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Vitamin D: A Review on Metabolism and Regulating Factors (Part I)

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ABSTRACT
Vitamin D although was identified in early years of 20th century as a vital component needed for the treatment of rickets, it remained unexplored for a long period. Key findings in recent years brought Vitamin D again in forefront and now it is considered to be the most important Vitamin. It acts as a hormone and is required by most of the cells of our body.
Before we discuss its functions one must be aware about the metabolism of Vitamin D. In this Review an attempt is made to provide detailed information on the metabolism and regulating factors of Vitamin D.
Keywords-*7-dehydrocholesterol, cholecalciferol , 25 hydroxyvitamin D3 , 1α,25(OH)2D3*.

INTRODUCTION

Vitamin D endocrine system is the most sensitive biological system used to sense the sunlight. It is important to know how this sunlight is converted to a metabolite which is circulated in the body. This metabolite known as Vitamin D was previously considered a "Vitamin" and later was found to function as a "Hormone." It is must to understand how this Vitamin was discovered, who chemically identified this Vitamin, how the structure of In-active and Active forms of Vitamin D were identified and how accidently Vitamin D Receptor (VDR) was discovered. This review article highlights the historical background. We have emphasized on synthesis of Vitamin D in detail. This review has also focused on the different up-regulating and down-regulating factors of Vitamin D. This will help us understand the importance of this Vitamin in our body,

HISTORICAL BACKGROUND

After first discovery of Vitamin in 1913[1] by McCollum and Davis, many outstanding contributions came up regarding Vitamin D. Most noteworthy was the 1st evidence of existence of Vitamin D by Sir Edward Mellanby in 1919. He created Rickets in dogs by giving them oatmeal feed and maintaining them indoor.[2] Huldshinsky in 1919

stated that rickets in children could be cured by ultraviolet light.[3] Steenbock and Black, Hess and Weinstock independently very clearly demonstrated that ultraviolet light is capable of converting an inactive substance found in foods, skin, and elsewhere into a substance that could heal rickets.[4, 5] In 1931 Askew et al[6] deduced the structure of Vitamin D_2 whereas the structure of Vitamin D_3 was determined through synthetic means by Windaus et al (1936)[7]. In 1967 the concept appeared that Vitamin D exists in inactive form in the blood and is converted to an active form.[8,9] By 1969 the circulating form of Vitamin D was isolated, chemically identified and synthesized.[10] Holick MF in 1971 isolated and identified
the final active form of Vitamin D_3.[11] Its structure was identified as 1α, 25- di hydroxyl vitamin D_3 by Semmler EJ in 1972.[12] Thus this $1,25(OH)_2D_3$ was considered as fully active hormonal form of Vitamin D which not only regulates calcium and phosphorus metabolism but also has non calcemic role. It was found to have very interesting and curious biologic actions on cells not associated with calcium metabolism. In an attempt to understand how the active form of Vitamin D carries out its function, Lawson DE in 1974[13] and Braumbaugh in 1975[14] discovered Vitamin D Receptor (The receptor specific for Vitamin D ligand)
Intensive research on Vitamin D has identified it as an exotic molecule essential for functioning of various cells.

METABOLISM (Figure I and Figure II)

The high energy ultraviolet B photons from sunlight, with energies between 290 and 315 nm penetrate into the skin where they are absorbed by epidermal and dermal stores of 7-dehydrocholesterol (Provitamin D_3)[15] a metabolite present in the skin (Figure II). 7-DHC is present in all layers of human skin. Approximately 65% of 7-DHC per unit area is found in the epidermis and the remaining 35% is in the dermis. However, the amount of previtamin D3 produced also depends on the number and energy of the photons reaching each layer of skin After absorption of Ultraviolet B photons there is bond cleavage of 7-dehydrocholesterol between carbons 9 and 10 to form a 9,10 secosterol - precholecalciferol a Previtamin D_3 (Figure I & Figure II).

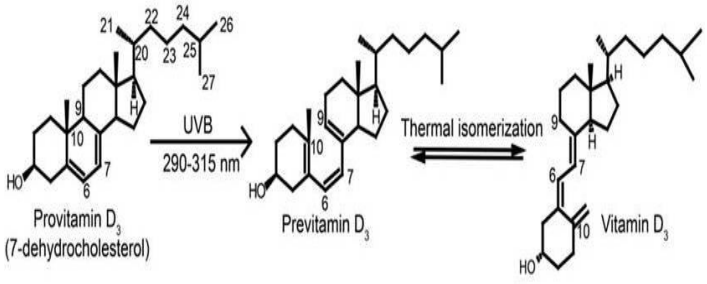

FIGURE I– CONVERSION OF PROVITAMIN D3 TO PREVITAMIN D3

This Previtamin D_3 is biologically inert and undergoes isomerization to form cholecalciferol (Figure II). Thus most of the precholecalciferol (Previtamin) initially formed in the skin is converted to cholecalciferol. The cholecalciferol from skin exits into the dermal capillary bed. In the capillaries, it is bound to the Vitamin D binding protein.[15] The excess cholecalciferol if formed in the skin, does not escape into circulation and is efficiently converted to 5, 6 trans-cholecalciferol (Supersterol I and Supersterol II).[16] The cholecalciferol which enters into circulation is taken to the hepatic parenchyma where it is hydroxylated to 25 hydroxyvitamin D_3 (25 OH D_3) by one of the several high capacity enzyme cytochrome P450s mainly CYP 27 (Vitamin D_3 Hydroxylase) (Figure II). This 25(OH) D_3 is the most plentiful and stable serum metabolite of Vitamin D, bound with high affinity to serum Vitamin D Binding Protein (DBP) and other members of the albumin superfamily of proteins.[17] It is a major circulating form of Vitamin D_3, present in plasma at concentrations of 10-40 ng /ml (25-125 nM).[18] The serum level of this metabolically inactive form is used to determine the status of Vitamin D in subjects.

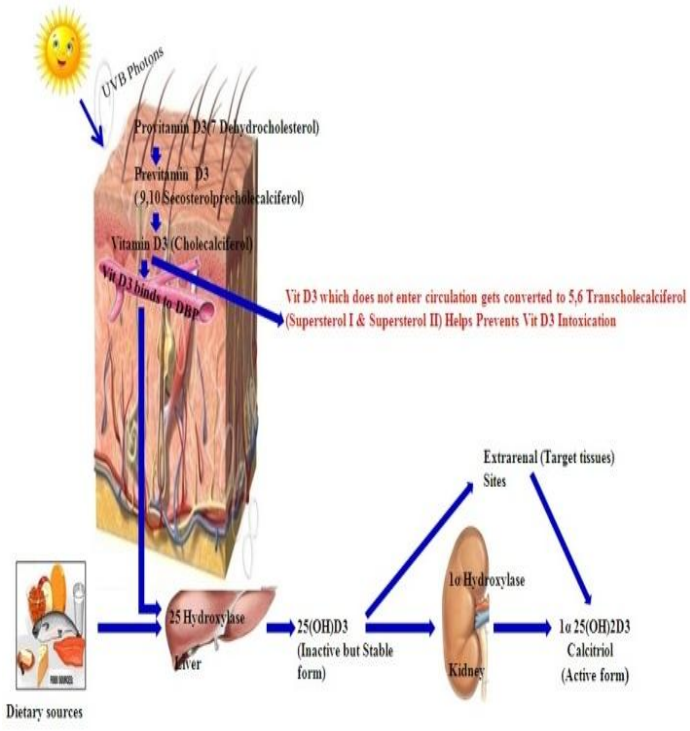

FIGURE II METABOLISM OF VITAMIN D3

Figure II shows absorption of UVB photons by metabolite present in skin and its isomerization to form Cholecalciferol which is hydroxylated in liver and kidneys to form active Vitamin D3.

The second step is activation of $25(OH)D_3$ to the active metabolite $1\alpha,25(OH)_2D_3$ (Calcitriol), known to take place by enzyme $25(OH)D_3$ 1α Hydroxylase (CYP1α) in the inner mitochondrial membranes of renal proximal tubular cells (Figure II). Once formed in kidneys it binds to Vitamin D Binding Protein in the blood with an affinity of 2 × 10-7 M, and has a serum half-life of 10 – 20 hours.[19] Most of the calcitriol is in bound form where as 0.4% is in the free form.[20, 21] Renal enzyme CYP1α (P-4501α) which is required for 2nd hydroxylation step shows close resemblance with hepatic enzyme CYP27 which is required for 1st hydroxylation step, therefore it is also termed as CYP27B1.[22]

Extrarenal sites of Calcitriol Synthesis

Calcitriol or active form of Vitamin D_3 is mainly synthesized in kidney from its inactive form. There are numerous reports about the additional extrarenal sites of calcitriol synthesis for intracrine and paracrine hormonal effects.[23] The enzyme 1αOHase (CYP27B1) required for this conversion is expressed by several target cells. Upon activation, these cells locally hydroxylate the inactive form $[25(OH)D_3]$ resulting in the autocrine production of calcitriol, the active form $[1\alpha,25(OH)_2D_3]$ [24].The cells which express the enzyme and locally produce active form are human monocytes and macrophages,[25,26] dermal and monocyte-derived dendritic cells, (DCs),[27, 28] B cells[29] and T cells.[30] In addition to immune cells, epidermal keratinocytes,[31, 32] osteoblasts and prostate epithelial cells[33, 34] also express both Vitamin D_3-metabolizing enzymes CYP27A1 and CYP27B1.[35] Thus, these cells too are capable of producing their own calcitriol from the precursor Vitamin D_3, which was shown in vitro[36] and in vivo.[37]

REGULATION OF VITAMIN D_3

Up regulation of Vitamin D3 (Figure III)

When plasma calcium and phosphorus concentrations decrease below the threshold level the transmembrane proteins found in parathyroid glands sense the calcium levels and stimulate the secretion of parathyroid hormone (PTH). This Parathyroid hormone (PTH) within seconds proceeds to osteoblasts and to proximal convoluted tubule cells in Kidney. In proximal convoluted tubule, PTH causes elevation of expression of enzyme Vitamin D_3 1αhydroxylase,[38] mediated through the action of Cyclic AMP.[39]

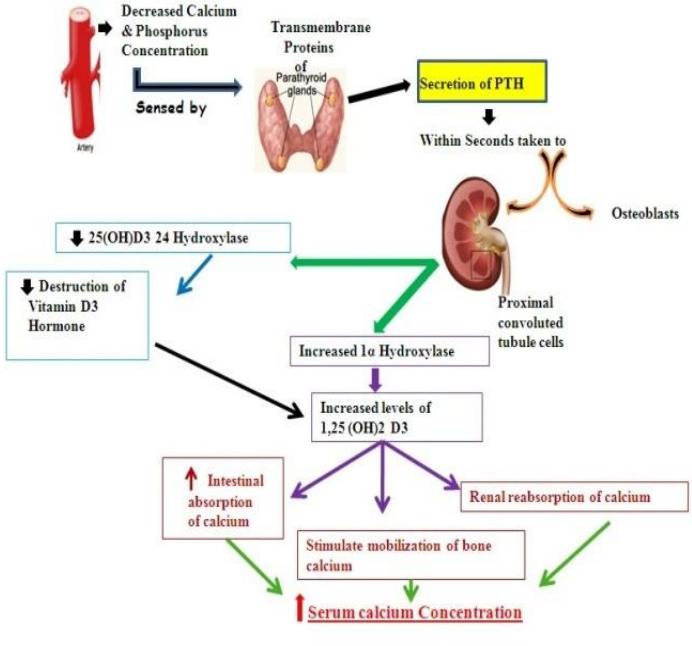

FIGURE III UPREGULATION OF VITAMIN D3

Figure III shows that decreased serum calcium stimulates PTH which further stimulate enzyme 1α hydroxylase and suppress 24 hydroxylase in kidneys leading to increased $1,25(OH)_2D_3$. This helps in increased absorption of calcium thus increasing the serum calcium.

Increase in enzyme 1α OHase causes synthesis of active form of Vitamin D_3 through hydroxylation of inactive form. At the same time the PTH markedly suppresses the 24-Hydroxylase (24OHase), the major enzyme involved in destruction of the Vitamin D hormone.[40] The mechanism of this suppression is not known, however there is a decrease in the mRNA encoding for the 24OHase. Above two actions result in marked elevation of plasma levels of $1,25(OH)_2D_3$.[41] This reaction of conversion of Inactive $[25(OH)D_3]$ to active $[1\alpha,25(OH)_2D_3]$ form by enzyme 1α hydroxylase is tightly regulated by the parathyroid hormone (PTH), calcium, phosphate, calcitonin, fibroblast growth factor 23 (FGF23), and calcitriol itself.[42] The active Vitamin D hormone, increases the intestinal absorption of calcium, and mobilization of bone calcium and renal reabsorption of calcium thus increasing the serum calcium concentration. When the serum calcium concentration exceeds, there is shut down of parathyroid gland induced cascade of events. Further the C- cells of the thyroid gland secrete the thirty two amino acid peptide calcitonin, which blocks the bone calcium mobilization thus lowering the serum calcium.[43] This decreases the danger of hypercalcemia which usually causes calcification of soft tissues especially kidney, heart, aorta, and intestine, causing organ failure and death. Calcitonin secretion also stimulates renal 1α hydroxylase to provide the Vitamin D hormone for non-calcemic needs under normo-calcemic conditions.[44]

Downregulation of Vitamin D_3

When there is high serum level of active form of Vitamin D_3 $[1\alpha,25(OH)_2D_3]$ the expression of 1αOHase is negatively regulated. Renno T. et al[45] in 1995 in their work using the perfused Vitamin D-deficient rat kidney, showed that the down regulation of 1α-hydroxylation takes 2–4 h after exposure to $1,25\text{-}(OH)_2D_3$ and is blocked by inhibitors of protein synthesis and transcription. The inactivation or catabolism of Vitamin D metabolites (Both active and Inactive forms of Vitamin D) takes place by multi-step inactivation pathways (C-23 and C-24 pathways) to less lipophilic calcitroic acid in target cells which is then excreted in the bile.[46] This inactivation is initiated by the multifunctional mitochondrial enzyme (CYP24A1), widely expressed and transcriptionally induced by the action of both ligands in a very rapid and sensitive manner[42] to generate either $24,25(OH)_2D_3$ or $1,24,25(OH)_3D_3$. The $24,25(OH)_2D_3$ generated has lower binding affinity to the nuclear Vitamin D Receptor (VDR).[47] Nevertheless, it has been shown to exert biological activities in parathyroid gland, bone metabolism and to activate the human osteocalcin gene.[48] The 24-hydroxylated metabolites are further degraded and eventually excreted as either calcitroic acid or 23-carboxyl derivatives.

CONCLUSION

Vitamin D, the most important vital element required by the body is derived from the UVB photons absorbed by the skin. From this review it is understood that the important biological effect of Vitamin D occurs only as a consequence of its metabolism in the epidermis and dermis and later its hydroxylation to form a family of daughter metabolites, including the key kidney-produced metabolite 1,25-dihydroxyvitamin D3. This is the most important metabolite required for functioning of each cell. It is clear that its production is modulated according to the organism's calcium and other endocrine needs. The circulating concentrations of calcium and 1, 25-dihydroxyvitamin D3 itself up regulates or down regulates its production. Also local production of 1, 25- dihydroxyvitamin D3 which generates biological responses in local cellular neighborhood, is possible if the local cells express 25 (OH) D3- 1α Hydroxylase.

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ABBREVIATIONS AND ACRONYMS

$1\alpha\ 25(OH)_2\ D_3$ - 1α25 dihydroxy D3
nm - Nano meter
$25(OH)D_3$ - 25 Hydroxyvitamin D_3
CYP- Cytochrome P
DBP- Vitamin D Binding Protein
ng/ ml - Nano gram/ Millilitre
nM- Nano mole
UVB Photons – Ultra Violet B Photons
1α OHase- 1α Hydroxylase
DC- Dendritic cells
PTH- Parathyroid Hormone
24 OHase- 24 Hydroxylase
FGF- Fibroblast Growth Factor
VDR – Vitamin D Receptor