVB exposure, the synthesized previtamin D₃ gets converted into biologically inert photo-isomers namely lumisterol and tachysterol. These isomers have a very low affinity to vitamin D binding proteins, and thus they remain at their site of synthesis in the epidermis and cannot be translocated into the blood stream. Moreover, they are lost with natural skin turnover, thus protecting the body from the risk of vitamin toxicity.5

The manifestations of vitamin D intoxication are nausea, vomiting, abdominal pain, anorexia, constipation, polydipsia, polyuria, myalgia, bone pain, osteoporosis, metastatic calcification, arrhythmia, and seizures.47 Treatment includes discontinuation of vitamin D intake, low calcium diet, intravenous fluids, diuretics, and steroids. However, the main aim of therapy revolves around management of hypercalcemia.47

VITAMIN D DEFICIENCY
Vitamin D deficiency has become a global pandemic and is highly prevalent in all age groups, including children, adolescents, adults, pregnant and lactating women.48 According to a systematic review of vitamin D status in healthy Indians, the mean 25-hydroxyvitamin D levels ranged from 3.15 ± 1.4 to 32.9 ± 33.7 ng/ml and vitamin D deficiency was prevalent in all parts of India.49 According to another study by Shivane et al.,50 the prevalence of vitamin D deficiency (< 20 ng/ml) in young healthy Indian adults was found to be 70%. Thus, despite being a country with abundant sunshine, India also faces the problem of vitamin D deficiency.

The high prevalence of hypovitaminosis can be attributed to multiple causes. Since sunlight is the major contributor to the body’s vitamin D stores, the major causes of vitamin D deficiency are lack of adequate exposure to sunlight, use of sunscreen and increased melanin content of the skin. It could also be due to lack of intake of vitamin D-rich foods or defect in intestinal absorption of vitamin D (fat malabsorption disorders or use of medications like cholestyramine which interfere with intestinal fat absorption).51 Other reasons are intake of drugs affecting vitamin D metabolism eg. glucocorticoids, anticonvulsants, and anti-HIV drugs. Vitamin D deficiency due lack of conversion of vitamin D into its biologically active form.52 Old age (reduced 7-dehydrocholesterol content of epidermis) and obesity (sequestration of vitamin D in the adipose tissues) are also risk factors for vitamin D deficiency.53

Vitamin D deficiency has many implications as vitamin D is intricately linked with maintenance of calcium homeostasis. It is associated with defect in mineralization of the skeleton and manifests either as rickets or osteomalacia in children and adults respectively.54 Vitamin D deficiency leads to a decrease in intestinal absorption of calcium and phosphate with resultant hypocalcemia stimulating the release of parathormone, thus producing secondary hyperparathyroidism. Parathormone causes calcium mobilization from the bones to restore the serum calcium levels, thus leading to the development of osteopenia and osteoporosis.55 A prospective cohort study in elderly individuals found that patients with low vitamin D levels had a higher risk of developing hip fractures compared to those with adequate vitamin D status.56 Another cohort study by De Boer et al.,57 has shown that low 25-hydroxyvitamin D status (<20 ng/ml) is associated with increased risk of hip fractures, myocardial infarction, cancer and death in a population of older adults over a follow-up period of 11 years. Studies have also shown that vitamin D deficiency is also associated with increased arterial stiffness and increased risk for adverse cardiovascular outcomes and all-cause mortality.58,59 A substantial body of evidence indicates the association between vitamin D deficiency and various malignancies like colon, breast and prostate cancers. Vitamin D deficiency is also associated with other diseases like inflammatory bowel disease, asthma, vitiligo, pemphigus vulgaris and atopic dermatitis.15,26

Vitamin D supplementation along with calcium in patient with low vitamin D levels is associated with improvement in bone mineral health and reduced risk for occurrence of fractures.63 However, it is not yet known whether supplementation of vitamin D would prevent the occurrence of non-skeletal diseases associated with its deficiency. Some studies have shown that vitamin D supplementation improves vascular functions and reduces oxidative stress in vitamin D deficient patients.64,65 A randomized controlled trial has demonstrated the beneficial effects of calcium and vitamin D supplementation in reducing cancer risk in post-menopausal women.66 There are also conflicting results with the use of vitamin D supplementation in prevention of cardiovascular diseases or cancer.67 Thus, further studies are warranted to establish whether
vitamin D supplementation is beneficial in providing non-skeletal benefits in patients with vitamin D deficiency.

CONCLUSION

Vitamin D is a fat soluble prohormone synthesized in our body with the help of UV-B radiation. It undergoes a process of two-step metabolic activation in the body, first 25-hydroxylation in the liver and followed by 1-alfa hydroxylation in the kidneys to form the biologically active metabolite 1,25 dihydroxycholecalciferol or calcitriol. Calcitriol binds to the vitamin D receptors and mediates its actions. Its major role is to maintain the bone mineral homeostasis and regulate the serum calcium levels. However, the presence of vitamin D receptors at sites other than those involved in bone mineral homeostasis and occurrence of extra renal 1-alfa hydroxylase enzyme led to the identification of the pleiotropic effects of vitamin D as an anti-inflammatory, anti-apoptotic, anti-fibrotic and immunomodulatory agent. The serum 25 hydroxyvitamin D levels are used as biomarkers to assess the vitamin D stores of an individual. Based on the serum 25 hydroxyvitamin D levels, individuals can be classified into vitamin D deficient, insufficient and those with normal vitamin D levels. Vitamin D toxicity refers to serum 25-hydroxyvitamin D levels >150 ng/ml and is predominantly due to excessive vitamin D supplementation. Vitamin D deficiency is highly prevalent and is associated with various diseases like osteoporosis, bone fractures, myocardial infarction and cancer. The studies regarding vitamin D supplementation in providing non-skeletal benefits is ambiguous and conflicting. Thus, further research is required in this field to uncover the potential benefits of the sunshine hormone in various non-skeletal diseases like cardiovascular diseases and cancer.

ACKNOWLEDGEMENT

I would like to thank Dr. Steven. A. Dkhar, Late Professor and Head, Department of Clinical Pharmacology, JIPMER, Puducherry, India, for his valuable support in writing this review.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

UVB: Ultraviolet B; MED: Minimal erythema dose; IU: International units; DBPs: Vitamin D binding proteins; CYP27B1: Cytochrome P27B1; VDR: Vitamin D receptors; RXR: Retinoid X receptor; VDRE: Vitamin D response elements; RDA: Recommended dietary allowances; IOM: Institute of Medicine; ICMR: Indian Council of Medical Research; HPLC: High performance liquid chromatography; RIA: Radioimmunoassay; ELISA: Enzyme-linked immunosorbent assay; LCMS/MS: Liquid chromatography–tandem mass spectrometry; EDTA: Ethylene-diamine-tetraacetic acid.

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