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CLINICAL STUDY

Vitamin D insufficiency is not associated with thyroid autoimmunity in Slovak women with Hashimoto´s disease

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ABSTRACT

The role of vitamin D (VD) in the etiopathogenesis of autoimmune diseases (AI) is extensively studied. However, its association with autoimmune thyroid disease (AITD) is still controversial.

AIM of this study was to assess the relationship between the vitamin D status and thyroid autoimmunity in Slovak premenopausal women with newly diagnosed AITD.

SUBJECTS AND METHODS: This prospective case-control study included 57 women with AITD and 41 age- and BMI-matched controls. All subjects were examined for summer and winter serum 25(OH)D, thyroid autoantibodies (a-TPO, a-TG), freeT4 and TSH concentrations. Thyroid volume was measured by ultrasound.

RESULTS: There were no significant differences in serum 25(OH)D between AITD and control groups. No significant correlation between 25(OH)D and thyroid autoantibodies was found either in the whole cohort or in AITD women. The prevalence of vitamin D insufficiency was 60.31 % in AITD women and 52.5 % in the control group. No significant association between VD and thyroid autoantibodies, thyroid hormones and thyroid volume was detected in this study.

CONCLUSION: Authors conclude that VD insufficiency is common in Slovak premenopausal women independently of the presence of AITD. Vitamin D insufficiency is not associated with thyroid autoimmunity in patients with early diagnosis of AITD *(Tab. 3, Ref. 31).* Text in PDF *www.elis.sk*

KEY WORDS: vitamin D, autoimmune thyroid disease, thyroid autoantibodies.

Introduction

Vitamin D is a steroid prohormone regulating calcium-phosphate homeostasis and bone metabolism. Recent studies have documented its importance in other biological processes such as cell growth and differentiation, cell maturation, apoptosis, etc. (1, 2). In addition to these multiple effects, vitamin D has been described as a potent modulator of the immune response. Its active form, calcitriol (1,25-hydroxyvitamin D), binds to the nuclear vitamin D receptor (VDR) which is expressed in various immune cells such as B and T lymphocytes, monocytes, macrophages, as well as in dendritic cells (3, 4).

Several studies have demonstrated an association between vitamin D deficiency and various organ-nonspecific as well as organ-specific autoimmune diseases including systemic connective tissue disorders, inflammatory bowel diseases, type 1 diabetes mellitus, Addison´s disease and autoimmune thyroiditis (5, 6).

Autoimmune thyroid disease (AITD) is the most common organ-specific autoimmune disorder characterized by the presence of antibodies against thyroid-specific components such as thyroglobulin (a-TG), thyroid peroxidase (a-TPO), thyrotropin receptor antigen (aTSHr) and sodium iodine symporter (NIS) in addition to a typical ultrasound picture. Among its clinical manifestations, Hashimoto´s thyroiditis (HT) is the most prevalent disease affecting approximately 5 % of the general population (7, 8). Simultaneously, HT is the most frequent cause of primary hypothyroidism in countries without iodine deficiency (8). The role of vitamin D as an environmental etiopathogenic factor in HT has been extensively studied in the past twenty years. However, the data are still controversial.

Several studies conducted in the past decade have documented that the low vitamin D status is associated with positivity of antithyroid antibodies, especially with a-TPO positivity, or with various degrees of thyroid insufficiency (9, 10). On the other hand, some researchers did not detect any relationship between vitamin D and thyroid autoimmunity or its function (11). The questions as to whether these discrepancies are related to different vitamin D status in various countries or other environmental and genetic factors, as well as those addressing the causality for that relationship, remain to be elucidated.

We hypothesized that the vitamin D insufficiency can be more prevalent in women with AITD as compared to healthy controls and might be related to higher serum thyroid autoan-

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tibodies concentration. The aim of this study was to assess the relationship of the vitamin D status to thyroid autoimmunity and function in Slovak premenopausal women and to compare the prevalence of vitamin D insufficiency in women with AITD and healthy controls.

Materials and methods

Altogether, 98 women in reproductive age were enrolled in this prospective observational case-control study. The average age of all subjects was 31 ± 0.9 years. All participants were divided into two groups based on the presence of autoimmune thyroid disease (AITD).

The first group included 57 subjects fulfilling the criteria for the diagnosis of AITD and were euthyroid, i.e., their hormonal status was indicative of normal thyroid function. None of them required replacement therapy with levothyroxine. The mean age of AITD group was 31 ± 0.9 years. The control group consisted of 41 healthy women with mean age of 31.7 ± 1.1 years.

Exclusion criteria for all women included morphological and/or functional thyroid abnormalities, polycystic ovary syndrome or other diseases associated with menstrual cycle disturbances and diabetes mellitus. All subjects had normal cardiac, kidney and liver functions and they did not take any medication that could affect the vitamin D serum concentration or calcium metabolism.

The study was approved by the Ethical Committee of the Hospital Šaca, Slovakia and all participants signed a written informed consent.

Blood samples were collected from all subjects for measuring serum 25(OH)D, total serum calcium, phosphate and PTH (parathyroid hormone) concentrations. Summer and winter measurements of 25(OH)D were taken in all subjects. Serum vitamin D levels obtained during the period from May to October were interpreted as summer VD levels (25(OH)D-s), while VD concentrations obtained during the period from November to April were considered as winter values (25(OH)D-w).

All subjects involved in the study were evaluated for thyroid autoimmunity and thyroid function. Serum autoantibodies against thyroperoxidase (a-TPO), thyroglobulin (a -TG), together with serum free thyroxine (fT4) and serum TSH levels were determined in all women participating in the study.

Thyroid ultrasonography was performed by the same endocrinologist using two-dimensional ultrasound device (ALOKA prosound α6) with a linear transducer (12 MHz). Thyroid volume (TV) was calculated as a sum of volumes of both right and left thyroid lobes. The volume of thyroid lobe was calculated using a formula as follows: length (mm) x width (mm) x 0.479. Hypoechoic thyroid gland on ultrasound together with an elevation of serum a-TPO and/or a-TG concentration represented the criteria for including women in the AITD group.

Laboratory investigations

Serum thyroid autoantibodies, TSH and PTH levels were determined by electrochemiluminescence immunoassay method (ECLIA) using kits Roche Diagnostics, Germany. Also, ECLIA was used to measure the serum 25(OH)D level, serum calcium and phosphate concentration.

Based on criteria reported by Holick et al, serum 25(OH)D levels lower than 50 nmol/l were classified as vitamin D deficiency, serum levels between 50 and 75 nmol/l as vitamin D insufficiency, and those of 75 nmol/l or higher were considered to be sufficient (1).

Statistical analysis

The SAS JMP version 13.0.0 (USA) software was used for statistical evaluation. Data are presented as mean ± SEM regardless of their distribution. For normally distributed variables Student´s T test was used to compare means between groups, whereas for non-normally distributed data, the non-parametric Mann-Whitney test was used to compare means among two groups. Linear regression analysis was used to detect correlations between variables. Values were considered to be statistically significant at $p \leq 0.05$. Differences in the prevalence of vitamin D insufficiency between two groups were assessed using χ^2 test.

Logistic regression analysis was applied for determining a potential association between vitamin D status and thyroid autoimmunity.

Results

The mean values of measured parameters in both control and age-matched AITD groups are presented in Table 1.

There were no significant differences in age and BMI between AITD and control groups. As expected, the patients with AITD had higher serum levels of a-TG (0.005), a-TPO (0.0001) and a slightly, but significantly higher serum TSH concentration (0.03) as compared to healthy subjects. The groups did not differ in thyroid volume, serum calcium, phosphate and PTH (Tab. 1). Also, significant differences were found neither in serum 25(OH) D-s (74.04 + 3.3 vs 73 + 28 nmol/l, p = 0.8) nor in serum 25(OH) D-w (56.2 + 3.1 vs 55.7 + 2.53 nmol/l, p = 0.9) between AITD women and controls.

Tab. 1. Mean values of measured parameters in the control group and group of women with AITD.

Parameter	Controls	AITD	p
age	31.65±1.06	30.97±0.9	0.6
BMI (kg/m^2)	25.73±0.9	23.85±0.74	0.1
TSH (mIU/l)	1.9±0.2	2.46±0.15	**0.03**
fT4 (pmol/l)	11.11±0.23	11.64±0.2	0.08
a-TPO (kIU/l)	1.05±19.62	120.76±16,3	**0.0001**
a-Tg (kIU/l)	0.67±25.08	93.32±20.83	**0.005**
25(OH)D -s (nmol/l)	74.04±3.3	73±2.8	0.8
25(OH)D-w (nmol/l)	56.2±3.1	55.7±2.53	0.9
Ca (mmol/l)	2.37±0.02	2.39±0.02	0.23
P (mmol/l)	1.1±0.04	1.13±0.04	0.6
PTH (ng/l)	37.4±2.4	37.4±2.0	0.999
TV (ml)	15.9±0.8	17.3±0.65	0.18

BMI – body mass index, TSH – thyroid stimulating hormone, fT4 – free thyroxine, a-TPO – antibodies against thyroperoxidase, a-TG – antibodies against thyroglobulin, 25(OH)D-s – serum concentration of 25 -hydroxyvitamin D in summer, 25(OH) D-w – serum concentration of 25 hydroxyvitamin D in winter, Ca – serum calcium concentration, P – serum phosphate concentration, PTH – parathyroid hormone, TV thyroid volume

Tab. 2. Correlations between 25(OH)D versus BMI and thyroid parameters in the whole cohort and AITD group.

All subjects	BMI	TSH	fT4	a-Tg	a-TPO	TV
VD-s R2	**0.2**	0.003	0.12	0.005	0.006	0.002
p	**0.001**	0.6	0.8	0.5	0.4	0.3
VD-w R2	**0.1**	0.001	0.01	0.01	0.003	0.002
p	**0.02**	0.89	0.24	0.4	0.9	0.2
AITD subjects						
VD-s R2	0.05	0.005	0.13	0.008	0.009	0.01
p	0.078	0.7	0.9	0.5	0.4	0.5
VD-w R2	0.2	0.002	0.01	0.01	0.004	0.03
p	0.4	0.8	0.17	0.4	0.9	0.57

BMI – body mass index, TSH – thyroid stimulating hormone, fT4 – free thyroxine, a-TPO – antibodies against thyroperoxidase, a-TG – antibodies against thyroglobulin, VD-s – summer vitamin D, VD-w – winter vitamin D, AITD – autoimmune thyroid disease

In the whole cohort, significant negative correlations between VD-s and BMI ($R^2 = 0.2$, $p = 0.001$) as well as between VD-w and BMI ($R^2 = 0.1$, $p = 0.02$) were demonstrated. On the other hand, no significant correlation was found between either 25(OH)D-s or 25(OH)D-w and thyroid autoantibodies (Tab. 2). In addition, VD-s and VD-w did not correlate with thyroid volume in the whole cohort of participants.

For the AITD group, no significant relationship of BMI with either serum VD-s or VD-w concentrations was demonstrated. We found no statistically significant correlation between VD-s/VD-w and thyroid autoantibodies (74.04 ± 3.3 vs 73 ± 2.8 nmol/l for VD-s and 56.2 ± 3.1 vs 55.7 ± 2.53 nmol/l for VD-w, respectively) (Tab. 2).

The whole cohort of participants was divided into two groups according to serum 25(OH)D-s levels. The first group included all women with serum 25(OH)D levels being lower than 75 nmol/l (VD insufficient), while the second group consisted of all subjects with serum 25(OH)D-s ≥ 75 nmol/l (VD normal). In the control group, only 3 of all subjects had their serum 25(OH)D concentrations in the normal range. Therefore, we did not proceed with subjecting 25(OH)D-w levels to further statistical analysis.

The prevalence of vitamin D insufficiency was 60.31 % (in 35 of 58 women), the prevalence among controls was 52.5 % (in 21 of 40 women). The difference did not reach statistical significance (p = 0.4).

As expected, women with VD insufficiency had higher BMI as compared to VD-sufficient women (p = 0.0002) (Tab. 3).

There were no statistically significant differences in serum a-TG (75 ± 22 vs 32.2 ± 25 kIU/l; p = 0.17) and a-TPO (88.3 ± 18.2 vs 50 ± 21 kIU/l; p = 0.13) concentrations between groups, despite the clear tendency to higher levels in VD-s-insufficient women. The same tendency was observed when dividing AITD subjects according to VD-s levels. As compared to controls, the 25(OH)D-s insufficient AITD women had higher a-TG levels (141.8 ± 27 vs 86.4 ± 34 kIU/l; p = 0.2) and a-TPO levels (116.3 ± 34 vs 60.9 ± 44 kIU/l; p = 0.3), although the differences did not reach the statistical significance (Tab. 3).

Using logistic regression analysis, we did not confirm any significant association between AITD and 25(OH)D-s in the whole cohort (OR = 0.8). Also, there was no significant association of vitamin D insufficiency with thyroid autoantibodies (OR = 0.15).

Tab. 3. The mean values of measured parameters in vitamin D-insufficient women and VD-normal women.

Parameter	All subjects			AITD		
	VD insuf. n = 56	VD normal n = 42	p	VD insuf. n = 36	VD normal n = 22	p
BMI (kg/m2)	26.4±0.7	22.2±0.8	**0,0002**	24.6±0.7	22.6±0.9	**0.08**
TSH (mIU/l)	2.3±0.2	2.2±0.2	0,8	2.6±0.2	2.3±0.2	0.3
fT4 (pmol/l)	11.4±0.2	11.4±0.2	0,9	11.6±0.3	11.7±0.4	0.9
a-TG (kIU/l)	75±22	32.2±25	0,17	141.8±27	86.4±34	0.2
a-TPO (kIU/l)	88.3±18.2	50±21	0,13	116.3±34	60.9±44	0.3

VD – vitamin D, BMI – body mass index, TSH – thyroid stimulating hormone, fT4 – free thyroxine, a-TPO – antibodies against thyroperoxidase, a-TG – antibodies against thyroglobulin

Discussion

In this study, we aimed to evaluate the relationship between the vitamin D status and thyroid autoimmunity in the population of premenopausal Slovak women with newly diagnosed AITD without thyroid dysfunction. Furthermore, we compared the prevalence of vitamin D insufficiency between premenopausal women with and without AITD in summer and winter measurements. The reference value for vitamin D concentration below 75 nmol/l was considered as vitamin D insufficiency (1).

The prevalence of vitamin D insufficiency in the patients with AITD was 60.31 % in summertime and higher in the wintertime. Because only 3 of all women had VD-w concentrations in normal range, we did not proceed with statistical evaluation of the groups. There were no significant differences between AITD and control group, in which the prevalence of VD insufficiency in the summertime was also high (52.5 %). These results are consistent with some previously published papers. Botelho et al demonstrated similar serum vitamin D concentrations in patients with HT and control group (12). Another study found differences neither in vitamin D deficiency nor in serum 25(OH)D levels between patients with AITD and healthy subjects (13). In their longitudinal study, Effraimidis et al found no statistically significant difference in the levels of VD in subjects with newly diagnosed a-TPO positivity as compared to controls. Authors concluded that vitamin D deficiency was not associated with the early stages of thyroid autoimmunity (11).

Recently published paper from Romania also showed results demonstrating that VD deficiency was high in both AITDs and controls (67 % vs 72 %), which however was not statistically significant (p = 0.464). These data are in agreement with our results and support our finding of high prevalence of VD deficiency in AITDs but also in controls (14). In addition, the study of Kivity et al observed that the prevalence of VD deficiency was similar between hypothyroid

patients with AITD and healthy subjects without AITD. However, in this study, anti-thyroid antibodies were more frequently elevated in patients with VD deficiency (15). Although our results indicate a tendency to higher titers of antithyroid antibodies in VD-insufficient women, this relation was very weak and did not reach statistical significance.

On the other hand, there are many studies that yielded opposite results. Unlike the current study, Turkish authors demonstrated that the prevalence of VD deficiency was higher (76 %) in HT patients than in the controls (35 %) (16). Also, another study identified lower 25(OH)D levels in subjects with HT when compared to age- and sex-matched controls (17).

In the present study, we did not confirm a significant correlation between serum VD levels and thyroid autoantibodies. Moreover, using logistic regression analysis we did not detect any association between vitamin D insufficiency and thyroid autoimmunity. There was also no significant association of VD levels with thyroid functional parameters such as serum fT4 and TSH concentrations.

In the past years, several studies have investigated the circulating levels of VD and their relation to thyroid autoimmunity in patients with AITD. Although some of them found a negative correlation between serum 25(OH) and anti-TPO antibodies, others did not demonstrate such a relationship (18–20). A weak association between VD insufficiency and AITD was identified in a study from India (21), while no correlation was observed between vitamin D and thyroid autoantibodies in Thai subjects (22). However, two studies from Korea demonstrated that low VD status was significantly associated with thyroid autoimmunity and dysfunction in the Korean population, especially in premenopausal women (23, 24). These findings are not in line with our results.

Recently two meta-analytic studies on the association of vitamin D and AITD were published. Wang et al analyzed data from twenty case-control studies, demonstrating that as compared to controls, AITD patients had lower levels of 25OHD and were more likely to be deficient in vitamin D. This study summarized that VD deficiency is prevalent in AITD patients and may play a role in the development of autoimmune thyroiditis (25). The question as to whether vitamin D deficiency can be a cause or consequence of AITD remains still unclear. In the second meta-analysis, serum vitamin D levels were significantly lower in hypothyroid patients, namely those with AITD and HT, as compared with healthy subjects (26). However, the data are still unconvincing, and do not allow to postulate a clear conclusion.

Finally, our study did not observe any association between vitamin D status and thyroid volume, which is in agreement with the study of Botelho et al (12) but different from another study that reported a significant negative correlation between VD insufficiency and TV patients with Graves disease, i.e., not in those with HT (27). In our study, there was also no significant correlation of vitamin D levels with serum concentration of FT4, TSH or PTH.

The explanation of these controversial results regarding the relationship between vitamin D status and Hashimoto´s thyroiditis, is considerably problematic. The most important explanation might be associated with the fact, that majority of Slovak women were VD insufficient, not only in winter, but also in the summertime. This could be the main factor possibly distinguishing the Slovak female population from women living in southern countries. Because almost all women included in the present study were vitamin D insufficient during wintertime, we did not use winter data for statistical analysis. Other factors such as sun exposure, diet, smoking, physical activity, etc., may participate in achieving different results (28). However, we did not take into account these factors, which can be one of several limitations of this study. The generally known negative correlation between BMI and VD concentrations could represent clear evidence for this consideration. VD deficiency is a common finding in obese subjects (29) and screening of VD levels in the obese population is recommended by some authors (30, 31).

Another limitation of this study lies in the fact that the study was performed during COVID-19 pandemic, i.e., the epidemic restrictions might partially influence the VD status in many of AITDs and control subjects.

Conclusion

The present study showed that vitamin D insufficiency is not associated with AITD in the population of Slovak premenopausal women. This study also demonstrated a high prevalence of vitamin D insufficiency in our female population regardless of the presence of autoimmune thyroid disease. We confirmed a significant negative correlation between vitamin D concentration and BMI, but found no correlation of vitamin D with parameters of thyroid autoimmunity or thyroid hormones. Thus, the relationship between VD status and AITD remains still controversial.

Learning points

- No significant differences in serum vitamin D concentration between AITD women and controls were observed.
- Vitamin D concentration did not correlate with thyroid autoantibodies in the AITD group and whole cohort.
- There was no association between vitamin D and thyroid volume in AITD patients.

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