

REVIEW

Vitamin D and Thyroid Diseases

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Summary

In this review we summarize recent opinions on the possible role of vitamin D in the risk of thyroid diseases development. It may be concluded from the available data that vitamin D deficiency, particularly levels below 12.5 ng/ml should be considered as an additional, but important risk factor for development of thyroid autoimmunity, both chronic autoimmune thyroiditis and Graves' disease. A higher risk of Graves' disease development is also associated with several polymorphisms in the gene encoding for vitamin D binding protein and for the specific receptor of active form of vitamin D – 1,25-(OH)₂D₃ in the respective target cells. Important for development of thyroid cancer appeared polymorphisms of genes encoding for vitamin D receptors and of genes encoding for the participating hydroxylating enzymes in thyroid tissue, leading to a diminished local 1,25-(OH)₂D₃ formation capacity with following alteration of antiproliferatory, antiapoptotic and prodifferentiating efficacy of the latter. Whether supplementation with high doses of vitamin D or its analogues possesses preventive or therapeutic effect is an object of intensive studies.

Key words

Vitamin D • Thyroid disease • Autoimmunity • Thyroid cancer

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Introduction

Nowadays one may encounter an increasing number of reports on the relationships between vitamin D deficiency and the risk of a number of systemic and organ diseases outside the bone system. Emphasized is especially its role in autoimmune (Agmon-Levin *et al.*

2013) and oncological diseases (De Mille 2014) and diabetes mellitus (Badenhoop *et al.* 2012), the importance of physiological saturation with vitamin D for normal fetal development during pregnancy and further postnatal life (Pérez López *et al.* 2015), the effects of vitamin D on the aging including mortality (Samefors *et al.* 2014) and its association with mental health (Kerr *et al.* 2015). In this review we tried to summarize and discuss recent opinions on the possible role of vitamin D in the risk of thyroid diseases development, as the most frequent endocrinopathies.

Physiology and pathophysiology of vitamin D saturation

Only 25(OH)D₃ (calcidiol) is being currently used in the world for clinical evaluation of the vitamin D saturation. It is considered as the real indicator of the total vitamin D stores. The 25(OH)D₃ levels are relatively stable for several days or weeks and oscillate in dependence on sun radiation rather than on vitamin D precursors intake from food. About 99 % of circulating 25(OH)D₃ is present in a bound form with vitamin D binding proteins, so that around 1 % of free vitamin D is available.

So far there is not unequivocal consensus in evaluation of physiological 25(OH)D₃ levels. Though the value 20 ng/ml is considered sufficient as concerns its skeletal effects, the values up to 30 ng/ml are still associated with manifestation of vitamin D deficiency in organs outside the bone system according to epidemiological data. The upper borderline of 25(OH)D₃ in blood from the point of view of a safe dose has not yet been established and is a subject of discussion.

Hormonal mechanism of vitamin D effects

Most of human cells is capable to exprime 1-alpha-hydroxylase (encoded by the *CYP27B1*) by which 25(OH)D₃, after its entering the cells, is further hydroxylated giving rise an active vitamin D form, 1,25-(OH)₂D₃ (calcitriol). Recent evidence, however supports the idea that circulating 1,25-(OH)₂D₃ levels in blood probably reflect only its formation in cells of proximal tubule of the kidney. The biological half-time of 1,25-(OH)₂D₃ is only 4-6 h. Its renal formation is regulated by circulating calcium and phosphate, parathormone and especially by the final product, calcitriol itself, and it is utilized preferably for bone metabolism. Other cells than those from renal tissues can express vitamin D receptor (VDR) as well as 1-alpha-hydroxylase, which allows the tissue specific up regulation of 1,25-(OH)₂D₃ formation according to their own needs.

Such a paracrine/autocrine regulation of tissue calcitriol formation, independent on parathormone, proceeds *via* different regulatory mechanisms than govern its renal formation. It may explain pleiotrophic effects of vitamin D on human organism. A necessary precondition for functioning of this non-skeletal component of vitamin D metabolism is a sufficient supply of its precursor, namely 25(OH)D₃ in the body and it may explain the negative impact of vitamin D deficiency for the whole organism. Mutation of genes encoding for tissue hydroxylases contributes significantly to cancer development. Biologically active 1,25-(OH)₂D₃ bound to special receptors penetrates to the cell nucleus. Here it gives rise to a final complex with retinoic acid, which interacts with vitamin D responsible elements in the promotor region of the regulated gene. The final effect is an activation or suppression of as many as 200-500 genes, representing about 3-5 % of the human genome. The active form of vitamin D functions here as classical hormone acting *via* nuclear receptors of the thyroid/gluco- or mineralocorticoid and other family.

With respect to the topics of this review, the most important are the genes, ensuring physiological function of the immune system, including innate as well as acquired immunity, and proteins responsible for cell growth and differentiation, antiproliferatory and/or antiphlogistic effects.

Chronic autoimmune thyroiditis

Chronic autoimmune thyroiditis is the most

frequent endocrinopathy. Using a competitive immunoassay procedure, the reported prevalence of detectable thyroid antibodies, primarily TPOAb levels, amounted 10-12 % of the healthy population. A hypochoic ultrasound pattern or an irregular echo pattern may precede TPOAb positivity in autoimmune thyroid disease and TPOAb may not be detected in about 20 % of individuals with ultrasound evidence of thyroid autoimmunity (Vanderpump 2011). In high risk groups such as older women, female with type 1 diabetes and in subjects with a positive family history, the prevalence reaches as much as 20-40 %.

The available data from studies on occurrence of vitamin D deficiency in relation to thyroid diseases mostly prove the association of vitamin D deficiency with higher incidence of autoimmune thyroiditis (Bizzaro and Shoenfeld 2015). More severe deficiency is often accompanied by thyroid hypofunction (Kivity *et al.* 2011, Tamer *et al.* 2011, Bozkurt *et al.* 2013). The levels of 25(OH)D₃ seem to be an independent factor influencing the presence of TPOAb positivity (Shin *et al.* 2014). The differences in vitamin D levels between children with autoimmune thyroiditis and healthy children are more pronounced than in adult population (Camurdan *et al.* 2012). Our own experience from examination of adult patients treated in the Institute of Endocrinology for autoimmune thyroiditis fully agrees with the data in the literature. The average initial value of 25(OH)D₃ in patients with newly onset of autoimmune thyroiditis was found in the range of a deep deficit (25(OH)D₃ – 11.4 (4.4-20.2 ng/ml), while in as many as 84 % patients the levels were lower than 10 ng/ml. In the subgroup patients with vitamin D levels below 10 ng/ml a hypofunction of the thyroid was found in 60 % at the time of diagnosis, while in patients with normal values of 25(OH)D₃ it occurred only in 20 %.

From the pathophysiological point of view chronic autoimmune thyroiditis and its forms represent organ-specific autoimmune disease. The key role in the development of autoimmune process play genetically dependent aberrant expression of HLA DR and other antigens on the thyreocyte surface, causing that these cells become prone to an autoimmune attack.

The unique immunomodulatory effect of 1,25-(OH)₂D₃ consists in influencing not only T-lymphocyte function, but also antigen presenting cells. In the experimental animals (mice) 1,25-(OH)₂D₃ stimulated fagocytosis and, on the other hand, suppressed the activity of macrophages and dendritic cells, resulting

in an decreased presentation of autoantigens. An active form of vitamin D, 1,25-(OH)₂D₃ significantly inhibited secretion of the key Th1 proinflammatory cytokines by antigen presenting cells resulting in inhibition of cytotoxic (cytotoxic) Th1 lymphocytes, and enhances Th2 cytokine (IL-4) production (Sterzl 2012).

An assumption that 1,25-(OH)₂D₃ can influence the course of autoimmune inflammation through this mechanism was confirmed experimentally. The experimental studies have proven direct protective effect of 1,25-(OH)₂D₃ in combination with suppression of an autoimmune inflammation, along with abovementioned influencing of T-lymphocytes and an impact on antigen presenting cells, especially dendritic cells.

Eliciting of such an immunomodulatory effect by using active 1,25-(OH)₂D₃ even in man supposes application of high (pharmacological) doses with undesired effects on bone remodeling and hypercalcemic states. Under development are therefore synthetic analogues of 1,25-(OH)₂D₃ with retained immunomodulatory activity, but with a reduced effect on calcium- and bone metabolism. Some of them appeared to prevent progression of autoimmune inflammation in experiment with NOD mice. Calcipotriol is recently used in human medicine in the treatment of psoriasis, and the same substance and its analogs are tested as potent antiproliferative agents on leukemia, breast and colon cancer (more details see in Wierzbicka *et al.* 2014).

The presence of 1,25-(OH)₂D₃ or its analogues in an *in vitro* system results in formation of dendritic cells with specific features: let us mention a decrease of IL 12, reduced CD80/CD86 expression and generally MHC II expression and, the most important, decreased stimulation of effector- and specific regulatory T-cells (Ferreira *et al.* 2014). These findings are recently examined under clinical condition (Nikolic and Roep 2013) consisting in an autotransfer of dendritic cells formed by peripheral monocytes in patients which were exposed *ex vivo* to high concentrations of 1,25-(OH)₂D₃ or its analogues. It appeared that immediately after the retransfer back to the patient these dendritic cells were capable to shift the immune system from attack towards a tolerance to affected cells. In spite still ambiguous and inconclusive results of the studies about association between a functional polymorphism in the vitamin D receptor (VDR) and autoimmune thyroiditis risk, it is worth to mention meta-analysis of relevant literature made recently by Feng *et al.* (2013). The authors found that the cumulative effect of VDR gene *BsmI* or *TaqI*

polymorphism in Europeans is significantly associated with autoimmune thyroiditis.

For details about the role vitamin D in the etiopathogenesis of autoimmune thyroiditis see Kivity *et al.* (2011), Effraimidis and Wiersinga (2014), Mazokopakis and Kotsiris (2014), Muscogiuri *et al.* (2014), Antonelli *et al.* (2015).

It may be concluded from the available data of both experimental and clinical studies that the values of vitamin D below 12.5 ng/ml should be considered an additional, but important risk factor for development of chronic autoimmune thyroiditis. Whether supplementation with high doses of vitamin D or its analogues possesses preventive or therapeutic effect is an object of intensive studies (Muscogiuri *et al.* 2015).

Graves' disease

Graves' disease (GD) is much more severe form of the thyroid gland autoimmunity than chronic autoimmune thyroiditis, mainly for negative impacts of high thyroid hormone levels on vital functions, which may be life threatening especially in aged people. Its occurrence is much lower in comparison to chronic autoimmune thyroiditis in normal population it is estimated 4 per 10 000 for women and 1 per 10 000 in men, but the age-specific incidence varies considerably (Vanderpump 2011).

Most of the available data point to a higher prevalence of 25(OH)D₃ deficiency also at this form of thyroid autoimmunity. More pronounced decreased levels of 25(OH)D₃ have been found mainly early after establishing of GD diagnosis (Yasuda *et al.* 2012). Higher deficit predicted later disease remission in some studies. Some authors who followed long-term development of the disease found significantly lower 25(OH)D₃ values in diseases in an active phase of GD in comparison to patients in a full remission (Yasuda *et al.* 2013). Inverse correlations were also described between 25(OH)D₃ levels and thyroid gland volume in GD patients (Yasuda *et al.* 2012).

Association of high thyroid hormone levels with low 1,25-(OH)₂D₃ level rose the question about the molecular mechanism behind it. Recent experiment with T₃-induced hyperthyroid mice revealed not only marked decrease of plasma 1,25-(OH)₂D₃, but also reduced renal mRNA expression of *CYP27B1* gene, the gene encoding for vitamin D 1-alpha-hydroxylase. This effect was independent on parathormone. Further promoter analysis

revealed that T₃ decreased the transcriptional activity of the *CYP27B1* gene through thyroid hormone receptors of both types (TR alpha and beta 1) and binding of thyroid hormone-receptor complex to DNA thyroid hormone responsive elements, in concert with retinoid X receptor. Of interest may be another finding of the authors that the negative thyroid hormone responsive elements overlap with some so called sterol regulatory elements, responsible for an opposite effect – a positive regulation of *CYP27B1* gene transcription (Kozai *et al.* 2013).

A higher risk of GD development is also associated with several polymorphisms in the gene encoding for VDR and for the specific receptor of active form of vitamin D – 1,25(OH)₂D₃ – in the respective target cells. Such polymorphisms were revealed in some populations with a higher risk of GD development, as for instance in Germany, Poland, or Egypt but not in Serbia (Ramos-Lopez *et al.* 2005, Kurylowicz *et al.* 2006, Abd El Gawad *et al.* 2012). Due to remarkable variability in individual risk polymorphisms, including their association with GD among populations, the clinical relevance of these findings is not significant. In conclusion, existing data support the idea about the role of vitamin D in GD development, but further epidemiological and especially intervention studies are needed.

Polymorphisms of genes encoding for vitamin D receptors and for vitamin D hydroxylating enzymes – relation to thyroid cancer

Important for development of thyroid cancer appeared polymorphisms of genes encoding for VDR, leading to a diminished local efficacy of 1,25(OH)₂D₃, with respect to remarkable antiproliferatory, antiapoptotic and prodifferentiating activity of the latter (Clinckspoor *et al.* 2013). Such polymorphisms were repeatedly found not only in thyroid cancers, the most common endocrine malignancy, but also have been reported to increase the risk of other tumors such as in breast, prostate, colon and others (Penna-Martinez *et al.* 2012). Similarly alterations

of 1,25-(OH)₂D₃ formation due to polymorphisms of genes encoding for the participating hydroxylating enzymes, resulting in its low levels were described in papillary, follicular as well as anaplastic thyroid cancers. The levels of 1,25-(OH)₂D₃ even correlated with cancer stages (I-IV) (Penna-Martinez *et al.* 2009, Stepien *et al.* 2010). Of great importance, emphasizing the relevance of the final hydroxylating step in the biosynthesis of the biologically active hormone, is the simultaneous absence of any association of thyroid cancer diagnosis or disease stage with 25(OH)D₃ levels, reported in most of these studies. In other words, thyroid cancer development does not depend probably on the total saturation with vitamin D (Jonklaas *et al.* 2013).

Conclusions

Based on our experience and data from the literature it may be expected that significant vitamin D deficiency would occur in the most of the subjects suffering from various forms of thyroid autoimmunity. The question arises, how to react to this situation. Whether to recommend sunning, bearing however many risks (skin aging, provoking of inflammation or even cancerogenic effect) and/or food supplements containing vitamin D precursors, or pharmacological substitution. Vitamin D supplementation should be offered to the deficient patients, the current opinion considers as optimal and at the same time safe a serum blood level of 25(OH)D₃ within the range 30-40 ng/ml (75-100 nmol/l). In the most valid studies such levels are believed to possess a number of beneficial effects. Whether supplementation with high doses of vitamin D or its analogues has preventive or therapeutic effect on thyroid autoimmunity is a subject of intensive studies.

Conflict of Interest

There is no conflict of interest.

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