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Vitamin D: A Review on Functions and Requirements (Part II)

Authors
Dr Vishakha S. Patil[1], Dr Rohini S. Mali[2], Dr Alpana Moghe[3]
[1]Dept of Periodontology, Bharati Vidyapeeth Deemed University, Dental College and Hospital, Pune, India
Email: *drvishakhap@gmail.com*
[2]Dept of Periodontology, Bharati Vidyapeeth Deemed University, Dental College and Hospital, Pune, India
Email: *rohinimali4@gmail.com*
[3]Dept of Cell and Molecular Biology, Rajiv Ganghi Institute of Information, Technology and Biotechnology, Bharati Vidyapeeth Deemed University, Pune, India
Email: *alpanasm@gmail.com*

ABSTRACT
Vitamin D a fat soluble vitamin is also a hormone which along with its effect on bone mineralization, exerts its effect on cells by binding to Vitamin D receptor present on most cell types in the body. Its broad spectrum of activities in skin, immune system, cell differentiation and development underlines its crucial role in regulation of metabolism. The present review is an attempt to provide compiled information on the crucial role played by this vitamin in controlling the functions of body tissues. This review also highlights necessary intake values, dietary sources, normal serum levels and toxicity associated with excess intake. The review article intends to spread the knowledge that vitamin D is absolutely critical for good health and disease prevention.

Keywords- *Inactive Vitamin D_3, Calcitriol, Vitamin D deficiency, Immune response, Cancer prevention.*

INTRODUCTION

Advanced knowledge of the biological and clinical importance of the steroid hormone 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] and its receptor, the Vitamin D Receptor (VDR), has resulted in significant contributions to good bone health. Over the past several decades, the biological sphere of influence of Vitamin D3,as defined by the tissue distribution of the VDR, has broadened at least 9-fold from the target organs required for calcium homeostasis (intestine, bone, kidney, and parathyroid). Now, research has shown that the pluripotent steroid hormone1,25(OH)2D3 initiates the physiologic responses of 36 cell types that possess the VDR. Thus new biological actions of 1,25 (OH)2D3 through the VDR has been identified. An attempt is made in this article to review all the actions of Vitamin D3. Also requirements and sources of Vitamin D3 are highlighted. So that, one gets an idea about the necessity of this hormone for proper functioning of our body.

FUNCTIONS OF VITAMIN D3

The mechanism by which an active Vitamin 1α $25(OH)_2$ D_3 exerts its effects has been extensively investigated. The Vitamin D system shows similar features like other ligand activated nuclear receptors such as the retinoic acid receptor (RAR) and thyroid hormone receptor (TR).[1] The biological effects of 1α $25(OH)_2D_3$ (Ligand) are mediated via binding to the

Vitamin D Receptor (VDR). Vitamin D Receptor (VDR) is a member of the steroid nuclear receptor super family found in Vitamin D targets. The VDR gene is positioned on human chromosome 12q. VDR can be divided by function into different domains (Figure I).

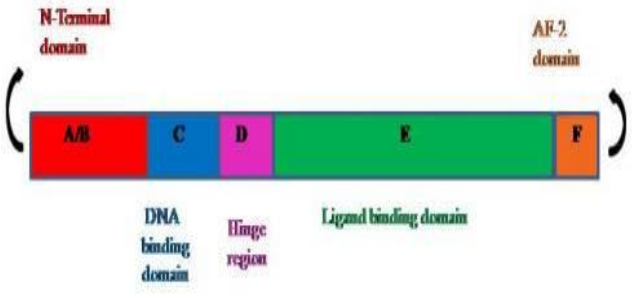

FIGURE I - VDR Domains

Amongst these domains the ligand binding domain is responsible for high affinity binding of ligand. Upon ligand binding the receptor dimerizes with retinoid X receptor (RXR). This complex binds to Vitamin D Responsive elements (VDRE) within the promoter regions of Vitamin D response genes (Figure II). Other proteins responsible for transcription are recruited and thus transcription takes place. Depending on co-activators or co-repressors transcriptional activity is either upregulated or downregulated.[2]

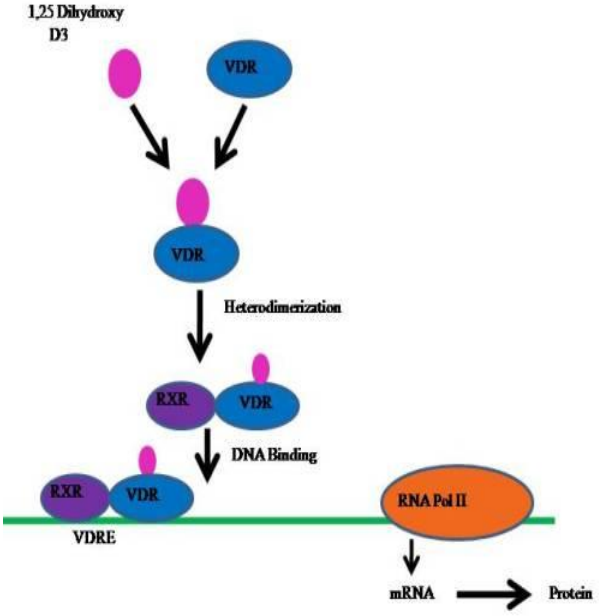

FIGURE II – BIOLOGICAL RESPONSE OF VITAMIN D3

VDR: Vitamin D Receptor, RXR: Retinoid X Receptor, VDRE: Vitamin D Responsive Element, RNA Pol II: RNA polymerase II

Mineralization of Skeleton

Vitamin D causes bone mineralization by the elevation of plasma calcium and phosphorus concentrations.[3] A major function of 1α $25(OH)_2$ D_3 is that it promotes intestinal absorption of calcium and phosphate. Along with PTH it also initiates the renal reabsorption of calcium in the distal tubule.[4] The above sources of calcium result in rise in blood calcium for support of mineralization and prevention of hypocalcemic tetany. $1\alpha25(OH)_2D_3$ may also have direct effects on the bone.[5] In vitro studies have shown that 1α $25(OH)_2$ D_3 stimulates osteoblasts, to differentiate and deposit calcified matrix.[6] The calcium concentration in blood is held constantly at 1 mmol ionized calcium or 10 mg/100 ml of total calcium. However when dietary sources are inadequate to maintain normocalcemia, 1,25-$(OH)_2D_3$ stimulates calcium mobilization from the bone by promoting the differentiation of precursor cells into mature, bone-resorbing osteoclasts.[7] The development of the giant osteoclast, plays a major role in bone remodeling, and bone resorption.[8] Vitamin D along with parathyroid hormone (PTH) stimulates osteoclast-mediated bone resorption.[9] Vitamin D and the PTH, as well as other factors, s timulate the transcription and production of RANKL, the ligand for the NFkB receptor. When this occurs, the osteoclast precursors are converted to mononuclear prefusion osteoclasts that differentiate and then become activated osteoclasts.

Regulation of Immunity

Vitamin D hormone is an immune system modulator, it stimulates the innate immune response in antigen presenting cells like macrophages and dendritic cells. When activated nonspecifically with mitogen or specifically with antigen, the macrophage becomes a target for vitamin D by expressing VDR and promotes antigen processing, phagocytosis, superoxide synthesis, interleukin 1beta and tumor necrosis factor alpha production, to rid the host of the offending agent.[10] Like the macrophage, mitogen or antigen activated lymphocytes also express the VDR.[10] VDR regulates the production of T-Cell helper 1 and 2 cytokines

and IL-17 thus influencing adaptive immunity and inflammation.[11] The TH1 cytokine interferon γ enhances the TLR2/1 induction of CYP27 B1, Cathelicidin. Cathelicidin have significant broad antimicrobial activity against both gram positive and gram negative bacteria.[12].1,25 dihydroxyvitamin D_3 induces antimicrobial peptide gene expression in isolated human keratinocytes, monocytes and neutrophils and human cell lines.[13]

Role in maintaining Periodontal health

Periodontitis even though is multifactorial disease, presence of specific bacteria and host immune response to bacterial insult is required for disease initiation and progression. It is characterized by alveolar bone loss. Both genetic and environmental factors enhance susceptibility to Periodontal disease.[14] Because vitamin D plays a role in bone maintenance and immunity there is biologic rationale to suspect that Vitamin D deficiency could negatively affect the Periodontium. From the Analysis of data of NHANES III (National health and Nutrition Examination Survey), it was revealed that higher levels of $25(OH)D_3$ reduced the risk of gingival inflammation by exerting anti-Inflammatory effects.[15] In a study by Garcia et al 2011,[16] Periodontal maintenance subjects taking calcium and Vitamin D supplements showed better periodontal health. As alveolar bone loss is a key feature in periodontitis some association studies involving Vitamin D Receptor have been conducted.[17, 18] considering the immunomodulatory effect of Vitamin D, it can be applied to periodontal health.[19]

Differentiation of cells:

The first important breakthrough was in 1981 when it was demonstrated that terminal differentiation of promyelocytes to the monocyte could be brought about by the Vitamin D hormone.[20] Along with differentiation of the promyelocytes it suppressed proliferation of those cells. This may be related to suppression of certain significant cell cycle proteins.[21] The $1,25(OH)_2D_3$ inhibits the growth of various normal as well as cancerous cell types by blocking G1/S transition which causes G1 phase cells to accumulate and accordingly S-Phase cell numbers to decrease.[22,23] It has been shown to cause G2/M arrest.[24] Along with its effect on different cell cycle regulators, $1,25(OH)_2D_3$ also controls genomic stability. The fact that cancer cell growth suppression and differentiation induced by $1,25(OH)_2D_3$ has raised the hope that $1,25(OH)_2D_3$, or an analog, may be useful in the treatment of malignant disease.[25]

Role in Reproduction

Ovarian cells have been found to contain VDR.[26] Furthermore, ovarian cells in vivo also accumulate $1,25(OH)_2D_3$.[27] It has been suggested that the ovary therefore is a target of Vitamin D action.

Role in Skin

Hosomi et al in 1983 [28] provided the first In-Vitro report that $1,25(OH)_2D_3$ induces keratinocyte differentiation. Holick and co-workers [29] also gave similar reports. Hyperproliferation of the keratinocyte and failure to differentiate was not found in Vitamin D-deficient animals [30] Differentiation property of $1,25(OH)_2D_3$ has been utilized in the treatment of hyperproliferative diseases of skin such as psoriasis.[31] During the differentiation process, it was found that there is an increase in the protein involukrin,[32] transglutamase activity [32] and cornified envelope formation.[33] The $1,25(OH)_2D_3$ produced by the keratinocyte itself, stimulate its differentiation.[34]

Other Actions

One more interesting area is autoimmune disease. In 1993 Yang S et al demonstrated that Vitamin D suppresses delayed hypersensitivity response.[35] In an experimental model of multiple sclerosis, super physiologic amounts of $1,25(OH)_2D_3$ completely blocked experimental autoimmune encephalom-yelitis.[36] Rheumatoid arthritis could also be suppressed by $1,25(OH)_2D_3$.[37] Vitamin D hormone also helped block type I diabetes in the non-obese diabetic mouse.[38]

REQUIREMENT AND SOURCES

Federal Governments Institute of Medicine (IOM) Food and Nutrition Board (Washington, DC [39]) at the end of 2010, proposed some improved recommendations (Table I). It increased the recommended dietary allowance for most adults from 200-600 IU (up to 800 IU for those 71 and older) to maintain healthy bones.

Table I: Vitamin D Dietary Reference Intakes

Vitamin D Dietary Reference Intakes				
Sr. No	**Life Stage Group**	**EAR**	**RDA**	**UL**
1.	Male 19-30 Years Old	400 IU	600 IU	4000 IU
2.	Male 31-50 Years Old	400 IU	600 IU	4000 IU
3.	Male 51-70 Years Old	400 IU	600 IU	4000 IU
4.	Male above 70 Years of Age	400 IU	800 IU	4000 IU
5.	Female 19-30 Years Old	400 IU	600 IU	4000 IU
6.	Female 31-50 Years Old	400 IU	600 IU	4000 IU
7.	Female 51-70 Years Old	400 IU	600 IU	4000 IU
8.	Female above 70 Years Age	400 IU	800 IU	4000 IU

EAR: Estimated Average Requirement (Intake that meets needs of50% of individual).
RDA: Recommended dietary Allowance (Intake that meets the needs of 97% to 98% of Individuals).
UL: Tolerable Upper Intake Level (Highest level of Intake that poses no adverse effects).
IU: International Units.

In the light of new research RDA guidelines are not sufficient. More units of Vitamin D are required every day to prevent risk of infection, cancer and various diseases.

In a conference held on November 3rd 2009 at University of Toronto, Ontario, Canada, Robert P Heaney, Reinhold Vieth, John White and Susan Whiting[40] had suggested Vitamin D recommendations as follows:

Table II: Vitamin D Recommendations

Vitamin D Recommendations		
Sr. No	**Age**	**Dosage**
1	Below 5	35 Units per pound per day
2	Age 5-10	2500 Units
3	Adults	4000-8000 Units
4	Pregnant Women	5000-10000 Units

Based on the most recent research, the current recommendation is 35 IUs of Vitamin D per pound of body weight. Bischoff-Ferrari HA in 2006 [41] indicated that the desirable 25(OH)D concentration is _75 nmol/L. Cholecalciferol (Vitamin D_3) is more potent than ergocalciferol (Vitamin D_2) and the safe upper intake level for Vitamin D_3 is 10,000 IU/d.

However Vitamin D requirements differ for each individual as Vitamin D status is dependent on numerous factors which affect absorption or production of Vitamin D_3 through skin. When skin is exposed to UV rays, precholecalciferol is formed which can isomerizes to cholecalciferol or photoisomerize into biologically inactive photoisomers, lumisterol and tachysterol.[42] Melanin pigmentation reduces the efficiency of sun mediated photosynthesis of precholecalciferol.[43,44] Age is another factor which declines production of adequate amounts of Vitamin D_3. Application of sunscreen also prevents cutaneous production of precholecalciferol.[45] Covering of skin with any type of clothing in any season prevents cutaneous production of cholecalciferol.[46]

Apart from its production in the skin, Vitamin D_3 has some dietary sources. The food sources are as follows: [47]

Table III: Food Sources

Food Sources		
Sr. No	**Food sources**	**Quantity (IU)**
1.	Oily fish and Fish liver oils (Cod Liver oil)(Best source) -1 tbs	1360 IU
2.	Sword Fish cooked 3 oz	566 IU
3.	Salmon cooked 3 oz	447 IU
4.	Liver, Beef cooked 3.5 oz	42 IU
5.	Egg 1whole (In the yolk)	41 IU
6.	Cheese (Swiss) 1 oz	06 IU

IU : International Unit, tbs : Table spoon, oz :Ounces

As Vitamin D_3 is fat soluble its absorption can be enhanced using nutritional oils like Flaxseed oil, evening Primrose oil, or fish oils in the diet. Subjects with chronic fat absorption problems should be investigated for Vitamin D and bone status. Use of Olestra diminishes absorption of fat soluble Vitamins A, D, E and K. Magnesium supplementation is required to convert Vitamin D_2 to D_3. It also acts as enzyme cofactor for converting cholecalciferol to Inactive and Active form of Vitamin D_3. Vitamin D absorption and /or metabolism are also interfered by Bile acid sequestrants like cholestyramine, corticosteroids, dilantin, barbiturates, phenobarbital, etidronate, tuberculosis drugs and mineral oils.

SERUM LEVELS

The normal Levels of 25 Hydroxy D_3 in blood are 30 ng/ml (75 nM) to 60 ng/ml(150 nM). Serum concentration of 25-hydroxyvitamin D_3 from 21 – 29 ng/ml is considered Insufficient and levels below 20 ng/ml (50 nM) are considered serious deficiency states. Levels greater than 150 ng/ml (374 nM) are believed to be toxic, and are associated with hypercalcemia, hypercalciuria and, hyperphosphatemia.[48] A review by Hathcock JN et al [49] in 2007 has discussed the risk assessment for Vitamin D. They focused on the risk of hypercalcemia and concluded that the Upper Intake Level (UL) for Vitamin D consumption by adults should be 10000 IU/d thus margin of safety for Vitamin D consumption for adults is more than 10 times any current recommended intakes.

TOXICITY

Following World War II, an outbreak of idiopathic hypercalcemia and related arterial supravascular stenosis was attributed to food fortification with Vitamin D.[50] Certainly, Vitamin D is potentially toxic when provided in large amounts. Toxicity results in hypercalcemia, nephrocalcinosis, aortic calcification, and other unwanted deposits of calcium and phosphorus in soft tissues.[51] A report indicated that 10,000 units of Vitamin D_3 per day is safe for 6 Months,[53] but we must remember that Vitamin D itself is stored and the danger of it accumulating in the adipose tissue and possibly resulting in toxicity in the future must be investigated.

CONCLUSION

The research on Vitamin D has increased tremendously. Vitamin D deficiency and insufficiency is pandemic and seen in essentially every country in the world. Lack of awareness about the importance of this deficiency has become very crucial. Its deficiency has led to increased risk of the most serious chronic illnesses such as cancer, type 2 diabetes, autoimmune diseases and infectious diseases in the world's population. Awareness is required in the medical community and public about the insidious consequences of Vitamin D deficiency. As there are very limited food sources and less exposure of skin to sun, daily intake is recommended. Importance of Vitamin D adequacy will definitely have a dramatic impact on the health and welfare of all children and adults and people should consume fortified food or should be given supplements of Vitamin D perhaps to ensure adequacy of essential element especially Vitamin D.

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ABBREVIATIONS AND ACRONYMS

1α $25(OH)_2$ D_3 - 1α25 dihydroxy D3
RAR - Retinoic Acid Receptor
TR - Thyroid hormone Receptor
VDR - Vitamin D Receptor
RXR - Retinoid X Receptor
VDRE - Vitamin D Responsive Element
RNA Pol II - Ribonucleic Acid polymerase II
mRNA - Messenger Ribonucleic Acid
PTH - Parathyroid Hormone
mmol - Milli mole
mg - Milligram
ml - Millilitre
RANKL - Receptor activator of nuclear factor kappa- B ligand
NFkB - Nuclear Factor kappa-light-chain enhancer of activated B cells
IL17 - Interleukin 17
TH1 - T helper 1
γ - Gamma
TLR - Toll like receptors
CYP 27 - Cytochrome P 27
NHANES - National Health and Nutrition Examination Survey
IU - International Units
IOM - Institute of Medicine
EAR - Estimated Average Requirement

RDA - Recommended Dietary Allowances
UL - Tolerable Upper Intake Level
nm/L - Nano mole/ Litre
IU/d - International Unit / Decilitre
UV rays- Ultraviolet rays
tbs – Table spoon
Oz - Ounces
ng/ ml - Nano gram/ millilitre
nM - Nano Mole