

Vitamin D: Structure and mechanism of action

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Abstract

Vitamin D has received more attention in recent years as a result of the resurgence of vitamin D deficiency and rickets as a global health issue, as well as compelling evidence in the laboratory indicating that 1,25-dihydroxy vitamin D3 [1,25(OH)2D3], the hormonally active form of vitamin D, generates several extraskelatal biological responses such as inhibition of breast, colon, and prostate cancer cell progression; effects on the cardiovascular system; and protects against. This review covers our present knowledge of vitamin D and its bioactivation, as well as fresh findings that have altered our understanding of vitamin D activity in both classical and nonclassical target tissues. This page also assesses vitamin D's alleged involvement in extraskelatal health, provides an overview of 1,25(OH)2D3 analogs that have been created, and highlights unanswered problems.

Keywords: Vitamin D; Structure; Metabolism; Cholecalciferol

1. Introduction.

Vitamin D was first classified as a vitamin in the twentieth century, but it is now classified as a prohormone. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the two most common forms of vitamin D. (cholecalciferol). Vitamin D3 is generated in human skin and taken through animal-based meals, primarily fish oils, but vitamin D2 is obtained from plant sources, is not entirely human-made, and is added to diets. Only the side chain structure of vitamin D2 and D3 differs. The differences have no effect on metabolism (i.e. activation), and both versions perform the same function as a prohormone. Vitamin D was discovered along with several other vitamins and is still considered a vitamin. However, research published in the second part of the twentieth century revealed that vitamin D is a prohormone, not a vitamin. Vitamin D is almost non-existent in the food supply. It is not found in plant materials (such as vegetables, fruits, or grains) and is only found in trace amounts in meats and other animal dietary sources, such as fish liver oils and plants.

2. Structure and synthesis of vitamin D

Vitamin D is a cyclopentano - perhydrop henanthrene structure secosteroid with a broken 9,10 carbon-carbon bond in the B ring. Cholecalciferol and ergocalciferols are two types of vitamin D and their metabolites. On exposure to the ultraviolet B part of sunlight, the parent chemical of the naturally occurring family, cholecalciferol (vitamin D3), is generated in the skin from 7-dehydrocholesterol. Vitamin D3 can be consumed from certain meals, including fatty fish, fish liver oils, and egg yolks, in addition to photosynthesis in the skin. Irradiation of ergosterol produced by yeasts produces vitamin D2 (ergocalciferol). A double bond between carbon 22 and carbon 23 and a methyl group on carbon 24 distinguish vitamin D2 from vitamin D3. Both families are included when vitamin D or its metabolites are written without a subscript [1]. In terms of biological activities, vitamin D2 is just a third as powerful as vitamin D3 [2, 3].

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To be active, vitamin D₃ generated in the epidermis must be processed further. The first step, 25-hydroxylation, is largely carried out in the liver, however, it is also present in other tissues. There are many 25-hydroxylases, as will be mentioned further below. The most common form of vitamin D in circulation is 25OHD. Vitamin D metabolites must be further hydroxylated in the 1 position by the enzyme CYP27B1 to acquire optimal biologic activity; 1,25(OH)₂D is the most potent metabolite of vitamin D and accounts for the majority of its biologic effects. Although unlike the 25-hydroxylase, the 1 hydroxylation occurs largely in the kidney, this enzyme is found in various organs. In the 24 positions, vitamin D and its metabolites, 25OHD and 1,25(OH)₂D, can also be hydroxylated. Because 1,25(OH)₂D and 1,24(OH)₂D have similar biologic potencies and 1,24,25(OH)₃D has about a tenth of the activity of 1,25(OH)₂D, this could help activate the metabolite or analogue. However, when metabolites containing a 25OH group are 24-hydroxylated, they undergo additional degradation. The next sections go over the specifics of these reactions [4].

3. Cutaneous Production of Vitamin D₃

The Kandutsch-Russell cholesterol pathway includes 7-dehydrocholesterol (7-DHC), a precursor to vitamin D. A multitude of variables, including vitamin D and cholesterol, govern the final enzymatic step mediated by 7-dehydrocholesterol reductase that converts 7-DHC to cholesterol, allowing for greater quantities of 7-DHC for conversion to vitamin D. [5]. Although it was known that irradiating 7-DHC produced pre-D₃ (which then undergoes a thermal rearrangement of the triene structure to generate D₃), lumisterol, and tachysterol, the physiologic regulation of this process was unknown until Holick and his colleagues' research [6-8].

They showed that the production of pre-D₃ under the impact of solar or UV irradiation (maximal effective wavelength between 290-310) is relatively quick, peaking within hours. Pre-D₃ is further converted to lumisterol and tachysterol by UV irradiation. The time it takes to reach this maximum concentration of pre-D₃ is correlated with the degree of epidermal pigmentation and the intensity of exposure, although neither factor affects the maximum level reached. Even though pre-D₃ levels have reached their maximum, the physiologically inactive lumisterol continues to accumulate as a result of prolonged UV exposure. Tachysterol is also produced, but unlike pre-D₃, it does not build when exposed to UV light for long periods. Lumisterol production is reversible, and it can be converted back to pre-D₃ as pre-D₃ levels decline. Around 0 degrees Celsius, no D₃ is generated; however, at 37 degrees Celsius, pre-D₃ is slowly transformed to D₃. Because of the delayed thermal conversion of pre-D₃ to D₃ and the conversion of lumisterol to pre-D₃, short exposure to sunlight should result in a prolonged synthesis of D₃ in the exposed skin. Because to the photoconversion of pre-D₃ to lumisterol and tachysterol, as well as the photoconversion of D₃ to suprasterols I and II and 5,6 transvitamin D₃, prolonged exposure to sunlight would not create dangerous quantities of D₃ [9].

Melanin in the epidermis can diminish the efficiency of sunlight in generating D₃ in the skin by absorbing UV irradiation. This could be one of the reasons why Blacks and Hispanics living in temperate climates have lower 25OHD levels (a well-documented surrogate measure for vitamin D levels in the body) [10]. Sunlight exposure boosts melanin formation, which is another way of preventing excess D₃ production. UV irradiation intensity is also necessary for optimal D₃ synthesis. The seasonal change in 25OHD levels is extremely noticeable, with greater levels in the summer and lower levels in the winter. The intensity of sunlight impacting exposed skin, and consequently the degree of this seasonal change, is determined by latitude.

From mid-October to mid-April, very little D₃ is created in exposed skin in Edmonton, Canada (52°N); Boston (42°N) has a somewhat longer period for effective D₃ production, but the skin in Los Angeles (34°N) and San Juan (18°N) may produce D₃ all year [11]. These findings pertain to the level of the sea. Because there is less UVB absorption in the atmosphere at higher elevations, skiers can manufacture vitamin D even on sunny days in the winter. During the summer, a bigger amount of the day is capable of synthesizing D₃ in the skin than at other times of the year, with peak D₃ production occurring about midday. In the covered parts, clothing [12] and sunscreens [13] efficiently limit D₃ production. This is one possible explanation for the observation that Bedouins in the Middle East, who completely cover their bodies with garments, are more prone to rickets and osteomalacia than Israeli Jews who had similar solar exposure [14].

4. Vitamin D Catabolism, Metabolites and Transport

Over 50 vitamin D metabolites have been identified in recent decades, with some of them attracting attention due to their biological activity. CYP24A1, which belongs to the mitochondrial P450 fraction and is encoded by the CYP24A1 gene on chromosome 20q13.2 [15], is the most well-known catabolic enzyme. Both 25OHD and 1,25(OH)₂D can be hydroxylated by CYP24A1, resulting in 24R,25(OH)₂D and 1,24,25(OH)₃D, respectively. The hydroxylation of these compounds is catalyzed by the same enzyme in numerous steps, generating a succession of 24—and 23—hydroxylated

derivatives. The inactive calcitric acid or 26,23-lactone eliminated with bile or urine are the end products. Calcitriol and FGF23 stimulate CYP24A1, while PTH and hypocalcemia inhibit it. CYP24A1 has been found in a variety of tissues that express VDR and is involved in the local control of vitamin D activity [16]. Idiopathic Infantile Hypercalcemia (IIH, OMIM 143880) is an uncommon condition caused by defective vitamin D catabolism and resultant hypercalcemia. Pathogenic variations of CYP24A1 have been identified. Biallelic variations (in homozygosis or heterozygosis) in particular exhibit a severe phenotype with hypercalcemia, which can often result in mortality in infants [17].

Other minor metabolic pathways have been described in addition to CYP24A1 and are continuously being investigated. The C-3 epimerization route was recently discovered, leading to the formation of many C-3 epimer metabolites in which the hydroxyl group on C3 is oriented alpha rather than beta in space. Epimeric metabolites are abundant in newborns and early children, but the physiological significance of this redundant pathway has yet to be determined [18]. Because there are so many metabolites, new and more precise analytical techniques are being developed. Since the introduction of high-performance liquid chromatography techniques in 1970, they have been steadily refined, and the most recent LC-MS-MS assay is now considered the "gold standard" approach [22].

This is due to the great sensitivity, repeatability, and accuracy of the method, the latter of which is influenced by the capacity to distinguish between 25OHD2 and 25OHD3, as well as their epimeric variants. Furthermore, it allows for simultaneous measurement of many vitamin D metabolites [23]. Vitamin D, 25OHD, 1,25(OH)2D, 24R,25(OH)2D, and C3-epi25 are the five intermediates now being measured with standardized procedures (OH) The Joint Committee on Traceability in Laboratory Medicine (JCTLM) database contains D and procedures[26]. The Nutritional Health and Nutrition Examination Survey [28] in the United States and the UK Food Standard Agency (FSA) in their National Diet and Nutrition Survey both recommended the use of LC-MS-MS for measuring vitamin D metabolites in 2009 [29].

The expectation is that LC-MS-MS will provide further insight into the complexity of vitamin D metabolites [30,31]. Vitamin D binding protein (DBP) with high affinity transports 85% of vitamin D metabolites, while albumin with low affinity transports 15% [14]. DBP, formerly known as Gc-globulin, is a multifunctional protein with a long evolutionary history invertebrates. DBP is a 458 amino acid single-chain protein encoded by the human gene DBP, which is found on chromosome 4 near other albumin family protein genes [14]. Even though 25OHD and 1,25(OH)2D have the highest affinity, all vitamin D metabolites can be bound by the same binding site of DBP [14]. Free 25OHD makes up 0.03 percent of the total amount of metabolites, while 1,25(OH)2D makes up 0.4 percent, and has long been thought to be the only active hormone that enters cells (free hormone theory) [14].

However, the free hormone concept has lately been re-examined in several organs, such as the kidney. Megalin, a large transmembrane protein found on the apical side of proximal tubule cells, has been demonstrated to act as a receptor for the combination vitamin D-DBP, along with tubulin and disabled-2 proteins [14]. According to this theory, knockout mice for Lrp2 (the gene that codes for megalin) develop severe osteomalacia and have a shorter lifespan, highlighting the importance of DBP binding capability in the kidney [14]. The relevance of this process in other tissues, on the other hand, is still being debated: megalin is expressed in various tissues where vitamin D has extraskeletal activities, but Megalin-mediated DBP uptake has yet to be fully defined. DBP operates as a huge pool reservoir of circulating 25OHD, which avoids vitamin D insufficiency when supply is inadequate, according to current evidence. Furthermore, DBP regulates vitamin D availability to cells in the kidney and, most likely, in other peripheral organs. [32].

5. Vitamin D Mechanism of Action

Genomic actions are reviewed in these articles [19, 20]. The VDR is responsible for all of 1,25(OH)2D's genomic effects. VDR is a transcription factor that belongs to the nuclear receptor family of steroid hormones. It has three domains: an N-terminal DNA binding domain with two zinc fingers that bind to DNA grooves at discrete sites (VDREs), a C-terminal ligand-binding domain, and a hinge region that connects the two domains. X-ray crystallography was used to solve the structure of the ligand-binding domain [21]. It's made up of 12 helices. The terminal helix functions as a gating mechanism, shutting around the integrated ligand and establishing an interface for coactivators, as well as aiding VDR's interaction with its heterodimer partner, RXR. Although VDRE sequences vary significantly, the majority of those with the strongest affinity for VDR are direct repeats of hexanucleotides with a 3 nt spacing between half-sites, a motif known as a DR3. Following VDR binding to its VDRE, coregulatory complexes needed for VDR's genomic action are recruited.

These complexes can be gene and cell-specific, allowing 1,25(OH)2D activity to be selective between cell types. These complexes contain a subunit that directly binds to the VDR via an LXXLL motif, as well as several subunits that contain enzyme activity, such as histone acetyltransferases (coactivators like the SRC family) or deacetylases (corepressors like SMRT and NCoR), methyltransferases and demethylases, ATPase-containing nucleosomal-remodeling activity (Mediator complex). Microarray, ChIP-chip, and ChIP-seq are recent approaches that have greatly expanded our

understanding of the vitamin D mechanism of action at the genomic level. In the mouse osteoblast, for example, 1,200 VDR binding sites were discovered under basal conditions (i.e., no 1,25(OH)₂D), while 8,000 sites were found after 1,25(OH)₂D administration [33]. In a second study, 2,776 VDR binding sites were discovered changing the expression of 229 genes in human lymphoblastoid cell lines treated with 1,25(OH)₂D [24].

When comparing data from different periods of 1,25(OH)₂D exposure, the profile of VDR binding sites and genes activated differs from cell to cell, with some but not total overlap [34]. Furthermore, VDR binding sites can be found everywhere in the genome, typically thousands of base pairs away from the gene under control. These sites are frequently discovered in conjunction with other transcription factor binding sites. RUNX2, C/EBPα, and C/EBPβ are among the proteins found in osteoblasts [25, 27]. A specific epigenetic histone signature involving methylation and/or acetylation of lysines within H3 and H4 is frequently observed at these locations [35]. Pike and Meyer (2010) [19] outlined six principles of VDR/RXR activity on target genomes in their recent review: “ 1) The active transcription unit is predominantly, but not exclusively, the VDR/RXR heterodimer; 2) VDR binding sites are predominantly, but not exclusively, classic hexamer half-sites separated by 3 base pairs; 3) VDR binding sites are predominantly, but not exclusively, classic hexamer half-sites separated by 3 base pairs; 4) Enhancers are promoterproximal (near), promoter distal (far), or a combination of the two concerning transcriptional start sites: many enhancers are clustered hundreds of kilobases from their target genes; 5) enhancers are modular in nature, with binding sites for a variety of transcription factors; 6) Enhancers in a genome are cell type-specific and extremely dynamic.’

6. Conclusion

Vitamin D's main purpose is to improve calcium absorption in the intestine. However, we are still learning about the mechanisms at work. The numerous methods by which 1,25(OH)₂D₃ functions in both the proximal and distal portions of the intestine require more characterization to develop new treatment approaches to maintain calcium homeostasis. Although laboratory evidence of 1,25(OH)₂D₃'s extraskeletal benefits is clear, conclusive clinical data supporting the use of vitamin D and analogs for the treatment or prevention of a variety of disease processes is still lacking. Although there are significant distinctions between human and mouse models, because many genes act similarly in both animals and humans, results in animal models may help to untangle complicated signaling pathways that are also affected in humans. These discoveries could lead to the discovery of new chemoprevention and chemotherapy targets.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict.

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