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The impact of vitamin D status and supplementation on thyroid autoimmunity

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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 pleiotropic 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 through 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”.

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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, $P_z = 0.001$ for B vs. b; OR = 0.854, 95% CI 0.757–0.963, $P_z = 0.010$ 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 autoimmunity, 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*, *rs2228570*, 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_3 and T_4 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]. Calcitriol 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]. Calcitriol 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 (TPMRSS4) 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 calcitriol 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.

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Вплив забезпечення вітаміном D на автоімунний стан щитоподібної залози

Резюме. Актуальність. Попри великий обсяг даних, що пов'язують вітамін D із серцево-судинною захворюваністю, автоімунітетом, раком та практично кожною системою органів, взаємозв'язок між вітаміном D та щитоподібною залозою залишається менш відомим аспектом у клінічній практиці. Причиною активного впливу вітаміну D є той факт, що рецептори вітаміну D (VDR) розміщені практично в кожній тканині та системі органів організму. **Мета:** висвітлити дані сучасної літератури про вплив вітаміну D та його забезпечення на автоімунітет щитоподібної залози. **Матеріали та методи.** Посилання на цей огляд були визначені за допомогою пошуку в PubMed за статтями, опублікованими з 2015 року по вересень 2020 року, із використанням термінів «щитоподібна залоза» та «вітамін D». **Результати.** Зареєстровано вірогідну обернену кореляцію між антитілами до тиреоїдної пероксидази (АТ-ТПО) та вмістом 25-гідроксिवітаміну D (25(OH)D) у сироватці крові. Наявність позитивних титрів АТ-ТПО більш поширена в осіб із дефіцитом вітаміну D. У великому обсязі медичної літератури наводяться результати спостережних

досліджень, що пов'язують вітамін D з автоімунітетом щитоподібної залози. Також наводяться дані інтервенційних досліджень, що підтверджують позитивний вплив вітаміну D на автоімунітет щитоподібної залози. Короткотерміновий прийом високих доз пероральних добавок вітаміну D сприяє зменшенню титрів АТ-ТПО. Деякі поліморфізми гена VDR пов'язані зі збільшенням випадків автоімунних розладів щитоподібної залози. Дані про те, чи призводить корекція дефіциту вітаміну D при автоімунних розладах щитоподібної залози до зниження потреби в левотироксині або карбімазолі відповідно при гіпотиреозі або хворобі Грейвса, відсутні. **Висновки.** Незважаючи на великий обсяг медичної літератури з обсерваційних досліджень, в яких пов'язують вітамін D з автоімунітетом щитоподібної залози, відсутні важливі конкретні клінічні дані про вплив додаткового призначення вітаміну D на основні клінічні кінцеві точки при цих розладах. Це повинно бути основною сферою досліджень у наступному десятилітті.

Ключові слова: щитоподібна залоза; автоімунітет; вітамін D; огляд

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Влияние обеспечения витамином D на аутоиммунное состояние щитовидной железы

Резюме. Актуальность. Несмотря на большой объем данных, связывающих витамин D с сердечно-сосудистой заболеваемостью, аутоиммунитетом, раком и практически каждой системой органов, взаимосвязь между витамином 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 обеспечения на аутоиммунитет щитовидной железы. **Материалы и методы.** Источники этого обзора были определены с помощью поиска в PubMed по статьям, опубликованным с 2015 года по сентябрь 2020 года, с использованием терминов «щитовидная железа» и «витамин D». **Результаты.** Зарегистрирована достоверная обратная корреляция между антителами к тиреоидной пероксидазе (АТ-ТПО) и содержанием 25-гидроксивитамина D (25(OH)D) в сыворотке крови. Наличие положительных титров АТ-ТПО более распространено у лиц с дефицитом витамина D. В большом объеме медицинской литературы приводятся результаты наблюдательных исследований, связыва-

ющих витамин D с аутоиммунитетом щитовидной железы. Также приводятся данные интервенционных исследований, подтверждающих положительное влияние витамина D на аутоиммунитет щитовидной железы. Краткосрочный прием высоких доз пероральных добавок витамина D содействует уменьшению титров АТ-ТПО. Некоторые полиморфизмы гена VDR связаны с увеличением случаев аутоиммунных расстройств щитовидной железы. Данные о том, приводит ли коррекция дефицита витамина D при аутоиммунных расстройствах щитовидной железы к снижению потребности в левотироксине или карбимазоле соответственно при гипотиреозе или болезни Грейвса, отсутствуют. **Выводы.** Несмотря на большой объем медицинской литературы по обсервационным исследованиям, в которых связывают витамин D с аутоиммунитетом щитовидной железы, отсутствуют важные конкретные клинические данные о влиянии дополнительного назначения витамина D на основные клинические конечные точки при этих расстройствах. Это должно быть основной сферой исследований в следующем десятилетии.

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