MINI REVIEW

Vitamin D and thyroid disease: to D or not to D?

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The main role of vitamin D is to maintain calcium and phosphorus homeostasis, thus preserving bone health.1 However, animal and human studies have demonstrated that vitamin D may also have a role in a variety of non-skeletal disorders. Recent evidence has demonstrated that vitamin D may also have a role in a variety of non-skeletal disorders such as endocrine diseases and in particular type 1 diabetes, type 2 diabetes, adrenal diseases and polycystic ovary syndrome. Low levels of vitamin D have also been associated with thyroid disease, such as Hashimoto’s thyroiditis. Similarly, patients with new-onset Graves’ disease were found to have decreased 25-hydroxyvitamin D concentrations. Impaired vitamin D signaling has been reported to encourage thyroid tumorigenesis. This review will focus on the role of vitamin D in thyroid diseases, both autoimmune diseases and thyroid cancer, and will summarize the results of vitamin D supplementation studies performed in patients with thyroid disorders. Although observational studies support a beneficial role of vitamin D in the management of thyroid disease, randomized controlled trials are required to provide insight into the efficacy and safety of vitamin D as a therapeutic tool for this dysfunction.

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INTRODUCTION

The most important role of vitamin D is to maintain calcium and phosphorus homeostasis and to preserve bone health.1 However, animal and human studies have demonstrated that vitamin D may also have a role in a variety of non-skeletal disorders. There is an increasing prevalence of hypovitaminosis D that gives rise to an emerging public health problem. In particular, a prevalence of vitamin D deficiency has been estimated ranging from 20 to 100% of American, Canadian and European elderly men and women.2-4 The same prevalence has been reported in children and young and middle-aged adults worldwide.5,6 Vitamin D has been involved in the pathogenesis of several endocrine conditions such as type 1 diabetes,7 type 2 diabetes,8 adrenal diseases9 and polycystic ovary syndrome.10 The involvement of vitamin D in thyroid disease has been suggested by pioneering studies performed in the eighties. In particular, McDonnell et al.11 found a strong homology between the molecular structure of vitamin D3 receptor and the receptor for thyroid hormone, which was due to two regions that they have in common: the first is a 70 amino acid, cysteine-rich sequence and the second region is a 62 amino acid one located towards the carboxyl terminus of the proteins. Later, Lamberg Allardt et al.12 demonstrated the existence of a functional 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] receptor in rat thyroid follicular cells (FRTL-5). The incubation of FRTL-5 with 1,25(OH)2D3 inhibited thyrotropin (TSH)-stimulated iodide uptake in a dose-dependent manner, indicating that 1,25(OH)2D3 has an effect on the physiological function of rat thyroid follicular cells in culture. These results were further confirmed by Berg et al.13 who reported a decrease in TSH stimulated production of the intracellular signalling molecule 3′,5′-cyclic adenosine monophosphate (cAMP), iodide uptake and cell growth of FRTL-5 when they were incubated with 1,25(OH)2D3 or with cholecalciferol analogues. However, the administration of 1,25(OH)2D3 for 3 days in rats was found not to have any effect on serum triiodothyronine (T3), thyroxine (T4) or TSH concentrations.14 These intriguing results laid the basis and encouraged the recent research on vitamin D and thyroid disease.

In particular, low vitamin D concentrations, certain vitamin D receptor (VDR) gene polymorphisms and pathologies of vitamin D-binding proteins and of their gene may favor the development of Hashimoto’s thyroiditis (HT).1,15 Women with new onset Graves’ disease (GD) have a reduced 25-hydroxvitamin D [25(OH)D] serum concentration, which also correlates with thyroid volume measured with ultrasonography.16 Furthermore, impaired 1,25(OH)2D3-VDR signaling has been reported to be associated with the onset and progression of thyroid cancer.17 The present review will focus on the association of vitamin D with autoimmune thyroid disease and thyroid cancer and the potential role for vitamin D supplementation in the therapy of thyroid disease.

VITAMIN D AND THYROID AUTOIMMUNE DISEASES

In vitro evidence

The molecular mechanism by which vitamin D exerts its action seems to be mediated by its binding to VDR, an intracellular receptor belonging to the steroid/thyroid nuclear receptor family, expressed by human immune cells, such as macrophages, dendritic cells and T and B lymphocytes. Vitamin D central target are dendritic cells (DCs).18 In particular, it has been shown that 1,25(OH)2D3 and calcifediol impair T-cell-stimulatory capacities of murine DC.19 DCs isolated from VDR knockout mice were not impaired in their T-cell-activating potential, demonstrating that the inhibitory effect of these vitamin D metabolites was...
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dependent on the presence of VDR. In particular, 1,25(OH)2D3 inhibited DC maturation as well as production of DC-derived cytokines, such as interleukin (IL)-12 and IL-23. In this way, 1,25 (OH)2D3 alters the Th balance and causes the differentiation of the T cells in a T-helper 2 phenotype, rather than in T helper 1 (Th1) and Th17 phenotype. DC-derived IL-10 release was enhanced, promoting its tolerogenic properties. Moreover, 1,25 (OH)2D3 decreased the production of inflammatory Th1 cytokines such as IL-2 and interferon-γ, which promote cell-mediated cytotoxicity leading to thyroid destruction in HT. In this regard, it is worth mentioning that the suppression of Th1 response by vitamin D may counteract the onset of GD, as Th1 dominance is worth mentioning that the suppression of Th1 response by vitamin D may counteract the onset of GD, as Th1 dominance seems to be involved in the induction of the disease. Finally, 1,25 (OH)2D3 inhibits Th17-derived cytokines IL-17 and IL-21 production, promoting the induction of regulatory rather than effector T cells.

Many studies point to a role of vitamin D in the development of thyroid autoimmune diseases (AITD), which has been also demonstrated in animal models. In particular, vitamin D has been reported to modulate hyperthyroidism induced in BALB/c mice by immunization with adenovirus, encoding thyrotropin receptor or its A-subunit. In fact, hyperthyroid BALB/c mice fed with a diet deprived of vitamin D showed fewer splenic B cells, decreased interferon-γ responses to mitogen and lack of memory T-cell responses to A-subunit protein. In addition, vitamin D-deprived animals developed persistent hyperthyroidism induced by adenovirus expressing the human TSHR_A subunit, demonstrating a clear role of vitamin D in modulating thyroid function in this animal model.

Human clinical studies

Regarding the association of vitamin D levels with antithyroid antibodies, lower 25(OH)D levels were found in subjects with higher levels of antithyroid antibodies compared with those who were negative for thyroid autoimmunity. Vitamin D deficiency has been diagnosed more frequently in AITD subjects, especially in those affected by HT, than in healthy subjects. In a study conducted by Tamer et al., 25(OH)D insufficiency (< 30 ng/ml) was found to be more common in subjects with HT than in controls. The association between hypovitaminosis D and thyroid autoimmunity has also been reported in a Chinese population by Choi et al. In particular the association between thyroid peroxidase antibody (TPOAb) and levels of 25(OH)D was found only in Chinese premenopausal women, but not in post-menopausal women or in men, thus suggesting that vitamin D may modulate thyroid autoimmunity through estrogens. Moreover, in female patients with newly onset GD, a significant relationship of low levels of 25(OH)D with increased thyroid volume was observed, suggesting that vitamin D status may be involved in the pathogenesis of the disease.

On the other hand, some studies failed to find an association between vitamin D deficiency and AITD. Chailurkit et al. did not find any relationship between 25(OH)D status and thyroglobulin antibody (TgAb) and TPOAb. Furthermore, an Asian Indian community-based survey found a significant but weak inverse correlation between serum 25(OH)D values and TPOAb titers, with an R^2 value of only 0.006, indicating that only 0.6% variation in thyroid autoimmunity was determined by 25(OH)D levels in the population. An inverse correlation between TPOAb production de novo and 25(OH)D levels was missing in a longitudinal study conducted on a Dutch female population. In addition, in the same population the Authors compared subjects with genetic susceptibility to AITD with healthy subjects. In both groups, 25 (OH)D levels were not lower in the cases than in the controls, showing that low vitamin D levels are not associated with thyroid autoimmunity in the early stages of the disease.

Regarding thyroid function, hypothyroid subjects showed both low 25(OH)D and serum calcium levels; interestingly, the degree and the severity of hypothyroidism were significantly associated with vitamin D levels. Yasuda et al. failed to find any association between thyroid function and vitamin D in subjects with GD. In addition, high 25(OH)D values were observed to be independently associated with low circulating TSH levels in middle-aged and elderly Chinese males with negative thyroid autoimmunity, independently of free T3 and free T4. Conversely, this association was not found in women.

Some studies evaluated the association between functional polymorphism in the VDR gene or vitamin D binding proteins and AITD risk. However, results are still ambiguous and inconclusive. A meta-analysis of eight studies, analyzing mainly females of various ethnicities (European, Asian and African) and including about 1000 cases and 1000 controls for each polymorphism studied, indicated that the BsmI or TaqI VDR polymorphism was significantly associated with AITD risk, whereas the Apal or FokI polymorphism was not. Allele analyses demonstrated that in Bsm polymorphism the B allele was more associated with AITD risk than the B allele. However, statistically significant heterogeneity was detected for Bsm polymorphism only when all the eligible studies were pooled in a meta-analysis. After a subgroup analysis by ethnicity, Europeans showed a strong decrease in heterogeneity, indicating that the genetic background might contribute to the observed heterogeneity. Regarding TaqI, no heterogeneity was detected in the subgroup analysis. Polymorphisms of the CYP27B1 gene that encodes the 1-α-hydroxylase enzyme, responsible for converting 25(OH)D to active 1,25(OH)2D3, were linked to autoimmune thyroid disease supporting the hypothesis of an association between vitamin D and AITD.

Section remarks

Most of the above data indicate a primary role of vitamin D deficiency in the pathogenesis of AITD. Vitamin D is able to trigger both innate and adaptive immune responses and to switch the immune system in a tolerogenic sense, avoiding the autoimmune response. However, further studies are needed to determine whether hypovitaminosis D is a key factor in the pathogenesis of AITD or, rather, a consequence of the disease.

VITAMIN D AND THYROID TUMORIGENESIS

Histochimical and in vitro evidence

The molecular basis of the hypothesized antitumoral effect of Vitamin D relies on the biological actions of 1,25(OH)2D3 through binding to the VDR, a nuclear hormone receptor, that is present, although variably, in benign and malignant thyroid tissue. The expression of VDR and 1-α-hydroxylase, that is, the activating enzyme of Vitamin D (also named CYP27B1), was found to be increased in papillary thyroid carcinoma (PTC) compared with normal thyroid tissue; in addition, VDR was significantly lower in lymph node PTC metastases compared with both normal thyroid tissue and primary PTC. These findings suggest that the increased local expression of vitamin D may be associated with differentiation, reduced proliferation and a generally favorable prognosis in PTC.

Similar results, indicating a local antitumor response of 1,25(OH)2D3 in early cancer stages, were later confirmed by Clinkspoor et al. who found an increased expression of VDR, CYP27B1 and CYP24A1, that is, the enzyme catalyzing vitamin D, in follicular adenoma and differentiated thyroid cancer compared with normal thyroid. These data suggest an increase in the local 1,25 (OH)2D3 metabolism in tumoral tissue compared with the normal one. Moreover, the Authors, comparing well-differentiated malignant thyroid tumours with benign tumours, observed significantly higher VDR, lower CYP24A1 and similar CYP27B1 expression, suggesting a stronger antitumor response in differentiated thyroid...
cancer, which results in an increase in the local availability of 1,25(\(\text{OH}\))\(_2\)D3. In addition, these Authors reported decreased VDR and CYP24A1 expression in PTC with lymph node metastasis, compared with nonmetastasized PTC; also in addition, in anaplastic thyroid cancer, VDR expression was often lost, whereas CYP27B1/CYP24A1 expression was comparable to DTC. Furthermore, in anaplastic thyroid cancer with high Ki67 expression or distant metastases at diagnosis, increased negative VDR/CYP24A1/CYP27B1 staining was evident.\(^{35}\) Of note, some Authors have suggested that the vitamin D system may also have a role in tumoral cell growth by affecting estrogen receptor expression, which is in turn involved in estrogen-induced cell growth in an estrogen receptor-type-specific manner. In fact, they found that a Vitamin D analog (JK 1624 F2) in three human thyroid cancer lines, that is, anaplastic, papillary and follicular carcinoma, was able to up- and downregulate, not only VDR receptor and 1,25(\(\text{OH}\))\(_2\)D3, but also ER\(_\beta\).\(^{36}\)

Several preclinical studies have reported that vitamin D and some analogs have antiproliferative effects on different thyroid cancer cell lines. In this regard, the effects of 1,25(\(\text{OH}\))\(_2\)D3 and of the superagonistic analog CD578 have been evaluated in various cell lines of thyroid cancer, such as anaplastic, undifferentiated and differentiated follicular thyroid cancer cells. Clear effects on growth arrest were observed, and absolute cell counts demonstrated a reduction in all cell lines after treatment with 1,25(\(\text{OH}\))\(_2\)D3. Growth inhibition was evident even after treatment with a 1000-fold lower concentration of analog CD578.\(^{37}\) Similarly, another group found that 1,25(\(\text{OH}\))\(_2\)D3 and its noncalciomimetic analog EB1089 exhibited antiproliferative effects in a dose-dependent manner on thyroid carcinoma cell growth, specifically on well- and poorly differentiated papillary, well-differentiated follicular carcinoma and anaplastic cell lines; interestingly, this report also showed that administration of 1,25(\(\text{OH}\))\(_2\)D3 increased the expression of p27, a tumor suppressor protein that has a critical role in the pathogenesis and prognosis of several human malignancies.\(^{38}\) This antiproliferative tendency was consistent with the findings both of Suzuki et al.,\(^{39}\) who demonstrated, in the thyroid anaplastic carcinoma cell line, the effectiveness of 22-oxacalcitriol, a vitamin D3 analog, in inhibiting tumoral cell growth and with the recent results of Bennett et al.,\(^{40}\) who observed cell growth inhibition by 25(OH)D3 or 1,25(OH)\(_2\)D3 in cancerous (papillary, follicular and anaplastic carcinoma) and in SV40-immortalized follicular cell lines.

However, a certain degree of inconsistency is present regarding the effect of 1,25(\(\text{OH}\))\(_2\)D3 on redifferentiation of thyroid cancer cells. As far as thyroglobulin is concerned, Liu et al.\(^{41}\) did not find any change, whereas other Authors reported an increase in this marker after 1,25(\(\text{OH}\))\(_2\)D3 treatment.\(^{42,43}\) Conversely, sodium iodide sumpporter mRNA levels were found to modestly increase after 1,25(\(\text{OH}\))\(_2\)D3 in two different studies;\(^{44,45}\) furthermore, one of these showed no change in thyroid-stimulating hormone receptor or thyroperoxidase mRNA expression.\(^{37}\)

As far as the antitumorigenic activity of vitamin D on C cells is concerned, findings are more controversial. Although consistent data report a decreasing effect of 1,25(\(\text{OH}\))\(_2\)D3 on calcitonin secretion and synthesis by C cell line derived from medullary thyroid carcinoma,\(^{46,47}\) findings on antiproliferative activity are very contradictory. In this regard, Zabel et al.\(^{48}\) demonstrated that 1,25(\(\text{OH}\))\(_2\)D3 and two analogs (PRI-1906 and PRI-2191) weakly inhibited proliferation of human and rat thyroid medullary carcinoma cells. On the contrary, other reports even identified a role for 1,25(\(\text{OH}\))\(_2\)D3 in stimulating the growth and proliferation of the same cell line,\(^{46,47}\) whereas yet another found that the growth of cells treated with 1,25(\(\text{OH}\))\(_2\)D3 or 24,25-dihydroxyvitamin D3 did not differ significantly from control-treated cells.\(^{49}\)

Finally, it is also worth noting that in vitro studies did not prove an effect of 1,25(\(\text{OH}\))\(_2\)D3 on the apoptosis of thyroid cancer cells, strongly suggesting that growth arrest was only because of the antiproliferative effects.\(^{50}\)

In vivo evidence

In vivo evidence on the antineoplastic activity of vitamin D, is quantitatively more limited. In 2005, some scientists investigated the pattern of xenografted thyroid cancer cells in severe combined immunodeficient mice and found that tumor weight and volume were reduced by 50% and 22%, respectively, after 1,25(\(\text{OH}\))\(_2\)D3 treatment. In addition, they reported that in fibronectin-downregulated cells the effect of the treatment was lesser, suggesting a role for fibronectin in mediating vitamin D3 actions on neoplastic cell growth.\(^{49}\) Another group, which implanted 5 × 10\(^6\) WRO cells, derived from human thyroid follicular carcinoma, in the neck of 4- to 5-week-old female severe combined immunodeficient mice, found that animals receiving 1,25(\(\text{OH}\))\(_2\)D3 exhibited a smaller mean tumor volume than the vehicle-treated ones. Furthermore, they confirmed the ability of Vitamin D3 to restore p27 accumulation in thyroid carcinoma cells.\(^{51}\)

Human clinical studies

Vitamin D deficiency has been reported in various types of cancer;\(^{52}\) however, clinical data are few and inconsistent in the case of thyroid cancer (Table 1). A recent retrospective cohort study from Canada demonstrated an association between 25(OH)D deficiency and the rate of diagnosis for well-differentiated thyroid cancer in patients undergoing thyroidectomy, with an increase in the malignancy rate from 37.5 to 75%, when comparing vitamin-deficient (n = 12) and vitamin-sufficient (n = 88) subjects, respectively, corresponding to a relative risk of 2.0 (P = 0.03, 95% confidence interval 1.07–2.66).\(^{53}\) A different group from Turkey also observed decreased levels of 25(OH)D and higher prevalence of 25(OH)D deficiency in 344 patients with papillary thyroid cancer compared with 116 healthy controls.\(^{54}\) Of note, in this work cases and controls differed greatly in number, but, at the same time, were matched for two confounding factors, such as age and body mass index. Another small study from Poland showed reduced levels only of 1,25(OH)\(_2\)D3 in peripheral blood from patients with thyroid cancer compared with normal controls, without any significant differences in the levels of 25(OH)D.\(^{55}\) Other researchers, however, by evaluating in total more than seven hundred subjects, did not find any associations between

<table>
<thead>
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<th>Study</th>
<th>Number of studied subjects</th>
<th>Primary end point</th>
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<tr>
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<td>92</td>
<td>AITD</td>
</tr>
<tr>
<td>Shin et al.(^{25})</td>
<td>304</td>
<td>AITD</td>
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<td>Choi et al.(^{26})</td>
<td>6685</td>
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<td>790</td>
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<td>Zhang et al.(^{31})</td>
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<td>62</td>
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Abbreviation: AITD, autoimmune thyroid disease.
the levels of 25(OH)D or the percentage of 25(OH)D deficiency and the rate of diagnosis or the stage of differentiated thyroid cancer. Only one isolated study, carried out on 30 cases and 32 controls, reported a positive association between vitamin D supplements and thyroid cancer, mostly because of a fourfold risk of medullary carcinoma.

VITAMIN D SUPPLEMENTATION IN THYROID DISEASES

Vitamin D supplementation is currently recommended for the treatment of hypovitaminosis D conditions. In particular, vitamin D deficiency is defined by the US Endocrine Society guideline as 25(OH)D less than 20 ng/ml (50 nmol/l), vitamin D insufficiency as 25(OH)D between 21 and 29 ng/ml, and the upper cutoff to minimize the risk of adverse effects as 25(OH)D equal to 100 ng/ml (250 nmol/l). The 25(OH)D levels recommended as ‘cutoffs’ differ in the US Institute of Medicine report, where a 25(OH)D concentration greater than 20 ng/ml (50 nmol/l) covers the requirements of the majority (>97.5%) of the population, and 50 ng/ml (125 nmol/l) is the upper safety margin for hypercalcemia. 25(OH)D is considered as the best indicator for monitoring vitamin D levels. This is the major circulating form of vitamin D, with a half-life of 2–3 weeks. 1,25(OH)2D3 does not reflect vitamin D status, as its half-life is ∼4 h only, its peripheral levels are 1000 times lower than 25(OH)D, and is tightly regulated by PTH, calcium and phosphate. Regarding screening for vitamin D deficiency, the US Endocrine Society guideline recommends it in individuals with specific conditions, who are at risk for this deficiency. None of potential thyroid diseases are included in the list of these conditions. According to the US Endocrine Society guideline, all adults require at least 600–800 IU daily dietary intake of vitamin D. In the case of deficiency or insufficiency, supplementation is needed and either vitamin D2 or vitamin D3 can be used. Adults who are vitamin D-deficient should be treated with 50 000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/ml. Supplementation should be continued by a maintenance therapy of 1500–2000 IU daily.

Although vitamin D has been shown to have a potential beneficial role in the treatment of various autoimmune diseases, the debate surrounding recommendations for vitamin D supplementation in autoimmune disease is still open. Evidence is even less clear as far as autoimmune thyroid disease is concerned.

Supplementation studies in animals

There is a real lack of vitamin D supplementation studies in the literature regarding autoimmune thyroid disease. The beneficial effect of supplementation with vitamin D on treatment or prevention of autoimmune thyroid disease has been demonstrated in experimental animal studies. In the first study, daily treatment with cyclosporin or 1,25(OH)2D3 alone resulted in a reduction of up to 26% of the severity of histological lesions in mice with experimental autoimmune thyroiditis. When mice were treated simultaneously with low doses of both cyclosporin and 1,25(OH)2D3, the outcome included a lower incidence of thyroid autoimmune pathology and a significantly milder clinical disease compared with the control group, without any changes in the levels of thyroid autoantibodies.

In a more recent study, the incidence of experimental autoimmune thyroiditis in mice, after administration of low dose of cyclosporine and 1,25(OH)2D3, decreased by 44.44% in the group studied for prevention and by 37.50% in the group studied for treatment. When severe autoimmune disease was examined, the incidence in the two groups decreased by 71.43% and 60.32%, respectively.

Section remarks

Considering the current available data along with the minimal side effects (that is, possible hypercalcemia after overtreatment, potential interactions with other drugs), careful vitamin D supplementation could be considered as a potential tool for the treatment of patients with autoimmune thyroid disease. However, this recommendation is not included in the US Endocrine Society guideline, obviously due to the lack of clinical trials performed in humans. Similarly to thyroid autoimmune disease, no clinical trials exist regarding the effect of vitamin D supplementation on thyroid cancer.

GENERAL REMARKS

Evidence on this issue deriving from clinical association studies must be taken with great caution. In fact, there are many confounding factors able to influence vitamin D concentration that have not always been properly considered in the relevant works and that can affect the relationship between vitamin D levels and thyroid diseases. As known, vitamin D metabolism may be influenced by exposure to sunlight, use of sunscreen, naturally dark skin tone, season, geographic latitude, clothing and institutionalization. Variability of vitamin D can be due also to physiological factors (for example, age, body mass index, extracellular volume and vitamin D binding globulin concentration and affinity). Moreover, other pathological or pharmacological causes of vitamin D deficiency, such as fat malabsorption syndromes, nephrotic syndrome, lymphomas, primary hyperparathyroidism and use of anticonvulsants and medications to treat AIDS/HIV, must be considered.

It is also worth mentioning that racial differences in vitamin D metabolism make total 25(OH)D not always the best parameter to truly indicate vitamin D deficiency. In fact, the mean levels of total 25(OH)D are usually lower in blacks than in whites, with the former having also lower levels of vitamin D binding globulins than the latter, thus resulting in similar concentrations of bioavailable 25(OH)D.

Moreover, there are several methods to measure vitamin D. The most widely used one for determining 25(OH)D is Diasorin RIA that recognizes both 25(OH)D2 and 25(OH)D3, although

| Table 2. Summary of available evidence that links vitamin D to thyroid disease |
|---|---|---|
| Diseases | Potential mechanisms | Observational studies | Clinical trials |
| Hashimoto's thyroiditis | Vitamin D promotes a Th2 phenotype while suppressing Th1 activity, and inhibits cytokine production, which is important in the development of Hashimoto's thyroiditis | !! !! !! !! | No |
| Graves' disease | Vitamin D seems to inhibit inflammatory responses in human thyroid cells and T-cell production of cytokine leading to the production of TSH receptor autoantibodies | !! !! | No |
| Thyroid cancer | Vitamin D, through binding to its receptor, seems to increase the expression of p27, a tumor suppressor protein that has a critical role in several human malignancies | !! | No |

Abbreviations: Th1, Th1 helper cells; Th2, Th2 helper cells. Number of !! denotes degree of available evidence (from low (!!) to very high (!!! !! !! !! !!)).
the calibration curves are constructed with 25(OH)D3. 65 High-performance liquid chromatography methods are less common and the main limitations for its use are represented by its laborious prepurification steps and the use of normal phase chromatography. 66 However, mass spectrometry is considered to be the most accurate of all methods because of its ability to separate and accurately quantify both 25(OH)D2 and 25(OH)D3. However, the main limit of this method is represented by the frequent issues with ion suppression, which could affect the measurements of small quantities of analytes. 67, 68

In view of these considerations, future protocols must rigorously consider all these aspects in order to clarify the real existence of this association.

CONCLUSION

Although several findings support the role of vitamin D in the pathogenesis of thyroid diseases (Table 2), no guidelines are currently available for or against recommending vitamin D supplementation in the prevention or therapy of thyroid disease, outside the current recommendations made by the Endocrine Society. However, because of the paucity of intervention studies, further clinical trials are needed before evidence-based recommendations can be made.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

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