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Vitamin D: A Mini review on Biochemical, Clinical, Physiological and Pathophysiological Aspects

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Abstract: Vitamin D is a pleiotropic secosteroid hormone with critical endocrine, paracrine, and autocrine functions. Beyond its classical role in calcium and phosphate homeostasis and bone mineralization, vitamin D regulates immune responses, cardiometabolic health, cancer biology, and neurocognitive function. This narrative review integrates recent advances in vitamin D biochemistry, physiology, and pathophysiology, including the FGF23–Klotho axis, vitamin D receptor (VDR) genomics and epigenomics, extrarenal vitamin D metabolism, and precision medicine approaches. Clinical implications for deficiency, supplementation, and therapeutic analogs are discussed. Emphasis will be directed toward the structural basis for understanding the mechanism of the two-step hydroxylation that activates vitamin D3, regulation of intestinal calcium absorption, kidney calcium and phosphate resorption, the molecular mechanisms of transcellular pathway, interrelationship of vitamin D with parathyroid hormone (PTH), calcitonin and other hormones, the involvement of vitamin D in diabetes, cancer and immune disorders.

Keywords: 1ά, 25(OH) 2 D3 ,24, 25-dihydroxycholecalciferol, , VDR, FGF23, calcium homeostasis, immunomodulation, cancer, cardiovascular disease, precision medicine. intestinal calcium transport. vitamin D analog PRI-1906: 4E)-24a-homo-(1S)-1, 25, renal 1 ά-hydroxylase, Type 2 diabetes and vitamin D insufficiency, congestive heart failure (CHF), Ca++ and PO4 --- absorption and resorption, bone, Intestine, and kidney, ectopic parathyroid adenoma, crystal structures of Vitamin D, Vitamin D receptors

INTRODUCTION

Vitamin D has evolved from being considered solely a bone-related nutrient to a multifunctional hormone influencing multiple organ systems. Advances in molecular biology, endocrinology, and genomics have expanded understanding of vitamin D metabolism and signaling. Widespread hypovitaminosis D remains a global public health issue, affecting diverse populations and contributing to skeletal and extra skeletal disease.

Biosynthesis of 1, 25-Dihydroxycholecalciferol (1 α25 (OH) 2D3) and Regulation of its Synthesis by Parathyroid hormone. Structural Implications

Vitamin D consists of two different compounds, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by plants while vitamin D3 as shown in Figure 1.1 is synthesized in the skin when 7- dehydrocholestrol, a substance normally in the skin is converted to vitamin D3 by ultraviolet-B rays (UVB) radiation(1). Subsequently, vitamin D requires activation by two-step hydroxylation reactions, the first at the 25 carbon atom

in the liver ; the reaction is catalyzed by 25-hydroxylase enzyme and then the second hydroxylation is in the in the proximal tubules of the kidneys at the first carbon, to a compound that has been known as the most active or hormonal form of the vitamin: 1α,25-dihydroxyvitamin D3(1 α25(OH)2D3), named calcitriol by 25 hydroxy-cholecalciferol 1α-hydroxylase(Figure 1.1). The first hydroxylation reaction in the liver is under feedback inhibition by its end product 25-hydroxycholecalciferol (2). This feedback regulation serves two major functions: a. It regulates the concentration of 25- hydroxycholecalicefrol in the plasma. Vitamin D3 intake can increase many times and yet the concentration of 25- hydroxycholecalciferol remains nearly normal. This high degree of feedback control prevents excessive action of vitamin D when it is present in too great a quantity. b. This controlled conversion of vitamin D3 to 25- hydroxycholecalciferol conserves Vitamin D stored in the liver for many months. The half- life of 25-hydroxyvitamin D3 (25-hydroxy D3) is about 15 days. Thus 25-hydroxy D3 may serve as storage form for 1 α 25(OH)2D3, which is much more biologically active but has a half-life of only about 15 hours (3). Therefore, in the absence of the kidneys, vitamin D loses almost all its effectiveness. The enzyme 25 hydroxycholecalciferol 1α-hydroxylase that catalyzes the conversion of 25-hydroxy D3 to 1 α25 (OH) 2D3 is carefully regulated by parathyroid hormone (PTH). In the absence of PTH, the activity of the enzyme is quite low and almost none of the 1 α 25(OH) 2D3 is formed. This enzyme is also regulated by plasma inorganic phosphate. High levels of inorganic phosphate reduce the activity, whereas low phosphate levels stimulate the enzyme. Only the final product, 1 α 25(OH) 2D3, is hormonally active (4-6), mediating its biological functions by binding to the vitamin D receptors (VDR). Activation of the VDR in the intestine, bone, kidney and parathyroid gland maintains calcium and phosphorus concentration in the blood and preserves bone mineral content (7)

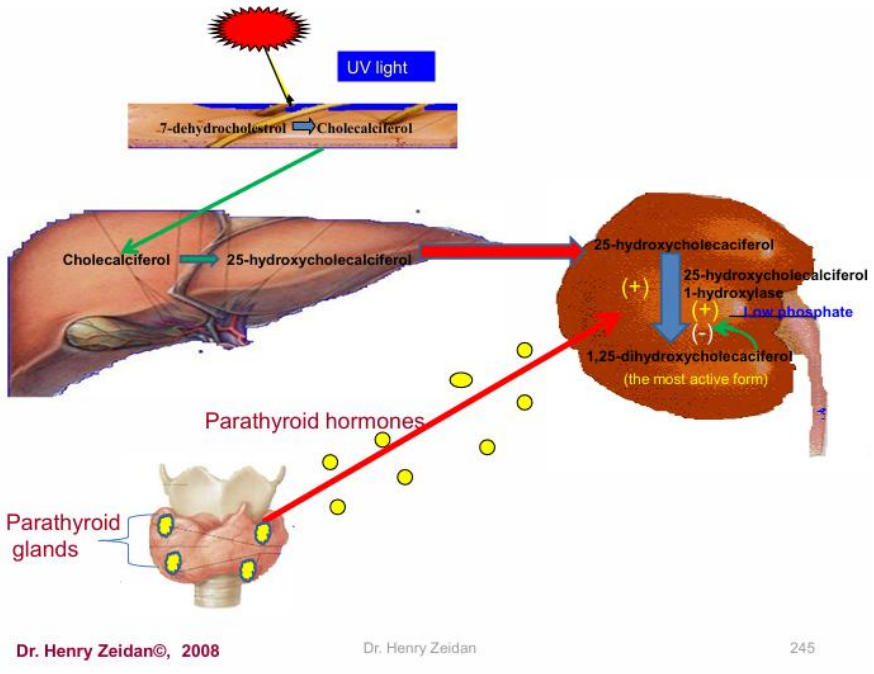

Figure 1: Synthesis of the functional forms of Vitamin D. In the liver, 25- hydroxy D3 is formed. In the proximal tubules of the kidneys 25-hydroxy D3 is converted to 1 α 25(OH) 2D3 (the most active form) by the enzyme 25 hydroxy- cholecalciferol 1α-hydroxylase. This enzyme is activated by parathyroid hormone (PTH) and low phosphate and is negatively modulated by its own product, 1, 25(OH) 2D3.

Studies by Sugimoto H et-al in 2008 provided the structural basis of activation of vitamin D3 by the kidney cytochrome P450 (CYP) enzymes and proposed an underlying mechanism for two step hydroxylation. The crystal structural analysis of the kidney CYP hydroxylase revealed the location and orientation of 1 α25 (OH) 2D3 observed in the enzyme (8). The compound 1α, 25(OH) 2D3 is positioned 11Ao from the iron atom along the I helix within the pocket (Figure 2). A comparison with the structure of wild-type bacterial CYP105A1 suggests that the loss of two hydrogen bonds in the bacterial mutant enzyme increases the adaptability of the B' and F' helices, creating a transient binding site. Further mutational analysis of the active site reveals that 25-and 1 αhydroxylation share residues that participate in these activities (Figures 2 and 3).

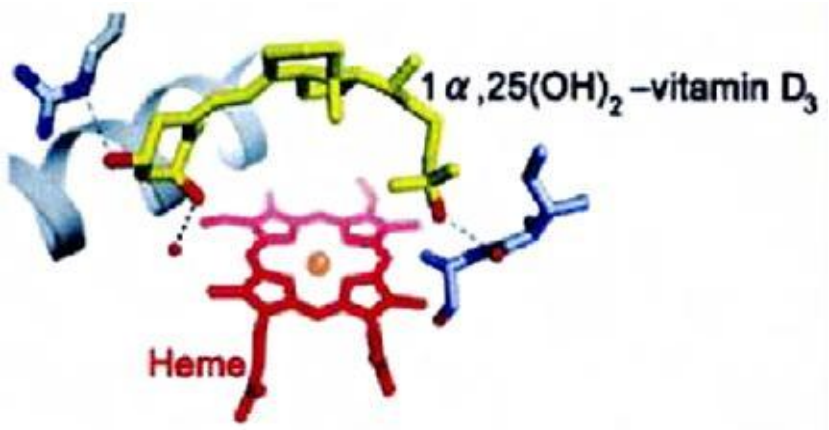

Figure 2: Crystal Structure of CYP105A1 in Complex with 1 ά 25- dihydroxyvitamin D3.

The compound 1α25 (OH)2D3 is positioned 11Ao from from the iron atom along 1 helix within the pocket. Reprinted with permission from Sugimoto et al, Biochemistry, published on Web 03/04/2008, copyright (2008) American Chemical Society.

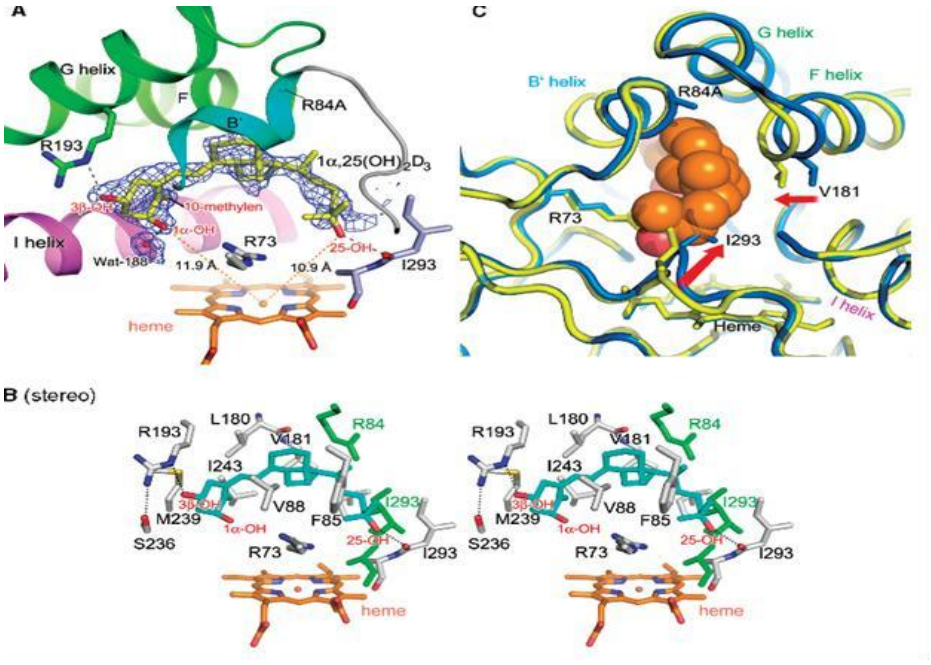

Figure 3

Figure 3: 1α25 (OH) 2D3-Binding site of the CYP105A 1 R84A mutant (are similar to that of VD3 in human CYP2R1). A) Electron- density map for 1α25 (OH) 2D3 was calculated as omit maps. The main chain of the protein is shown using a ribbon model. Arg73 and Arg G 193 and Ille293 an Ala294 are shown as stick models. The heme and 1α 25(OH)2D3 are shown using orange and yellow stick models, respectively. The nitrogen and the oxygen atoms are shown in blue and red, respectively. The helices are indicated by the colors shown above. Amino acid residues involved in the interaction with 1α25 (OH)2D3 are shown in stick models. The carbon atoms of the protein residues of R84A mutant, heme, and 1α25 (OH)2D3 are shown in white, orange, and cyan, respectively. The side chain of Arg84 and Ille 293 and Ala294 regions of the enzyme (noncomplexed form) are superimposed as a green stick model. Hydrogen bonds are shown as dotted lines between donor and acceptor. C) Conformational change upon 1α25 (OH)2D3 binding is shown. Main-chain trace of the 1α25 (OH)2D3-complexed form (yellow) and noncomplexed form (light blue) are superimposed. The heme, Arg73, Ala84, Val181, and IIe293 are shown using a stick model. The bound 1α25 (OH)2D3 is represented by the spheres. This Figure is Reprinted with permission from Sugimoto et al, Biochemistry, published on Web 03/04/2008. Copyright (2008) American Chemical Society.

The Role of Calcium Ion Concentration on the Production of 1, 25-Dihydroxycholecalciferol

The regulation of calcium metabolism by vitamin D is complex, requiring at least three additional hormones including parathyroid hormone (PTH), calcitonin and thyroxine which are discussed later.

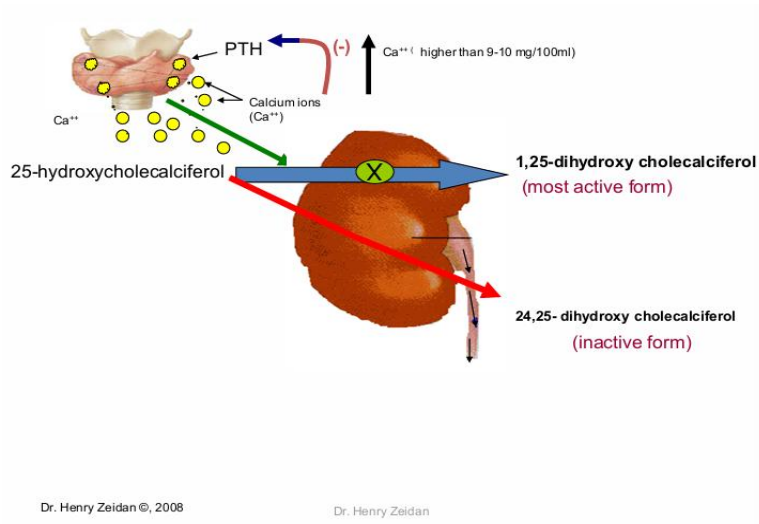

Figure 4: Production of 24, 25-dihydroxycholecalciferol (the inactive form). A high level of calcium ion concentration will depress the production of PTH. Under this condition, 25-hydroxy VD_3 is converted to 24, 25 dihydroxy VD_3. This form is inactive.

The production of the most active form of vitamin D, 1α 25(OH)2D3 is inversely affected by the concentration of calcium in the plasma. As seen in Figures 4 and 5 that increasing calcium ion concentration has an inhibitory effect on production of PTH which is needed to activate 25 hydroxy-cholcalciferol 1α-hydroxylase enzyme(9). This enzyme

catalyzes the conversion of 25- hydroxycholecalciferol to 1, 25-dihydroxycholecalciferol. Therefore, when the plasma calcium concentration is too high, the production of 1α 25(OH)2D3 is highly inhibited. The 25-hydroxycholecalciferol is converted into 24, 25-dihydroxycholecaleciferol by an enzyme called 24α-hydroxylase. This form is an inactive form and is excreted in the urine.

Regulation of Calcium Ions (Ca^{++}) by Parathyroid, Calcitonin, Thyroid, Estrogen and Glucocorticoid Hormones

Parathyroid hormone (PTH) plays a major role in the maintenance of the extracellular Ca++ concentration, adjusting minute by minute changes in the blood calcium concentration. When the extracellular Ca++ concentration is low, the parathyroid glands secrete PTH to the circulation and then PTH binds to the PTH receptor producing (PTHrP) receptor, mainly in the bone and kidney stimulating bone resorption and Ca++ reabsorption respectively (10).

IN SUMMARY

Vitamin D exists in two primary forms: vitamin D3 (cholecalciferol), synthesized in the skin from 7 dehydrocholesterol under ultraviolet-B (UVB) radiation, and vitamin D2 (ergocalciferol), derived from plant sources. Both forms undergo two-step hydroxylation for activation.

Hepatic and Renal Hydroxylation

In the liver, vitamin D is hydroxylated by CYP2R1 and CYP27A1 to form 25 hydroxyvitamin D [25(OH)D], the major circulating storage form. In the kidney proximal tubules, CYP27B1 converts 25(OH)D to the biologically active hormone 1α,25 dihydroxyvitamin D (calcitriol).

Regulation by PTH, Calcium, Phosphate, and FGF23

Parathyroid hormone (PTH) stimulates renal CYP27B1, increasing calcitriol synthesis. Serum calcium and phosphate levels exert feedback regulation. The fibroblast growth factor 23 (FGF23)–Klotho axis suppresses CYP27B1 and induces CYP24A1, forming a bone–kidney endocrine feedback system crucial for mineral metabolism.

Vitamin D Catabolism

CYP24A1 mediates 24 hydroxylation of calcitriol, producing inactive metabolites. Genetic defects in CYP24A1 cause hypercalcemia and nephrolithiasis, highlighting the clinical significance of vitamin D degradation pathways.

Vitamin D Receptor and Molecular Mechanisms of Action

The vitamin D receptor (VDR) is a nuclear transcription factor expressed in more than 40 tissues. Calcitriol-bound VDR forms a heterodimer with retinoid X receptor (RXR) and binds vitamin D response elements (VDREs) in target genes.

Genomic Actions

Genomic actions regulate calcium transport proteins such as TRPV6, calbindin-D9k, and PMCA1b, as well as osteocalcin and RANKL, influencing bone remodeling.

Non-Genomic Actions

Rapid non-genomic signaling involves membrane-associated VDR, intracellular calcium signaling, MAPK pathways, and modulation of insulin secretion.

Epigenetic Regulation

Vitamin D influences DNA methylation, histone modifications, and microRNA expression, linking vitamin D signaling to immune tolerance, cancer biology, and metabolic regulation

VITAMIN D: PHYSIOLOGICAL ASPECTS

The most active form of vitamin D, 1, 25(OH) 2 D3, plays a major function in maintaining calcium homeostasis. 1, 25(OH)2 D3 facilitates and increases both absorption of calcium and phosphorus by the small intestine and their resorption from bone. At the intestinal level, PTH seems to act indirectly on intestinal Ca++ absorption by stimulation of renal 1 ά-hydroxylase and thereby, increasing [1, 25(OH) 2 D3 dependent absorption of Ca++ from the intestine (11). Calcitonin believed to stimulate intestinal calcium absorption through an increase in 1, 25(OH)2D3 circulating levels, however so far there have been no reports of pathologies caused by either calcitonin deficiency or excess(12). It is believed that this hormonal action on calcium absorption facilitates and acts as a transport mediator of the phosphate (13).

Furthermore, it increases calcium and phosphate absorption by the epithelial cells of the renal tubules, thereby tending to decrease excretion of these substances in the urine (Figure 5). Cross et- al (14) concluded from their studies that thyroid hormones increase the genomic action of 1, 25(OH)2D3 in the intestine. In a recent study by Kumar V and Prassad R (15) concluded that thyroid hormones stimulate calcium transport system and Ca++ uptake by brush border membrane vesicles. The authors have shown that Na+ /Ca++ exchanger activity is highly regulated by thyroxine hormones. Numerous investigators believe that thyroid hormones and vitamin D have a cooperative effect not only on intestinal calcium transport but also on intestinal phosphate movement (14). Finally, Vitamin D with PTH plays a major role in bone remodeling (Figure 5 and 6).).

In summary, Vitamin D has several effects on the intestines, kidneys, and bones that increase absorption of calcium and phosphate into the extracellular fluid and contribute to feedback regulation of these substances. These effects are as follow:

1. In Bone: It facilitates resorption of calcium and phosphate.
2. In the intestine: It increases the absorption of dietary calcium and phosphate.
3. In the kidney: It stimulates calcium absorption.

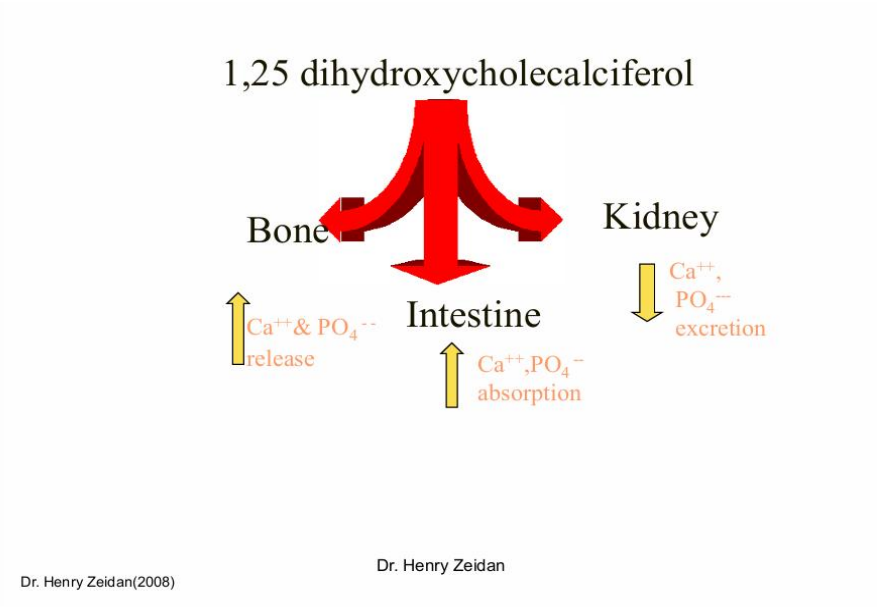

Figure 5: Summary of the hormonal effects of 1, 25-dihydroxycholecalciferol [1.25(OH) 2 D3] on Ca++ and PO4-- absorption and resorption in bone, Intestine and kidney.

The exact molecular mechanisms responsible for 1 ά, 25(OH) 2 D3 dependent intestinal calcium transport are not fully understood. Numerous investigators have shown that 1ά,25(OH)2 D3 is the major controlling hormone of intestinal calcium absorption and as the body's demand for calcium increases from a diet deficient in calcium, from growth, or from pregnancy, the synthesis of 1ά,25(OH)2 D3 is increased, stimulating the rate of calcium absorption(16-18).

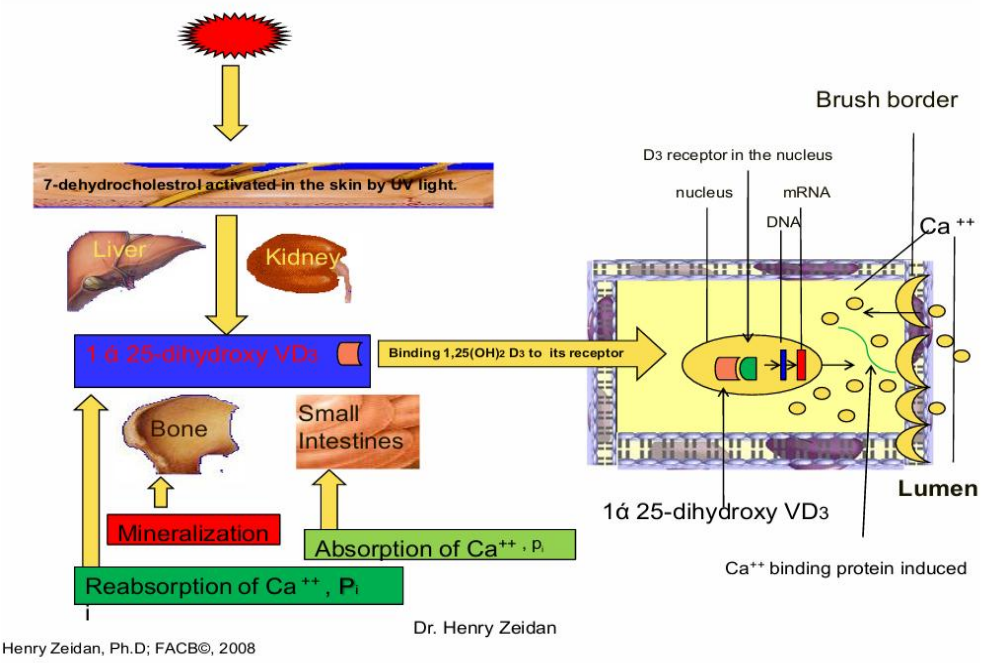

Figure 6: The mode of Action of The Vitamin D system- The role of 1ά,25(OH)2 D3 in stimulating intestinal calcium transport.

Raval-Pendya et-al have reported that active intestinal calcium transport is trans-cellular and believed to take place in three component 1ά, 25(OH) 2 D3 highly regulated steps: entry across the brush border membrane, intracellular diffusion, and extrusion across the basolateral membrane(18). As it has been reported by the authors and numerous investigators that the calcium binding protein calbindin is induced by 1ά, 25(OH) 2 D3 in the intestine, and acts to facilitate the diffusion of calcium through the cell interior toward the basolateral membrane (19). The detailed mechanism for the activation of calbindin protein by 1ά,25(OH)2 D3 and the mode of action of the most active form of the vitamin is shown in Figure 6

In summary, the physiological Roles of Vitamin D are as follows:

Calcium and Phosphate Homeostasis

Vitamin D increases intestinal absorption of calcium and phosphate, enhances renal tubular reabsorption, and regulates osteoblast and osteoclast differentiation through RANK/RANKL/osteoprotegerin pathways.

Immune System Regulation

Vitamin D induces antimicrobial peptides (cathelicidin, defensins) and modulates T-cell differentiation, promoting regulatory T cells and suppressing pro-inflammatory Th1 and Th17 responses.

Cardiometabolic Effects

Vitamin D affects endothelial function, blood pressure regulation, insulin sensitivity, and lipid metabolism. Observational studies link deficiency to metabolic syndrome, diabetes, and cardiovascular disease, though randomized trials show mixed results.

Neurocognitive and Neurodevelopmental Roles

VDR expression in the hippocampus and cortex suggests roles in neurodevelopment, neuroplasticity, and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

PATHOPHYSIOLOGICAL ASPECTS

Investigations by Zittermann, A et- al in 2007 have demonstrated that low vitamin D status may contribute to the pathogenesis of congestive heart failure (CHF). Furthermore, their results demonstrated that CHF patients and controls differed in several vitamin D-associated lifestyle factors and in alcohol consumption during earlier periods of their lives (20). In an elegant first case report on ectopic thymic parathyroid adenoma in a patient presenting with rickets by Pitukcheewanont P et- al in 2008, the authors have demonstrated that hyperparathyroidism – induced hypercalcaemia may be masked by severe vitamin D deficiency. The authors reported that prolonged treatment with ergocalciferol after removal of the parathyroid adenoma was necessary to normalize iPTH and replenish vitamin

D store. Furthermore, the authors concluded that with vitamin D therapy, hypocalcemia becomes evident and the diagnosis of primary hyperparathyroidism can be made . Different types of cancer cells present may prevent vitamin D to bind to its receptors and may interfere with the enzymatic system involved in both vitamin D synthesis and regulation(21). The active form 1ά, 25(OH) 2 D3, can induce differentiation, inhibit proliferation, and modulate immune responsiveness of breast and a wide variety of female genital cell types (22). Faustino R and Lo'pez P in 2008 have reported that for several types of cancer (e.g., breast and vulva), the relative risk of mortality is higher if there is hypovitaminosis D, suggesting that maintenance of adequate vitamin D levels is more important in limiting tumor progression than in preventing tumor initiation(23). In 2007, Wietrzyk J et al have demonstrated that the 14 new vitamin D analog PRI-1906: 4E)-24a-homo-(1S)-1, 25 dihydroxy ergocalciferol is new vitamin D analog PRI-1906: 4E)-24a-homo-(1S)-1, 25 dihydroxy ergocalciferol is more effective than calcitriol or PR1-2191-1, 24-dihydroxyvitamin D3 as a potential anticancer agent, when used in combination therapy with cytostatic agents. However, further research is needed to elucidate the future precise place of vitamin D in both cancer prevention and treatment (24). Sugden, JA et al in 2007 have demonstrated that vitamin D insufficiency is common in patients with Type 2 diabetes. A single large dose of oral vitamin D2 improves endothelial function in patients with Type 2 diabetes and vitamin D insufficiency (25).

PATHOPHYSIOLOGICAL IMPLICATIONS

Skeletal Disorders

Vitamin D deficiency causes rickets in children and osteomalacia in adults and contributes to osteoporosis and fracture risk in older populations(26).

Cardiovascular and Metabolic Disorders

Low serum 25(OH)D levels are associated with hypertension, atherosclerosis, and insulin resistance, although causality remains under investigation(27).

Cancer Biology

Calcitriol inhibits proliferation, induces differentiation and apoptosis, and modulates angiogenesis in breast, prostate, colorectal, and gynecologic cancers.

Novel vitamin D analogs with reduced hypercalcemic effects are being investigated as anticancer agents(28).

Immune and Infectious Diseases

Vitamin D modulates innate and adaptive immunity and has been studied in autoimmune diseases and viral infections including COVID 19. Meta-analyses suggest supplementation may reduce respiratory infection risk, particularly in deficient individuals(29,30).

Clinical Implications and Supplementation

Current guidelines recommend maintaining serum 25(OH)D levels between 20–50 ng/mL, with higher targets for high-risk populations. Supplementation strategies vary based on age, body mass index, malabsorption syndromes, and chronic kidney disease. Hypervitaminosis D can cause hypercalcemia, nephrolithiasis, and vascular calcification, emphasizing the need for individualized dosing(31-34),. Precision medicine approaches incorporate polymorphisms in VDR, CYP2R1, CYP24A1, and GC genes to personalize vitamin D supplementation and predict clinical response(35-36)

FUTURE DIRECTIONS

Future research should focus on tissue-specific vitamin D metabolism, epigenomic mechanisms, large randomized clinical trials for chronic disease outcomes, and development of selective VDR modulators. Integration of genomics and metabolomics will advance personalized vitamin D therapy.

CONCLUSION

Vitamin D is a multifunctional hormone essential for skeletal health and systemic physiological regulation. Advances in molecular biology have expanded understanding of vitamin D signaling networks, revealing its role in immunity, metabolism, cardiovascular health, and cancer. Continued translational research and precision medicine approaches will refine therapeutic applications and public health strategies.

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