Article title: Vitamin D

Regulation, Metabolism, AndFunction

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Vitamin D

Regulation, Metabolism

And

Function

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Contents	PAGES
Introduction	2
Regulation vitamin D	2
Vitamin D Metabolism	4
Functions of vitamin D	7
1-Vitamin D Role in Mineral Metabolism:	
2-Vitamin D Effects on Nonskeletal Tissues:	9
Summary	11
References	12

Introduction

Interest in vitamin D has dramatically increased over the past several decades. From the beginning, vitamin D was incorrectly named a vitamin when later it was discovered to be a member of the steroid hormone family. Over time, the vitamin D receptor was discovered along its major circulating form, 25-hydroxyvitamin D, and its hormonal ligand, 1,25-dihydroxyvitamin D. Classically, vitamin D was known to be important for enhancing intestinal absorption of calcium; however, interest grew in vitamin D when it was determined that vitamin D may be utilized by other tissues of the body .

Vitamin D₃ is made in the skin from 7-dehydrocholesterol under the influence of UV light. Vitamin D₂ (ergocalciferol) is derived from the plant sterol ergosterol. Vitamin D is metabolized first to 25-hydroxyvitamin D (25OHD), then to the hormonal form 1,25-dihydroxyvitamin D (1,25(OH)₂D). CYP2R1 is the most important 25-hydroxylase; CYP27B1 is the key 1-hydroxylase. Both 25OHD and 1,25(OH)₂D are catabolized by CYP24A1. 1,25(OH)₂D is the ligand for the vitamin D receptor (VDR), a transcription factor, binding to sites in the DNA called vitamin D response elements (VDREs). There are thousands of these binding sites regulating hundreds of genes in a cell-specific fashion. VDR-regulated transcription is dependent on comodulators, the profile of which is also cell specific. Analogs of 1,25(OH)₂D are being developed to target specific diseases with minimal side effects.(Bikle , 2014)

Regulation of Vitamin D

During exposure to solar UVB radiation, 7-dehydrocholesterol in the skin is converted to previtamin D₃, which is immediately converted to vitamin D₃ in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D₃ and vitamin D₃ into inactive photoproducts. Vitamin D₂ and vitamin D₃ from dietary sources are incorporated into chylomicrons and transported by the lymphatic

system into the venous circulation. Vitamin D (hereafter, “D” represents D2 or D3) made in the skin or ingested in the diet can be in the kidneys by 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) to the biologically active form 1,25(OH) $_2$ D. stored in and then released from fat cells as shown in figure [1].

Figure 1: Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus, and bone metabolism. <http://doctorsgates.blogspot.com/2011/08/synthesis-and-metabolism-of-vitamin-d.html>

Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25(OH)D. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng/mL [50 to 250 nmol/L], the preferred range is 30 to 60 ng/mL [75 to 150 nmol/L].) This form of vitamin D is biologically inactive and must be converted.

Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25(OH)₂D. 1,25(OH)₂D decreases its own synthesis through negative feedback and decreases the synthesis and secretion of PTH by the parathyroid glands. 1,25(OH)₂D increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)₂D to the water-soluble biologically inactive calcitroic acid, which is excreted in the bile.

1,25(OH)₂D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25(OH)₂D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of RANKL.

RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate Ca²⁺ and phosphorus (HPO₄^{2–}) levels promote the mineralization of the skeleton. (**Doctors Gates, 2011**).

Vitamin D Metabolism Synthesis and activation: vitamin D₃ synthesis plateaus at about 10–15 % of the original 7 DHC content. Once formed, vitamin D₃ is preferentially bound to the

vitamin D-binding protein (DBP), allowing its translocation into the general circulation (**Holick , *et al* ., 1981**).

Skin synthesis is limited by various determinants, including pigmentation, age, zenith angle of the sun, poor air quality and % of the skin surface area available for exposure. A recent study of sun-protective behaviour in the USA showed that wearing long sleeves or staying in the shade reduced vitamin D status (**Linoss , *et al* .,2011**). Surprisingly sun screen use, even those with a high sun protection factor (SPF), did not significantly affect vitamin D status; however, self-reported use does not necessarily imply total skin coverage.

There have been numerous studies looking at skin pigmentation as a predominant factor for reducing vitamin D synthesis (**Hall , *et al* ., 2010**).In addition to cutaneous synthesis, vitamin D can be obtained from the diet in the form of vitamin D3 (chole-calciferol) or occasionally as vitamin D2 (ergocalciferol).Whereas vitamin D3 is obtained from animal sources, vitamin D2 is present in fungi and mushrooms irradiated with UVB.

In this article, vitamin D will denote the name of both types of molecules unless it is important to distinguish between these two forms. Vitamin D2 is deemed by some to be an “unnatural” form of vitamin D (**Houghton and Vieth , 2006**). In terms of efficacy, a recent systematic review and meta-analysis showed that a bolus dose of vitamin D3 raises25(OH)D more than a similar amount of vitamin D2,although this difference was not seen with daily supple-mentation of more modest doses (**Tripkovic, *et al* ., 2012**).

Vitamin D2 is considered as an active substance and is not excluded as a source of dietary vitamin D by the Endocrine Society (**Holick , *etal* ., 2011**).

Before entering the circulation, ingested vitamin D is absorbed and then transported in chylomicrons. Once in the circulation, it binds DBP until it is released into the liver where it undergoes hydroxylation of the carbon molecule in the 25 position by one of four hepatic cyto-chrome P-450 enzymes.

Three of them are microsomal forms, CYP2R1, CYP2J2 and CYP3A4, with CYP2R1 being the most physiologically important as this is the only 25-hydroxylase that causes rickets when it is non-functional. The fourth enzyme, CYP27A1, is mitochondrial **.(Whiting ,et al .,2008; Schuster , 2011)**. Circulating form of vitamin D and the last metabolite prior to conversion to the active form. Serum levels of 25(OH) D reflect both dietary and skin contributions as well as body stores. The serum concentration of 25(OH)D constitutes the main validated biomarker of vitamin D status.

For the endocrine functions of vitamin D, the proximal tubule of the kidney is the main site for CYP27B1 (1 α -hydroxylase) activity. This enzyme is responsible for conversion of 25(OH)D to the active metabolite 1 α ,25(OH) $_2$ D (calcitriol). Once made in the kidney, this active metabolite enters the general circulation, allowing it to act in distant organs and cells in a hormone-like manner.

The two primary functions of circulating 1 α ,25(OH) $_2$ D are

- (1) to increase the efficiency of intestinal calcium and phosphorus absorption and
- (2) to induce preosteoclasts to become mature osteoclasts. Other known roles include down-regulation of renin production in the kidney and stimulation of insulin secretion in the beta islet cells of the pancreas **(Holick , 2007)**.

Extra renal conversion of 25(OH) D to 1 α ,25(OH) $_2$ D can occur in numerous organs or tissues such as the muscles , prostate, immune system or pancreas, all of which express CYP27B1. These “ectopic” sites can thus supply local needs of active vitamin D in a paracrine/autocrine manner.

The most well-known example of this is its production in the macrophage cells of the antimicrobial pep-tide cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*.

Functions of vitamin D

1-Vitamin D Role in Mineral Metabolism:

That includes activation of intestinal calcium absorption, promotion of bone formation (probably by regulating the expression of several bone growth factors) and resorption, kidney calcium resorption, and inhibition of PTH production (by direct effects on parathyroid cells and indirectly by increasing calcium blood levels)

The most known effect of activated vitamin D is to increase intestinal calcium absorption (**Bikle , 1990; Wasserman and Fullmer , 1995; Hoenderop *et al.*, 2005**). Calcium enters the microvillus of the intestinal epithelial cell through TRPV6 calcium channel and then binds to a specific protein, calmodulin (CaM) that is itself bound to brush border myosin I (BBMI). The calcium/CaM complex moves into the terminal web where the calcium is picked up by another specific protein, calbindin (CaBP), and transported through the cytoplasm inside endocytic vesicles. At the basolateral membrane, the calcium is pumped out of the cell by the Ca-ATPase. Activated vitamin D enhances intestinal calcium absorption by inducing most of the mechanisms involved in the microvillus active intestinal calcium transport (TRPV6, CaBP, Ca-ATPase, and the amount of CaM bound to BBMI in the brush border).

Activated vitamin D increases calcium resorption also in kidney with a mechanism that is similar to that found in intestinal microvillus (**Friedman and Gesek , 1995; Biber *et al.*, 2013**). In fact, the molecules critical for calcium reabsorption in the distal tubule appear to be the VDR, calbindin, TRPV5, and the Ca-ATPase.

More difficult has been to determinate whether activated vitamin D has also a role in bone metabolism (**Underwood and De Luca , 1984; Suda *et al.*, 1992; Takeda *et al.*, 1999; Panda *et al.*, 2004**). VDR is found in osteoblasts, and activated vitamin D promotes the differentiation of osteoblasts and increases the production of proteins such as alkaline phosphatase and osteocalcin that are markers of bone formation. Activated vitamin D also increases the production of RANKL so activating the formation of osteoclasts. Patients with

vitamin D deficiency present an increase of several bone factors that are linked to bone resorption and formation. However, the rickets resulting from vitamin D deficiency or VDR mutations can be corrected by supplying adequate amounts of calcium and phosphate, and it suggests that the direct vitamin D effect on bone is relatively modest as shown in figure 2 .

Probably, more important for bone metabolism are the indirect effects of vitamin D. In particular, part of the skeletal phenotype in vitamin D deficiency is due to the hyperparathyroidism that develops in the vitamin D deficient state. The relationships between activated vitamin D availability and PTH secretion are complex (**Demay *et al.*, 1992; Liu *et al.*, 1996; Hawa *et al.*, 1996**). PTH stimulates the production of 1, 25(OH)₂-vitamin D and in turn 1, 25(OH)₂-vitamin D inhibits the production of PTH. This seems to be a direct effect of activated vitamin D on PTH producing cells because within the promoter of the PTH gene is a region that binds the VDR and mediates the suppression of the PTH promoter by 1,25(OH)₂-vitamin D. However, calcium alters the ability of activated vitamin D to regulate PTH gene expression. Calcium is a potent inhibitor of PTH production and secretion, acting through the calcium sensing receptor (CaSR) on the plasma membrane of the parathyroid cell. 1, 25(OH)₂-Vitamin D induces the CaSR in the parathyroid gland making it more sensitive to calcium.

Figure 2 : Effects of activated vitamin D on bone formation and mineralization
Carmina E. (2017)

In states of severe vitamin D deficiency, the reduction of calcium availability has the main effect on bone inducing bone demineralization and, as consequence of it, patients develop rickets if children and osteomalacia if adults. States of mild vitamin D deficiency increase bone turnover and bone loss determining a condition of osteoporosis. It is probable that the effects of mild vitamin D deficiency on bone are mainly mediated by a direct effect on parathyroid cells with a consequent PTH increase. In fact, in these patients, serum calcium is normal, while circulating PTH is moderately increased and it has been used to monitor the vitamin D deficiency.

2-Vitamin D Effects on Nonskeletal Tissues:

While the importance of vitamin D on calcium metabolism and bone maintenance is well proven, in recent years a large debate has occurred regarding possible important extra-skeletal effects of activated vitamin D (**Rosen *et al.* 2012; Cipriani *et al.*, 2015**). In fact, vitamin D receptors have been found in most tissues (**Rosen *et al.*, 2012; Lee *et al.*, 1994; Bikle , 2012**), and many studies have shown that activated vitamin D may influence many biological function including cell differentiation and proliferation in many tissues, immune system responses, and some hormone secretions as shown in figure 3. (**Carlberg and Campbell , 2013; Rosen *et al.*, 2012**).

Figure 3 : Effects of activated vitamin D on nonskeletal tissues.
Carmina E. (2017)

One of the main nonskeletal biologic functions of activated vitamin D is the regulation of immune function. Nuclear receptors for vitamin D (VDR) have been found in many cells of the immune system including macrophages, dendritic cells, and activated T and B lymphocytes (**van Etten and Mathieu , 2005**). In general, activated vitamin D enhances the innate immune response, whereas it inhibits the adaptive immune response by reducing T cell proliferation, shifting the balance of T cell differentiation from the Th1 and Th17 pathways to Th2 and Treg pathways, and inhibiting the maturation of dendritic cells (DC) important for antigen presentation. Because autoimmune diseases are characterized by excessive Th17 activation, normal availability of activated vitamin D may be essential for preventive excessive inflammatory responses and avoiding the onset of autoimmune diseases (**Froicu *et al.*, 2003; van Etten and Mathieu , 2005; Adorini and Penna , 2008**). While vitamin D analogs have shown the ability to improve some disorders like psoriasis, studies in most autoimmune disorders have produced inconclusive results.

It has been suggested that activated vitamin D may protect against insurgence or progression of some cancers by stimulating several inhibitors of cell proliferation. Epidemiologic studies have shown a negative correlation between sun exposure and vitamin D availability and a number of cancers but mainly cancers of the colon, breast, and prostate. The preventive effect of vitamin D seems particularly important for colon cancer, but activated vitamin D may also reduce the progression and/or the mortality of breast and prostate cancers, too. However, the results of several trials with high doses of vitamin D have been disappointing because no improvement in patients affected by different forms of cancer was observed (**Jacobs *et al.*, 2016**).

Activated vitamin D may stimulate some hormone secretion. In particular, it may enhance insulin secretion and protect pancreatic beta cells against cytokine-mediated destruction; Both VDR and calbindin are found in pancreatic beta cells. Epidemiological studies have shown that low vitamin D levels are associated to increased risk

for type 1 and type 2 diabetes mellitus, rising the hope that vitamin D supplementation may reduce the prevalence or the clinical expression of the different forms of diabetes. However, results of randomized controlled trials with vitamin D in patients having type II diabetes have been disappointing because no improvement of the disorder was observed.

Finally, a deficiency of activated vitamin D has been involved in cardiovascular diseases. Mechanisms related to a better control or a lower prevalence of hypertension has been suggested, but activation of inflammatory processes and increased atherogenic processes may be also involved. However, as for other disorders that have been linked to vitamin D deficiency, the results of several trials of vitamin D supplementation have been negative, and in some cases the possibility that high doses of vitamin D could be harmful has been raised .

Summary

Vitamin D is formed by the effect of ultraviolet exposure but requires two hydroxylations (in liver and kidney) to be activated and be able to determine biologic effects. Biologic effects require the link of activated vitamin D with specific receptors that are present in a large number of tissues. The main receptor (VDR) is a nuclear receptor and the complex activated vitamin D – VDR activates multiple gene transcriptions. Other receptors may be found in cell membrane and may determine non genomic effects like calcium transportation across cell membrane.

Activated vitamin D is one of the main regulators of mineral metabolism and bone homeostasis by increasing active calcium absorption in intestinal microvilli and in kidney. These effects are mainly mediated by the link to VDR because require synthesis of multiple proteins. Activated vitamin D may also directly increase bone formation and reduces bone resorption but these effects are mainly mediated by its effect on reducing PTH secretion.

Different cutoffs of 25OH vitamin D have been suggested, but a cutoff of 25 ng/ml seems the most reasonable and corresponds to initial bone damage.

Activated vitamin D has many extra-skeletal actions and in particular may regulate cell proliferation, immune function, and some hormone production.

Epidemiologic studies have shown a negative correlation between vitamin D availability or levels and several chronic diseases including cancer of the colon, type II diabetes, some autoimmune and cardiovascular diseases.

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