Review Article

Vitamin-D and Thyroid : Permissive effects of vitamin-D on thyroid autoimmunity and cancer

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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 pleotropic effects of vitamin-D on thyroid function and thyroid disorders. References for this review were identified through searches of PubMed, Medline, and Embase for articles published to November 2017 using the terms "thyroid" [MeSH Terms] AND "vitamin-D" [MeSH Terms] OR "thyroid" [All Fields] AND "vitamin-D" [All Fields]. Significant inverse correlation was documented between anti-thyroid peroxidase antibody (TPOAb) and serum 25-hydroxy-vitamin-D (25OHD) titers. TPOAb positivity is more prevalent in the vitamin D deficient individuals. Certain vitamin-D receptor (VDR) gene polymorphism have been linked to increased occurrence of autoimmune thyroid disorders (AITD). Short-term high dose oral vitamin-D supplementation reduces TPOAb titers. 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 analogues for treating thyroid cancer. In spite of large volume of medical literature from observational and cross-sectional studies linking vitamin-D with thyroid autoimmunity and cancer, meaning 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.

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Key words **: Vitamin-D, thyroid, autoimmunity, cancer**

The last 2 decades has 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 pleotropic effects of vitamin-D on thyroid function and thyroid disorders.

- **A large volume of data is available from cross-sectional and observational studies linking vitamin-D with thyroid autoimmunity and cancer.**
- **Limitations of these studies : (a) Studied with small number of patients, (b) heterogeneity of dosage, (c) preparation of vitamin-D, and (d) short duration of follow-up.**
- **Hence there is an urgent need for such large, multi-centric studies to evaluate the clinical end points.**
- **Such study should be the primary area of research in the next decade.**

Materials and Methods

References for this review were identified through searches of PubMed, Medline, and Embase for articles published to November 2017 using the terms "thyroid" [MeSH Terms] AND "vitamin-D" [MeSH Terms] OR "thy-

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roid" [All Fields] AND "vitamin-D" [All Fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

Results

Vitamin-D and Thyroid Autoimmunity (Observational Studies) :

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[13]. 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)[14]. Low vitamin-D has been linked to increased autoimmune thyroid disorders (AITD) in women with PCOS[15]. In a meta-analysis involving 20 different case-control studies, it as 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)[16]. 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)[17].

Vitamin-D and Thyroid Autoimmunity (Interventional Studies) :

Daily cholecalciferol supplementation of 1000U/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[18]. 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 hypothyroidism as compared to only 16% reduction in the control group[19]. 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[20]. There is literature also available to suggest lack of vitamin-D supplementation on TPOAb titers[21]. However limitation of this study included use of low dose of vitamin-D (400-1000IU/day) for 16 weeks and all the patients continued to be vitamin-D deficient at the end of the study (25OHD levels increased from 26nmol/L at the study onset to 49 nmol/L at the end of the study)[21]. 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. Vitamin-D receptor (VDR) polymorphism has also been documented to be an independent risk factor for Graves' disease in the Chinese Han population[22].

Vitamin-D and Thyroid Cancer :

Lower circulating levels of calcitriol (the active form of vitamin-D) have been documented in patients with differentiated thyroid carcinoma[23]. 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[23]. 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[24]. 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)[22]. The haplotype Tabf is believed to be associated with an increased FTC risk[25].

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)[26]. VDR expression in human thyroid cancer cells has been linked to increased ECM protein-1 (ECM1) and type II transmembrane serine protease-4 (TPMRSS4) expression, which are tissue markers of increased local invasion and metastasis[27], 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[28]. 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[28].

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[29,30].

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