Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Review Article
Volume 11 Issue 2 - June 2018
DOI: 10.19080/CTOIJ.2018.11.555807

Canc Therapy & Oncol Int J

A Review of the Role Portrayed by Vitamin D in Cancer

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Submission: May 07, 2018; **Published:** June 25, 2018

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Abstract

Vitamin D, also known as calcitriol, is not only one of the fat soluble vitamins but is a versatile hormone. Besides taking part in calcium homeostasis in the body and taking care of the bone health, it performs a number of important functions in the body. It can be synthesized by the body in presence of sunlight as well as can be derived from few dietary sources. Recently it has been observed that deficiency of vitamin D is rampant in general population around the world. Deficiency of vitamin D [1,25-$(OH)_2D_3$] has now been associated with a variety of clinical diseases including cancer. Though the exact mechanism involved is not clear yet, a number of theories have been put forward for the role played by vitamin D in protection against cancer. For this effect, important actions include anti-inflammatory, anti-proliferative, anti-angiogenic and pro-apoptotic which are able to abet cancer at any stage. Anti-cancer action of vitamin D is seen in prevention of all the stages of carcinogenesis. It helps to improve the efficacy of chemotherapy as well as radiotherapy in the treatment while helping in minimizing or avoiding the adverse effect associated. But further research is still needed to establish all the claims.

Keywords: Vitamin D; Anti-cancer activity; Anti-proliferative; Anti-inflammatory; Pro-apoptotic; Radiosensitization

Introduction

There is a recent surge in the interest of estimating, analyzing and associating vitamin D deficiency with a variety of clinical disorders. Vitamin D, a fat-soluble vitamin, is considered a prohormone because the body can synthesize vitamin D from its precursor (cholesterol) when exposed to ultraviolet light at a wavelength between 290-315 nm. Active form of vitamin D is 1,25-dihydroxy cholecalciferol/ 1,25-dihydroxy vitamin D_3 [1,25-$(OH)_2D_3$] or calcitriol. This metabolite interacts with its ubiquitous nuclear vitamin D receptor (VDR) to regulate the transcription of a wide spectrum of genes involved in calcium and phosphate homeostasis as well as in cell division and differentiation. It is these latter actions that have attracted tumor biologists to explore the effects of vitamin D and to use it as an antiproliferative agent in cancer cells *in vitro* and *in vivo* [1]. Adequate circulating levels of active form of this vitamin need to be maintained for normal functioning of all the systems of the body irrespective of age and gender. Insufficient levels of vitamin D may affect any system and produce the related clinical abnormality [2].

Lately, the scientific evidence is accumulating to demonstrate the insufficiency of vitamin D globally. Factors, which play a crucial role in the worldwide prevalence of vitamin D insufficiency, vary among countries; but in all cases involve limitations in either or both cutaneous synthesis and dietary sources of vitamin D. A rough estimate indicates that about 1 billion people globally are vitamin D deficient and vitamin D deficiency is quite common in regions and countries including North America, Northern Europe, Saudi Arabia, United Arab Emirates, Australia, Turkey, India and Lebanon [3] Besides the regulation of calcium and phosphorus levels in the body, a variety of diverse functions have been assigned to vitamin D. Therefore, its deficiency is bound to be implicated in a number of clinical chronic disorders like heart disease, bone disorder, cancer, infectious, inflammatory and autoimmune diseases, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and type-I diabetes mellitus etc. [3]. Many mechanisms have been put forward for its role in causation of different disorders but this review has been targeted to throw some light on the association between vitamin D deficiency and development of cancer. The general aspects pertaining to its metabolism and assessment will be discussed first.

Discussion

Metabolism of vitamin D

The major sources for vitamin D include sun exposure (predominant source), foods like fatty fish, beef liver, cheese,

egg yolk, cod liver oil and mushrooms etc. [4] Vitamin D_3 can be synthesized in the skin from the precursor 7-dehydroxycholesterol or be derived in the form of vitamin D_3 or vitamin D_2 (collectively known as vitamin D) from dietary sources. Vitamin D and its metabolites are mostly hydrophobic and thus require a protein (vitamin D–binding protein) for their transport in the aqueous environment of the bloodstream to sites of storage (adipose tissue) or sites of activation (liver and kidney) or sites of action. Vitamin D undergoes its first step of activation with help of 25-hydroxylase to produce 25-hydroxy vitamin D_3 in the liver, a step carried out by both liver mitochondrial (CYP27A1) and microsomal cytochrome P450 isoforms CYP2R1,CYP3A4, and CYP2J3 [5-7].

The circulating metabolite, 25-hydroxyvitamin D_3, is activated to the hormonal form, 1,25-$(OH)_2D_3$, primarily in the kidney. Patients with chronic renal failure exhibit frank rickets or osteomalacia due to a deficiency of circulating 1,25-$(OH)_2D_3$ caused by lack of renal 1α-hydroxylase [8,9]. The main component of the 1 α-hydroxylase enzyme is the cytochrome P450, CYP27B1, which is strongly down-regulated by its product, 1,25-$(OH)_2D_3$ and up-regulated by parathyroid hormone (PTH) as part of the calcium homeostatic loop and up-regulated by fibroblast-like growth factor 23 as part of the phosphate homeostatic loop [10,11].

Assessment of vitamin D Levels

Though 1,25$(OH)_2D_3$ is the active form of vitamin D but 25$(OH)D_3$ is the predominantly analyzed form. It is because of the fact that serum 25$(OH)D_3$ is the major circulating form of vitamin D and has a half-life of 2 to 3 weeks compared with 1,25$(OH)_2D$, which has a circulating half-life of 4 hours and a concentration 1,000 times lower than that of 25(OH)D. Besides, vitamin D deficiency is associated with a compensatory increase of PTH secretion, which stimulates the kidneys to produce more 1,25$(OH)_2D_3$. Thus, when 25$(OH)D_3$ levels fall due to vitamin D deficiency, the concentrations of 1,25$(OH)_2D_3$ may remain within normal limits and in some cases, they might even be elevated. In suspected renal impairment and inherited disorders of 25$(OH)D_3$ and phosphate metabolism, both 25$(OH)D_3$ and 1,25$(OH)_2D_3$ should be measured. There are multiple assays available to measure 25$(OH)D_3$ but with great variability in results. Therefore, treatment should target a goal above normal reference levels (Table 1) to ensure adequate levels of 25$(OH)D_3$ [12-15].

Table 1: Reference range for vitamin D [66].

Normal vitamin D levels	30-100 ng/mL
Vitamin D deficiency	< 20 ng/mL
Vitamin D insufficiency	21 to 29 ng/mL
Vitamin D toxicity	>100ng/mL

Vitamin D_2 *versus* Vitamin D_3

The natural form of vitamin D in all animals and the form synthesized in human skin on exposure to sunlight is cholecalciferol, vitamin D_3. Ergocalciferol (vitamin D_2) is a synthetic product derived by irradiation of plant sterols/ ergosterol. Initially, the two forms of the vitamin were considered to be interchangeable and equivalent, however, since the availability of the measurement of serum 25$(OH)D_3$ as an indicator of vitamin D functional status, it has become clear that vitamin D_2 is substantially less potent than vitamin D_3. These two seem to be absorbed from the intestine and to be 25-hydroxylated in the liver with equal efficiency; however, vitamin D_2 seems to up regulate several 24-hydroxylases, leading to increased metabolic degradation of both the administered D_2 and endogenous D_3. Thus, although it is certainly possible to treat patients satisfactorily with vitamin D_2, ergocalciferol seems to have no advantage over vitamin D_3 (cholecalciferol), which is the natural form of the vitamin and is less expensive [16-19].

Vitamin D and Cancer

Vitamin D deficiency is known principally for its association with bone disorders, but its newly recognized association with risk of several types of cancer is receiving considerable attention [20-22]. The high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggests that vitamin D deficiency may account for several thousand premature deaths from colon, breast, ovarian and prostate cancer annually [23,24]. Vitamin D deficiency has been found to be associated with different stages of cancer. The vitamin D receptor (VDR) is essential to initiate various signaling pathways that are induced by 1,25(OH)2D_3 and have been shown to play a substantial role in its anti-cancer activity. There are several reports suggesting that VDR expression is gradually reduced when the stage of malignancy advances and certain VDR polymorphisms are associated with increased cancer risk [25,26]. It has also been reported that locally circulating 25$(OH)D_3$ can be converted into 1,25(OH)2D_3 by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), which is not only expressed in kidney but in many other tissues such as colon, breast, prostate, placenta and different cells of the immune system suggesting the role played by these tissues in the metabolism of vitamin D [27]. The anti-cancer activities of 1,25(OH)2D_3 include the effects of its local synthesis, which induces autocrine/ paracrine actions within the tumors as well as endocrine actions of circulating 1,25(OH)2D_3 [28]. A number of molecular mechanisms have been put forward to demonstrate the association of vitamin D and cancer.

Mechanisms for anti-cancer actions of vitamin D

Various actions of vitamin D to contribute towards its anti-cancer property are as under:

Anti-proliferative Actions

In most cell types that express a functional VDR, exposure to 1,25(OH)2D_3 results in the accumulation of cells in the G0/ G1 phase of the cell cycle. The transition from G to S-phase is controlled by the pocket proteins retinoblastoma (Rb), p107 and p130. The phosphorylation status of these proteins determines their association with members of the E2F family of transcriptional

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regulators that play a pivotal role in mediating gene expression during cell proliferation. In quiescent and early G1 cells, E2F4 and E2F5 act as transcriptional repressors by associating with p107 and p130. In proliferating cells, pocket proteins get phosphorylated and upon release by Rb, E2Fs 1-3 function as transcriptional activators inducing the transcription of target genes that regulate cell cycle progression. Dephosphorylation of Rb by $1,25(OH)2D_3$ results in the modulation of the expression and the activity of a number of genes. In general, activated cyclin/cyclin dependent kinase (CDK) complexes phosphorylate Rb and a loss of their kinase activity generates hypo or dephosphorylated Rb. Thus, both the expression of cyclins (D1, E, A) and CDKs (2,4,6) can be decreased by $1,25(OH)2D_3$ [29,30].

The expression of the CDK inhibitors (CDKIs) p19, p21 and p27 are increased after treatment with $1,25(OH)2D_3$, and this effect is cell type specific. In different cancer cell lines, increased p27 protein levels are attained by secondary effects that increase the half-life of the protein. Vitamin D reduces phosphorylation of Thr187 residue of p27, which is important for its recognition by the ubiquitin-ligase SKP2 and rendering it less prone to degradation. The levels of protein SKP2 have also been found decreased by $1,25(OH)2D_3$ [30,31]. It has also been reported that in HL60 cells, $1,25(OH)2D_3$ controls p27 levels by decreasing the expression of miR181s, a microRNA known to target p27 as well as regulating miR-106b expression to control p21 expression [32,33].

Apoptosis

Vitamin D can trigger the intrinsic, mitochondria-dependent pathway that induces cell death though the effect is not uniform for all types of cells. Depending on the cell type, $1,25(OH)2D_3$ decreases the expression of the anti-apoptotic factors (Bcl-2, Bcl-XL) and increases the pro-apoptotic equivalents (Bax, Bak), thus, directing the cells towards apoptosis [34]. In prostate cancer (PCa) and breast cancer (BCa) cells, vitamin D activates the intrinsic pathway of apoptosis causing the disruption of mitochondrial function, cytochrome release and production of reactive oxygen species [35,36]. In some cells $1,25(OH)2D_3$ also directly activates caspases to induce apoptosis [37,38]. In addition, vitamin D analogues have been shown to enhance cancer cell death in response to radiotherapy and chemotherapy [39,40].

Inhibition of Tumour spread

$1,25(OH)2D_3$ reduces the invasive and metastatic potential of many malignant cells as demonstrated in murine models of prostate and lung cancer by inhibiting angiogenesis [41]. The formation of new blood vessels is an important ability of malignant cells to guarantee their oxygen supply and tumor suppressors often interfere with this process. The mechanisms underlying this effect include the inhibition of angiogenesis and the regulation of the expression of key molecules involved in invasion and metastasis like the components of the plasminogen activator (PA) system and matrix metalloproteinases (MMPs), decreasing the expression of tenascin-C, an extracellular matrix protein that promotes growth, invasion and angiogenesis, down-regulation of the expression of α6 and β4 integrins and increase in the expression of E-cadherin, a tumor suppressor gene whose expression is inversely correlated to metastatic potential [42-45]. Vitamin D-mediated suppression of MMP-9 activity and increase in tissue inhibitor of metalloproteinase-1 (TIMP-1) also decrease the invasive potential of PCa cells [46].

$1,25(OH)2D_3$ inhibits the proliferation of endothelial cells and reduces vascular endothelial growth factor (VEGF)-induced endothelial cell growth and elongation. VEGF is a key mediator involved in positive regulation of the formation of new vessels [47]. In addition, vitamin D modulated bone resorption also plays an important role in metastasis in PCa and BCa cells [48].

Anti-inflammatory Action

Chronic inflammation, triggered by a variety of stimuli such as injury, infection, carcinogens, autoimmune disease, the development of tumors, hormonal factors and so forth, has been recognized as a risk factor for cancer development. Cancer-related inflammation is characterized by the presence of inflammatory cells at the tumor sites and over-expression of inflammatory mediators such as cytokines, chemokines, prostaglandins (PGs) and reactive oxygen and nitrogen species in tumor tissue. Many of these proinflammatory mediators activate angiogenic switches usually under the control of vascular endothelial growth factor (VEGF) and thereby promote tumor progression, metastasis, and invasion [49-51].

Vitamin D regulation of gene expression leads to the inhibition of the synthesis and biologic actions of prostaglandins (PGs) by inhibiting the expression of gene for the enzyme cyclooxygenase-2 and increasing the synthesis of catabolic enzyme 15-hyroxyprostaglandin dehydrogenase [52]. It also suppresses the activation and signaling of nuclear factor kappa B (NFκB), a transcription factor that regulates the expression of genes involved in inflammatory and immune responses and cellular proliferation and is believed to play a key role in the process leading from inflammation to carcinogenesis [53,54].

$1,25(OH)2D_3$ has been reported to increase the expression of MAP kinase phosphatase MKP5, a member of the dual specificity MKP family of enzymes that dephosphorylate and thereby inactivate, MAPKs in normal human prostate epithelial cells. This action leads to downstream anti-inflammatory responses by causing the dephosphorylation and inactivation of the p38 stress-induced kinase, resulting in a decrease in the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) [55].

Role of vitamin D in Cancer Treatment

$1,25(OH)2D_3$ deficiency has, definitely, a role to play in the causation, growth and spread of the tumour cells but its supplementation has been reported to increase the efficiency of different treatment modalities used for cancer. $1,25(OH)2D_3$ has been demonstrated to enhance the sensitivity of PCa cells

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to ionizing radiation significantly by selectively suppressing radiation-mediated RelB activation and via suppression of the NFκB pathway [56]. There is also considerable evidence that vitamin D potentiates the antitumor activity of a wide variety of cytotoxic chemotherapy agents. In addition, the induction of p73 by 1,25(OH)2D_3 seems to contribute to the synergistic activity of vitamin D and platinum analogues and some antimetabolites [57]. Vitamin D status may have a significant bearing in cancer outcome also as higher mortality in patients with colorectal carcinoma was found to be associated with groups having lower vitamin D levels [58]. Chemotherapy for colorectal rectal carcinoma has been reported to induce a state of vitamin D insufficiency or deficiency [59]. The role of vitamin D in preventing adverse effects of chemotherapy is controversial and is an area of interest for further research [60,61].

Treatment with vitamin D has been found to increase radiosensitization of tumour cells as reported by some recent studies. In a study on non small cell lung carcinoma, it was found that vitamin D radiosensitized A549 cells by significantly decreasing the cell colony formation ability by producing enhanced G2/M cell cycle arrest and promoting apoptosis [62]. Similarly increased radiosensitization has been reported in prostate carcinoma cells with vitamin D or vitamin D analogue supplementation [63,64]. 1,25(OH)2D_3 has been reported to be effective against adverse effects associated with radiotherapy. In a recent report, vitamin D deficiency has been found to be associated with increased severity of radiation-induced acute proctitis in cancer patients [65].

Conclusion

Besides putting forward so many mechanisms for anti-cancer property of vitamin D, the effects of vitamin D on carcinogenesis or cancer progression remain incompletely understood. However, a great body of information about the association between vitamin D deficiency and increased cancer risk, together with the known benefits of maintaining adequate 25(OH)D_3 serum levels for cancer prevention, treatment and improving the efficiency of different therapeutic modalities in the oncology field, warrant further research regarding this natural antineoplastic hormone. Recent research has focused on the use and invent of vitamin D analogs that have potential for more potent anti-proliferative effects on cancer cells with fewer hypercalcemic side effects.

Conflict of Interest

None.

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How to cite this article: Rakesh Dhankhar, Kiran Dahiya, Raunak Ahlawat, Priya Dahiya, Sunder Singh, Keerti Gupta. A Review of the Role Portrayed by Vitamin D in Cancer. Canc Therapy & Oncol Int J. 2018; 11(2): 555807. DOI: 10.19080/CTOIJ.2018.11.555807

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DOI: 10.19080/CTOIJ.2018.11.555804

How to cite this article: Rakesh Dhankhar, Kiran Dahiya, Raunak Ahlawat, Priya Dahiya, Sunder Singh, Keerti Gupta. A Review of the Role Portrayed by Vitamin D in Cancer. Canc Therapy & Oncol Int J. 2018; 11(2): 555807. DOI: 10.19080/CTOIJ.2018.11.555807