



## Review

## Role of vitamin D and vitamin D receptor (VDR) in oral cancer

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## ABSTRACT

Oral cancer is known as one of the most common cancers, with a poor prognosis, related to delayed clinical diagnosis, either due to the lack of particular biomarkers related to the disease or costly therapeutic alternatives. Vitamin D executes its functions by interacting with the vitamin D receptor (VDR), both in healthy and diseased individuals, including oral cancer. This review discusses the role of vitamin D and VDR on tumorigenesis, emphasizing on oral cancer. Furthermore, regulation of VDR expression, mechanisms of anticancer effects of calcitriol, oral cancer chemoresistance and its relation with VDR and polymorphisms of VDR gene will be discussed. The manuscript is prepared mainly using the information collected from PubMed and MEDLINE.

## 1. Introduction

Vitamin D and its receptor (VDR) earned increasing importance during the last two decades as they play an essential role in the calcium and phosphate metabolism and also homeostasis [1]. On the other hand, the importance of attention to vitamin D as well as VDR increased whenever it was revealed to effect noteworthy clinical problems such as diabetes, cardiovascular disease, and cancers [2–4].

Recently, the role of vitamin D to various disease progressions and mortality of cancer has drawn attention in epidemiological and pre-clinical studies. The higher level of circulating vitamin D is strongly related to reducing the risk of progression a variety type of cancers (bladder, breast, colorectal, gastric, ovarian, kidney, hematological, lung, prostate, head and neck, pancreatic liver, and also skin cancers). It has been shown that vitamin D could inhibit the proliferation and differentiation of tumor cells. The active form of the fat-soluble metabolite, 1 $\alpha$ ,25(OH) $_2$ D $_3$ , exert its performance on various tissues with binding to the nuclear vitamin D receptor (VDR) [5]. Moreover, the presence of VDR expression in a number of malignant tumor tissues is reflective of the role of VDR in influencing cancer etiology. On the other hand, it has been illustrated that the activity of the VDR-vitamin D complex could be altered by VDR polymorphisms [6–8].

Oral cancer is a type of malignant neoplasm that involving the lip or

oral cavity. Because oral squamous cell carcinoma (OSCC) consists of more than 90% of oral cancers, it is conventionally defined as OSCC [9]. The timely detection and immediate treatment is the most effective procedure to decrease morbidity and mortality in oral cancer [10]. More recently, prevention and also treatments efficacious of vitamin D has been examined in the wide range of cancers. The data obtained from preclinical studies strongly support the cancer prevention properties of vitamin D because of its pro-apoptotic, anti-proliferative and anti-angiogenic performances against the wide range of cancer cells [11].

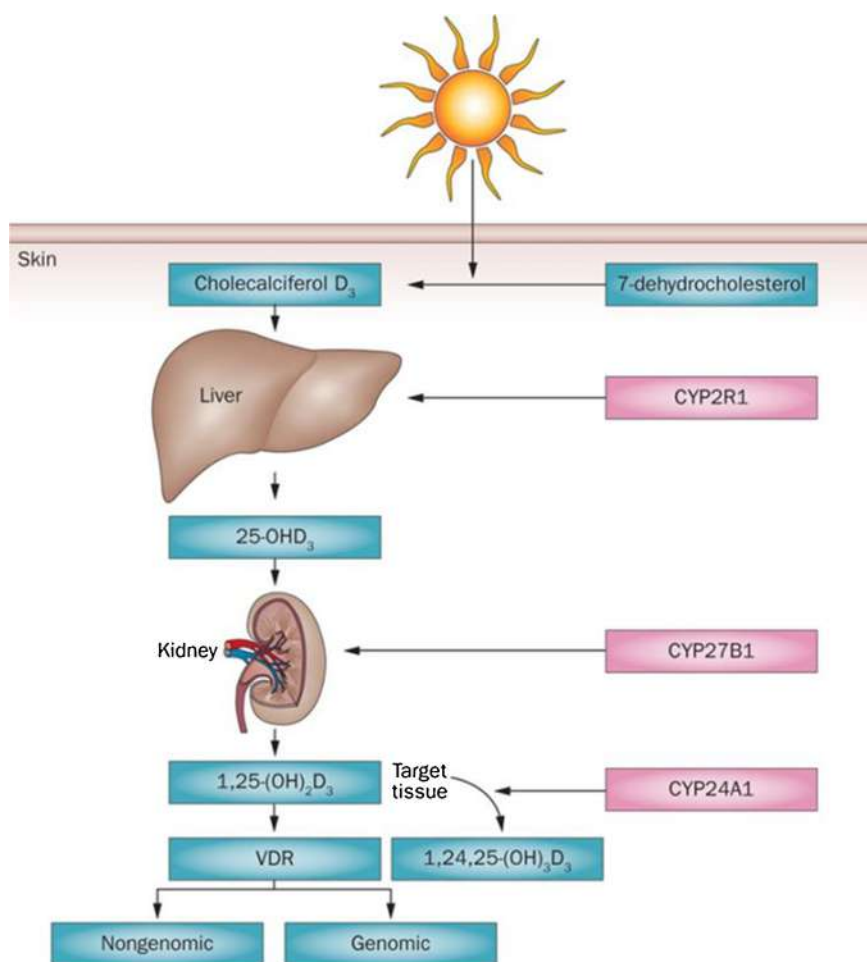
As regards to the numerous studies have been supported on the vitamin D, and its receptor plays a vital role in cancer's etiology, nevertheless, no comprehensive review on the association between oral cancer and vitamin D/VDR system is available. In this article, we reviewed the updated evidence related to the role of this system in oral cancers. Information is collected from the National Library of Medicine's PubMed database, and we discussed the role of vitamin D and VDR in oral cancer [6].

## 2. Vitamin D synthesis

A group of fat-soluble secosteroids that known as vitamin D is responsible for rising absorption of phosphate, magnesium, and calcium,

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**Fig. 1.** Systemic vitamin D metabolism (adapted from ref. [18] with permission). Vitamin D synthesis commonly starts in the skin tissue, where 7-dehydrocholesterol converts to cholecalciferol by ultraviolet B radiation. Cholecalciferol D<sub>3</sub> is an inactive form, and before the active 1 $\alpha$ ,25-dihydroxy vitamin D<sub>3</sub> (calcitriol) is formed, it undergoes two hydroxylation steps. Hepatic CYP2R1 mediated 25-hydroxylation and renal CYP27B1 mediated 1 $\alpha$ -hydroxylation. 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> that is the active form of vitamin D that couple to the vitamin D receptor (VDR) and mediates fast effects by additional ligand (nongenomic), binding pocket, or genomic effects by the genomic pocket. 24-hydroxylation inactivated all of the vitamin D circulating forms.

in the intestine [12]. In human, vitamin D<sub>3</sub> (known as cholecalciferol) and vitamin D<sub>2</sub> (known as ergocalciferol) are the most important compounds in this group [13]. There are two different ways Vitamin D is acquired: dietary source and non-dietary source from sunlight exposure [14,15]. The UVB radiation exactly regulated the vitamin D synthesis. At first, in the epithelium of the bowel with starts oxidation the cholesterol to 7-dehydrocholesterol, create pro-vitamin D<sub>3</sub>. Followed by the pro-vitamin D<sub>3</sub> transferred to skin and with the effect of ultraviolet radiation at wavelengths from 270 to 300 nm converted to pre-vitamin D<sub>3</sub>. Followed by pre-vitamin D<sub>3</sub> isomerizes to vitamin D<sub>3</sub> and cholecalciferol, in a temperature-dependent reaction. Activation of vitamin D<sub>3</sub> happens by two hydroxylations and create 1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub> (calcitriol that is as the biological active form of vitamin D) [16]. By the microsomal and mitochondrial vitamin D 25-hydroxylases (CYP27A1), calcitriol first one takes place in the liver. The 25(OH) D (calcidiol) is ordinarily applicable in different studies to estimate the vitamin D level as it has physiological higher concentration [8]. The second hydroxylation is performed by 1-hydroxylase (CYP27B1) in the renal mitochondria (Fig. 1). Furthermore, 24-hydroxylation inactivated all the circulating forms of vitamin D [16,17]. It is noteworthy, the synthesis of calcitriol is not only done in renal cells, even can as well as be established in skin, keratinocytes, prostate and cancer cells [9,10,11,12].

### 2.1. VDR related genomic mechanism of calcitriol action

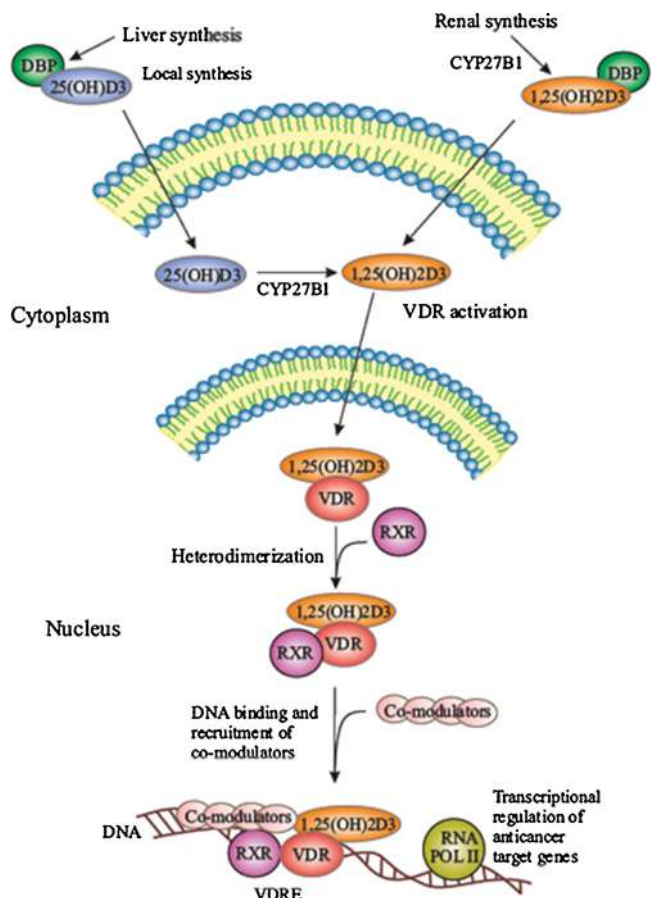
The biological actions of calcitriol are mostly exerted through genomic actions mediated by the VDR (Fig. 2). Initially, calcitriol joins to the VDR, so retinoid X receptor (RXR) induce its dimerization, then formed a complex to vitamin D response elements (VDREs) binds into several regulatory areas which are located in promoter sites and distal

regions of target genes that enrollment as co-modulators [18–22]. The calcitriol has been shown several rapid cellular actions through nongenomic related pathways [23]. As well as, it needs the VDR and the endoplasmic reticulum stress protein57 (ERP57; also known as 1,25D<sub>3</sub>-MARRS and GRP58) [24], that involved in the protection of calcitriol *versus* DNA damage that was induced by sunlight and also skin cancer [25].

### 3. VDR

The vitamin D receptor is a member of the nuclear receptors' superfamily with its gene long 75 kb that is mapped on long arm of the chromosome 12 [26]. The previous evidence demonstrated the functions of VDR are much wider than the commonly known functions of vitamin D or calcium metabolism. The importance of VDR has been shown as an inflammatory mediator; its role is also suggested in estrogen-related pathways and insulin-like growth factor signaling by *in vitro* and *in vivo* studies [27]. In addition, the existence of VDR in the numerous tumor tissues is suggestive of its role in tumorigenesis [6].

During the last decade, our understanding of 1,25(OH)<sub>2</sub>D<sub>3</sub> metabolism, as well as biological activities, has significantly improved. In the twentieth century, it has been reported that VDR plays an important role in maintaining skeletal health and calcium homeostasis. Additionally, VDR is related to other effects: anti-inflammatory and anti-fibrosis status, diabetic nephropathy prevention, reduction of proteinuria, hypertension and atherosclerosis, alignment of proliferation and differentiation [28–37]. It seems that the identification of VDR in tissues is essential to realize the physiopathological importance of vitamin D and may have the potential for the development of innovative modalities for targeted therapy. Interestingly, since VDR was



**Fig. 2.** VDR related genomic mechanism of calcitriol action. Both 25-(OH)D<sub>3</sub> (calcidiol) and 1,25-(OH)<sub>2</sub>D<sub>3</sub> (calcitriol) circulate bound to a specific carrier protein as known vitamin D binding protein (DBP). Conversion of 25-(OH)D<sub>3</sub> to 1,25-(OH)<sub>2</sub>D<sub>3</sub> mediated with a CYP27B1 enzyme in the target cells. The 1,25-(OH)<sub>2</sub>D<sub>3</sub> biological activities are mediated by VDR protein. Binding of 1,25-(OH)<sub>2</sub>D<sub>3</sub> to VDR and retinoid X receptor (RXR) dimerization and its transportation to the nucleus. The complex of ligand-bound VDR–RXR couple to vitamin D response elements (VDREs) in several regulatory regions which is located in the target genes promoters, following on this causes the employment of co-activators or co-repressors, which respectively cause positive or negative regulations in transcription of target genes.

discovered three decades ago, more than fifty targets have been identified relating to vitamin D functions [38–41].

### 3.1. Regulation of VDR expression

The regulation of VDR expression is multifaceted; formed by environment, genetics, and epigenetics. Studying the interactions and association roles of these facets for gene regulation could be facilitated to the better understanding of the predisposition and evolution of VDR-related diseases such as cancer. Various environmental factors control the VDR, among which are age, diet, sun exposure, infection and pollution [42–46]. The VDR gene heterogeneity in several diseases and populations maybe owing to divergent lineages to evolutionary relationships causing in distinct clusters of diverse geography [47]. Instead, VDR DNA shows a regulation role in infections, cancer and some other diseases by several epigenetic mechanisms such as methylation [48]. It was illustrated the VDR gene regulated through various hormones including retinoic acid, parathyroid hormone (PTH) and glucocorticoids [49,50]. Maybe the most interesting aspect is the capability of 1,25(OH)<sub>2</sub>D<sub>3</sub> to raise the expression of the VDR gene. Identically, VDR levels autoregulate by 1,25(OH)<sub>2</sub>D<sub>3</sub> over both transcriptional [51–53] and posttranslational [53,54] regulations. In the other case,

the ligand interactions with its receptor led to increasing the stability of the VDR protein, of which the mechanism remains to be determined although the studies suggest that several enhancers located within the gene itself directly involved in autoregulation of the VDR gene by 1,25-(OH)<sub>2</sub>D<sub>3</sub>. These studies prepared for starting to need further investigation related to VDR gene regulation [55].

## 4. Cancer prevention and anti-cancer effects of vitamin D

Natural vitamin D or synthetic compounds of vitamin D [56,57] have been shown to induce apoptosis of cancer cells and likely to play a promising role in cancer therapy. Numerous studies have proposed a strong relationship between low serum vitamin D levels and increased risk of cancer [58,59], especially by the strongest evidence in breast and colorectal cancer. Furthermore, a higher level of vitamin D intake is related to a lower risk of breast cancer [60]. More recently evidence indicated that 10,000 IU/d of calcitriol is the safe upper intake level [61] that is significantly more potent than ergocalciferol (vitamin D<sub>2</sub>). Because of the 1,25(OH)<sub>2</sub>D<sub>3</sub> multi-involved roles in the protection and regulation of normal cellular phenotypes and functions, it has been included as an anti-cancer agent.

The vitamin D anti-cancer activities have clearly demonstrated in the *in vitro* and *in vivo* animal model. In 1981, Colston et al. [62] presented inhibition the growth of malignant melanoma cells by the calcitriol, and Abe et al. [63]. In additional studies, reported that calcitriol led to the differentiation of HL60 leukemia cells to the macrophages lineage. The *in vitro* and *in vivo* anti-cancer ability of calcitriol has been reported in various tumors [18,21,64–69]. Genomics and proteomics screening approaches recognized a comprehensive array of VDR target genes which it intercedes the anti-cancer effects attributed to calcitriol [70–75].

The experimental evidences suggest a relationship between serum calcitriol concentration in the optimal level of 80 nmol/L (~32 ng/ml) and prevention of cancer [61,76]. According to the vitamin D status in the populations of Central Europe (CE), determined by the levels of 25-OH vitamin D are typically below the 30 ng/mL. The 25-OH vitamin D values in the wintertime of the CE population are around 21–23 ng/mL in all studied age groups, with a considerable increase in August that reaching to 42 ng/mL for children between aged 0 and 9 years, but 21 ng/mL for the elderly aged from 80 to 89 years [77]. Specially focusing on head and neck squamous cell carcinoma (HNSCC), in a study by Arem et al. [78] investigated that there is no relation between a median serum 25-OH vitamin D level at 31 nmol/L (~12 ng/ml) and oropharynx cancer in Finnish men (including n = 131 patients with OSCC).

## 5. Common basic mechanisms of the anti-cancer effects of calcitriol

The potential anti-cancer mechanisms of calcitriol illustrate in Fig. 3.

### 5.1. Induction of apoptosis

In many but not exactly all kind of cancer cells calcitriol induce apoptosis by means of cell type-specific mechanisms, mainly through induction the intrinsic pathway of apoptosis, especially *via* suppressing the expression of anti-apoptotic genes, for example, *BCL2*, and also by the pro-apoptotic genes like *BAX* stimulation [79,80]. Evaluation of critical apoptosis-regulatory genes in total RNA derived from oral cancer cell lines has revealed the occurrence of programmed cell death after calcitriol treatment. In this context, calcitriol could induces the expression of *caspase 2*, *8* and *BAX* genes in a concentration dependent manner in oral cancer *in vitro* [81]. In addition, these events mediate the activation of downstream protease pathways that lead to cell removal by apoptosis [79,82]. Calcitriol-induced apoptosis delayed

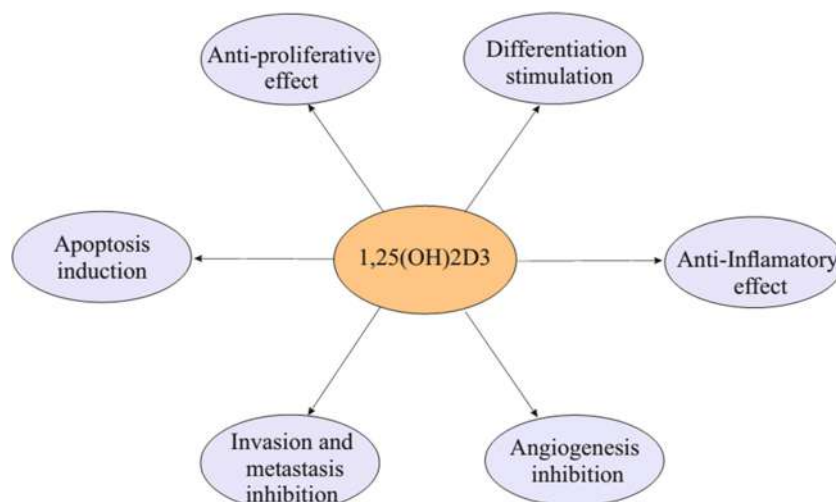


Fig. 3. Common anti-cancer mechanisms of calcitriol.

mammary gland epithelial maturation in VDR-null mice, suggest a potential role of physiological apoptosis during the development of normal mammary [83].

### 5.2. Anti-proliferative effects

Cyclin-dependent kinases (CDKs) play an essential role in the regulation of the cell cycle [84]. Cyclin-dependent kinase inhibitors are considered as potential anticancer agents. Calcitriol stimulates up-regulation of the cyclin-dependent kinase (CDK) inhibitors, such as p21 and p27, and reduce the activity of CDK, thus leading to the retinoblastoma protein dephosphorylation and eventual G0/G1 cell cycle arrest [85–88].

Calcitriol stimulates suppression of the mitogenic signaling through some growth factors such as insulin-like growth factor1 (IGF1) through upregulation of IGF-binding protein 3 (IGFBP3) and epidermal growth factor (EGF), along with increasing the expression of growth inhibitors, for example, transforming growth factor- $\beta$  (TGF $\beta$ ) [89,90]. Additionally, calcitriol modulates the intracellular kinase pathways, for example, PI3K, p38 MAPK, and ERK and also suppress the proto-oncogene MYC [87,91]. Calcitriol treatment has been shown to induce the expression of cell-cycle regulatory genes such as *ornithine decarboxylase*, *c-myc* and *p53* in oral squamous cell carcinoma cell lines (SCC15, CAL27, SCC25,) [81]. The high telomerase activity may indicate high proliferation rate as seen in human cancer cells; calcitriol and analogs involved the inhibition of high telomerase activity through decreasing telomerase reverse transcriptase (TERT) mRNA expression [92]. Calcitriol also induces miR-498 that play a role in the down-regulation of TERT mRNA in some cancer cells [93].

In addition to direct anti-proliferative effects, calcitriol has been shown to mediate the chemo-preventative impact of growth inhibitors in an upward trend. Erlotinib as an epidermal growth factor receptor (EGFR) pathway inhibitor has gained importance in head and neck carcinogenesis. The latter pathway is an early event in squamous cancer initiation. Calcitriol has effectively increased the inhibitory effects of erlotinib in tumor growth of patient-derived xenograft model of HNSCC [94].

### 5.3. Anti-inflammatory effects

Vitamin D induces anti-inflammatory by suppression of prostaglandin action through suppression of cyclooxygenase 2 expression, stress kinases, nuclear factor KB (NF- $\kappa$ B) signaling, and increasing tissue inhibitor of metalloproteinases 1 and E-cadherin response. Antiproliferation by a decrease in cyclin-dependent kinases, cyclins,

MYC and RB expression, and an increase in P21 and P27 expression and intracellular kinase pathway modulations such as MAPK, ERK, P38 and P13 pathways. Inflammation involved the expansion and progression of several cancers [95].

Calcitriol shows valuable anti-inflammatory activities in many cancers [69,96]. Some of important mechanisms consist of: (i) the inhibition of the prostaglandin synthesis (prostaglandins are one of the more significant contributors to the inflammatory process) by repressing the expression of cyclooxygenase 2 (COX2) and also prostaglandin signaling (through enhancing the catabolic enzyme 15-hydroxyprostaglandin dehydrogenase expression), as well as down-regulating the expression of prostaglandin receptors [97,98]; (ii) The inhibition of p38 stress kinase signaling (the p38 is one of the main MAP kinases and MAP kinase pathway, a key inflammatory signal mechanism in eukaryotic cells) through the up-regulation of MAPK phosphatase 5 and consequent down regulation the production of pro-inflammatory cytokine [99]; (iii) The suppression of NF- $\kappa$ B signaling [100–102].

Calcitriol supplementation in patients with HNSCC for 3 weeks between cancer diagnosis and surgical intervention has prolonged the recurrence time in a clinical study in which the anti-inflammatory property of calcitriol has been shown to have a fundamental role [103].

### 5.4. Stimulation of differentiation

Some cancer cells obtain a minor malignant, and more mature and normal phenotype in response to calcitriol, which indicates a pro-differentiating effect [104]. For examples, human myeloid leukemia cells inducing into macrophages and monocytes in the last stage of differentiation [88], induction of the differentiation markers for example lipid droplets, casein and some adhesion proteins in breast cancer cells [105], in prostate cancer cells increasing expression of E-cadherin, bone morphogenetic protein6 (BMP6) and prostate-specific antigen (PSA) as well as the induction the differentiation markers in colonic epithelial cell in colon cancer [104]. Other pro-differentiation effects of calcitriol are cell type-specific mechanisms consist of the regulation of JUN N-terminal kinase,  $\beta$  catenin, NF- $\kappa$ B signaling pathways and PI3K, in addition to the regulation the activity of the some transcription factors such as the CCAAT/enhancer-binding protein (C/EBP) and the activator protein 1 complex [19,104].

### 5.5. Inhibition of angiogenesis

Calcitriol plays a critical role in suppression of angiogenesis through inhibition of vascular endothelial growth factor (VEGF which is an essential contributor in angiogenesis) expression through repression of



interleukin-8 (IL-8) through an NF- $\kappa$ B-dependent manner and transcription alhypoxia-inducible factor1alpha (HIF1A) [105,106]. Additionally, calcitriol enhancing expression of pro-angiogenic factors such as VEGF, platelet-derived growth factor (PDGF), HIF1 $\alpha$  and angiopoietin1 in tumors of VDR-null mice recommend these molecules regulate through calcitriol-VDR [107]. Other studies showed that calcitriol has a potential anti-proliferative action directly on tumor-derived endothelial cells [107]. Furthermore, it has an indirect role in decreasing COX2-generated prostaglandin E2 (PGE2) which favors angiogenesis by increasing HIF1 $\alpha$  synthesis in cancer cells [108]. Besides, different studies have investigated the efficacy of calcitriol analogs in cancer prevention. Calcitriol has been shown to prohibit oral squamous cell carcinoma cell growth through inhibition of NF- $\kappa$ B and HbP17/FGFBP-1 signaling cascades which are crucial in cancer angiogenesis [109].

### 5.6. Inhibition of invasion and metastasis

Metastasis is the important cause of mortality in patients with cancer. In recent decades, a significant advancement in understanding the cellular and molecular basis of invasion and metastasis in cancer is achieved [110]. This section summarizes some invasion and metastasis inhibition mechanisms of calcitriol. The plasminogen activator system and matrix metalloproteinases are important promoters of cancer cell metastasis and invasion that have been illustrated the calcitriol regulate the expression of these components [111]. One of the extracellular matrix proteins is tenascin-C which it increases angiogenesis and invasion of cancer cells. Calcitriol inhibits from the expression of tenascin-C RNA in several normal or malignant epithelial cell lines [112]. Laminin receptors such as  $\alpha$ 6 and  $\beta$ 4 integrins are related to promotion of migration and invasion of cancer cells, calcitriol decrease expression of these receptors [113]. Matrix metalloproteinase 9 (MMP9) is associated with cancer, because of its role in extracellular matrix angiogenesis and remodeling and its increase in metastatic cancer cells [114]. Calcitriol inhibits the activity of MMP9, and up-regulate tissue inhibitor of metalloproteinase1 (TIMP1) expression [115]. One of the tumor suppressor genes is *E-cadherin* which it is reversely related with metastatic potential. Calcitriol increases expression of *E-cadherin* gene, therefore inhibit invasion and metastasis of cancer cells [116].

The glutathione peroxidase-1 (GPX1) gene is related to the progression of tumour. Downregulating GPX1 expression inhibited salivary adenoid cystic carcinoma (SACC) cell proliferation, motility, chemoresistance, and urokinase plasminogen activator (uPA) secretion, but stimulated apoptosis via the NF- $\kappa$ B pathway. Pre-processing calcitriol suppressed the expression of NF- $\kappa$ B/GPX1/uPA, and subsequently inhibited cell motility in SACC cells [117].

## 6. Cancer and vitamin D: molecular pathological epidemiology (MPE)

An emerging field that known as MPE, provides a notable background in medical research by creating an effective link between environment or lifestyle and molecular pathologies or immunity of diseases, as well as contribute the biomarker, tailored prevention, precision medicine, and programs for treatment. In another word, the connected immunology-MPE model can provide a positive contribution to improve understanding about the interactions between environment-tumour and immune system, and also valuable immunosuppression and immunotherapy strategies in precision medicine. Proof of evidence demonstrates that adjustable agents like the levels of vitamin D influence cancer risk as well as immune system performances [118,119]. The essential role of immune system and inflammation is undeniable in etiology of cancer and also in post-transplant malignancies because of long-term immunosuppression. Additionally, dietary or intake of supplemental vitamin D and the levels of systemic vitamin D have been related to lower risks of cancer incidence and mortality [118].

In order to become clearer the roles of vitamin D in cancer prevention and immune modulation, a study with the base of immuno-MPE was focused to assess the relation between the plasma vitamin D levels and the incidence of colorectal carcinoma subtypes that classified through immune response conditions [120].

Gastrointestinal cancer due to given rich microbiota and intestinal related immune tissue and especially the carcinogenic role of inflammation in intestinal, signify exemplary diseases for the immunology-MPE model. Referring to principle studies on colorectal cancer specifies the clear insights the immunomodulating effects of vitamin D. Therefore, the capacity of vitamin D for cancer prevention is more specifically stronger for cancer that showed high-level of lymphocytic infiltrates. A likely reason for this phenomenon is that some immune cells are able to convert 25-hydroxyvitamin D [25(OH)D] to bioactive form, 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub> [1,25(OH)<sub>2</sub>D<sub>3</sub>], which can create a inhibitory effect against progression of neoplastic in patients with elicit high-level lymphocytic response to appear tumors [120,121]. On the other hand, higher 25 (OH) D levels were inversely related to the risk of colorectal cancer, irrespective the VDR expression levels in tumour cells [122]. Furthermore, there is recently epidemiologic evidence that extensive support the significance of enough vitamin D administration, including sunlight exposure, of the prevention of the various types of cancer [123].

## 7. Oral cancer

Oral cancer is malignant neoplasia which arises on the lip or oral cavity. Oral squamous cell carcinomas (OSCC) is important cancer which involves more than 90% of all oral cancers [124,125]. Although the mortality and incidence rates of oral cancer have reduced in industrialized countries such as the United States among recent decades, nevertheless, it has been observed increasing rate in other nations and worldwide, in general [126–128]. In developing economies due to workplace environment and social mobility have increased along with disposable revenues, the accessibility to alcohol and tobacco products has been related to increasing rates of oral cancers [129–131]. Comprehensive studies about the main risk factors related to the development of oral cancers in the United States have determined that alcohol consumption and, to a more extent, tobacco use, when combined, probably reason of 80% of oral cancer risk [128,130,132].

However, these researches have also revealed that over demographic subgroups in the population, such as stark diverse by age are varied incidence and mortality rates, but much higher rates demonstrated among minorities and sharp rises observed among females [133–137].

Oral infection related to the human papillomavirus (HPV) is another significant risk factor for pharyngeal and oral cancers (OPCs) [135]. Oral HPV infection is probably related to particular demographic subgroups, including men in addition to certain minority subgroups, that can cause some of the different geographic and geospatial OPC trends observed [136,138]. The elimination of important risk factors even after an oral cancer diagnosis can improve the prognosis, and there is evidence that such actions may decrease the risk of second tumors formation and recurrences in existing oral cancer patients [139].

## 8. Oral cancer, vitamin D deficiency and VDR

The OSCC development is a multi-step process that influences the important cellular pathways involved in the development of tumor and growth. It was demonstrated a variety of exogenous and endogenous incitements are leading to a multifaceted series of molecular changes contributing to cancer progression [140–142]. The anti-neoplastic activity of calcitriol was illustrated in-vitro and in-vivo studies in a wide range of cancer-related abnormalities including head and neck cancer and specifically in OSCC [143–150].

Furthermore, calcitriol has the potential to affect to cytostatic

chemotherapy and increase induction apoptosis in OSCC cells [151]. Studying the relation between the level of vitamin D in serum and its receptor (VDR) seems to be appropriate for guiding supportive treatment for individuals with precancerous lesions and OSCC patients.

Induction of apoptosis in tumors and precancerous lesions that presented VDR (VDR+) (e.g., oral lichen planus or leukoplakia) through vitamin D could be beneficial for chemoprevention or may have functioned as a stimulator of apoptosis in the treatment of OSCC [57]. This hypothesis has to be assessed by clinical studies. In a Cutaneous Squamous Cell Carcinoma Murine Model, oral calcitriol supplementation caused an increasing Photodynamic therapy-induced cancer cell death [152]. Hence, application of topical and systemically vitamin D (or in combination with vitamin A derivatives) probably considered as a possible novel, low side effect and adjuvant cancer treatment procedure, which can be easily presented it for VDR+ patients to the usual supplementation of clinical oral cancer treatment without any extra risk. Specifically, regard to the hypothesis of the field cancerization [153–155] it has seemed vitamin D applied *via* systemically as the tissue of the gastrointestinal tract is very significant display toward the two major exogenous carcinogenic factors, tobacco, and alcohol. While the stimulation of carcinogenic continue may lead to second meta-chronous tumors in related sites [156].

Grimm et al. assessed the possibility of biologically active calcitriol or its analogs effects as a new potential target on oral tissue, so they studied to evaluate the expression of VDR in oral cancers OSCC. Their study showed evidence that reduced VDR expression in OSCC probably related to tumor reversion. Interestingly, cancer cells of a putative CD44+ cancer stem cell VDR+ demonstrating a significant potential for the OSCC treatment. However, their outcomes could not make any conclusion on the VDR function. Application of calcitriol or its analogs as adjuvant chemoprevention can provide an effective agent for targeting adjuvant residual tumor cells and will probably help in the optimization of clinical treatment of cancer patients [157]. In another study by Sonkar et al. that examined vitamin D levels and VDR expression in the normal oral mucosa, oral cancer, and leukoplakia patients. Briefly, patients with advanced oral cancer threaten by chemoradiotherapy were assessed for the vitamin D supplementation effect on several observable quality of life (QOL) parameters, for instance, swallowing performance, oral mucositis, and overall QOL. The scores of vitamin D were considerably lower in oral cancer and leukoplakia patients as compared to healthy controls. Importantly, Vitamin D supplementation considerably decreased the toxicities correlated with therapy of advanced oral cancer, therefore improving QOL and decreasing morbidity. Sonkar study showed VDR expression increased in oral cancer, oral neoplastic lesions and premalignant lesions [158].

Deficiency and insufficiency of Vitamin D are more common in patients with oral neoplastic lesions with a priori at diagnosis. Since deficiency of vitamin D might determine increased morbidity risk of patients which is related with treatment, should be paid close attention to the repair of deficiency of vitamin D in nutrition before therapy procedures, particularly in a palliative situation. Lipworth et al. reported that dietary vitamin D intake is related to a reduced risk of squamous cell carcinoma of the esophagus (SCCE) and likely related to a decreased risk of oral and pharyngeal cancers, which were most displayed between heavy alcohol consumers and heavy smokers [159]. One of the important events happens in many cancers such as oropharyngeal cancer (OPC), applying some special effects on the metabolism of vitamin D such as changing the availability or affecting the on quality of binding to VDR. The evidence obtained from a variety of specific cancers reveal reduced VDR expression [20,160,161]. Ras activation is common in many OPC cancers, furthermore, there are some studied demonstrated that activation of Ras may weaken the activity of vitamin D-related transcription, whenever cytochrome p450 24 (CYP 24), the mitochondrial enzyme which causes decreasing of vitamin D metabolites, perhaps up-regulated and also functionally active in several cancers [162–164].

Another study confirmed that mutations of the CYP24 degraded risk of oral cancer in comparison to normal type, after adjusting for smoking status, alcohol consumption, age, and gender [165]. It seems that the rate of effect of calcitriol on gene expression be tissue-specific characteristics possibly could be explained by the varying results obtained from *in vitro* studies of gene expression in some head and neck cell lines (SC15, SCC9, SCC25 and SCC4) and squamous cell carcinoma (SCC), affected by calcitriol, which established diverse sensitivities in cell lines ranging from about 50% growth inhibition for SCC9 to the completely cell-cycle arrest at G<sub>0</sub>/G<sub>1</sub> in SCC25 [166]. The more than 4500 target genes screening in SCC25 cells demonstrated 38 genes up-regulated (at least 1.5 fold), consist of protein kinases, growth factors, cell adhesion proteins, cytoskeleton proteins, some intracellular signaling molecules and also transcription factors related to regulating of cell-cycle growth and arrest [167,168].

## 9. Benefits of sunlight exposure on oral cancer

Indeed, the amount of vitamin D is little in majority of foods unless they are s enriched, that shows humans need to sunlight to obtain enough vitamin D stores. For example, although in the United States an eight glass of fortified milk contains 100 IU of vitamin D, enough sun exposure of the skin to cause a slight pinkness in Caucasian skin lead to synthesis the about an oral dose of 20,000 IU of vitamin D [169,170]. Regarding these findings, may explain that the epidemiologic studies with increased sun exposure among certain populations and in certain geographic areas were related to decrease risk at all tumor sites and cancer mortality. Data that obtained from more than 100 countries have revealed the strong, negative relations between solar UV-B exposure for 15 types of malignancies and noteworthy effects observed among nine other cancers, consist of the larynx and oral cavity/pharynx cancers [20,169–173].

## 10. Polymorphisms in VDR gene, cancer risk, and prognosis in oral cancer

The studies showed the variations near key genes involved in hydroxylation and transportation of vitamin D and cholesterol synthesis have related with the status of vitamin D. Evaluation of genetic variation of these loci demonstrated in high risk of vitamin D insufficiency individuals. Recently, a large number of studies paid close attention to the relevance of restriction fragment length polymorphisms in the VDR gene in different types of cancer. It has been considered that polymorphisms in VDR possibly influence both prognosis and risk and occurrence of cancer. Although, surveys often show inconclusive results in investigating the relations between specific VDR polymorphisms and different types of cancer [93]. It have been reported that there are significant associations in VDR polymorphisms within cancers of bladder (Fok1), colorectal (Fok1, Bsm1), ovary (Fok1, Apa1), skin (Fok1, Bsm1, A-1210), renal cell carcinoma (Taq1, Apa1), prostate (Bsm1, Fok1, Taq1, poly (A)) and breast (Taq1, Fok1, Bsm1, Apa1, poly (A)). But, contradictory results have been reported for the most of malignancies [124]. A study of genome-wide relation to recognizing genes related with deficiency of vitamin D has determined special single nucleotide polymorphisms (SNPs) in numerous genes that could foresee the levels of circulating 25-OH vitamin D [174]. SNPs in the VDR gene may also influence both the cancer progression and risk of cancer occurrence. Małodobra-Mazur et al. study illustrated a genetic correlation between the risk and occurrence of oral cavity carcinoma and rs2238135 in the VDR gene [175].

Another study by Bektaş et al. determined that in the distribution of VDR Taq I genotype was a significant difference in OSCC patients compared with healthy controls. VDR Tt genotype in OSCC patients was demonstrated to be at considerably higher risk than persons with other genotypes. Especially, female with OSCC was subjected to a higher risk for oral cancer. These findings indicate that the VDR Taq I

polymorphism might relate to susceptibility to OSCC and it probably helped as a prevention method in the future [176]. The genetic polymorphisms of VDR and genes that involved in the metabolism of vitamin D such as *CYP24B1* and *CYP27B1* might influence susceptibility to OSCC. Additionally, Zeljic et al. study indicated that polymorphism of *CYP24A1* gene might be affected on the susceptibility to oral cancer and polymorphism of *VDR FokI* gene can be an area of interest as a prognostic marker, as it has been shown that it is related to worse survival [165].

### 11. Oral cancer chemoresistance and its relation with VDR

Chemoresistance is a likely cause of relapse and metastasis, confronting the progress of clinical outcome in cancer patients, and remains as one of the main challengeable obstacles to cancer therapy [177–181]. The main reason for mortality and morbidity in OSCC is poor chemotherapy response and fundamental resistance to the majority of anti-cancer drugs [182,183]. It was demonstrated resistance to apoptosis is as a key factor for the tumorigenesis of OSCC, which is related to tumor recurrence and radio-, and chemotherapy resistance [184–186]. Hence overcoming the resistance to treatment of oral neoplastic lesions is a major challenge. Achievement of such therapeutic effective agents that led to more accurately identify so might help create an improved response and consequently reduce the return of oral cancer [158]. Vitamin D is one example of these agents, which has been illustrated have induced apoptosis, anti-proliferative and anti-invasive properties in some cancer cell types such as OSCC and oral precancerous lesions [143,148,150,187,188]. It is also hypothesized that the combination of vitamin D with chemotherapy of oral cancer showed increasing effectiveness [151]. Studying serum vitamin D level and its corresponding VDR seems to be appropriate for guiding supportive therapy for patients with pre-cancerous lesions and OSCC. The low VDR expression is also an adverse prognostic sign for OSCC patient's survival [157]. Moreover, Grimm and coworkers measured and correlated serum vitamin D levels (calcidiol) with tissue-related VDR expression in OSCC patients. The natural or synthetic vitamin D compounds induce apoptosis in oral pre-cancerous lesions, and OSCC could be useful for chemoprevention [56]. Additionally, locally or systemically applied to these compounds probably leads to more sensitization of OSCC to apoptosis associated with radio-, and chemotherapy treatment [140].

### 12. Discussion

Recent studies focused on the vitamin D effects on the prevention and treatment of the wide range of cancers is reported elsewhere. Preclinical studies strongly support the importance of vitamin D in prevention of cancer by exerting a wide range of cellular functions, including pro-apoptotic, anti-angiogenic, anti-inflammatory, anti-proliferative, anti-invasion and anti-metastatic effects on cancer cells [70]. The active form of vitamin D, calcitriol, which exerts bioactivities by binding to the nuclear VDR in different tissues. Of clinical importance, a wide range of tumor tissues express the VDR, and that the receptor has the potential to influences cancer etiology [11].

Oral calcitriol supplementation able to increase the effectiveness of photodynamic therapy on tumor cell death of cutaneous squamous cell carcinoma in a murine model [152]. Hence, topical or/and systemically applied vitamin D may offer a new nontoxic, adjuvant to the treatment of cancer, which can be easily present with classic protocols without any supplementary clinical cancer therapy risk for VDR+ patients. Calcitriol has been illustrated to increase expression of the *VDR gene* and protein in different cell types *in vitro* [189,190]. It has been proposed that calcitriol administration lead to enhance VDR expression due to an improved receptor protein lifetime and/or raise the *VDR genes* transcription [53,190]. We know the keratinocytes able to synthesize the biologically active calcitriol. However, we don't make sure that oral precancerous or OSCCs have this ability as well. Additionally,

tumor-infiltrating leucocytes and oral precancerous/tumor cells expressed inflammatory cytokines/peptides that may upregulate VDR expression in adjacent cells [191].

Study of Yuan et al. [192] strongly supports an important role for signaling of vitamin D in the pathophysiology of oral keratinocyte *in vitro* and *in vivo*, but a deficiency of vitamin D alone seems to be inadequate to stimulate carcinogenesis and change homeostasis of oral epithelia. Afzal et al. [193] demonstrated a low plasma level of 25-hydroxyvitamin D with increased risk of smoking-related cancer including head and neck squamous cell carcinoma (HNSCC). In this base, vitamin D may reversely alter the carcinogenicity of tobacco smoke chemical. Authors hypothesize that especially smokers may benefit from Vitamin D intake as more than 80% of OSCC are related to tobacco abuse.

As suggested for multistep carcinogenesis [142] it is indistinct based on the actual literature whether vitamin D can be standardized useful for chemoprevention in the therapy of precursor lesions or development of OSCC, but it provides a clear rationale for more researches in the OSCC carcinogenesis [140]. VDR is important in different cancer types. It is essential to note, all polymorphisms of the *VDR gene* haven't the same relation with cancer, and the importance of each polymorphism determined with the cancer site. Given these relations, it is essential to evaluate the relationship among other polymorphisms in other areas of the *VDR gene* and cancer. Since VDR is involved in several pathways, it is essential to assess the relations between VDR and other environmental factors, lifestyle and diet as they relate to cancer. VDR gene as a key element of further researches is acquiring a better understanding of its functionality [194].

### 13. Conclusion

The main purpose of this review article is to summarize the possible role of vitamin D in the development of oral cancer. Although the anti-cancer effects of vitamin D showed by several *in vitro* and *in vivo* studies, new evidence indicates these effects are regulated by several other factors. Further studies are required to evaluate the effects of the vitamin D system (both ligand and receptor) on the evolvement of oral cancer, and potential benefits of alleviating vitamin D deficiency on tumor growth and progression. The information provided in this article would be useful to oral epidemiologists, oral health care providers, as well as oral oncologists as they attempt to improve oral health outcomes of patients.

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