Vitamin D and Thyroid Cancer

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Abstract

Accumulating evidence demonstrated that the active form of vitamin D, 1,25(OH)2D3, has antiproliferative, anti-apoptotic and prodifferentiating effects in several tumor types in preclinical studies. Several studies reported the impact of vitamin D on cancer risk particularly in breast and colorectal cancer, however, its effect on thyroid cancer is less known. This review focuses on the relationship of vitamin D and thyroid cancer under the light of the literature. Thyroid cancer is the most common endocrine cancer and also vitamin D deficiency is a common condition throughout the world. Some clinical studies showed that vitamin D deficiency is higher in patients with thyroid cancer. Preclinical studies evidenced that vitamin D has an effect on differentiation, reduction in tumor burden, and prevention of metastatic growth in thyroid cancer used alone or in combination with anticancer drugs. However, further clinical studies are needed to understand its impact on prognosis of thyroid cancer.

Keywords: Vitamin D, thyroid cancer, calcitriol.

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Introduction

Thyroid cancer is the most common endocrine cancer and its incidence is on the rise throughout the world (1-3). It is 2-4 times more frequent in females than in males but the incidence is similar between genders before puberty and after the female menopause (3). The vast majority of thyroid cancer is differentiated thyroid cancer (85% papillary cancer, 10% follicular cancer). Anaplastic and medullary thyroid carcinomas are seen rarely. The main reported causes of thyroid cancer is radioactive iodine exposure, previous childhood radiation to the head and neck, female gender, family history of thyroid cancer and iodine intake status (1,4). Accumulating evidence sourced from observational, epidemiological and preclinical studies showed that vitamin D deficiency increases the risk of developing many extraskeletal diseases including multiple malignancies. Among malignancies, colorectal cancer has the most clear association with circulating vitamin D levels (5). According to few data conducted on relationship between vitamin D deficiency and thyroid cancer and data from these studies had controversial results. Vitamin D is the precursor of the steroid hormone calcitriol (also called as 1,25-dihydroxy-vitamin D3 (1,25(OH)2D3) that mediates several actions in many cells of the body (6). CYP24A1 (24-hydroxylase) and CYP27B1 are cytochrome enzymes that have a role in steps of yielding calcitriol from vitamin D. The circulating form of vitamin D is 25(OH)D3 and its level in the blood is used for monitoring the vitamin D status of a patient. The defined levels for deficiency is set 75 nmol/L (30 ng/ml) by the Endocrine Society and 50 nmol/L (20ng/ml) by the Institute of Medicine (7,8). People have to receive adequate sunlight in order to maintain adequate vitamin D levels. However, this is not possible for many people due to various life conditions. Therefore, vitamin D deficiency is a very common condition throughout the world. Vitamin D might be one of the undetermined etiology leading to an increase of thyroid cancer prevalence in addition to the increased imaging of the neck. In this review, we focused on the studies about vitamin D and thyroid cancer to elucidate the role of vitamin D in the development, progression, prognosis and treatment of thyroid cancer.

Calcitriol and cancer development

Calcitriol is the predominant active metabolite of vitamin D and initiates or suppresses gene transcription by binding to the nuclear vitamin D receptor (VDR) (9). VDR is found in both the cytoplasm and nucleus of the most cells of the body but the expression level sometimes can be at low concentration (10,11). Calcitriol regulates indirectly or directly the human genome and induces CYP24A1 (6). Current data have been demonstrated that calcitriol diminishes tumor development through effects on cell proliferation, apoptosis, differentiation, inflammation, invasion, metastases, and angiogenesis (6). Calcitriol prevents the transition from the gap 1 (G1) to the synthesis (S) of the cycle. Known antiproliferative effects are increase in p21 and p27 expression and
decrease in cyclin-dependent kinase (CDK), CYCLINS, MYC and RB expression. It affects apoptosis by inhibiting BCL-2 and BCL-XL or increasing the expression of BAX, BAK, BAD (12,13). The effects of calcitriol are not only via genomic pathways but also several non-genomic pathways like upregulation of insulin growth factor binding protein 3 (IGFBP3) and transforming growth factor-β (TGF-β) and downregulation of the epidermal growth factor (EGFR) described (14-16). Besides this, inhibition of expression of cyclooxygenase-2 (COX2), prostaglandin receptors, stress kinase and NF-kB signaling and increase in the expression of 15-PGDH (hydroxyprostaglandin dehydrogenase 15-NAD) is shown (17). Additionally, it inhibits angiogenesis by decreasing vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 (HIF-1) and interleukin-8 (IL-8) levels (18,19). High expression of CYP24A1 occurs in several cancer lines and upregulation of this enzyme concludes poor clinical outcome (20). Expression level and activity of CYP27B1 change according to the organ, the tumor grade and cell differentiation (6,21). Another effect of vitamin D metabolites and analogs on cancerous cells is to regulate the activity and expression of estrogen receptors (22).

**VDR and local vitamin D metabolism in thyroid cancer**

VDR is present in both thyrocytes and C cells (23). In a preclinical study done in rats demonstrated that high doses of calcitriol has not changed thyroid stimulating hormone (TSH) and levothyroxine (T4) levels (24). In another study done in VDR KO mice, only slightly decreased levels of serum TSH were found. In the same study, increased thyroidal calcitonin expression and serum calcitonin levels were found higher (25). Expression of VDR and CYP27B1 protein were found enhanced in PTC compared with normal thyroid tissue particularly in areas of lymphocyte infiltration (26). VDR gene polymorphisms occur frequently, but the importance of it has not been systematically evaluated in terms of function and protein expression. An association has been observed between the VDR polymorphism and certain cancers such as prostate, breast, colon cancer and malign melanoma (27). The affect of VDR polymorphism in thyroid cancer is investigated in few studies. The first study in differentiated thyroid carcinoma was done by Martinez et al. They reported that the alleles AA and FF of the Apal and FokI VDR polymorphisms and the haplotype Tabf provide protection from follicular carcinoma, but the haplotype Tabf increases follicular carcinoma risk (28). A case control study with a large number of patients conducted by the same author investigated the genes, CYP24A1 and CYP27B1 together with vitamin D levels. The CYP27B1 gene was similar between the groups but in the haplotype analysis, a rare haplotype gene was found protective against papillary thyroid carcinoma. But a higher risk for differentiated carcinoma was observed by haplotypes within the CYP24A1 together with vitamin D deficiency and a reduced conversion to calcitriol (29). Clinckspoor et al. investigated VDR and expression of CYP24A1 and CYP27B1 in normal thyroid, follicular adenoma, differentiated thyroid carcinoma and anaplastic thyroid cancer. VDR, CYP24A1 and CYP27B1 expression was found higher in follicular adenoma and differentiated thyroid carcinoma than with normal thyroid. However, in PTC with lymph node metastases, VDR and CYP24A1 were found less than with non-metastasized PTC. In anaplastic thyroid carcinoma, high VDR expression was rare, but CYP24A1 and CYP27B1 expression was similar to differentiated thyroid carcinoma. Additionally, more negative staining were observed in ATC with high Ki67 expression and distant metastases at diagnosis (30).

**Epidemiological Studies on Vitamin D and Thyroid Cancer**

Currently, few studies published on the issue of the relationship of vitamin D levels and thyroid cancer in the literature. Jonklaas et al. reported a pilot study conducted in the United States and found no associations between vitamin D concentration and thyroid cancer diagnosis. Furthermore, vitamin D levels were not associated with disease stage or any other prognostic variables (31). Stepien et al. investigated vitamin D metabolism by evaluating 25(OH)D3 and 1,25(OH)2D3 in patients with thyroid cancer and compared with nontoxic control group. 1-25(OH)2D3 levels were found significantly different between groups also according to the cancer stage of the patients that patients with stage 4 had the lowest 1,25(OH)2D3 levels. However, no significant difference were found in 25(OH)D3 levels between groups (32). Laney et al. also evaluated the prevalence of vitamin D deficiency between thyroid nodular goiter and cancer patients and found similar results. In this study vitamin D deficiency was defined as <30 ng/ml and the percentage of patients with vitamin D deficiency was not different between groups. They also evaluated vitamin D levels according to the histologic type of thyroid cancer and no significant difference were found (33). Roskies et al. investigated the malignancy rate according to the...
vitamin D level, and found two times more vitamin D deficiency compared to vitamin D sufficient patients. In vitamin D sufficiency, the malignancy rate was 37.5% whereas this rate rose to 75% in vitamin D deficiency group. They defined vitamin D deficiency as <37.5 nmol/L (34). Sahin et al. reported the results of comparison between thyroid cancer patients and healthy controls in terms of vitamin D deficiency including large number of study (n=235) and control (n=116) participants. They defined the vitamin D deficiency as <20 ng/ml and found decreased vitamin D levels and more frequent vitamin D deficiency in the thyroid cancer patients according to the control group. Furthermore, vitamin D levels were not significantly different between micro- and macropapillary thyroid cancers and also between classical and follicular type of thyroid carcinoma. Additionally, no relationship was found between vitamin D deficiency and thyroid cancer prognosis (35) (Table 1).

There are only two studies demonstrating the relationship of vitamin D supplement intake and thyroid cancer conducted in the United States. Mack et al. observed no relationship between use of weekly vitamin D in females aged 15-54 years (36). In contrast to this case control study, another study found that regular usage of vitamin D leads to an increase in thyroid cancer risk in both of gender (37). Therefore, there is no clear evidence for or against to use of vitamin supplements to protect people from thyroid cancer (38).

**Preclinical and clinical intervention trials with Vitamin D in thyroid cancer**

Accumulating evidence from animal, preclinical and observational studies demonstrated that vitamin D therapy might be a chance to treat thyroid cancer particularly patients with advanced differentiated thyroid cancer or anaplastic thyroid cancer. In an in-vitro study, 1,25(OH)2D3 and the superagonistic vitamin D analog CD578 alone or in combination with paclitaxel (a taxane) and suberoylanilide hydroxamic acid (a potent histone deacetylase inhibitor, SAHA) provided an additive and synergistic effect on the inhibition of proliferation. A modest increase was observed in sodium iodide symporter and thyroglobulin mRNA expression however, thyroid stimulating hormone receptor or thyroid peroxide mRNA expression not changed (39). Affect of calcitriol administration to the thyroid cancer cells in a mouse model was resulted in an increase in cellular differentiation, reduction in tumor burden, and prevention of metastatic growth (40). Another study showed that calcitriol and analogues inhibited proliferation of thyroid medullary carcinoma in human and rat cell lines indicating their effect on the process of calcitonin expression (41).

In a 65-year-old Japanese woman diagnosed extremely locally-advanced thyroid cancer underwent an oral administration of vitamin D3 (0.5µg/body/day, Alphacalcidiol) and was found to retard the tumor growth and more increase in serum thyroglobulin levels. Also, the patient had no side effects related to the use of Alphacalcidiol (42). There is no other paper reporting the affect of vitamin D treatment on thyroid cancer as clinical evidence.

**Conclusions**

The rise in the prevalence of thyroid cancer is mainly related with the advances in imaging modalities but the other possible causes like vitamin D deficiency is also investigated. Vitamin D deficiency is a common condition throughout the world and it is higher in patients in thyroid cancer than in healthy population. In the case of anaplastic thyroid cancer and persistent or recurrent differentiated thyroid cancer, surgery and/or ablation treatment is not enough to provide disease cure. In these patients, treatment modalities that have redifferantiating and antiproliferative effects are needed. 1,25(OH)2D3 is known to have many anticancer effects including also these effects. To avoid hypercalcemia due to the vitamin D therapy, clinical applicable vitamin D analogues has been designed to provide anticancer effects at physiologically concentrations. In vitro studies showed that these drugs can be combined with certain anticancer drugs to achieve an additive and synergistic effect. Clinical outcomes of vitamin D deficiency and the effect of vitamin D therapy on prognosis is not well known not only in thyroid cancer but also in breast and colorectal cancer that are the most studied cancers until now. Therefore, more in vivo preclinical and randomized clinical studies are needed to confirm the impact of vitamin D therapy in thyroid cancer.
Table 1: Articles on vitamin D and thyroid cancer.

<table>
<thead>
<tr>
<th>Study (references)</th>
<th>Site</th>
<th>No. of patients</th>
<th>Time of drawing the sample</th>
<th>25(OH)D3 levels</th>
<th>1-25(OH)2D3 levels (pg/ml)</th>
<th>Compariso n with controls*</th>
<th>Variat i on by disease stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonklaas et al. 2013 (32)</td>
<td>USA</td>
<td>48</td>
<td>Before diagnosis</td>
<td>26.5±9.9 ng/ml</td>
<td>NA</td>
<td>n=17, p=0.08</td>
<td>No</td>
</tr>
<tr>
<td>Stepien et al. 2010 (33)</td>
<td>Poland</td>
<td>50</td>
<td>Before surgery</td>
<td>Not mentioned</td>
<td>16.0±4.0</td>
<td>n=26, p&gt;0.05</td>
<td>With 1-25(OH)2D3 levels</td>
</tr>
<tr>
<td>Laney et al. 2010 (34)</td>
<td>USA</td>
<td>69</td>
<td>After diagnosis</td>
<td>NAα</td>
<td>NA</td>
<td>n=42, p&gt;0.05</td>
<td>No</td>
</tr>
<tr>
<td>Sahin et al. 2013 (36)</td>
<td>Turkey</td>
<td>235</td>
<td>After diagnosis</td>
<td>17±16 ng/ml</td>
<td>NA</td>
<td>n=116, p=0.004</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Comparison of 25(OH)D3 levels between patients with thyroid cancer and benign thyroid nodular disease. NA: Not applicable.

References


