Review Article

Vitamin D, Thyroid Autoimmunity and Cancer: An Interplay of Different Factors

Deep Dutta, Meha Sharma[1], Sameer Aggarwal[2], Ritin Mohindra[3], Saptarshi Bhattacharya[4], Sanjay Kalra[5]

Departments of Endocrinology and [1]Rheumatology, CEDAR Super-Specialty Clinics, Dwarka, Gujarat, [2]Department of Endocrinology, Apex Super-Specialty Hospital, Rohtak, Haryana, [3]Department of Medicine, PGIMER, Chandigarh, [4]Department of Endocrinology, Max Superspecialty Hospital, Patparganj, New Delhi, [5]Department of Endocrinology, Bharti Hospital, Karnal, Haryana, India

Abstract

Background and Aims: In spite of large volume of data linking Vitamin D with cardiovascular morbidity, autoimmunity, cancer, and virtually every organ system, Vitamin D and thyroid is a lesser-known aspect of Vitamin D in clinical practice. This article intends to highlight the current literature on the impact of Vitamin D status and supplementation on thyroid autoimmunity and cancer. **Methods:** References for this review were identified through searches of PubMed for articles published to from 1950 to August 2019 using the terms "thyroid" [MeSH Terms] AND "Vitamin D" [MeSH Terms] OR "thyroid" [All Fields] AND "Vitamin D" [All Fields]. **Results:** Significant inverse correlation was documented between anti-thyroid peroxidase antibody (TPOAb) and serum 25-hydroxy-Vitamin D (25OHD). TPOAb positivity is more prevalent in Vitamin D deficient individuals. A large volume of medical literature is available from observational studies linking Vitamin D with thyroid autoimmunity. Data from interventional studies documenting beneficial effects of Vitamin D on thyroid autoimmunity is also available, but lesser than that from observational studies. Short-term high dose oral Vitamin D supplementation reduces TPOAb titers. Certain Vitamin D receptor (VDR) gene polymorphism have been linked to increased occurrence of autoimmune thyroid disorders (AITD). Vitamin D deficiency, decreased circulating calcitriol has been linked to increased thyroid cancer. Certain VDR gene polymorphisms have been linked with increased as well as decreased occurrence of thyroid cancer. Data is scant on use of Vitamin D and its analogues for treating thyroid cancer. **Conclusion:** In spite of large volume of medical literature from observational studies linking Vitamin D with thyroid autoimmunity and cancer, meaningful concrete clinical data on impact of Vitamin D supplementation on hard clinical end points in these disorders is lacking, and should be the primary area of research in the next decade.

Keywords: Autoimmunity, cancer, thyroid, Vitamin D

Introduction

The last two decades have seen an exponential increase in medical literature (basic, translational and clinical studies) linking Vitamin D to various organ systems in the body. Apart from the classical and well known impact of Vitamin D on bone and muscle health,[1,2] Vitamin D is believed to have a beneficial effect on endothelial dysfunction (microalbuminuria),[3] cardiovascular function and events,[4] insulin resistance,[5] diabetes prevention,[6] better immune function and response to anti-tubercular therapy in patients with tuberculosis,[7] immune-modulatory effects in patients with autoimmune disorders (lupus, rheumatoid arthritis),[8] prevention and remission of multiple sclerosis,[9] better response to immunotherapy in patients post organ transplantation,[10] gonadal function,[11] among the growing list of pleotropic effects of Vitamin D. The reason for this almost ubiquitous role of Vitamin D is perhaps because Vitamin D receptor (VDR) is virtually expressed in every tissue and organ system of the body.[12] Vitamin D mediates its effect though VDR and activation of VDR-responsive genes. Vitamin D and thyroid is however a less known and discussed aspect of Vitamin D in clinical practice. This article intends to highlight the current literature on the impact of Vitamin D status and supplementation on thyroid autoimmunity and cancer.

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Address for correspondence: Dr. Deep Dutta, Department of Endocrinology, Center for Endocrinology Diabetes Arthritis and Rheumatism Super-specialty Clinics, Sector-13, Dwarka, New Delhi - 110 078, India.
E-mail: deepdutta2000@yahoo.com

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Methods

References for this review were identified through searches of PubMed for articles published to from 1950 to August 2019 using the terms "thyroid" [MeSH Terms] and "Vitamin D" [MeSH Terms] OR "thyroid" [All Fields] AND "Vitamin D" [All Fields]. A total of 1481 articles were found. The title of all the articles were manually screened. 491 articles were removed as they were primarily dealing with parathyroid. 271 articles which were not of human origin were excluded. 92 articles related to diabetes were removed. 33 articles related to pregnancy were removed. This resulted in 594 articles which were manually evaluated for inclusion in the review. The search was not restricted to English-language literature.

Results

Vitamin D and thyroid autoimmunity

Pathophysiology

Autoimmune thyroid disease (AITD) is believed to be a polygenic disorder.[13] Both genetic predisposition and environmental factors have a role in the genesis of AITD. These include thyroid specific genes, immunomodulatory genes, selenium, iodine, radiation, smoking, infections, among many others that are yet to be defined.[13] Vitamin D enhances the innate immune response while exerting an inhibitory action on the adaptive immune system.[13] Activated Vitamin D (calcitriol) has been demonstrated to modulate the cytokine mileau from a pro-inflammatory to a more tolerogenic immune status.[14] Calcitriol inhibits Th1 and Th17 cell proliferation and differentiation; inhibits production of inflammatory cytokines (IL-2, interferon-γ, IL-17, IL-21), and promotes production of anti-inflammatory Th2 cytokines (IL-3, IL-4, IL-5, and IL-10).[13,14] Calcitriol also inhibits the B-cell differentiation into plasma cells and production of immunoglobulins.[14] The immunomodulatory properties of Vitamin D raises the possibility of role of Vitamin D in different autoimmune disorders including the AITD.

Vitamin D and thyroid autoimmunity (animal studies)

Vitamin D deficient but not Vitamin D sufficient BALB/c (Bagg and Albino, laboratory bred) mice developed persistent hyperthyroidism after immunization with thyroid stimulating hormone receptor antibody (TSHR Ab).[15] Calcitriol has been demonstrated to reduce thyroid autoantibodies production along with resolution of pathologic changes in the thyroid glands of Wistar rats.[16] Calcitriol had a synergistic effect when added to cyclosporine for prevention of experimental autoimmune thyroiditis in CBA mice.[17]

Vitamin D and thyroid autoimmunity (human observational studies)

A total of 21 studies involving more than 3890 patients with AITD have been published till date evaluating the relationship between Vitamin D status and severity of thyroid autoimmunity as evaluated by autoantibody titers.[18-34] These studies are often limited by small number of patients, different criteria used for defining Vitamin D deficiency/insufficiency and different criteria for AITD. Studies with more than 100 patients/controls have been elaborated in Table 1.

A weak but statistically significant inverse correlation was documented between anti-thyroid peroxidase antibody (TPOAb) and serum 25-hydroxy-Vitamin D (25OHD) titers in a study from New Delhi India in 2009.[18] In the Korea National Health and Nutrition Examination Survey involving 4141 participants, anti-thyroid peroxidase antibody (TPOAb) positivity was more prevalent in the vitamin D deficient group (9.1%) as compared to the sufficient groups (5.3%; $P < 0.01$).[19] Low Vitamin D has been linked to increased autoimmune thyroid disorders (AITD) in women with PCOS.[35] In a meta-analysis involving 20 different case-control studies, it was observed that patients with AITD (Graves disease and Hashimoto's thyroiditis) had significantly lower serum Vitamin D levels and were more likely to be deficient in 25OHD (OR 2.99, 95% CI: 1.88, 4.74).[36]

In another meta-analysis, VDR gene TaqI (rs731236) and BsmI (rs1544410) polymorphisms were significantly associated with AITD risk (OR = 0.801 95% CI 0.705-0.910, Pz = 0.001 for B vs. b; OR = 0.854, 95% CI 0.757-0.963, Pz = 0.010 for t vs. T respectively).[37]

Vitamin D deficiency has been linked with increased systemic inflammation. Increased systemic inflammation has been linked with increased insulin resistance, metabolic syndrome and obesity. In a genetically predisposed individual to thyroid autoimmunity, Vitamin D deficiency and metabolic syndrome has been linked to increased systemic inflammation and Hashimoto's thyroiditis.[38] Vitamin D deficiency has been linked to increased risk of gestational diabetes and neonatal intensive care admission in women with thyroid autoimmunity.[39]

In a study from Poland, atorvastatin therapy of 20-40 mg/day over a period of 6 months was associated with significant reduction in thyroid autoantibody titers only in people who were Vitamin D sufficient, suggestive an indirect beneficial impact of Vitamin D sufficiency on thyroid autoimmunity.[40] In a meta-analysis, specific Vitamin D receptor (VDR) polymorphisms like VDR rs731236, rs1544410, rs2228570, and rs7975232 were significantly associated with risk for autoimmune thyroid disease.[41] Vitamin D receptor (VDR) polymorphism has also been documented to be an independent risk factor for Graves' disease in the Chinese Han population.[42]

Vitamin D and thyroid autoimmunity (human interventional studies)

Daily cholecalciferol supplementation of 1000 U/d for 1 month was associated with a significant reduction in TPOAb and anti-thyroglobulin antibody (TgAb) titers in a cohort of 46 patients from Turkey.[43] In a randomized controlled trial, we demonstrated a significant 46% reduction in TPOAb titers following 3 months of weekly 60,000 U weekly of cholecalciferol supplementation in newly diagnosed, Vitamin D deficient, treatment naïve primary and subclinical

Table 1: Key outcomes of observational studies evaluating the relationship between Vitamin D status and thyroid autoimmunity

Authors	Participants	Vit-D criteria used	Key Observations
Goswami *et al*., 2009[18]	642 students, teachers and staff	<25 ng/ml	Weak inverse correlation between serum 25OHD and TPOAb titers (*r* -0.08)
Kim M *et al*. 2017[19]	4141	<20 ng/ml vs. >20 ng/ml	TPOAb positivity in vit-D deficiency and sufficiency groups 9.1% and 5.3% respectively
Wang *et al*. 2015[20]	1714	-	Significant negative correlation (*r* -0.12) between serum 25OHD and TGAb titers in women
Effraimidis *et al*., 2012[21]	803	-	No relation observed between vit-D levels and early stages of thyroid autoimmunity
Choi *et al*., 2014[22]	673 TPOAb (+), 6012 TPOAb (-)	<25 (deficiency: D); 25-75 (insufficiency; I); >75 nmol/L (Sufficiency: S)	21.2% 15.5% and 12.6% people with vit-D D, I and S had TPOAb (+); 25OHD levels in TPOAb (+) and (-) were 50.7 and 56.4 nmol/L respectively
Kim, 2016[23]	221 HT, 148 GD, 407 NC	<75 nmol/L	48.9%, 41.9% and 37.1% of HT, GD and NC respectively had 25 OHD <75 nmol/L
Unal *et al*., 2014[24]	254 HT, 27 GD, 124 NC	<25 (deficiency: D); 25-75 (insufficiency; I); >75 nmol/L (Sufficiency: S)	25 OHD 14.9±8.6 ng/ml, 19.4±10.1 ng/ml and 22.5±15.4 ng/ml in HT, GD and NC respectively; 25OHD inversely correlated with TGAb (*r* = –0.136, P=0.025), TPOAb (*r* = –0.176, *P*=0.003)
Evliyaoglu *et al*., 2015[25]	90 HT; 79 HC	<50 nmol/L	71.1% of HT and 51.9% of HC had vit-D deficiency
Bozkurt *et al*., 2013[26]	180 euthyroid HT, 180 newly diagnosed HT, 180 HC	<25 nmol/L	Occurrence of severe Vitamin D deficiency was 48.3% vs. 35% vs. 20.5% respectively
Muscogiuri *et al*., 2016[27]	168 elderly people	<50 nmol/L	Occurrence of AITD was 28% vs. 8% in vit-D deficient vs. non deficient groups
Botelho *et al*. 2018[28]	88 HT, 71 HC		No difference in serum 25OHD between HT and HC
Yasuda *et al*., 2013[29]	36 active GD, 18 inactive GD, 49HC	-	No difference in 25OHD levels; 36.2 vs. 45.4 vs. 46.4 nmol/L
Tamer *et al*., 2011[30]	161 HT, 162 HC	<75 nmol/L	Occurrence of vit-D insufficiency was 91.9% in HT, 63% in HC
Shin *et al*., 2014[31]	111 AITD, 193 non-AITD patients	-	25OHD levels 31.5 nmol/L in AITD, 36.2 nmol/L in non-AITD; Correlation between 25OHD and TPOAb (*r* = -0.252)
Camurdan *et al*., 2012[32]	78 HT, 74 HC	<32.5 nmol/L	73.1% of HT and 17.6% of HC had vit-D deficiency; correlation between 25OHD and TPOAb (*r* = -0.3)
D'Aurizio *et al*., 2015[33]	100 AITD, 126 HC	<50 nmol/L	No difference
Mangaraj S *et al*., 2019[34]	84 GD, 42HC	<20 ng/ml	GD had significantly lower 25OHD (19.2 ng/ml) compared to HC 23.8 ng/ml; no correlation of 25OHD with TPOAb, thyroid hormones

TPOAb: Anti-thyroid antibody; TGAb: Anti-thyroglobulin antibody; 25OHD: Serum 25-hydroxy Vitamin D; HT: Hashimoto's thyroidtitis; GD: Graves Disease; NC: Normal controls; HC: Healthy control; AITD: Autoimmune thyroid disorder; OR: Odds ratio

hypothyroidism as compared to only 16% reduction in the control group.[44] Beneficial effects of Vitamin D supplementation on TPOAb titers (viz. reduction in antibody titers) following Vitamin D supplementation have also been documented even in Vitamin D sufficient patients with Hashimoto's thyroiditis, in a study from Poland.[45] In that study, the reductions were more pronounced for TPOAb titers as compared to TgAb titers.[45] In a placebo controlled randomized controlled trial (RCT) study from Iran in which 21 women with Hashimoto's thyroiditis were randomized to receive either cholecalciferol (50,000 U) or placebo pearls for 3 months, a significant reduction in anti-thyroglobulin antibody (TGAb) and TSH titers were noted at the end of the study, without any impact on TPOAb, T3 and T4 hormone levels[46] However whether this reduction in TSH levels over a short period of time of 3 months translating to reduction in long term levothyroxine requirements needs further evaluation in longer studies.

In a small study on euthyroid men with thyroid autoimmunity, both Vitamin D vs. selenium supplementation were associated with equivalent reduction in thyroid antibody titer over a period of 6 months, suggesting their independent beneficial impact on thyroid autoimmunity.[47] In another study by the same group, in a cohort of 47 euthyroid patients with thyroid autoimmunity, Vitamin D supplementation of 4000 IU for 6 months was associated with significant reductions in circulating levels of TPOAb and thyroglobulin antibody titers, and the effect was more pronounced in people who had been treated with selenomethionine (200 μg daily) in the prior 1 year, suggesting perhaps an adjunctive effect of Vitamin D with selenium supplementation.[48] In a meta-analysis comprising of 6 RCTs and involving 344 patients with AITD, Vitamin D supplementation was associated with significant reductions in TPOAb and TgAb titers at 6 months follow-up.[49] In a RCT involving 251 apparently healthy individuals, low dose vitamin supplementation (400 IU/day and 1000 IU/day) as compared

to placebo did not result in any significant change in TPOAb and TSH titers at 16 weeks of follow-up.[50] Limitations of this study include the fact that most of the patients in these studies were healthy individuals without AITD and had TPOAb titers in the normal range. Also the serum 25OHD levels in the supplementation groups increased from 26 to 49 nmol/L at the end of the study, which continued to be in the Vitamin D deficiency range.[50] It can be said that the very low dose Vitamin D used in this study, did not result in any meaningful changes in the serum 25OHD, and hence no meaningful changes in TPOAb titers is expected. This study also highlighted that blanket blind Vitamin D supplementation in people without AITD may not have any meaningful impact on TPOAb titers and TSH levels.

However, whether this beneficial impact on TPOAb titers following Vitamin D supplementation actually translates to a lower levothyroxine requirement in the long run is not known and needs long-term follow-up studies.

In this regard, it is interesting to consider that in a small study from Iran, it was noted that Vitamin D supplementation over 12 weeks in people with primary hypothyroidism was associated with an independent reduction in serum TSH levels. However, a reduction in levothyroxine requirement was not documented in this study.[51]

Vitamin D and thyroid cancer

Pathophysiology

Vitamin D through Vitamin D receptor (VDR) has both direct and indirect effects on cellular proliferation, differentiation, apoptosis, inflammation, invasion, angiogenesis, and metastasis.[52] Calcitriol increases the expression of cyclin dependent kinase inhibitors (CDKI), which have potent negative impact on cell proliferation.[53] Vitamin D influences microRNA expression which also has an additional negative influence on cell growth and proliferation.[54] Calcitriol induces caspase expression along with other pro-apoptotic proteins (BAX, BAK, and BAD), thus promoting apoptosis of tumor cells.[54]

Vitamin D and thyroid cancer (cell culture and animal studies)

Calcitriol has been shown to inhibit the proliferation of thyroid cancer stem cells.[55] Calcitriol reduced tumor size and prevented metastatic growth in SCID mice that were implanted with human thyroid follicular carcinoma-derived (WRO) cells.[56] Vitamin D receptor (VDR) polymorphisms has been demonstrated to have an impact on Vitamin D metabolism in thyroid tissue, which may modulate the anti-tumor effect of Vitamin D in papillary thyroid cancer (PTC).[57] VDR expression in human thyroid cancer cells has been linked to increased ECM protein-1 (ECM1) and type II trans-membrane serine protease-4 (TPMRSS4) expression, which are tissue markers of increased local invasion and metastasis,[58] highlighting the potential role of Vitamin D analogues in down regulating VDR and thus having a beneficial impact on thyroid cancer. Studies have shown that the efficacy of VDR agonist therapy to decrease viable thyroid cancer cell count depends on the FF FokI VDR genotype polymorphisms.[59] Higher baseline 24-hydroxylase levels were also associated with relative resistance to calcitriol and other VDR agonists (DP006) in inhibiting and killing thyroid cancer cells.[59]

Vitamin D and thyroid cancer (human studies)

Lower circulating levels of calcitriol (the active form of Vitamin D) have been documented in patients with differentiated thyroid carcinoma.[60] In a study involving 212 patients with thyroid nodules, presence of Vitamin D deficiency (25OHD <37.5 nmol/L) in the peroperative state was associated with higher occurrence of malignancy on post-operative histopathologic evaluation (75% vs. 37.5%).[61] A significantly lower serum 25OHD was documented in 344 patients with papillary thyroid cancer as compared to healthy controls.[62] In 548 women undergoing thyroidectomy for papillary thyroid cancer, the pre-surgery serum 25OHD was significantly lower in patients with tumor diameter more than 1 cm and/or tumor metastasis.[63] In another study, serum calcitriol was significantly lower in 172 patients with DTC when compared to 321 healthy controls.[64] The same authors demonstrated an association between differentiated thyroid cancer and low 25OHD and calcitriol levels in certain CYP24A1 haplotypes.[65]

A significant number of negative literatures are also available where they have found no relation between the Vitamin D status and the occurrence and severity of thyroid malignancy. Preoperative serum 25OHD was not a predictor of disease aggressiveness or poor outcomes among 820 patients with papillary thyroid cancer.[66] In another study involving 433 patients with thyroid nodules who underwent thyroidectomy, quartiles of serum 25OHD was not a predictor of malignancy or benign lesions.[67] In a study involving 410 patients with thyroid nodules, Vitamin D deficiency was not a predictor of malignancy detected either during needle aspiration or following thyroidectomy.[13] Population screening of 5186 individuals revealed that serum 25OHD was not a predictor of malignancy in the general population.[68] In another study involving 177 patients with papillary thyroid cancer, it was not the Vitamin D or adipocytokine status, but the occurrence of obesity, especially central obesity, which was the strongest predictor of malignancy.[69]

Genetic polymorphisms of VDR, cytochrome P450, and factors, which modulate Vitamin D metabolism, signaling and action, play an important role in the pathogenesis of different cancers including thyroid cancer.[60] Increased activity of vitamin D-inactivating CYP24A1 gene in papillary thyroid cancer (PTC) has been linked to increased tumor malignity (mainly vascular invasion, lymph node metastasis, tumor size), suggesting that CYP24A1 may be directly involved in thyroid carcinogenesis.[70] Polymorphism of VDR of alleles AA and FF of the ApaI (rs7975232), FokI (rs10735810) and haplotype tABF are believed to confer protection from follicular thyroid carcinoma (FTC).[50]

The haplotype tABF is believed to be associated with an increased FTC risk.[71]

Sirtuin 1 histon deacethylase (SIRT1) is believed to link the vitamin D pathway with regulation of transcription factor FOXO3a, a key player in cell cycle regulation and apoptosis.[72] In a study from Germany, FOXO3a rs9400239T and rs4945816C, which has been linked with thyroid malignancy, was also documented to be a risk factor for Hashimoto's thyroiditis.[58] Vitamin D is believed to exert its antiproliferative effects through its impact on vitamin D-SIRT1-FOXO3a axis.[72] In a case control study involving 276 Chinese Han people, a high level of circulating 25-hydroxy-Vitamin D was associated with decreased risks for thyroid cancer.[73] In a meta-analysis involving 14 different studies, lower serum 25-hydroxyvitamin D levels, especially in the Vitamin D deficiency range was associated with increased risk for thyroid cancer.[74]

Summary

To conclude, a large volume of medical literature is available from cross-sectional and observational studies linking Vitamin D with thyroid autoimmunity. Data from interventional studies documenting beneficial effects of Vitamin D supplementation on thyroid autoimmunity is also available, but lesser than that from cross-sectional and observational studies. Limitations of these interventional studies include small number of patients evaluated, heterogeneity of dosage and preparation of Vitamin D used in these studies, short duration of follow-up, and end points primarily being reduction in titers of thyroid auto-antibodies. Data on whether correction of Vitamin D deficiency in AITD results in reduction in the requirement of levothyroxine or carbimazole in hypothyroidism or Graves' disease respectively is not available. Hence there is an urgent need for large, multi-centric studies to evaluate the impact of Vitamin D supplementation on meaningful long-term clinical end points in AITD. Similarly, in spite of large volume of literature available linking Vitamin D deficiency, VDR gene polymorphisms, calcitriol metabolism with thyroid cancer, there is scant data from interventional studies on the same, which should be the major area for research in the next decade. However it must be realized that as of today, Vitamin D should not be considered as a panacea for all illness including thyroid disorders. Rampant unmonitored Vitamin D supplementation, especially parental has been associated with an exponential increase in the occurrence of Vitamin D intoxication in the last one decade, which is easily avoidable, as it is a difficult to treat condition with significant morbidity.[75,76]

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Conflicts of interest

There are no conflicts of interest.

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