

©Borgis

*Magdalena Kochman

Vitamin D and autoimmune thyroid diseases

Witamina D a autoimmunizacyjne choroby tarczycy

Department of Endocrinology, Centre of Postgraduate Medical Education, Bielański Hospital, Warsaw
Head of Department: Professor Wojciech Zgliczyński, MD, PhD

Keywords

vitamin D, autoimmune thyroid disease, Hashimoto's thyroiditis, postpartum thyroiditis, Graves' disease

Słowa kluczowe

witamina D, autoimmunizacyjna choroba tarczycy, choroba Hashimoto, poporodowe zapalenie tarczycy, choroba Gravesa-Basedowa

Conflict of interest

Konflikt interesów

None

Brak konfliktu interesów

Address/adres:

*Magdalena Kochman
Klinika Endokrynologii
Centrum Medyczne
Kształcenia Podyplomowego
Szpital Bielański
ul. Ceglowska 80, 01-809 Warszawa
tel./fax +48 (22) 834-31-31
mkochman@cmkp.edu.pl

INTRODUCTION

Vitamin D is a steroid prohormone, mainly synthesized in the skin, which, after conversion to an active metabolite, regulates calcium and phosphorus metabolism and bone homeostasis. Currently, multiple data suggest, that it has also many extra-skeletal actions. Vitamin D deficiency may play an important role in pathogenesis of infections, autoimmune diseases, metabolic syndromes, cardiovascular diseases, cancers and all-cause mortality (1, 2). In recent years there have been many studies published, which showed vitamin D associations with autoimmune thyroid diseases,

Summary

Vitamin D is one of the most important factors regulating calcium and phosphorus homeostasis and bone metabolism. In the last years increasing evidences suggest an important role of vitamin D deficiency in many extra-skeletal disorders, such as metabolic syndromes, cardiovascular diseases, cancers, infections and autoimmune disorders, including rheumatoid arthritis, Crohn disease, multiple sclerosis and type 1 diabetes mellitus. Many studies has shown also an association of vitamin D deficiency with occurrence and development of autoimmune thyroid diseases including Hashimoto's thyroiditis, postpartum thyroiditis and Graves' disease. In recent years there are increasing data indicating that vitamin D supplementation may prevent these pathologies or alleviate their course. Some studies suggest also that vitamin D may influence thyroid function. This review presents current data on the relationship of vitamin D and thyroid autoimmunization and function. The effects of vitamin D supplementation on the development and progression of autoimmune thyroid disease have also been discussed.

Streszczenie

Witamina D jest jednym z głównych czynników regulujących homeostazę wapnia i fosforu oraz metabolizm kostny. W ostatnich latach coraz więcej dowodów wskazuje na ważną rolę niedoboru witaminy D w wielu schorzeniach spoza układu kostnego, takich jak zespoły metaboliczne, choroby układu sercowo-naczyniowego, nowotwory, infekcje oraz zaburzenia autoimmunizacyjne, w tym reumatoidalne zapalenie stawów, choroba Leśniowskiego-Crohna, stwardnienie rozsiane czy cukrzyca typu 1. Wiele badań wykazało także związek między niedoborem witaminy D a chorobami autoimmunizacyjnymi tarczycy, w tym zapaleniem tarczycy Hashimoto, poporodowym zapaleniem tarczycy i chorobą Gravesa-Basedowa. W ostatnich latach coraz więcej danych wskazuje na to, że uzupełnianie niedoboru witaminy D może zapobiegać tym patologiom lub łagodzić ich przebieg. Niektóre badania sugerują także, że witamina D może mieć wpływ na czynność hormonalną gruczołu tarczowego. W artykule przedstawiono najnowsze doniesienia dotyczące związku witaminy D z procesami autoimmunizacyjnymi w tarczycy i jej czynnością hormonalną. Omówiono także wpływ suplementacji witaminą D na rozwój i przebieg autoimmunizacyjnych chorób tarczycy.

es, including Hashimoto's thyroiditis (HT), postpartum thyroiditis (PPT) and Graves' disease (GD) (3, 4).

Vitamin D occurs in two different forms, as cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). Cholecalciferol is mainly synthesized in the skin upon exposure to ultraviolet B radiation by 7-dehydrocholesterol reductase (DHCR7), but it can be also obtained from few dietary sources (mainly fatty fish). Ergocalciferol is derived from dietary sources – it is synthesized by plants and fungi (2). Both forms are transported to the liver and there hydroxylated to 25-hydroxyvitamin D (25(OH)D₃, calcidiol) by

25-hydroxylase (CYP27A1, CYP2R1), which has little biological activity, but is the main storage form of vitamin D. Calcidiol is converted to active hormone, calcitriol ($1,25(\text{OH})_2\text{D}_3$) by 1α -hydroxylase (CYP27B1), which is mainly expressed in kidney. This enzyme is stimulated by parathormone (PTH) and inhibited by high $1,25(\text{OH})_2\text{D}_3$ concentration and fibroblast growth factor 23 (FGF23). Calcitriol is inactivated by 24-hydroxylase (CYP24A1) (1, 2). Calcitriol is also produced from calcidiol by several other cell types (including immune cells), which express 1α -hydroxylase, without the above regulatory feedback, as an autocrine or paracrine cytokine (1). The main factor determining extrarenal $1,25(\text{OH})_2\text{D}_3$ synthesis seems to be $25(\text{OH})\text{D}_3$ concentration (5). There have been found many associations between serum calcidiol level, rather than calcitriol concentration, and extraskeletal health outcomes (5). Both calcidiol and calcitriol are highly hydrophobic molecules, stored in the adipose tissue and circulating in blood bound mainly to vitamin D binding protein (DBP) (85 and 88%, respectively) and, with lower affinity, to albumin (15 and 12%, respectively) (6, 7). Less than 1% of calcitriol is free and can bind to nuclear vitamin D receptor (VDR), which acts on vitamin D response element (VDRE) of multiple target genes to exert its effects (8). VDR is found in most cells and tissues, including the thyroid (1, 8, 9). $1,25(\text{OH})_2\text{D}_3$ decreases cellular proliferation, induces differentiation and apoptosis, influences angiogenesis, and modulates the immune system (1, 2). A membrane-bound VDR has been also hypothesized, which would mediate rapid, non-genomic actions of $1,25(\text{OH})_2\text{D}_3$ (8).

Vitamin D is a potent immunomodulator. Most immune cells, including macrophages, antigen-presenting cells (APCs), lymphocytes T and B, express not only VDR, but also 1α -hydroxylase (2, 10). Generally, vitamin D activates the innate system and regulates the acquired immune response (2, 11). It inhibits major histocompatibility complex class II molecules expression on dendritic cells surface and modulates cytokine secretion, shifting the balance from a Th1 and Th17 to a Th2 phenotype (2, 10). Calcitriol also inhibits B cell proliferation, differentiation of B cells into plasma cells, immunoglobulin secretion and formation of memory B cells, as well as induces B cell apoptosis (2, 10). To summarize, vitamin D promotes immunotolerance, and, therefore, could be beneficial in autoimmune disorders (1, 2, 10).

Not only vitamin D status, but also polymorphism of genes involved in vitamin D metabolism, transport and activity was shown to be associated to susceptibility to autoimmune disorders (10).

This review presents the current data regarding the role of vitamin D in autoimmune thyroid diseases.

VITAMIN D STATUS AND THYROID FUNCTION

The thyroid gland secretes mainly thyroxine (T4) and, in less extent, triiodothyronine (T3), which are crucial for maintaining specific function of multiple cell

types and tissues and stimulating metabolism. Thyroid function is controlled by thyrotropin (thyroid stimulating hormone – TSH) released by the pituitary. The data on associations between vitamin D status and TSH or thyroid hormone concentrations are very limited and often divergent.

Animal studies

Experiments on rats showed, that those fed with severely vitamin D deficient diet had lower TSH, but similar T4 levels to vitamin D sufficient animals. However, administration of high doses of calcitriol did not influence TSH or T4 concentrations (12). In streptozotocin-induced diabetic rats inhibited peripheral conversion of FT4 into FT3 secondary to reduction in deiodinase 2 (D_2) expression was observed. Vitamin D greatly corrected the alterations in thyroid profile and D_2 expression (13).

Human studies

In human, when hospitalized patients without history of thyroid diseases were studied, TSH levels did not differ between those with $25(\text{OH})\text{D}_3$ very low (≤ 10 ng/ml) and high (≥ 40 ng/dl) concentrations (9). On the contrary, in two normal population-based studies, high vitamin D status was associated with lower TSH levels. In a Thai cohort it was observed only in young subjects (14), while in Chinese – also in middle-aged and elderly ones (15). In postmenopausal women suppressed TSH was also associated with higher vitamin D levels, however the relationship was not linear (16). On the other hand, in a population of euthyroid adults Barchetta et al. showed a strong association between vitamin D deficiency and higher TSH levels ($p = 0.01$) (17). Those and other authors suggested, that reported seasonality in TSH secretion was associated with vitamin D status (17, 18).

Hypothyroidism was, according to Mackawy et al., as well as to Kim, associated with hypovitaminosis D (19, 20), however others did not confirm these observations (21, 22).

Bouillon et al. reported, that in hypothyroid patients serum calcidiol levels were comparable to normal subjects, while calcitriol concentrations were significantly increased (73 ± 28 ng/l vs. 42 ± 13 ng/l in control subjects; $p < 0.001$), probably secondary to high parathyroid hormone levels (53 ± 17 mU/l vs. 26 ± 9 mU/l in controls; $p < 0.001$) (21).

Very recently, in a large retrospective Canadian cohort study regarding the influence of vitamin D supplementation on thyroid function, baseline mean $25(\text{OH})\text{D}_3$ concentration was significantly lower in hypothyroid subjects than in healthy controls (27.2 vs. 32.8 ng/ml) (18). Interestingly, in type 2 diabetic patients Calvo-Romero and Ramiro-Lozano found slightly higher serum thyrotropin levels in vitamin D deficient subjects (at the limit of statistical significance), however, with no effect of correction of vitamin D deficiency on TSH concentrations (23).

In untreated hyperthyroid patients unaltered calcidiol, low calcitriol and high $24,25(\text{OH})_2\text{D}_3$ concentrations were observed (21, 24, 25). It was explained to be a result of high bone turnover causing secondary hypoparathyroidism or of competitive inhibition of calcitriol synthesis by $24,25(\text{OH})_2\text{D}_3$.

However, recently, in women with gestational transient thyrotoxicosis $25(\text{OH})\text{D}_3$ concentrations were found to be significantly lower than in pregnant female with normal thyroid function (26, 27). Moreover, Pan et al. showed, that calcidiol levels correlated positively with TSH and negatively with FT4 and FT3 concentrations (27).

VITAMIN D STATUS AND AUTOIMMUNE THYROID DISEASES

Autoimmune thyroid diseases are the most common organ-specific autoimmune disorders. Hashimoto thyroiditis, also known as chronic lymphocytic thyroiditis, is a typical T-cell mediated autoimmune disease, in which intrathyroidal infiltration of B and T lymphocytes is observed. It is well established, that type 1 T helper (Th1) lymphocytes participate in the development of HD. Cytokines secreted by Th1 cells activate cytotoxic T-lymphocytes and natural killer (NK) cells, leading to thyrocyte destruction. Nowadays increasing data indicate important role of other mechanisms in pathogenesis of HT (including autoantibodies, other subgroups of T helper cells such as Th17, regulatory T cells, disturbances of the process of apoptosis) (28). In Graves' disease only a mild lymphocytic infiltration with type 2 T helper (Th2) cell subtype predominance is observed. Th2 cells induce the production of antibodies to the receptor for TSH (TRAb), which are crucial in pathophysiology of GD. The ability of vitamin D to modulate adaptive immune system may influence the pathogenesis of autoimmune thyroid disorders.

Animal studies

In mice previously sensitized with porcine thyroglobulin intraperitoneal injections of calcitriol and intragastrical administration of cyclosporine A reduced severity of autoimmune thyroiditis, and, when applied together, even prevented thyroid disease (29, 30). In rats with experimental autoimmune thyroiditis, $1,25(\text{OH})_2\text{D}_3$ also prevented or ameliorated structural disruption of thyroid gland and corrected cytokine disequilibrium (31). In mouse model of Graves' disease, persistent hyperthyroidism was observed in vitamin D deficient, but not in vitamin D sufficient animals immunized with TSH receptor. Interestingly, before immunization vitamin D deficient mice had lower T4 concentrations. These results suggest direct modulation of thyroid function by vitamin D (32).

Human studies

In the last years, several clinical studies indicated an association between vitamin D deficiency and autoimmune thyroid diseases (AITD) defined as elevated

antithyroid antibodies with or without characteristic ultrasonographic features (diffuse parenchymal hypoechogenicity and/or heterogeneous echogenic pattern of thyroid gland) (20, 33-38). Many authors observed that subjects with low vitamin D concentration had more frequently elevated anti-TPO antibodies (33-37, 39) and/or anti-TG antibodies (35, 36, 40, 41). In patients with AITD anti-TPO titers were highest among subjects with lowest calcidiol concentrations (42). A meta-analysis of 20 case-control studies made by Wang et al. in 2015, showed that patients with AITD have lower calcidiol levels and are more often vitamin D deficient compared to controls (43). The same results were obtained in 90 Turkish children with AITD and HT (aged 12.3 ± 2.9 years) compared to 79 age-matched healthy controls (11.9 ± 2.3 years) (44). Recently, in a group of Italian elderly subjects (168 patients, aged 81.6 ± 9.4 years) a significantly higher prevalence of AITD was observed in vitamin D deficient subjects ($25(\text{OH})\text{D}_3 < 20$ ng/ml) than in those with normal calcidiol levels (28 vs. 8%, respectively, $p = 0.002$). In addition, in subjects with AITD a significant correlations between $25(\text{OH})\text{D}_3$ and anti-TPO antibodies ($r = -0.27$, $p = 0.03$) as well as FT3 ($r = 0.35$, $p = 0.006$), but not anti-TG antibodies, TSH or FT4 were observed (45). Interestingly, Choi et al. in a cross-sectional study on 6685 subjects observed that serum calcidiol levels were significantly lower in pre-menopausal, but not in post-menopausal women with AITD (36). It may suggest connections between vitamin D and estrogens in the development of AITD.

However, no difference in the prevalence of vitamin D deficiency ($25(\text{OH})\text{D}_3 < 20$ ng/ml) between 100 patients with AITD (52 HT, 48 GD) and 126 healthy controls was observed by D'Aurizio et al. (11). Likewise, the relationship between low vitamin D levels and the presence of anti-TPO and anti-TG antibodies was not always observed (14, 37, 38, 41). Goswami et al. in a group of 642 subjects from India revealed only a weak inverse correlation between serum calcidiol and anti-TPO concentrations ($r = -0.08$, $p = 0.04$), but no association between vitamin D deficiency ($25(\text{OH})\text{D}_3 < 10$ ng/ml) and anti-TPO positivity (33). In the study of Yasmeh et al. the mean $25(\text{OH})\text{D}_3$ levels were not significantly different in AITD males and healthy controls (14.24 vs. 13.26 ng/ml) and were even higher in females with AITD than in healthy ones (30.75 vs. 27.56 ng/ml). AITD females were more often vitamin D sufficient (51.7 vs. 31.1%) than control females. Furthermore, in males, a significant positive correlation between $25(\text{OH})\text{D}_3$ and anti-TPO antibodies was observed ($r = 0.436$, $p = 0.016$) (46). The authors concluded that AITD is not associated with higher prevalence of vitamin D deficiency.

Since the majority of authors observed, however, an inverse correlation between anti-thyroid antibodies and calcidiol levels (33, 35-37, 39, 41), a suggestion that vitamin D deficiency is one of the potential factors in pathogenesis of autoimmune thyroid disorders

occured. In contrast to those results, in a study regarding women from the Amsterdam AITD cohort (first- and second-degree relatives of overt AITD patients, euthyroid and without thyroid antibodies), neither the whole group nor a subgroup of subjects, which during a 5-year follow-up developed anti-thyroid antibodies, had lower 25(OH)D₃ levels than age-matched controls. Interestingly, seronegative cohort subjects had even significantly higher calcidiol concentrations when compared to controls (47). Therefore, the authors concluded, that early stages of thyroid autoimmunity are not associated with low vitamin D levels.

There was no difference in calcidiol levels in children and adolescents with type 1 diabetes mellitus with and without thyroid antibodies (48).

In an elderly population with a high prevalence of vitamin D deficiency/insufficiency patients with type 2 diabetes were found to be 2.5 times more likely to have AITD compared to a nondiabetic individuals, but, interestingly, the higher the serum 25(OH)D₃ levels were, the higher this chance was (49). In women with polycystic ovary syndrome (PCOS), 25(OH)D₃ levels were significantly lower in subjects with AITD than in those without AITD ($p = 0.02$). However, in women with PCOS and AITD no correlation was found between calcidiol and thyroid antibodies, TSH nor thyroid hormone levels (50).

HASHIMOTO'S THYROIDITIS

In the majority of studies regarding Hashimoto's thyroiditis (HT), in HT patients calcidiol concentrations were lower and the prevalence of vitamin D deficiency was higher when compared with healthy controls (34, 35, 40, 51-53). It was confirmed in meta-analysis performed by Wang et al. for the subgroup of patients with HT (43).

When patients with HT were compared to subjects with non-autoimmune thyroid diseases, both vitamin D deficiency (25(OH)D₃ < 10 ng/ml) (34) and its insufficiency (25(OH)D₃ < 30 ng/ml) (20) were more often in HT subjects. Tamer et al. observed a trend for a higher prevalence of vitamin D insufficiency (25(OH)D₃ < 30 ng/ml) in patients with overt (94%) and subclinical hypothyroidism (98%) than in those with euthyroidism (86%), but the differences were not significant ($p = 0.083$) (52). Kim demonstrated, that patients HT and with overt hypothyroidism had significantly more often vitamin D insufficiency (60.4 vs. 44.1 and 21.7%, respectively, $p < 0.001$) and lower 25(OH)D₃ levels (80.1 ± 47.7 vs. 99.34 ± 61.2 and 110.3 ± 69.9 nmol/l, respectively, $p = 0.009$) compared with those with euthyroidism and subclinical hypothyroidism (20). In the study of Ke et al. vitamin D deficiency, defined as serum 25(OH)D₃ < 20 ng/ml, was also significantly more often in HT patients with overt hypothyroidism treated with L-thyroxine compared with euthyroid mild HT patients (70.3 vs. 55.4%, $p < 0.05$) (53). In the study of Mazokopakis et al. including 218 HT patients there was a significant negative correlation only between serum 25(OH)D₃ and anti-TPO concen-

trations and anti-TPO levels were significantly higher in 186 vitamin D deficient subjects compared to 32 those with no vitamin D deficiency (364 ± 181 IU/ml vs. 115.8 ± 37.1 IU/ml, $p < 0.0001$) (37). Bozkurt et al. found not only correlation of severity of vitamin D deficiency with antibody levels, but also with duration of HT as well as thyroid volume, suggesting a potential role of vitamin D in development and progression of HT (40).

Only few studies were performed to assess vitamin D status in children with HT. Camurdan et al., as well as Evliyaoğlu et al., observed that children with newly diagnosed HT had significantly lower 25(OH)D₃ concentrations and higher prevalence of vitamin D deficiency (defined as 25(OH)D₃ < 15.2 ng/ml and ≤ 20 ng/ml, respectively) than healthy controls (44, 54). The results were confirmed Sönmezgöz et al. in a group of 136 Turkish children (68 with HT and 68 controls) (55). In the study of Evliyaoğlu et al. vitamin D deficient children had more than 2 times increased risk of HT (OR 2.28, 95% CI 1.21-4.3) (44). However, none of these studies was able to show the relationship between vitamin D deficiency and the severity of thyroid dysfunction (44, 54, 55). Lower calcidiol levels and higher rates of vitamin D deficiency were observed also in a study on Egyptian children with HT. Additionally, the difference in 25(OH)D₃ concentrations was more evident between patients with overt hypothyroidism and controls than between those with subclinical hypothyroidism and controls ($p < 0.01$). There were significant negative correlations between serum 25(OH)D₃ and age, duration of the disease, BMI, anti-TPOAb, anti-TGAb and TSH ($p < 0.001$ each). On the other hand, serum calcidiol correlated positively with FT4 levels. However, after adjustment for other potential confounding factors; age, sex and BMI, 25(OH)D₃ concentration was not an independent risk factor for the progression of subclinical to overt hypothyroidism (56).

VITAMIN D STATUS AND POSTPARTUM THYROIDITIS

In a study of Krysiak et al. calcidiol levels were significantly lower in hypothyroid ($n = 14$) and euthyroid ($n = 14$) women with postpartum thyroiditis (PPT) than in subjects with non-autoimmune hypothyroidism ($n = 16$) and euthyroid controls ($n = 15$), respectively. Lower 25(OH)D₃ concentrations were also observed in hypothyroid patients with PPT compared to those with preserved thyroid function and women with non-AITD compared to healthy ones. Calcidiol levels inversely correlated with anti-TPO and anti-TG antibody titers. After L-thyroxine therapy of hypothyroid subjects an increase of 25(OH)D₃ concentrations occurred, but only in PPT patients (57). In another study the same group confirmed that L-thyroxine treated PPT female ($n = 38$) had lower 25(OH)D₃ levels than healthy controls ($n = 21$) and anti-TG and anti-TPO antibody levels inversely correlated with calcidiol concentrations (58). Ma et al. in a nested case-control study also showed that previously euthyroid subjects diag-

nosed with PPT ($n = 57$) had significantly lower serum 25(OH) D_3 levels ($p < 0.001$) and higher vitamin D deficiency prevalence (92.98 vs. 78.07%, $p = 0.014$) than euthyroid non-PPT mothers ($n = 114$) before delivery. In a multivariate regression analysis lower serum 25(OH) D_3 levels were an independent risk factor for PPT (OR = 1.09, 95% CI 1.05-1.43, $p < 0.001$). Every 5 nmol/l decrease in serum 25(OH) D_3 concentrations was associated with a 1.51-fold increase in PPT risk (95% CI 1.25-1.82). However, in this study predelivery calcidiol levels were not associated with TSH, anti-TPO or anti-TG levels (38).

GRAVES' DISEASE

The relationship between GD and vitamin D status was less explored. In the study of Kivity et al. vitamin D deficiency was more prevalent in 22 subjects with GD (64%) than in healthy controls (30%, $p < 0.01$), but was not significantly different when compared with non-AITD patients (52%, $p = 0.08$). The authors observed also a tendency to lower TSH values in vitamin D deficient subjects with GD (34). In newly diagnosed patients with GD lower mean 25(OH) D_3 concentration and higher prevalence of vitamin D deficiency was observed when compared to healthy controls (35, 38, 59). Additionally, in GD subjects Yasuda et al. found a significant correlation between calcidiol levels and thyroid volume ($r = -0.45$, $p = 0.05$), but not thyroid function or TRAb (59). Similarly Shin et al. did not observe correlation between TRAb and 25(OH) D_3 levels (39). On the contrary, Zhang revealed lower serum calcidiol concentrations in GD TRAb-positive patients than in GD TRAb-negative subjects and healthy controls, as well as inverse correlation between 25(OH) D_3 and TRAb levels, suggesting a possible link between vitamin D status and increased thyroid autoimmunity in GD patients (60). In the study of Ma et al. higher 25(OH) D_3 levels were weakly associated with lower TRAb ($r = -0.25$, $p = 0.036$). Lower serum calcidiol levels were associated with an increased risk of GD (OR = 1.09, 95% CI 1.03-1.15, $p = 0.001$). In multivariate logistic regression analysis, every 5 nmol/l decrease in serum 25(OH) D_3 concentration was associated with a 1.55-fold (95% CI 1.18-2.02) increase in GD risk (38). Other authors, however did not observe differences in vitamin D status between subjects with GD and non-AITD patients (20) or healthy subjects (11, 53). In two meta-analyses including 13 and 26 studies patients with GD had lower 25(OH) D_3 compared to controls (SMD = -1.04, 95% CI: -1.52 to -0.57 and SMD = -0.77, 95% CI -1.12 to -0.42, respectively), and were more likely to have vitamin D deficiency (OR = 3.50, 95% CI 1.86-6.56 and OR = 2.24, 95% CI 1.31-3.81, respectively) (43, 61). Xu et al. pointed out that high heterogeneity of the results of the studies included to those meta-analyses ($I^2 = 84.1\%$, $p < 0.001$) was partially related to various 25(OH) D_3 assay methods used (61).

Interestingly, Yasuda et al. reported also, that serum calcidiol levels were significantly lower in 36 GD pa-

tients who could not achieve remission for more than 4 years after the initiation of anti-thyroid drug therapy when compared to 18 GD subjects remaining in remission for more than 1 year and 49 controls (14.5 ± 2.9 vs. 18.2 ± 5.1 ng/ml, $p < 0.005$, and 18.6 ± 5.3 ng/ml, $p < 0.0005$). However, the authors found no significant association between serum 25(OH) D_3 levels and serum TRAb levels in non-remission group (62). Ahn et al. observed that low calcidiol levels (≤ 14.23 ng/ml) were associated with a higher probability of GD recurrence after anti-thyroid drug discontinuation (HR 3.016; 95% CI 1.163-7.819) (63). In the study of Li et al. on 128 GD patients who received radioiodine therapy (RIT) serum 25(OH) D_3 were significantly lower and in patients who failed than in those who succeeded in RIT. In Cox regression analysis serum 25(OH) D_3 level < 20 ng/ml was an independent risk factor for predicting failure of RIT in GD patients (relative risk = 8.83, 95% CI 3.34-23.38, $p < 0.001$) (64).

VITAMIN D-RELATED GENES AND AUTOIMMUNE THYROID DISEASES

Polymorphism of the VDR gene may vitally affect its activity. Therefore, the associations between the VDR gene polymorphism and the risk of AITD were largely investigated, although the results are still inconsistent. In the meta-analysis of 7 studies (3 Caucasian, 4 Asian) regarding VDR gene polymorphisms (Apal, BsmI, FokI and TaqI) and GD Apal, BsmI and FokI polymorphisms in the VDR gene were associated with susceptibility to GD in Asian populations, while no association was found between VDR polymorphisms and GD in Caucasian populations (65). According to more recent meta-analysis of Feng et al. including 8 studies (5 European, 2 Asian and 1 African) the BsmI or TaqI polymorphisms significantly decrease the risk of AITD (including HT and GD), while the Apal or FokI polymorphism do not. In the subgroup of Europeans, the decreased risk of AITD remained for the B or t variant (66). Inoue et al. showed, that in 139 patients with GD the frequency of the TT genotype for the TaqI was higher than in 116 subjects with HT and the frequency of the C allele for the Apal was higher than in 76 healthy controls. In HT patients the frequency of the CC genotype for the FokI was higher than in GD patients and controls (67). Meng et al. in 417 GD patients reported also increased frequency of allele A for the Apal when compared to 301 healthy controls (68). In 2017 the meta-analysis of 11 studies (5 Caucasian, 6 Asian) regarding VDR and HT was published by Wang et al. It showed, that only the FokI polymorphism was significantly associated with the increased risk of HT in Asian population, but not in Caucasians; and the TaqI, Apal and BsmI polymorphisms had no positive association with the risk of HT neither in the overall population, nor when stratified by ethnicity (69).

The role of DBP gene polymorphisms in AITD was studied by Pani et al., who showed, that an intron 8 (TAAA)N polymorphism was correlated with

GD, but not with HT (70). Kuryłowicz et al. in 332 Polish patients with GD observed significantly higher frequency of single nucleotide polymorphism (SNP) ACG --> AAG (Thr --> Lys) at codon 420 of the DBP gene when compared to healthy controls (34.2 vs. 25.7%, $p = 0.005$; OR = 1.50; 95% CI 1.13-1.99). Moreover, the codon 420 Lys allele correlated with lower 25(OH) D₃ serum concentration. However, in this study the codon 416 alleles and intron 8 (TAAA)N variants were not associated with susceptibility to nor with clinical phenotype of GD (71). Inoue et al. showed, that the frequency of the Gc1Gc1 genotype for the DBP gene polymorphism was lower in subjects with intractable GD than in GD patients in remission ($p = 0.0093$). They also observed, that GD in remission was associated with higher frequency of the AG genotype for the CYP2R1 polymorphism than intractable GD (67).

Patients with GD (92 families) and HT (106 families) were also genotyped for a C/T polymorphism in intron 6 of the CYP27B1 gene by Pani et al., but no associations were found (72). Two SNPs in the intron 6 (+2838 C/T) and the promoter (-1260 C/A) of the CYP27B1 gene were analyzed by Lopez et al. in 139 HT and 334 GD patients. The SNP in the intron 6 was associated with HT but not with GD, while in the promoter – with both autoimmune diseases (73). Kuryłowicz and Badenhoop confirmed an association of the same SNP in CYP27B1 gene promoter with GD in 326 Polish patients compared to 175 controls (74).

VITAMIN D TREATMENT AND AUTOIMMUNE THYROID DISEASES

In recent years several studies regarding vitamin D supplementation in AITD have been published. Mazokopakis et al. showed, that a 4-month oral vitamin D supplementation (1200-4000 IU/day) in 186 vitamin D deficient HT patients caused a significant decrease (20.3%, $p < 0.0001$) in serum anti-TPO antibody levels (37). In an open-labeled randomized controlled trial of Chaudhary et al. including patients with newly diagnosed AITD a 8-week vitamin D supplementation (60 000 IU/week) resulted in a significant fall in anti-TPO levels when compared to subjects not receiving vitamin D (-46.73 vs. -16.6%, $p = 0.028$). The percentage of subjects with anti-TPO titer decrease of at least 25% was higher among patients receiving vitamin D than in those without vitamin D supplementation (68 vs. 44%, $p = 0.015$) (42). Simsek et al. showed a significant decrease in anti-TPO ($p = 0.02$) and anti-TG ($p = 0.03$) concentrations in 46 AITD subjects (37 with HT and 9 with GD) receiving vitamin D in relatively low doses (1000 IU/day) for 1 month, not observed in the group of 36 AITD patients (31 with HT and 5 with GD) not supplemented with vitamin D (75). Ucan et al. also revealed, that vitamin D supplementation (50 000 IU/week for eight weeks) in vitamin D deficient euthyroid HT subjects sig-

nificantly decreased thyroid autoantibody titers. Moreover, in this group vitamin D therapy improved HDL cholesterol concentrations (76). Recently, Krysiak et al. revealed, that also in vitamin D sufficient (25(OH)D₃ > 30 ng/ml) L-thyroxine treated women with HT a 6-month oral vitamin D therapy (2000 IU daily) resulted in reduction in anti-TPO and (in less extend) anti-TG antibody titers (77). These findings suggest that vitamin D supplementation could contribute to the treatment of patients with HT. However, none of them showed influence of vitamin D therapy on thyroid function. Moreover, in a double-blind randomized placebo-controlled study of Anaraki et al., including 56 vitamin D deficient HT subjects, a 12-week oral vitamin D supplementation (50 000 IU/week) significantly influenced neither TSH nor anti-TPO levels (78). In another study of the same group regarding 65 vitamin D deficient HT patients vitamin D supplementation did not improve metabolic markers (including fasting plasma glucose, glycated hemoglobin, total cholesterol, triglycerides and high-density lipoproteins), insulin resistance, nor insulin secretion (79). On the other hand, in Canadian community-based study including over 11 000 participants, after 1 year of vitamin D supplementation individualized to achieve optimal vitamin status, defined as serum calcidiol concentrations ≥ 40 ng/ml a significant decrease in the percentage of hypothyroid subjects was observed – from 2% (23% including subclinical hypothyroidism) of participants at baseline to 0.4% (or 6% with subclinical) at follow-up. In this study serum 25(OH)D₃ concentrations ≥ 50 ng/ml were associated with a 30% reduced risk of hypothyroidism and a 32% reduced risk of elevated anti-thyroid antibodies. Moreover, calcidiol concentration was a significant positive predictor of improved thyroid function. The authors concluded, that vitamin D supplementation may be safe and economical approach to improve thyroid function and may protect from developing thyroid disease (18).

In PPT females treated with L-thyroxine Krysiak et al. showed that vitamin D supplementation reduced anti-TPO antibody titers, especially in vitamin D deficient subjects (58).

CONCLUSIONS

In conclusion, the majority of the studies have reported an association between low vitamin D status and increased risk of thyroid autoimmunity. It remains unclear whether vitamin D deficiency contributes to the pathogenesis of AITDs or is a consequence of the diseases. Recent data suggest that vitamin D supplementation may be a safe and economical approach to improve thyroid function and protect from developing autoimmune thyroid diseases. Further randomized controlled studies are needed to determine whether vitamin D supplementation may prevent AITDs or modulate their evolution.

BIBLIOGRAPHY

1. Holick MF: Vitamin D deficiency. *N Engl J Med* 2007; 357(3): 266-281.

2. Makariou S, Liberopoulos EN, Elisaf M, Challa A: Novel roles of vitamin D in disease: what is new in 2011? *Eur J Intern Med* 2011; 22(4): 355-362.

3. Kmieć P, Sworczak K: Vitamin D in thyroid disorders. *Exp Clin Endocrinol Diabetes* 2015; 123(7): 386-393.
4. Kim D: The role of vitamin D in thyroid diseases. *Int J Mol Sci* 2017; 18(9): pii: E1949.
5. Jones G: Extrarenal vitamin D activation and interactions between vitamin D₂, vitamin D₃, and vitamin D analogs. *Annu Rev Nutr* 2013; 33: 23-44.
6. Bikle DD, Siiteri PK, Ryzen E, Haddad JG: Serum protein binding of 1,25-dihydroxyvitamin D: a reevaluation by direct measurement of free metabolite levels. *J Clin Endocrinol Metab* 1985; 61(5): 969-975.
7. Gomme PT, Bertolini J: Therapeutic potential of vitamin D-binding protein. *Trends Biotechnol* 2004; 22: 340-345.
8. Norman AW: Minireview: vitamin D receptor: new assignments for an already busy receptor. *Endocrinology* 2006; 147(12): 5542-5548.
9. Clinckspoor I, Gérard AC, Van Sande J et al.: The vitamin D receptor in thyroid development and function. *Eur Thyroid J* 2012; 1(3): 168-175.
10. Bizzaro G, Antico A, Fortunato A, Bizzaro N: Vitamin D and Autoimmune Diseases: Is Vitamin D Receptor (VDR) Polymorphism the Culprit? *Isr Med Assoc J* 2017; 19(7): 438-443.
11. D'Aurizio F, Villalta D, Metus P et al.: Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? *Autoimmun Rev* 2015; 14(5): 363-369.
12. Törnquist K, Lambert-Allardt C: Systemic effects of 1,25-dihydroxyvitamin D₃ on the pituitary-hypothalamic axis in rats. *Acta Endocrinol (Copenh)* 1987; 115(2): 225-228.
13. Alrefaie Z, Awad H: Effect of vitamin D₃ on thyroid function and deiodinase 2 expression in diabetic rats. *Arch Physiol Biochem* 2015; 121(5): 206-209.
14. Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B: High vitamin D status in younger individuals is associated with low circulating thyrotropin. *Thyroid* 2013; 23(1): 25-30.
15. Zhang Q, Wang Z, Sun M et al.: Association of high vitamin d status with low circulating thyroid-stimulating hormone independent of thyroid hormone levels in middle-aged and elderly males. *Int J Endocrinol* 2014; 2014: 631819.
16. Niafar M, Pourafkari L, Aminmzaffari S, Nader ND: Association of Vitamin D Deficiency and Thyroid Function in Postmenopausal Women. *Adv Pharm Bull* 2016; 6(4): 639-644.
17. Barchetta I, Baroni MG, Leonetti F et al.: TSH levels are associated with vitamin D status and seasonality in an adult population of euthyroid adults. *Clin Exp Med* 2015; 15(3): 389-396.
18. Mirhosseini N, Brunel L, Muscogiuri G, Kimball S: Physiological serum 25-hydroxyvitamin D concentrations are associated with improved thyroid function-observations from a community-based program. *Endocrine* 2017; 58(3): 563-557.
19. Mackawy AM, Al-Ayed BM, Al-Rashidi BM: Vitamin d deficiency and its association with thyroid disease. *Int J Health Sci (Qassim)* 2013; 7(3): 267-275.
20. Kim D: Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis. *Hormones (Athens)* 2016; 15(3): 385-393.
21. Bouillon R, Muls E, De Moor P: Influence of thyroid function on the serum concentration of 1,25-dihydroxyvitamin D₃. *J Clin Endocrinol Metab* 1980; 51(4): 793-797.
22. Musa IR, Gasim GI, Khan S et al.: No Association between 25 (OH) Vitamin D Level And Hypothyroidism among Females. *Open Access Maced J Med Sci* 2017; 5(2): 126-130.
23. Calvo-Romero JM, Ramiro-Lozano JM: Vitamin D and thyrotropin in type 2 diabetic patients. *Diabetes Metab Syndr* 2017; 11(4): 279-280.
24. Jastrup B, Mosekilde L, Melsen F et al.: Serum levels of vitamin D metabolites and bone remodelling in hyperthyroidism. *Metabolism* 1982; 31(2): 126-132.
25. MacFarlane IA, Mawer EB, Berry J, Hann J: Vitamin D metabolism in hyperthyroidism. *Clin Endocrinol (Oxf)* 1982; 17(1): 51-59.
26. Küçükler FK, Şimşek Y, Gökem Ü et al.: Relationship between gestational transient thyrotoxicosis and vitamin D. *Turk J Med Sci* 2016; 46(5): 1374-1378.
27. Pan Y, Zhong S, Liu Q et al.: Investigating the relationship between 25-hydroxyvitamin D and thyroid function in second-trimester pregnant women. *Gynecol Endocrinol* 2017 Oct 26: 1-4.
28. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Roliński J: Immune disorders in Hashimoto's thyroiditis: what do we know so far? *J Immunol Res* 2015; 2015: 979167.
29. Fournier C, Gepner P, Sadouk M, Charreire J: *In vivo* beneficial effects of cyclosporin A and 1,25-dihydroxyvitamin D₃ on the induction of experimental autoimmune thyroiditis. *Clin Immunol Immunopathol* 1990; 54(1): 53-63.
30. Chen W, Lin H, Wang M: Immune intervention effects on the induction of experimental autoimmune thyroiditis. *J Huazhong Univ Sci Technolog Med Sci* 2002; 22(4): 343-354.
31. Liu S, Xiong F, Liu EM et al.: Effects of 1,25-dihydroxyvitamin D₃ in rats with experimental autoimmune thyroiditis. *Nan Fang Yi Ke Da Xue Xue Bao* 2010; 30(7): 1573-1576.
32. Misharin A, Hewison M, Chen CR et al.: Vitamin D deficiency modulates Graves' hyperthyroidism induced in BALB/c mice by thyrotropin receptor immunization. *Endocrinology* 2009; 150(2): 1051-1060.
33. Goswami R, Marwaha RK, Gupta N et al.: Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey. *Br J Nutr* 2009; 102(3): 382-386.
34. Kivity S, Agmon-Levin N, Zisapli M et al.: Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol* 2011; 8(3): 243-247.
35. Unal AD, Tarcin O, Parildar H et al.: Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. *Cent Eur J Immunol* 2014; 39(4): 493-497.
36. Choi YM, Kim WG, Kim TY et al.: Low levels of serum vitamin D₃ are associated with autoimmune thyroid disease in pre-menopausal women. *Thyroid* 2014; 24(4): 655-661.
37. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC et al.: Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis? *Hell J Nucl Med* 2015; 18(3): 222-227.
38. Ma J, Wu D, Li C et al.: Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases. *Medicine (Baltimore)* 2015; 94(39): e1639.
39. Shin DY, Kim KJ, Kim D et al.: Low serum vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. *Yonsei Med J* 2014; 55(2): 476-481.
40. Bozkurt NC, Karbek B, Ucan B et al.: The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. *Endocr Pract* 2013; 19(3): 479-484.
41. Wang X, Zynat J, Guo Y et al.: Low Serum Vitamin D Is Associated with Anti-Thyroid-Globulin Antibody in Female Individuals. *Int J Endocrinol* 2015; 2015: 285290.
42. Chaudhary S, Dutta D, Kumar M et al.: Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. *Indian J Endocrinol Metab* 2016; 20(3): 391-398.
43. Wang J, Lv S, Chen G et al.: Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015; 7(4): 2485-2498.
44. Evliyaoğlu O, Acar M, Özcabı B et al.: Vitamin D Deficiency and Hashimoto's Thyroiditis in Children and Adolescents: a Critical Vitamin D Level for This Association? *J Clin Res Pediatr Endocrinol* 2015; 7(2): 128-133.
45. Muscogiuri G, Mari D, Prolo S et al.: 25 Hydroxyvitamin D Deficiency and Its Relationship to Autoimmune Thyroid Disease in the Elderly. *Int J Environ Res Public Health* 2016; 13(9): 850.
46. Yasmeh J, Farpour F, Rizzo V et al.: Hashimoto thyroiditis is not associated with vitamin D deficiency. *Endocr Pract* 2016; 22(7): 809-813.
47. Effraimidis G, Badenhoop K, Tijssen JG, Wiersinga WM: Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. *Eur J Endocrinol* 2012; 167(1): 43-48.
48. Demir K, Keskin M, Kör Y et al.: Autoimmune thyroiditis in children and adolescents with type 1 diabetes mellitus is associated with elevated IgG4 but not with low vitamin D. *Hormones (Athens)* 2014; 13(3): 361-368.
49. Toulis K, Tsekmekidou X, Potolidis E et al.: Thyroid Autoimmunity in the Context of Type 2 Diabetes Mellitus: Implications for Vitamin D. *Int J Endocrinol* 2015; 2015: 710363.
50. Muscogiuri G, Palomba S, Caggiano M et al.: Low 25 (OH) vitamin D levels are associated with autoimmune thyroid disease in polycystic ovary syndrome. *Endocrine* 2016; 53(2): 538-542.
51. Mansournia N, Mansournia MA, Saeedi S, Dehghan J: The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis. *J Endocrinol Invest* 2014; 37(5): 473-476.
52. Tamer G, Arik S, Tamer I, Coksert D: Relative vitamin D insufficiency in Hashimoto's thyroiditis. *Thyroid* 2011; 21(8): 891-896.
53. Ke W, Sun T, Zhang Y et al.: 25-Hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. *Endocr J* 2017; 64(6): 581-587.
54. Camurdan OM, Döğer E, Bideci A et al.: Vitamin D status in children with Hashimoto thyroiditis. *J Pediatr Endocrinol Metab* 2012; 25(5-6): 467-470.
55. Sönmezgöz E, Ozer S, Yılmaz R et al.: Hypovitaminosis D in Children with Hashimoto's Thyroiditis. *Rev Med Chil* 2016; 144(5): 611-616.
56. Metwalley KA, Farghaly HS, Sherief T, Hussein A: Vitamin D status in children and adolescents with autoimmune thyroiditis. *J Endocrinol Invest* 2016; 39(7): 793-797.
57. Krysiak R, Kowalska B, Okopień B: Serum 25-Hydroxyvitamin D and Parathyroid Hormone Levels in Non-Lactating Women with Post-Partum Thyroiditis: The Effect of L-Thyroxine Treatment. *Basic Clin Pharmacol Toxicol* 2015; 116(6): 503-507.
58. Krysiak R, Kowalcze K, Okopień B: The effect of vitamin D on thyroid autoimmunity in non-lactating women with postpartum thyroiditis. *Eur J Clin Nutr* 2016; 70(5): 637-639.
59. Yasuda T, Okamoto Y, Hamada N et al.: Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. *Endocrine* 2012; 42(3): 739-741.

60. Zhang H, Liang L, Xie Z: Low Vitamin D Status is Associated with Increased Thyrotropin-Receptor Antibody Titer in Graves Disease. *Endocr Pract* 2015; 21(3): 258-263.
61. Xu MY, Cao B, Yin J et al.: Vitamin D and Graves' disease: a meta-analysis update. *Nutrients* 2015; 7(5): 3813-3827.
62. Yasuda T, Okamoto Y, Hamada N et al.: Serum vitamin D levels are decreased in patients without remission of Graves' disease. *Endocrine* 2013; 43(1): 230-232.
63. Ahn HY, Chung YJ, Cho BY: Serum 25-hydroxyvitamin D might be an independent prognostic factor for Graves disease recurrence. *Medicine (Baltimore)* 2017; 96(31): e7700.
64. Li X, Wang G, Lu Z et al.: Serum 25-hydroxyvitamin D predict prognosis in radioiodine therapy of Graves' disease. *J Endocrinol Invest* 2015; 38(7): 753-759.
65. Zhou H, Xu C, Gu M: Vitamin D receptor (VDR) gene polymorphisms and Graves' disease: a meta-analysis. *Clin Endocrinol (Oxf)* 2009; 70(6): 938-945.
66. Feng M, Li H, Chen SF et al.: Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. *Endocrine* 2013; 43(2): 318-326.
67. Inoue N, Watanabe M, Ishido N et al.: The functional polymorphisms of VDR, GC and CYP2R1 are involved in the pathogenesis of autoimmune thyroid diseases. *Clin Exp Immunol* 2014; 178(2): 262-269.
68. Meng S, He ST, Jiang WJ et al.: Genetic susceptibility to autoimmune thyroid diseases in a Chinese Han population: Role of vitamin D receptor gene polymorphisms. *Ann Endocrinol (Paris)* 2015; 76(6): 684-689.
69. Wang X, Cheng W, Ma Y, Zhu J: Vitamin D receptor gene FokI but not TaqI, ApaI, BsmI polymorphism is associated with Hashimoto's thyroiditis: a meta-analysis. *Scientific Reports* 2017; 7: 41540.
70. Pani MA, Regulla K, Segni M et al.: A polymorphism within the vitamin D-binding protein gene is associated with Graves' disease but not with Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 2002; 87(6): 2564-2567.
71. Kuryłowicz A, Ramos-Lopez E, Bednarczuk T, Badenhop K: Vitamin D-binding protein (DBP) gene polymorphism is associated with Graves' disease and the vitamin D status in a Polish population study. *Exp Clin Endocrinol Diabetes* 2006; 114(6): 329-335.
72. Pani MA, Regulla K, Segni M et al.: Vitamin D 1alpha-hydroxylase (CYP1alpha) polymorphism in Graves' disease, Hashimoto's thyroiditis and type 1 diabetes mellitus. *Eur J Endocrinol* 2002; 146(6): 777-781.
73. Lopez ER, Zwermann O, Segni M et al.: A promoter polymorphism of the CYP27B1 gene is associated with Addison's disease, Hashimoto's thyroiditis, Graves' disease and type 1 diabetes mellitus in Germans. *Eur J Endocrinol* 2004; 151(2): 193-197.
74. Kuryłowicz A, Badenhop K: CYP27B1 gene polymorphism is associated with Graves' disease in a Polish population study. *Thyroid* 2005; 15(9): 1107-1108.
75. Simsek Y, Cakır I, Yetmis M et al.: Effects of vitamin D treatment on thyroid autoimmunity. *J Res Med Sci* 2016; 21: 85.
76. Ucan B, Sahin M, Sayki Arslan M et al.: Vitamin D Treatment in Patients with Hashimoto's Thyroiditis may Decrease the Development of Hypothyroidism. *Int J Vitam Nutr Res* 2017: 1-9.
77. Krysiak R, Szkróbka W, Okopień B: The Effect of Vitamin D on Thyroid Autoimmunity in Levothyroxine-Treated Women with Hashimoto's Thyroiditis and Normal Vitamin D Status. *Exp Clin Endocrinol Diabetes* 2017; 125(4): 229-233.
78. Anaraki PV, Aminorroaya A, Amini M et al.: Effect of Vitamin D deficiency treatment on thyroid function and autoimmunity markers in Hashimoto's thyroiditis: A double-blind randomized placebo-controlled clinical trial. *J Res Med Sci* 2017; 22: 103.
79. Anaraki PV, Aminorroaya A, Amini M et al.: Effects of Vitamin D deficiency treatment on metabolic markers in Hashimoto thyroiditis patients. *J Res Med Sci* 2017; 22: 5.

otrzymano/received: 10.11.2017
zaakceptowano/accepted: 30.11.2017