The impact of vitamin D status and supplementation on thyroid autoimmunity

Abstract. Background. In spite of large volume of data linking vitamin D (VD) with cardiovascular morbidity, autoimmunity, cancer, and virtually every organ system, VD and thyroid is a lesser-known aspect of VD in clinical practice. The reason for this almost ubiquitous role of VD is perhaps because VD receptor (VDR) is virtually expressed in every tissue and organ system of the body. This review intends to highlight the current literature on the impact of VD status and supplementation on thyroid autoimmunity. Materials and methods. References for this review were identified through searches of PubMed for articles published to from 2015 to September 2020 using the terms “thyroid” and “Vitamin D”. Results. Significant inverse correlation was documented between anti-thyroid peroxidase antibody (TPO Ab) and serum 25-hydroxyvitamin D 25(OH)D. TPO Ab positivity is more prevalent in VD deficient individuals. A large volume of medical literature is available from observational studies linking VD with thyroid autoimmunity. Data from interventional studies documenting beneficial effects of VD on thyroid autoimmunity is also available, but lesser than that from observational studies. Short-term high dose oral VD supplementation reduces TPO Ab titers. Certain VDR gene polymorphism has been linked to increased occurrence of autoimmune thyroid disorders (AITD). 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. Conclusions. In spite of large volume of medical literature from observational studies linking VD with thyroid autoimmunity, meaningful concrete clinical data on impact of VD supplementation on hard clinical end points in these disorders is lacking, and should be the primary area of research in the next decade.

Keywords: thyroid; autoimmunity; vitamin D; review

Introduction

The last two decades have seen an exponential increase in medical literature (basic, translational and clinical studies) linking Vitamin D (VD) to various organ systems in the body. Apart from the classical and well-known impact of VD on bone and muscle health [1, 2]. VD is believed to have a beneficial effect on endothelial dysfunction (microalbuminuria) [3], cardiovascular function and events [4], insulin resistance [5], diabetes mellitus (DM) 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], gonadal function [10] among the growing list of pleotropic effects of VD.

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 [11, 12]. Vitamin D mediates its effect though VDR and activation of VDR-responsive genes. VD and thyroid are however a less known and discussed aspect of VD in clinical practice.

This article intends to highlight the current literature on the impact of Vitamin D status and supplementation on thyroid autoimmunity.

Materials and methods

References for this review were identified through searches of PubMed for articles published to from 2015 to September 2020 using the terms “thyroid” and “Vitamin D”. © 2020. The Authors. This is an open access article under the terms of the Creative Commons Attribution 4.0 International License, CC BY, which allows others to freely distribute the published article, with the obligatory reference to the authors of original works and original publication in this journal.

For correspondence: Ivan Pankiv, MD, PhD, Associate Professor at the Department of clinical immunology, allergology and endocrinology, Bukovinian State Medical University, Teatralna sq., 2, Chernivtsi, 58002, Ukraine; e-mail: ip@bsmu.edu.ua

Full list of author information is available at the end of the article.
Results

**Vitamin D and thyroid autoimmunity**

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 [14]. Vitamin D enhances the innate immune response while exerting an inhibitory action on the adaptive immune system [15]. Activated Vitamin D (calcitriol) has been demonstrated to modulate the cytokine milieu from a pro-inflammatory to a more tolerogenic immune status [16]. 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) [17]. Calcitriol also inhibits the B-cell differentiation into plasma cells and production of immunoglobulins [18].

The immunomodulatory properties of Vitamin D raises the possibility of role of Vitamin D in different autoimmune disorders including the AITD. Vitamin D deficient but not Vitamin D sufficient BALB/c mice developed persistent hyperthyroidism after immunization with thyroid stimulating hormone receptor antibody (TSHR Ab) [19]. Calcitriol has been demonstrated to reduce thyroid autoantibodies production along with resolution of pathologic changes in the thyroid glands of Wistar rats [20]. Calcitriol had a synergistic effect when added to cyclosporine for prevention of experimental autoimmune thyroiditis in CBA mice [21].

Studies have been published till date evaluating the relationship between Vitamin D status and severity of thyroid autoimmunity as evaluated by autoantibody titers [22–24]. These studies are often limited by small number of patients, different criteria used for defining Vitamin D deficiency/insufficiency and different criteria for AITD.

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) [25]. Low Vitamin D has been linked to increased AITD in women with polycystic ovary syndrome (PCOS) [26]. 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) [27]. 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) [28].

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 autoimmune, Vitamin D deficiency and metabolic syndrome has been linked to increased systemic inflammation and Hashimoto’s thyroiditis [29].

Vitamin D deficiency has been linked to increased risk of gestational diabetes and neonatal intensive care admission in women with thyroid autoimmunity [30]. 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 [31]. In a meta-analysis, specific VDR polymorphisms like VDR rs731236, rs1544410, rs22283570, and rs7975232 were significantly associated with risk for autoimmune thyroid disease [32].

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 [33].

In a randomized controlled trial authors demonstrated a significant 46 % reduction in TPOAb titers following 3 months of weekly 60,000 IU 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 [34]. 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 our study [35].

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 IU) or placebo pearls for 3 months, a significant reduction in TGAb and TSH titers were noted at the end of the study, without any impact on TPOAb, T, and T4 hormone levels [36]. 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 meta-analysis involving 344 patients with AITD, Vitamin D supplementation was associated with significant reductions in TPOAb and TgAb titers at 6 months follow-up [37]. 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 [38]. 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 25(OH)D 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 [38]. 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 25(OH)D, and hence no meaningful changes in TPOAb titers were 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 [39].

Vitamin D through VDR has both direct and indirect effects on cellular proliferation, differentiation, apoptosis, inflammation, invasion, angiogenesis, and metastasis [40]. Calciotriol increases the expression of cyclin dependent kinase inhibitors (CDKI), which have potent negative impact on cell proliferation [41]. Vitamin D influences microRNA expression which also has an additional negative influence on cell growth and proliferation [42].

Calcitriol induces caspase expression along with other pro-apoptotic proteins (BAX, BAK, and BAD), thus promoting apoptosis of tumor cells [43]. Calciotriol has been shown to inhibit the proliferation of thyroid cancer stem cells [44]. 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) [45]. VDR expression in human thyroid cancer cells has been linked to increased ECM protein-1 (ECM1) and type II trans-membrane serine protease-4 (TPMRS54) expression, which are tissue markers of increased local invasion and metastasis, highlighting the potential role of Vitamin D analogues in down regulating VDR and thus having a beneficial impact on thyroid cancer [46]. Lower circulating levels of calciotriol have been documented in patients with differentiated thyroid carcinoma [47].

Conclusions
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.

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

References
1. Amrein K, Scherkel M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020 Nov;74(11):1498-1513. doi: 10.1038/s41430-020-0558-y.
2. Chareongum N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020 Jul 15;12(7):2097. doi: 10.3390/nu12072097.
3. Liyanage P, Lekamwasam S, Weerarathna TP, Liyanage C. Effect of Vitamin D therapy on urinary albumin excretion, renal functions, and plasma renin among patients with diabetic nephropathy: A randomized, double-blind clinical trial. J Postgrad Med. 2018 Jan-Mar;64(1):10.15. doi: 10.4103/jpgm;jpgm_598_16.
4. Nishta A, Toutouza M, Machairas N, Mariolis A, Philippou A, Kouvelisieris M. Vitamin D in Cardiovascular Disease. In Vivo. 2018 Sep-Oct;32(5):977-981. doi: 10.21873/inivo.113358.
5. Pankiv VI, Yuzevenko Tyu, Pavlovskova NY, Pankiv IV. Effect of vitamin D on insulin resistance and anthropometric parameters in patients with type 2 diabetes mellitus. Clinical Endocrinology and Endocrine Surgery. 2019;1(65):53-58. doi:10.30978/CEES-2019-1-33.
6. Gröber U, Holick MF. Diabetes Prevention: Vitamin D Supplementation May Not Provide Any Protection If There Is No Evidence of Deficiency! Nutrients. 2019 Nov 4;11(11):2651. doi: 10.3390/nu11112651.
7. Aibana O, Huang CC, Aboud S, et al. Vitamin D status and risk of incident tuberculosis disease: A nested case-control study, systematic review, and individual-participant data meta-analysis. PLoS Med. 2019 Sep 11;16(9):e1002907. doi: 10.1371/journal.pmed.1002907.
8. Meena N, Singh Chawla SP, Garg R, Battu A, Kanw A. Assessment of Vitamin D in Rheumatoid Arthritis and Its Correlation with Disease Activity. J Nat Sci Biol Med. 2018 Jan-Jun;9(1):54-58. doi: 10.4103/jnsbm.jnsbm_128_17.
9. Feige J, Moser T, Bieler L, Schwenker K, Hauer L, Sellner J. Vitamin D Supplementation in Multiple Sclerosis: A Critical Analysis of Potentials and Threats. Nutrients. 2020 Mar;12(3):783. doi:10.3390/nu12030783.
10. Karras S, Anagnostis P, Kotou K, Goulis DG. Vitamin D and gonadal function in men: a potential inverse U-shaped association? Androlgy. 2016 May;4(3):542-4. doi: 10.1111/andr.12173.
11. Bass JJ, Nakhuda A, Deane CS, et al. Overexpression of the vitamin D receptor (VDR) induces skeletal muscle hypertrophy. Mol Metab. 2020 Dec;42:101059. doi: 10.1016/j.molmet.2020.101059.
12. Quesada-Gomez JM, Entrenas-Castillo M, Bouillon R. Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166. J Steroid Biochem Mol Biol. 2020 Sep;202:105719. doi: 10.1016/j.jsbmb.2020.105719.
13. Kyriss EM, Kanaka-Gantenbein C. Autoimmune Thyroid Disease in Specific Genetic Syndromes in Childhood and Adolescence. Front Endocrinol (Lausanne). 2020 Aug 19;11:543. doi: 10.3389/fendo.2020.00543.
14. Hirota S, Marui S, Migliari D. Does autoimmune thyroid disorder act as a predisposing factor in the development of oral lichen planus? Oral Dis. 2020 Apr 4. doi: 10.1111/odi.13339.
15. Martens PJ, Gusemann C, Verspyck A, Mathieu AC. Vitamin D’s Effect on Immune Function. Nutrients. 2020 Apr 28;12(5):1248. doi: 10.3390/nu12051248.
16. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. Nutrients. 2020 Jun 16;12(1):236. doi: 10.3390/nu1201236.
17. Dutta D, Sharma M, Aggarwal S, Mohindra B, Bhattacharya S, Kalra S. Vitamin D, Thyroid Autoimmunity and Cancer: An Interplay of Different Factors. Indian J Endocrinol Metab. 2019 Sep-Oct;23(5):507-513.
18. Kim D. The Role of Vitamin D in Thyroid Diseases. Int J Mol Sci. 2017 Sep 12;18(9):1949. doi: 10.3390/ijms18091949.

19. Vanherwegem AS, Gyselens C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. Endocrinol Metab Clin North Am. 2017 Dec;46(4):1061-1094. doi: 10.1016/j.ecl.2017.07.010.

20. Alrefaie Z, Awad H. Effect of vitamin D3 on thyroid function and de-iodinase 2 expression in diabetic rats. Arch Physiol Biochem. 2015;121(5):206-9. doi: 10.3109/13813455.2015.1107101.

21. Lowry MB, Guo C, Zhang Y, et al. A mouse model for vitamin D-induced human cathelicidin antimicrobial peptide gene expression. J Steroid Biochem Mol Biol. 2020 Apr;198:105522. doi: 10.1016/j.jsbmb.2019.105522.

22. Mascoguiri G, Mari D, Prulo S, et al. 25 Hydroxyvitamin D Deficiency and Its Relationship to Autoimmune Thyroid Disease in the Elderly. Int J Environ Res Public Health. 2016 Aug 26;13(9):850. doi: 10.3390/ijerph13090850.

23. Cakir I, Yetmis M, Dizdar OS, Baspinar O, Gokay F. The relationship between 25 hydroxy vitamin D3 and thyroid antibodies with thyroid benign-malign neoplasms. Niger J Clin Pract. 2019 Sep;22(9):1224-1228. doi: 10.4103/njcp.njcp_440_18.

24. Peng W, Wang K, Zheng R, Derwahl M. 1,25 dihydroxyvitamin D3 inhibits the proliferation of thyroid cancer stem-like cells via cell cycle arrest. Endocr Res. 2016 May;42(5):536-541. doi: 10.1016/j.endocr.2014.09.013.

25. Yildiz S, Ekinci O, Ucier R. The relationship between 25 hydroxy Vitamin D3 and thyroid antibodies with thyroid benign-malign neoplasms. Niger J Clin Pract. 2019 Sep;22(9):1224-1228. doi: 10.4103/njcp.njcp_440_18.

26. Bozdağ H, Akdeniz E. Does severe vitamin D deficiency impact obstetric outcomes in pregnant women with thyroid autoimmune? J Matern Fetal Neonatal Med. 2020 Apr;33(8):1359-1369. doi: 10.1080/08024240.2018.1517420.

27. Bozdag H, Akdeniz E. Does severe vitamin D deficiency impact obstetric outcomes in pregnant women with thyroid autoimmune? J Matern Fetal Neonatal Med. 2020 Apr;33(8):1359-1369. doi: 10.1080/08024240.2018.1517420.

28. Yavropoulou MP, Panagiotou G, Topouridou K, et al. Vitamin D receptor expression is linked to potential markers of human thyroid papillary carcinoma. J Steroid Biochem Mol Biol. 2016 May;159:26-30. doi: 10.1016/j.jsbmb.2016.02.016.

29. Danilovic DL, Ferraz-de-Souza B, Fabri AW, Santana NO, Kulcsar MA, Cernea CR, Marui S, Hoff AO. 25-Hydroxyvitamin D and TSH as Risk Factors or Prognostic Markers in Thyroid Carcinoma. PLoS One. 2016 Oct 13;11(10):e0164550. doi: 10.1371/journal.pone.0164550.

Received 27.10.2020
Revised 30.11.2020
Accepted 07.12.2020
Влияние обеспечения витамином D на аутоиммунное состояние щитовидной железы

Резюме. Актуальность. Несмотря на больший объем данных, связывающих витамин D с сердечно-сосудистой заболеваемостью, аутоиммунитетом, раком и практически каждой системой органов, взаимосвязь витамина D и щитовидной железой остается менее известным аспектом в клинической практике. Причиной активного влияния витамина D является тот факт, что рецепторы витамина D (VDR) размещены практически в каждой ткани и системе органов организма. Цель: осветить данные современной литературы о влиянии витамина D и его обеспечении на аутоиммунный статус щитовидной железы. Материалы и методы. Источниками этого обзора были опубликованные за 2015 год и ранее данные об аутоиммунных исследованиях, в которых витамин D был связан с аутоиммунным состоянием щитовидной железы. Среди ключевых данных были данные о корреляции витамина D с аутоиммунным состоянием щитовидной железы. Также приводятся данные интервенционных исследований, подтверждающих положительное влияние витамина D на аутоиммунитет щитовидной железы. Краткосрочный прием витамина D в дозах, равных дозам тиреоидных препаратов, приводит к снижению потребности в левотироксине, что подтверждается краткосрочными исследованиями.

Ключевые слова: щитовидная железа; аутоиммунитет; витамин D; обзор