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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Relationship between low vitamin D levels with Hashimoto thyroiditis

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SUMMARY

Introduction/Objective Vitamin D not only plays a role in calcium and phosphorus metabolism, but also has antiproliferative, prodifferentiation, anti-inflammatory and immunomodulatory effects.
The aim of this study was to investigate the association between vitamin D deficiency in individuals with autoimmune Hashimoto's thyroiditis.

Methods A total of 156 patients were enrolled and divided into two groups. First group included 108 patients with 25 (OH) D insufficiency, and second included 48 individuals with normal 25 (OH) D levels. All participants underwent a detailed clinical examination, laboratory tests for thyroid function [T3, fT4, TSH, thyroid antibodies (TPO-Ab, and TG-Ab)], as well as ultrasound scanning (thyroid volume and Doppler characteristics).

Results The patients with vitamin D insufficiency (n = 108 (69.2%)) were predominantly female and had a higher body mass index than the patients with normal vitamin D levels. The group with vitamin D insufficiency had statistically significantly higher TSH levels. The prevalence of positive thyroid antibodies was higher in the vitamin D insufficiency group, while thyroid volume, superior thyroid artery, and inferior thyroid arteries resistance index, as well as the prevalence of positive circular dichroism signals, were significantly higher in the vitamin D insufficiency group. Out of the 156 subjects, 44 were diagnosed with thyroiditis (28.2%). The mean serum level of 25 (OH) D was statistically notably lower in patients with thyroiditis (20.23 ± 8.10 ng/mL) than in the group without thyroiditis (25.44 ± 8.38 ng/mL), $p < 0.001$.

Conclusion There was an association between vitamin D insufficiency and hypothyroidism in subjects with Hashimoto's thyroiditis.

Keywords: vitamin D; insufficiency; Hashimoto's thyroiditis

INTRODUCTION

The vitamin D group consists of several related cholesterol-derived steroid compounds, the most important of which are vitamins D2 and D3. Vitamin D2 is a substituted part of vitamin D from foods and dietary supplements, while vitamin D3 is formed in the skin from 7-dehydrocholesterol under the influence of UVB from the solar spectrum. Thus, its synthesis is influenced by various factors such as skin pigmentation, lifestyle, etc. Vitamin D is synthesized as a biologically inactive precursor and exerts its physiological effects after two metabolic hydroxylation reactions [1, 2].

The main roles of vitamin D are the maintenance of calcium and phosphate homeostasis in the body as well as bone metabolism (deposition and resorption). In addition, vitamin D has been observed to play an important role in other diseases (autoimmune, malignancy, infectious and cardiovascular diseases) due to its binding to vitamin D receptor [3, 4].

Vitamin D supplementation plays a significant role in reducing inflammatory processes and suppressing the progression of autoimmune diseases in the treatment of obesity-related diseases (such as diabetes mellitus), in which obese people are frequently deficient in vitamin D [5–8].

Chronic lymphocytic thyroiditis (HT) is an autoimmune disease of the thyroid gland in which there is a gradual deterioration of the tissue of the gland itself. The incidence of HT is increasing in the world. In the early stages of thyroiditis, symptoms may be mild or even imperceptible, so the disease often goes undetected. The potential health, social, and/or economic benefits would likely be greater if diagnosis was not delayed. Diagnosis is based on laboratory indicators (hormone status and presence of thyroid antibodies) [9].

The relationship between vitamin D and autoimmune thyroid diseases has not been adequately elucidated. Therefore, several studies have been conducted to investigate the effects of serum vitamin D deficiency on autoimmune thyroid diseases and vitamin D supplementation in the prevention and treatment of these diseases, and conflicting results have been obtained [10, 11].

The results of some studies do not indicate an association between serum vitamin D deficiency and autoimmune thyroid disease [12, 13]. Other studies have found an association and have shown that low serum vitamin D levels in people with autoimmune thyroid disease lead to elevated TSH levels as well as increased anti-thyroid antibodies, goiter, and abnormal function [14, 15].

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The incidence of HT is increasing worldwide, and it is considered the most common autoimmune thyroid disease [16]. Given the multifactorial pathogenesis, a number of studies have been conducted linking genetic and other factors leading to the disease. Antiproliferative and immunomodulatory roles of vitamin D, as well as the presence of vitamin D receptor in most immune cells, are thought to play an important role in autoimmune thyroid diseases [17, 18].

The aim of this study was to analyze the relationship between vitamin D deficiency and thyroid function and its morphological features, anti-thyroid antibody levels, and the incidence of Hashimoto's thyroiditis.

METHODS

In this cross-sectional study, 156 medical records of patients who visited the Institute for Health Protection of Workers "Medical System Belgrade" in Belgrade as part of the annual systematic review from March 2019 to September 2020 were evaluated. The study was approved by the MSB Ethics Committee and was in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. A total of 156 patients were enrolled and divided into two groups. First group included 108 patients (69.2%) with 25 (OH) D insufficiency (< 30 ng/ml), and second included 48 individuals (30.8%) with normal 25 (OH) D levels (≥ (30 ng/ml) [4]. All participants underwent a detailed clinical examination, laboratory tests for thyroid function, as well as ultrasound scanning. Patients underwent testing for thyroid function T3, fT4, TSH, thyroid antibodies (TPO-Ab, and TG-Ab) and serum 25 (OH) D levels. In addition, all patients underwent thyroid ultrasonography to determine thyroid volume, Doppler pattern of signal intensity, and peak systolic velocity (PSV) and resistance index (RI) of the superior thyroid arteries (ATS) and inferior thyroid arteries (ATI).

The study included a total of 156 patients, 44 with HT (28.2%) and 112 without HT (71.8%), according to the presence of thyroid antibodies. The diagnosis of 44 patients with thyroiditis was based on TPO-Ab (> 100 mIU/L) and / or TG -Ab positivity (> 70 mIU/L) [4]. In addition, all subjects were divided into three groups according to thyroid status. The first group consisted of patients with overt hypothyroidism with serum TSH > 10 mIU/L and fT4 < 10.04 pmol/L or patients receiving levothyroxine regardless of their thyroid function status. The second group consisted of patients with subclinical hypothyroidism in whom serum levels of fT4 were between (10–24.97 pmol/L) and serum levels of TSH were between (4–10 mIU/L). The third group consisted of euthyroid patients with normal serum levels of fT4 and TSH (0.25–4.0 mIU/L).

Serum T3, fT4 and TPO Ab, TG Ab were tested by radioimmunoassay, while TSH were measured with a fluoroimmunometric assay (DELFIA). Electro-chemiluminescence binding assay (ECLIA) was used for 25 (OH) D level.

Thyroid ultrasound examinations were performed using a Toshiba aplio XG ultrasound scanner (Canon Medical Systems Corporation, Otawara, Tochigi, Japan) with a 12 MHz linear transducer.

Patients with metabolic bone disease, hyperparathyroidism, renal and liver disease, as well as patients taking medications that could affect vitamin D metabolism were excluded from the study.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA) and MedCalc Version 11.4.2 (MedCalc Software Ltd., Ostend, Belgium). Comparison of categorical variables between groups was performed with the χ^2 test. Continuous variables are expressed as mean ± standard deviation. Student's t-test and single factorial ANOVA were used to compare continuous variables between two or more groups when normally distributed, as well as the Kruskal–Wallis test for ordinal data and the Mann–Whitney U test without normal distribution. Pearson's correlation analysis was performed to investigate the correlation between vitamin D and biochemical parameters. $p < 0.05$ was considered statistically significant for all tests.

RESULTS

The study included a total of 156 subjects [108 females (69.2%) and 48 males (30.8%)]. The mean age was 46.04 years, and the mean body mass index (BMI) was 26.2 kg/m^2. The mean serum level of 25 (OH) D was 23.97 ng/mL. The prevalence of vitamin D insufficiency was 63.5% respectively.

The patients with vitamin D insufficiency (n = 108) (69.2%) were predominantly female and had a higher BMI than the patients with normal vitamin D levels. The group with vitamin D insufficiency had statistically significantly higher TSH levels. The prevalence of positive thyroid antibodies was higher in the group with vitamin D insufficiency. Thyroid volume determined by ultrasound was statistically notably higher in the group with vitamin D insufficiency, as was the prevalence of Doppler signal positivity. The PSV of the ATS and ATI was significantly lower, while the RI of the ATS and ATI was significantly higher in the vitamin D insufficiency group compared with the control group.

There were no statistically significant differences in the concentrations of T3, fT4, TPO-Ab, TG-Ab, and age between the group with normal and insufficient vitamin D levels (Table 1).

Of 156 respondents, 44 (or 28.2%) had thyroiditis, while 112 (or 71.8%) did not have thyroiditis. The patients with thyroiditis were predominantly female and had a higher BMI. The mean serum 25 (OH) D level in patients with thyroiditis (20.23 ± 8.10 ng/ml) was statistically significantly lower compared with the group without thyroiditis (25.44 ± 8.38 ng/ml) $p < 0.001$. The level of fT4 was significantly lower in the thyroiditis group, while the concentrations of TSH, TPO-Ab, TG-Ab, were higher in the thyroiditis group, which was expected. Thyroid volume was statistically significantly higher in the thyroiditis group, as was the prevalence of Doppler signal positivity. The PSV of ATS and ATI, as well as the RI of ATS and ATI were

statistically significantly higher in the thyroiditis group than in the control group (Table 2, Figure 1).

Table 1. Laboratory and ultrasound characteristics of the thyroid gland in subjects with insufficiency and normal 25 (OH) D levels

Parameters	Insufficiency 25 (OH)D < (30 ng/ml) [n = 108]	Normal 25 (OH)D ≥ (30 ng/ml) [n = 48]	p-value
Age(years)	45.95 ± 9.89	46.23 ± 10.16	0.874
Female sex (n)	**85 (78.7%)**	**23 (47.9%)**	**< 0.001**
BMI (kg/m^2)	**27.3 ± 4.1**	**25.3 ± 3.3**	**0.002**
T3 (nmol/L)	1.79 ± 0.29	1.72 ± 0.56	0.431
fT4 (pmol/L)	13.56 ± 5.74	14.82 ± 3.88	0.827
TSH (μIU/ml)	**4.58 ± 3.88**	**3.05 ± 2.90**	**0.020**
TG-Ab (IU/ml)	99.3 ± 327.7	54.4 ± 107.1	0.113
TPO-Ab (IU/ml)	32.35 ± 87.52	41.01 ± 118.20	0.186
Prevalence of TPO-Ab or TG-Ab positivity(n)	**37 (34.3%)**	**7 (14.6%)**	0.02
Thyroid volume (ml)	9.97 ± 1.03	9.69 ± 0.94	0.028
Prevalence of Doppler signal positivity(n)	19 (17.6%)	7 (14.6%)	0.031
PSV ATS (cm/s)	30.42 ± 7.44	33.18 ± 6.62	0.022
PSV ATI (cm/s)	31.58 ± 6.93	32.84 ± 6.21	0.045
RI ATS (mean ± SD)	0.673 ± 0.05	0.612 ± 0.06	0.002
RI ATI (mean ± SD)	0.702 ± 0.07	0.643 ± 0.06	0.005

25 (OH)D – 25 hydroxyvitamin D; BMI – body mass index; T3 – triiodothyronine; T4 –thyroxine; fT4 – free thyroxine; TSH – thyroid-stimulating hormone; TG-Ab – thyroglobulin antibody; TPO-Ab – thyroid-peroxidase antibody; PSV ATS – peak systolic velocity-*arteria thyreoidea superior*; PSV ATI – peak systolic velocity *arteria thyreoidea inferior*; RI ATS – resistant index *arteria thyreoidea superior*; RI ATI – resistant index *arteria thyreoidea inferior*

Table 2. Laboratory and ultrasound characteristics of the thyroid gland in subjects with and without thyroiditis

Parameters	With thyroiditis n = 44	Without thyroiditis n = 112	p-value
Age (years)	46.29 ± 9.40	45.94 ± 10.19	0.840
Female sex (n)	**35 (79.5%)**	**73 (65.2%)**	**< 0.001**
BMI (kg/m^2)	**27.8 ± 3.5**	**24.3 ± 2.4**	**0.001**
25 (OH)D (ng/ml)	**20.23 ± 8.10**	**25.44 ± 8.38**	**< 0.001**
T3 (nmol/L)	1.81 ± 0.32	1.76 ± 0.41	0.509
fT4 (pmol/L)	**11.78 ± 6.23**	**14.79 ± 4.58**	**0.025**
TSH (μIU/ml)	**6.41 ± 4**	**3.20 ± 3.01**	**< 0.001**
TG-Ab (IU/ml)	**321.67 ± 524.23**	**15.69 ± 17.21**	< 0.001
TPO-Ab (IU/ml)	111.60 ± 159.96	4.43 ± 4.52	< 0.001
Thyroid volume (ml)	10.10 ± 1.02	9.65 ± 0.93	0.016
Prevalence of Doppler signal positivity (n)	19 (43.2%)	7 (6.2%)	< 0.001
PSV ATS (cm/s)	35.33 ± 8.21	30.15 ± 7.25	0.001
PSV ATI (cm/s)	36.29 ± 9.42	33.58 ± 8.69	0.02
RI ATS (mean ± SD)	0.828 ± 0.06	0.698 ± 0.06	0.001
RI ATI (mean ± SD)	0.794 ± 0.06	0.685 ± 0.05	0.001

25 (OH)D – 25 hydroxyvitamin D; BMI – body mass index; T3 – triiodothyronine; T4 – thyroxine; fT4 – free thyroxine; TSH – thyroid-stimulating hormone; TG-Ab – thyroglobulin antibody; TPO-Ab – thyroid-peroxidase antibody; PSV ATS – peak systolic velocity- *arteria thyreoidea superior*; PSV ATI – peak systolic velocity *arteria thyreoidea inferior*; RI ATS – resistant index *arteria thyreoidea superior*; RI ATI – resistant index *arteria thyreoidea inferior*

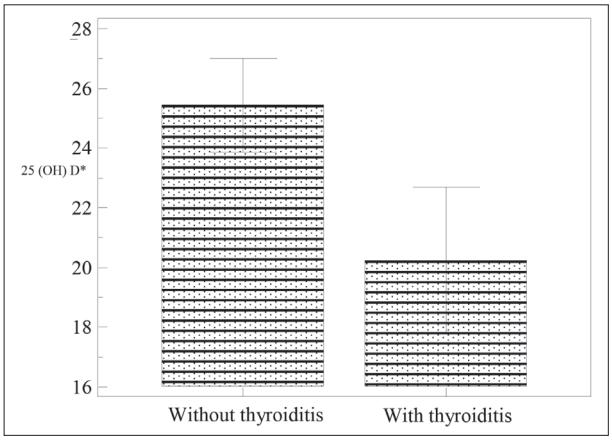

Figure 1. Concentrations of 25 (OH) D in subjects with and without thyroiditis;

*titer 25 (OH) D (ng/ml)

In terms of thyroid function, all subjects were divided into three groups. The first group consisted of patients with overt hypothyroidism, in whom serum levels of TSH > were 10 mIU/L and fT4 < were 10.04 pmol/L, or patients who received levothyroxine regardless of the status of thyroid function [40 patients (25.6%)]. The second group consisted of patients with subclinical hypothyroidism, in whom serum fT4 levels ranged from 10 to 24.97 pmol/L, and elevated serum TSH levels of 4–10 mIU/L (13 patients (8.3%)). The third group consisted of euthyroid subjects with normal serum fT4 and TSH levels (0.25–4 mIU/L) (103 subjects (66%)).

There was a statistically significant difference in 25 (OH) D levels between the group of euthyroid subjects (25.11 ng/ml) and the group with overt hypothyroidism (21.07 ng/ml) (p = 0.04). There was no statistically significant difference in the 25 (OH) D level between the group of euthyroid and subclinical hypothyroid patients (23.85 ng/ml) and between the subclinical hypothyroid patients and the patients with overt hypothyroidism (Table 3).

The mean thyroid volume was statistically significantly higher in the group of patients with overt hypothyroidism than in euthyroid patients, while the prevalence of Doppler signal positivity was higher in the groups with subclinical and overt hypothyroidism than in euthyroid patients. (Table 3, Figure 2)

Serum 25 (OH) D concentrations were significantly negatively correlated with serum TSH levels (r = - 0.284, p < 0.001), and BMI (r = - 0.228, p = 0.01), suggesting that lower 25 (OH) D concentration values were associated with subclinical, or overt hypothyroidism, as well as with obese people (Tables 1 and 3).

DISCUSSION

In this study, the vitamin D insufficiency group was predominantly female, with higher BMI, higher TSH levels. The 25 (OH) D level was significantly lower in the group with HT and in subjects with overt hypothyroidism compared

Table 3. Biochemical and ultrasound characteristics of the thyroid gland in subjects with different hormonal status

Parameters	25 (OH)D (ng/ml)[1]	Thyroid volume (ml)[2]	Prevalence of Doppler signal positivity (n)
Euthyroid status (n = 103)	25.11*	9.62*	11 (10.7%)*
Subclinical hypothyroidism (n = 13)	23.85	10.02	4 (30.8%)
Overt hypothyroidism (n = 40)	21.07*	10.09*	11 (27.5%)
*p-value	0.04	0.04	0.01

25 (OH)D – 25 hydroxyvitamin D;
[1]mean serum 25 (OH)D levels (ng/ml);
[2]ultrasound mean thyroid volume values

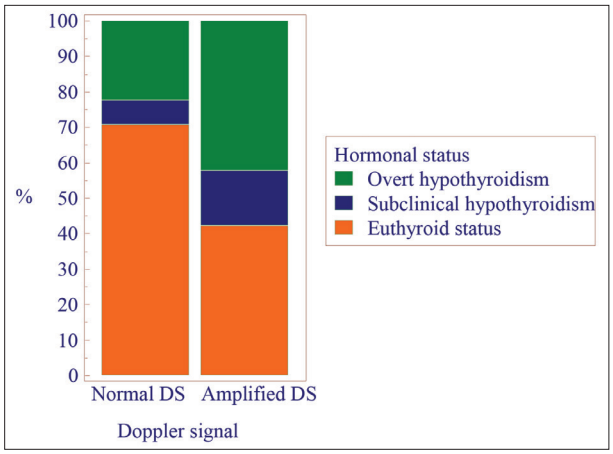

Figure 2. Doppler signal at different thyroid hormonal status

with the euthyroid subjects. We also obtained a higher prevalence of positivity of TPO-Ab and TG-Ab in the group with vitamin D insufficiency (p = 0.02), while the concentrations of TG-Ab and TPO-Ab showed no significant difference between the group with insufficiency and normal vitamin D levels. Some studies showed a negative correlation between vitamin D levels and TG -Ab concentrations in female subjects with HT, suggesting that vitamin D deficiency is higher in women with HT than in men, which is consistent with our findings [17, 19].

One of the first researchers to find an association between vitamin D and autoimmune thyroid disease was Kivity [20], and then further studies were conducted showing this association. Kivity et al. [20] showed that vitamin D deficiency was higher in respondents with HT than in those without HT. They also showed that vitamin D insufficiency correlated with the presence of thyroid antibodies. Some studies also show a negative correlation between the levels of TPO-Ab and TG-Ab and vitamin D insufficiency. In our study there was no statistically significant difference between thyroid antibodies titer and 25 (OH) D levels (TG Ab p = 0.113; TPO Ab p = 0.186) [21, 22].

Although we did not obtain a statistically significant difference between thyroid antibodies titer and 25 (OH) D levels, the prevalence of thyroid antibody positivity was higher in the vitamin D insufficiency group (p = 0.02), as in a study by Kim [4].

However, in the study by Yasmeh et al. [23], the results were different. They showed the association of normal and higher vitamin D levels in women with autoimmune thyroid disease compared to the control group. They also showed a positive correlation between vitamin D and TPO-Ab levels in men, which is not consistent with our results [23].

In our study, we obtained significantly higher TSH levels in the vitamin D insufficiency group compared to the group with normal vitamin D level (TSH = 4.58 ± 3.88 *vs*. TSH = 3.05 ± 2.90; p = 0.02), which is in agreement with the results of Chao et al. [15] and Sulejmanovic et al. [19].

The association between vitamin D insufficiency and HT has been demonstrated in many studies, but few indicate a higher prevalence of vitamin D deficiency in HT patients with overt hypothyroidism compared to subclinical hypothyroidism and euthyroid individuals [4, 24]. In our study, we found no statistically significant difference in vitamin D levels between overt hypothyroidism and subclinical hypothyroidism, but it existed between overt hypothyroidism and euthyroid individuals (p = 0.04), which is consistent with the study of Kim [4], which showed a statistically significant difference in vitamin D levels between overt hypothyroidism and euthyroid and subclinical hypothyroidism. It showed that patients with overt hypothyroidism and HT had lower vitamin D levels than patients without HT [4].

In contrast to these findings, some investigators found no association between vitamin D insufficiency and autoimmune thyroid disease and concluded that vitamin D insufficiency is not associated with the early stages of autoimmunity [13, 25].

It is not yet known whether vitamin D deficiency is a cause or a consequence of HT. Botelho et al. [26] showed that vitamin D levels were similar in patients with HT and without HT, and lower fT4 levels were considered a predictor of vitamin D deficiency for HT. In our study, we also showed lower fT4 levels in the vitamin D deficient group, but with no statistically significant difference (p = 0.827). Thyroid hormone levels play an important role in maintaining normal vitamin D levels. A positive correlation of fT4 with vitamin D suggests that levothyroxine substitution in HT is important for maintaining normal vitamin D levels and preventing serum insufficiency and deficiency [26]. Some studies also suggest that vitamin D supplementation lowers concentrations of TG-Ab and TPO-Ab, as well as TSH levels, especially in women with HT, who receive levothyroxine replacement therapy and have low serum vitamin D levels [24, 27].

In our study, we determined statistically significant differences in BMI in individuals with vitamin D insufficiency (p = 0.002, and in the group with thyroiditis p = 0.001). BMI was significantly higher in the group with vitamin D insufficiency than in the control group. In the study by De Pergola et al. [28] they pointed out the negative correlation between vitamin D and BMI and suggested that all obese people with vitamin D insufficiency should be screened for TPO-Ab and TG-Ab. Obese people with HT should also have their vitamin D levels checked [28].

Prolonged thyroiditis leads to increased vascularization of the parenchyma, formation of fibrous septa in the lobes, and a gradual decrease in thyroid volume [4, 12]. In our

study, patients with vitamin D insufficiency had lower flow rates and higher RI by ATS and ATI compared to the group with sufficient vitamin D.

Nalbant et al. [29] showed that the PSV of ATS and ATI was significantly higher in the group with sufficient vitamin D level than in the group with vitamin D insufficiency. There is a negative correlation between RI and vitamin D insufficiency, which is consistent with our results. They concluded that vitamin D deficiency leads to decreased blood supply to the thyroid gland as well as increased microvascular resistance in patients with HT [29].

In our study, the prevalence of circular dichroism positivity as well as thyroid volume is significantly higher in HT patients with vitamin D insufficiency. El Rawi et al. [30] compared ultrasound parameters of the thyroid gland in patients with HT and vitamin D insufficiency. They showed that vitamin D levels were lower in patients with HT with overt hypothyroidism and were inversely proportional to TSH, TPO-Ab and TG -Ab levels and thyroid volume. Low vitamin D levels are associated with increased vascularization, which is consistent with the results we obtained [30].

CONCLUSION

This study demonstrated a correlation between vitamin D insufficiency and hypothyroidism and an association with a positive prevalence of increased vascularization and greater thyroid volume in individuals with Hashimoto's thyroiditis. Further randomized controlled trials are needed to determine whether a causal relationship exists and to investigate the potential use of vitamin D in the treatment of autoimmune thyroid disease.

Conflict of interest: None declared.

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Повезаност нивоа витамина *D* са Хашимотовим тиреоидитисом

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САЖЕТАК

Увод/Циљ Осим улоге витамина *D* у метаболизму калцијума и фосфора, он остварује и антипролиферативне, диференцијалне, антиинфламаторне и имуномодулаторне ефекте. Циљ ове студије је био да се испита повезаност инсуфицијенције витамина *D* код особа са аутоимуним Хашимотовим тиреоидитисом.

Методе Испитивано је 156 болесника подељених у две групе. Прву групу чинило је 108 болесника са инсуфицијенцијом 25 (*OH*) *D*, а другу 48 особа са нормалним нивоом 25 (*OH*) *D*. Сви испитаници су подвргнути детаљном клиничком прегледу, лабораторијским тестовима функције штитасте жлезде [*T3*, *fT4*, *TSH*, тироидна антитела (*TPO-At*, і *TG-At*)], као и ултразвучном скенирању (запремина штитасте жлезде и карактеристике Доплерове дијагностике).

Резултати Испитаници са инсуфицијенцијом витамина *D* [*n* = 108 (69,2%)] били су претежно женског пола и имали су виши индекс телесне масе од оних са нормалним нивоом витамина *D*. Група са инсуфицијенцијом витамина *D* имала је статистички значајно виши ниво *TSH*. Преваленција позитивности аутоантитела на штитасту жлезду је била већа у групи са инсуфицијенцијом витамина *D*, док су волумени штитасте жлезде, индекси отпора горње тироидне артерије и доње тироидне артерије, као и преваленце позитивности сигнала циркуларног дихроизма, били статистички значајно већи у групи са инсуфицијенцијом витамина *D*. Међу 156 испитаника, њих 44 је имало дијагнозу тиреоидитиса (28,2%). Средњи нивои серумских 25 (*OH*) *D* код болесника са тиреоидитисом (20,23 ± 8,10 *ng/ml*) били су статистички значајно нижи у односу на групу без тиреоидитиса (25,44 ± 8,38 *ng/ml*), $p < 0,001$.

Закључак Постојала је повезаност између инсуфицијенције витамина *D* и хипотиреоидизма код особа са Хашимотовим тироидитисом.

Кључне речи: витамин *D*; инсуфицијенција; Хашимотов тиреоидитис