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BENEFICIAL ROLE OF VITAMIN D IN COMMON CANCERS: IS THE EVIDENCE COMPELLING ENOUGH?

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Abstract – *Background:* *Vitamin D is a fat-soluble vitamin having well known effects on bone health and calcium homeostasis. Vitamin D3 (cholecalciferol) is the chemical form of vitamin D in humans, synthesized from photochemical conversion of 7-dehydrocholesterol in the skin. It is activated by hydroxylation in the liver and kidney to form 1,25-dihydroxyvitamin D3 (calcitriol), which exerts its biochemical and physiological effects through the vitamin D receptor (VDR). In addition to maintenance of skeletal mineral balance, vitamin D has multiple other roles in the body including regulation of cell cycle, cellular differentiation and immune functions, neuroprotection, antioxidant action, xenobiotic metabolism as well as antimicrobial, anti-inflammatory and antitumor effects.*

Materials and Methods: *Vitamin D is involved in the expression of several genes having oncogenic potential. The anti-cancer effects of vitamin D are mediated via its stimulation of apoptosis and cell differentiation and inhibition of invasion, metastasis and angiogenesis.*

In the last two decades, numerous studies have addressed the potential of vitamin D in curtailing development and progression of multiple malignancies and/or improving their prognosis. Most of the data accumulated over this time has linked lack of exposure to sunlight and deficiency of vitamin D to an increased risk of several cancer types but a few studies have yielded conflicting results particularly on the therapeutic role of vitamin D supplementation.

Results: *Recent findings have provided detailed insights into the mechanism of anti-cancer actions of vitamin D. Disruption of the VDR signalling pathway at multiple levels seems to be at the core of oncologic transformation in various types of cancers. Based on the available mechanistic evidence, future research trials using novel pharmacological interventions targeting the vitamin D pathway need to be instituted in order to derive conclusive clinical recommendations.*

Conclusions: *At present, adequacy of vitamin D status appears to be a pertinent factor in mitigating the risk of cancer development, thus maintenance of vitamin D levels through appropriate sun exposure and dietary intake is advisable.*

KEYWORDS: *Vitamin D, Anti-cancer, Supplementation, Hypovitaminosis D.*

INTRODUCTION

The Nobel Prize winning chemist Adolf Windaus discovered vitamin D which was subsequently identified as a remedy for prevention and reversal of the bone disease rickets[1]. Vitamin D is a fat-soluble secosterol occurring in two principal forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), of which vitamin D3 is the prohormone having multiple roles in human physiology. The predominant source of vitamin D3 is ultraviolet radiation-induced photochemical conversion of its precursor 7-dehydrocholestrol in the skin[2]. Vitamin D3 is biologically inert and two successive hepatic and re-

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nal hydroxylation steps produce its active hormonal form 1,25-dihydroxyvitamin D3, also known as calcitriol. 25-hydroxyvitamin D3, or calcidiol, formed after hydroxylation of vitamin D3 in the liver is the serum marker typically employed for estimation of vitamin D status in routine clinical practice[2]. 85-90% of circulating 25-hydroxyvitamin D3 is tightly bound to vitamin D-binding protein (DBP), 10-15% is loosely bound to albumin and less than 0.03% is free[3]. Vitamin D plays pivotal roles in skeletal mineral homeostasis, including intestinal absorption of calcium and phosphate, skeletal mobilization of calcium and renal reabsorption of calcium[4]. Vitamin D is also involved in several noncalcemic extraskeletal functions in the body including cellular proliferation and differentiation, immunomodulation, neuroprotection, antioxidant defense, xenobiotic detoxification, antimicrobial, anti-inflammatory and anticancer actions (Figure 1) [2,5].

The effects of vitamin D are exerted through a single vitamin D receptor (VDR), which is a member of the class II steroid hormones. It has a C-domain (DNA-binding), an E-domain (ligand-binding), and an F-domain, which is one of the activating domains[6]. Calcitriol (activated vitamin D) binds to VDR in the cytosol forming a dimer that gets translocated into the nucleus. The nuclear retinoid X receptor (RXR) binds to the calcitriol-VDR dimer and then the complex triggers gene expression by binding to the vitamin D responsive element (VDRE) (Figure 2). Vitamin D regulates the expression of nearly two hundred genes, some of which are implicated in oncogenic mechanisms. Vitamin D exerts antineoplastic effects by inducing cell differentiation, promoting apoptosis, decreasing angiogenesis, preventing invasion and inhibiting metastasis. Additionally, the gene for CYP24A1, the primary enzyme for the metabolic degradation of active Vitamin D3, is considered a putative oncogene[7, 8].

Numerous studies have attempted to explore the role of vitamin D in oncological transformation. Low sunlight exposure and hypovitaminosis D have been linked, albeit somewhat inconsistently, with the increased risk of cancers through scientific evidence gathered over the past few decades[9]. Vitamin D supplementation, in particular, has yielded variable results across different types of cancers[10, 11]. The current review summarizes the recent work on the antitumor potential of vitamin D in common malignancies including skin, lung, breast, prostate, colorectal and hepatocellular cancers.

SKIN CANCER

Skin is the primary tissue involved in the metabolism of vitamin D. Vitamin D synthesis in the skin is dependent upon ultraviolet exposure. However, exposure to the sun is also known to predispose to skin cancer as evident from geographical variations in incidence and a higher risk in fair-skinned people[12]. Skin cancer, including both melanoma and non-melanoma, is one of the most common type of malignancies[13, 14]. *In vitro* studies have shown an inhibitory role of vitamin D in the development of several skin cancer types including melanoma, basal cell carcinoma and squamous cell carcinoma. Disruption of molecular signalling pathways involving vitamin D and calcium receptors has been linked to epidermal tumorigenesis in murine models. Clinical studies, however, have yielded inconsistent results with some showing lower vitamin D levels as a risk factor for skin cancer, while others suggesting the opposite[15-17]. Eid et al[18] showed increased baseline serum vitamin D levels to be associated with an elevated risk of non-melanoma skin cancer but ultraviolet exposure was stated to be a potentially strong confounder. In another study, increased incidence of basal cell carcinoma and melanoma and a non-statistically significant decreased incidence of squamous cell carcinoma

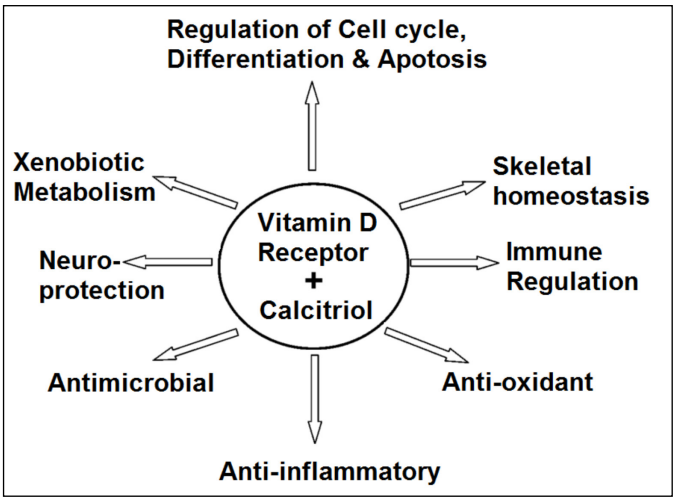

Fig. 1. Functions of activated vitamin D (calcitriol) signalling pathway.

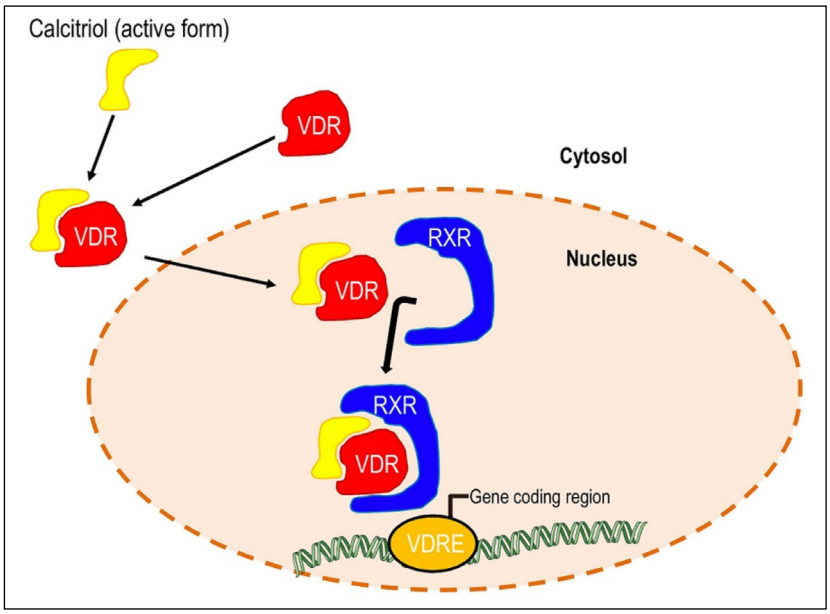

Fig. 2. Mechanism of action of vitamin D. Calcitriol, being lipid-soluble, enters the cell and binds to vitamin D receptor (VDR) in the cytosol. The calcitriol-VDR dimer is translocated into the nucleus where nuclear retinoid X receptor (RXR) binds to it. The resulting complex activates gene expression by binding to vitamin D responsive element (VDRE).

was observed with high baseline serum vitamin D levels[19]. These conflicting observations suggest a role of complex factors including ultraviolet sun exposure and skin color.

Data generated from a meta-analysis evaluating the association of blood vitamin D levels and dietary intake with the risk of melanoma and non-melanoma skin cancers suggested an inverse association between circulating vitamin D and melanoma thickness at the time of diagnosis but dietary or supplemental vitamin D was not associated with the incidence of skin cancer[20]. Another large American study by Park et al[21] did not find a protective role of oral vitamin D on cutaneous carcinogenesis. In their prospective study assessing the association of vitamin D intake with the risk of skin cancer, vitamin D intake was shown to be associated with increased risk of basal cell carcinoma, but no associations were found with melanoma and squamous cell carcinoma. A delicate equilibrium of intricate factors like sun exposure, vitamin D levels and skin color appears to determine vulnerability to skin carcinogenesis. The complexity of the relationship between these factors warrants more studies to derive unambiguous clinical recommendations regarding the role of vitamin D in skin cancer.

LUNG CANCER

Lung cancer is a major malignancy with a high disease burden, causing more than a million deaths worldwide every year[13, 14]. The role of vitamin D in lung carcinoma has been recognized relatively recently. In a Czech study assessing serum vitamin D levels in multiple cancer groups, very low vitamin D levels were observed in patients with lung cancer[22]. Zhang et al[23] showed an inverse association between serum vitamin D and lung cancer risk. In a meta-analysis by Liu et al[24], an inverse correlation was shown between overall risk of lung cancer and high vitamin D (or calcium) intake and serum vitamin D levels individually. High serum levels were also shown to reduce lung cancer mortality while a positive trend was observed in the relationship between serum vitamin D concentration and survival. It was further revealed that non-smokers had higher vitamin D levels, which correlated negatively with lung cancer risk. Dietary vitamin D intake was associated with a reduced risk reduction for non-small cell lung cancer In a case-control study[25].

A dose-response meta-analysis of prospective cohort studies reported a significant association between circulating vitamin D and lung cancer risk and mortality, but serum vitamin D was not associated with overall lung cancer survival. It was further shown that an increase of 10nmol/L in the circulating vitamin D levels led to 8% and 7% reduction in the risk of lung cancer and lung cancer mortality respectively[26]. Recent findings from a randomized double-blind trial of patients with non-small cell lung cancer comparing vitamin D supplements (1,200 IU/day) with placebo over a one year period suggested improvement in survival of patients with lower vitamin D levels receiving vitamin D supplementation[27].

The current evidence suggests that high intake and high serum levels of vitamin D may lower the risk of lung cancer risk and improve prognosis, but further studies are needed to illustrate the preventative potential of vitamin D supplementation in lung cancer.

BREAST CANCER

Breast cancer is the most common malignant tumor in women and dietary factors are thought to exert influence in more than one-third of the diagnosed females[13, 14]. Dietary measures such as reduction in the consumption of alcohol, red meat and fats along with increase in the intake of vitamin D and fibre have been highlighted as potentially beneficial in reducing the risk of breast cancer[28]. VDR found in breast epithelial cells, plays physiological roles in the mammary gland during milk production through regulation of calcium transport and hormone differentiation[29]. Several vitamin D-responsive targets have been identified in cancerous mammary cells through genomic profiling including the role of VDR signalling in modulation of cell cycle events, cell differentiation and apoptosis as well as regulation of metabolic and immune effects influencing tumor microenvironment[30]. Suppression of CYP24A1 gene, the enzyme product of which causes catabolic inactivation of vitamin D in target tissues, enhances apoptosis and inhibits growth in breast cancer cells by increasing the bioavailability of active vitamin D[31]. Huss et al[32] evaluated the covariation between expression of VDR and prognostic factors of breast cancer in a tissue microarray of invasive breast tumors. Both intranuclear and cytoplasmic expression of VDR in breast cancer cells was positively associated with favorable prognostic characteristics such as lower grade, smaller tumor size and positive estrogen and progesterone receptor expression. Positive VDR expression was also associated with a low risk of breast cancer deaths.

Data from most observational and epidemiologic studies are supportive of an inverse relationship between serum vitamin D levels and the risk of breast cancer risk[29]. A high incidence of hypovitaminosis D has been shown in breast cancer patients[22]. A systematic review by Estebanez at al[33]. showed a protective effect of serum vitamin D on breast cancer in premenopausal women. However, no association was found between vitamin D intake and the development of breast cancer. Pooled findings from a recent meta-analysis of observational studies suggested a direct association between deficiency of circulating vitamin D and breast cancer while total and supplemental vitamin D intake had an inverse relationship with breast cancer[34]. Further research employing the latest genomic, proteomic and metabolomic techniques is required to elucidate the possible protective mechanisms of action of vitamin D against breast cancer development. Clinical trials designed to definitively assess the association of vitamin D levels and intake with the risk, recurrence and survival in breast cancer are also warranted.

PROSTATE CANCER

Prostate cancer (PC) is a major malignancy afflicting men and one of the leading causes of cancer mortality worldwide[13, 14]. A study reported that the association of low levels of vitamin D with a high risk of prostate tumors for the first time, based on the observations of reduced PC mortality rates in patients with more ultraviolet light exposure[35]. Numerous studies have since been conducted evaluating vitamin D deficiency, either due to dietary insufficiency or low ultraviolet exposure, as a risk factor for PC[36]. While most of these studies have implicated low circulating vitamin D levels in the progression of PC, a few have borne controversial results. Vitamin D supplementation has been shown to confer a beneficial impact on patients with low-risk PC under active surveillance[37]. However, calcium- rich diets have been linked to accelerated progression of early stage PC. The opposing roles for calcium and vitamin D in the development, progression and prognosis of PC suggest a complex interplay between these nutrients[38]. Results from a recent meta-analysis indicated a reduction in all-cause mortality and PC-specific mortality in patients with higher circulating vitamin D levels[39]. A systemic review of randomized clinical trials by Petrou et al[40] suggested dose-dependent clinical benefits of vitamin D supplementation in combination with standard cancer-specific therapies. Vitamin D supplementation in PC has been shown to positively alter the redox status with potential to improve disease outcomes. However, an undesirable accumulation of metal ions in the erythrocytes of PC patients has also been documented which may affect the cancer outcomes in an adverse manner[41].

Therapeutic activation of vitamin D signalling, either by vitamin D alone or in combination with other antineoplastic agents, seems to be a plausible prevention strategy but the available data do not provide conclusive information[42]. Furthermore, considering the androgen-dependent nature of PC, it is highly pertinent to evaluate the role of testosterone signalling as an intermediate mechanism in the relationship between vitamin D and PC progression[43]. Existing data support the need to further demonstrate the mechanistic and therapeutic roles of vitamin D in the pathogenesis of PC.

COLORECTAL CANCER

Colorectal cancer (CRC) is a common malignant neoplasm and one of the leading causes of cancer related mortality the world over[13,14]. Garland and Garland proposed a protective role of vitamin D against CRC in 1980 and numerous studies conducted since

then have suggested that higher circulating vitamin D levels lower the risk of CRC[44,45]. Hypovitaminosis D is common in patients with newly diagnosed CRC. Furthermore, chemotherapy and surgical resection of CRC have also been shown to induce fall in serum vitamin D concentration[46, 47]. A systematic review of epidemiological studies assessing serum vitamin D concentration and the risk for CRC reported an inverse relation between the two[48]. A recent pooled analysis by McCullough et al[49] showed higher serum vitamin D levels to be associated with a marked reduction in CRC risk in women. A lower risk was also observed for men, but it was not statistically significant.

Mechanistic studies have shown that calcitriol, the active metabolite of vitamin D, mediates a range of potential protective effects against CRC through the VDR. These include suppressing proliferation and promoting differentiation of cancer cells, modulating immune cell function, inhibiting gene expression and tumorigenic actions of cancer-associated fibroblasts and altering intestinal flora[50]. In a recent analysis by Fedriko et al[51], genomic variants in the vitamin D signalling and their altered transcriptional activity depending on the serum vitamin levels were suggested to be associated with colorectal tumorigenesis. Another genetic study of VDR polymorphisms showed certain polymorphisms to be correlated with serum vitamin D and calcium concentration in patients with CRC, thereby suggesting a role of vitamin D in the onset of CRC. Homozygous genotype (aa) of the rs7975232 VDR single nucleotide polymorphism was found associated with serum vitamin D levels in CRC patients and the heterozygous genotype (Tt) of the rs731236VDR single nucleotide polymorphism correlated with serum Ca levels[52]. Low serum levels of vitamin D were shown to be associated with poorer survival in CRC patients, particularly those with homozygous genotype (GG) of the rs11568820 VDR single nucleotide polymorphism[47].

Recently, high-dose vitamin D was shown to improve clinical outcomes in patients with metastatic CRC receiving standard chemotherapy[53]. An Iranian study also showed a reduced risk of CRC with dietary vitamin D, but no such association was observed with calcium intake[54]. Previously, a meta-analysis of randomized controlled trials of vitamin D supplementation and the incidence and mortality of CRC showed vitamin D supplementation to be beneficial in terms of reducing the risk of mortality only[55].

Epidemiologic evidence accrued over the years is suggestive of a protective effect of vitamin D on CRC, but supplementation does not seem to provide benefit as would be expected, particularly in terms of reduction in the incidence of CRC. Randomised trials of vitamin D supplementation designed to account for confounding factors like sun exposure, seasonal influences, skin color and dietary intake are required to determine the preventative and therapeutic potential of vitamin D in CRC.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the primary liver malignancy, accounting for more than 80% of all patients with liver cancer. It is one of the most common cancers globally and despite the recent advancements in treatment modalities, HCC is a major cause of cancer related mortality due to its poor prognosis[13, 14]. Association of vitamin D and HCC has been a subject of investigation for quite some time now but the evidence garnered remains unclear[56,57].

A recent cross-sectional study reported vitamin D deficiency, decreased VDR levels and downregulation of autophagy and host-mediated apoptosis in HCC patients with hepatitis C viral infection, suggesting a role of VDR axis in the development of HCC related to viral hepatitis[58]. Buonomo et al[59] reported hypovitaminosis D to be common in HCC patients with a negative impact on the overall survival of patients with liver cirrhosis regardless of the presence of HCC. In another study, higher serum levels of bioavailable vitamin D (free and albumin-bound fractions only), rather than total circulating vitamin D, were shown to be associated with improved survival in HCC[60]. Wu at al[61] have recently demonstrated that vitamin D deficiency at baseline is associated with poor tumor response in patients receiving transarterial chemoembolization (TACE) as first-line therapy for advanced HCC.

Vitamin D has been shown to enhance the antitumor activity of 5-Fluorouracil and improve liver function in a rat model of HCC by modulating the expression of transforming growth factor beta 1 (TGF-β1), caspase-3, and nuclear factor erythroid 2-related factor 2 (NrF2)[62]. Another study has shown vitamin D to be able to re-sensitize HCC cell lines resistant to treatment with everolimus, an inhibitor of mechanistic target of rapamycin (mTOR). Vitamin D reverses resistance to everolimus by upregulation of miR-375 and consequent down-regulation of several oncogenes responsible for drug resistance and epithelial mesenchymal transition in HCC[63].

Genomic analysis has demonstrated association between the single nucleotide polymorphism of VDR gene at FokI locus and increased susceptibility of HCC in patients with chronic hepatitis B infection. The polymorphism is also useful in evaluating the severity of HCC through its association with its clinicopathological characteristics[64,65]. Conversely, CYP2R1 polymorphism responsible for higher vita-

min D levels, has been associated with progression to HCC in patients infected with hepatitis C virus[66].

Recent biochemical, genomic, animal and clinical data have highlighted the involvement of vitamin D pathway in the pathogenesis and prognosis of HCC in various clinical contexts. Therapeutic regimens comprising of vitamin D analogues in combination with standard anti-cancer therapies for HCC have showed promising results[67]. Nonetheless, there is a need for more mechanistic studies and clinical trials to provide convincing evidence on the role of vitamin D in HCC.

OTHER COMMON CANCERS

Vitamin D has been studied in various other common cancers owing to its involvement in multiple cellular processes whose disruption can trigger oncogenesis, Data on the relationship of vitamin D with urological cancers other than PC are limited[68]. Studies have demonstrated that low serum vitamin D is associated with an increased risk of bladder cancer, suggesting a potential protective effect of vitamin D against bladder cancer[69-71]. A recent Chinese study suggested a protective effect of a higher serum vitamin levels against renal cell carcinoma, with each 10 ng/mL increase in vitamin D concentration corresponding to a 12% decrease in cancer risk[72]. VDR has been shown to function as a tumour suppressor in cell lines of renal cell carcinoma by regulating the expression of the transient receptor potential vanilloid subfamily 5 (TRPV5) which is a highly selective calcium channel protein mainly found in the kidney[73].

A beneficial role of vitamin D has also been suggested in cancers of the digestive tract[74,75]. However, recent work does not support a therapeutic role of vitamin D in gastrointestinal malignancies[76]. A protective effect of sunlight exposure against non-Hodgkin's lymphoma has been demonstrated but association with serum and/or dietary vitamin D was not found[77]. Attaining normal serum levels of vitamin D following supplementation has been shown to improve event-free survival in patients with diffuse large B-cell lymphoma receiving rituximab-based treatment[78]. Vitamin D supplementation does not seem to improve progression-free survival in patients with Hodgkin's lymphoma[79].

Hypovitaminosis D is very common in patients with head and neck cancers. Higher serum vitamin D levels are associated with decreased risk of head and neck cancers and improved survival. Inadequate vitamin D intake has been shown to increase the risk of mortality and recurrence in patients with head and neck cancers. Vitamin D has the potential to serve as an adjuvant to traditional chemotherapeutic agents for head and neck malignancies, lending synergistic support to antitumorigenic immune responses for improving prognosis[80-83].

CONCLUSIONS

The role of vitamin D in prevention of neoplastic transformation and progression has been debated extensively for over two decades now. Hypovitaminosis D has been highlighted as a risk factor for multiple cancer types, but its therapeutic potential has generated mixed results. The recent emergence of biochemical and genomic evidence points to disturbances in the vitamin D signalling pathway as one of the reasons for oncogenic change. Future work should be aimed at elaboration of these molecular mechanisms of vitamin D which are likely to offer clinically useful insights. Based on the existing knowledge, it is reasonable to suggest maintenance of serum vitamin D levels within normal range to extract potential anti-cancer benefits of vitamin D.

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Conflict of Interest:

The authors declare no conflict of interest.

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