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The role of vitamin D in women with Hashimoto's thyroiditis

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Abstract

Introduction: Autoimmune thyroid diseases (AITD), including Hashimoto's thyroiditis (HT), are the most common organ-specific autoimmune disorders. Vitamin D (vit-D) is a steroid molecule, mainly produced in the skin, which regulates the expression of many genes. The vitamin D receptor (VDR) is found in most tissues and cells in the body. Many studies suggests that vit-D deficiency, which is common worldwide, could also play an important role in autoimmune diseases, including HT. The aim of our study was to show the potential differences in vit-D levels between healthy women and individuals with hypothyroidism and HT. Additionally, we assessed the correlation between vit-D concentration and the level of TSH and anti-thyroid antibodies in females diagnosed with HT.

Material and methods: The study group included 370 subjects. The group was divided into 3 subgroups: (125 — healthy individuals, 111 — hypothyreosis, 134 — HT). Anthropometric measurements including height and weight were obtained in all participants. Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of body height (in metres). The measurement of the thyroid gland was performed using an ultrasound scan with a 10-MHz linear probe by one endocrinologist (Vivid S60N).

Results: We noticed that a lower level of vit-D was connected with a higher level of TSH in each subgroup. There was also strong, negative correlation between TSH and vit-D levels in all the study groups. Moreover, there was a weak, negative correlation between antithyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (anti-TG) and vit-D levels in females with HT regardless of vit-D status: < 20 ng/mL, 20–30 ng/mL, and > 30 ng/mL.

Conclusions: To our knowledge, the current study is the first in Poland to compare vit-D status in healthy patients and patients with hypothyroidism, taking into account the level of antibodies (anti-TPO and anti-TG). The results of our study suggest that vit-D supplementation in patients with hypothyroidism, especially in the course of AITD, although determining its optimal, safe dose requires further research.

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Key words: *vitamin D; Hashimoto's thyroiditis; hypothyreosis*

Introduction

Autoimmune thyroid diseases (AITD), including Hashimoto's thyroiditis (HT), are the most common organ-specific autoimmune disorders [1]. HT is polygenic disease resulting from a combination of genetic predisposition and environmental triggers (iodine, selenium, drugs, irradiation, smoking, infections, stress, etc.), characterized by lymphocytic infiltration into the thyroid gland and production of thyroid-specific autoantibodies [1, 2]. The clinical hallmark of HT is hypothyroidism, determined by lymphocytic destruction of the thyroid gland [3].

Vitamin D (vit-D) is a steroid molecule, mainly produced in the skin, which regulates the expression of many genes [4]. The vitamin D receptor (VDR) is found in most tissues and cells in the body. Many studies suggests that vit-D deficiency, which is common worldwide, could also play an important role in autoimmune diseases, including HT [4, 5]. However, the results are not consistent.

The aim of our study was to show the potential differences in vit-D levels between healthy women and individuals with hypothyroidism and HT. Additionally, we assessed the correlation between vit-D concentration and the level of TSH and anti-thyroid antibodies in females diagnosed with HT.

Material and methods

Participants

The study group included 370 subjects. The group was divided into 3 subgroups: (125 — healthy individuals, 111 — hypothyreosis, 134 — HT). All patients were recruited in the 12 months from March 2021 to January 2022 by the Cardiometabolic Centre Gierach-Med in Bydgoszcz, Poland and the Department of Endocrinology and Diabetology Collegium Medicum University of Nicolaus Copernicus in Bydgoszcz, Poland and provided verbal consent to participate in the study. The mean age of the women studied was 38.2 years, and the standard deviation was ± 4.6 years.

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Table 1. *Characteristics of the study group divided into subgroups according to thyroid function*

Parameters	Total	Healthy individuals	Hypothyreosis	Hashimoto's thyroiditis	p
N	370	125	111	134	NS
Average age ± SD [y]	38.2 ± 4.6	37.9 ± 3.6	39.2 ± 4.8	39.4 ± 5.3	NS
Vit-D level ± SD [ng/mL]	30.18 ± 13.1	34.38 ± 12.6	31.15 ± 10.6	27.01 ± 14.4	< 0.001
Calcium level ± SD [2.25–2.65] [mmol/L]	2.35 ± 0.09	2.37 ± 0.12	2.38 ± 0.11	2.32 ± 0.11	NS
TSH level ± SD [0.3–4.5] [μIU/mL]	**2.41 ± 0.9**	**1.98 ± 0.46**	**3.98 ± 1.2**	**3.77 ± 1.3**	**< 0.001**
fT4 level ± SD [12–22] [pmol/L]	16.94 ± 2.7	17.6 ± 2.4	15.8 ± 2.2	16.9 ± 3.1	NS
BMI [kg/m^2] ± SD	27.6 ± 2.3	26.9 ± 2.1	27.8 ± 2.4	28.2 ± 2.5	NS
L-thyroxine dose [μg] ± SD	–	–	76.3 ± 13.2	55.7 ± 11.8	NS

SD — standard deviation; vit-D — vitamin D; TSH — thyroid-stimulating hormone; fT4 — free thyroxine; BMI — body mass index; NS — non-significant

Anthropometric measurements including height and weight were obtained in all participants. Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of body height (in metres).

The mean dose of L-thyroxine during the study was 55.7 μg per day with a standard deviation (SD) of ± 11.8 μg in hypothyreosis group, and 76.3 μg per day with a SD of ± 13.2 μg in the HT group. Exclusion criteria for the study were postmenopausal women, smoking, patients using drugs that may affect thyroid functions like lithium, amiodarone, steroids, beta blockers, or interferon, patients using drugs that might affect body water-lipid homeostasis like diuretics or oral contraceptives, patients with chronic renal failure, hepatic failure, congestive heart diseases, malnutrition, or malignant diseases, pregnant women, and patients with other known endocrine disorders.

Thyroid gland ultrasonography

The measurement of the thyroid gland was performed using an ultrasound scan (US) with a 10-MHz linear probe using the Vivid S60N. The US was performed in a lying position with the head tilted back in a darkened room. The structure of the thyroid gland and its dimensions were assessed by one endocrinologist.

Biochemical analyses

Venous blood samples were collected from fasting patients for biochemical analyses (thyroid-stimulating hormone [TSH], free triiodothyroinine [fT3], free thyroxine [fT4], antithyroid peroxidase antibody [anti-TPO], antithyroglobulin antibody [anti-TG], calcium, and vit-D). Hypothyreosis was diagnosed on the basis of typical clinical symptoms (tiredness, weakness, dry skin, feeling cold, etc.), decreased fT3, and/or fT4 and increased TSH. This group included patients after thyroidectomy, radioiodine treatment, and other thyroid developmental causes. HT was recognized also on the basis of typical clinical symptoms (weakness, tiredness, dry skin, etc.) connected with decreased fT3 and/or fT4 and increased TSH and additionally the presence of anti-thyroid antibodies, with or without ultrasonography. All tests were performed at the Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum, Bydgoszcz, Poland using a Horiba ABX Pentra 400 analyser (Horiba ABX, Montpelier, France).

Statistical analyses

Statistical analysis was performed using Statistica 10.0 software (StatSoft Poland, Bydgoszcz). The results were expressed as mean ± standard deviation (SD). The Kruskal-Wallis test for independent variables was used for the comparison of the groups, followed by the ANOVA test. The results were considered statistically significant when $p < 0.001$.

Ethic approval

The research protocol was approved by the Ethics Committee at the University Hospital in Bydgoszcz — permission number KB/224/2021. All subjects gave their informed consent for participation in the study. The characteristics of the study groups are presented in Table 1.

Results

We noticed that lower level of vit-D is connected with higher level of TSH in each subgroup (Tab. 2).

Additionally, we marked the correlation between vit-D and TSH and anti-thyroid antibodies (anti-TPO and anti-TG).

There was a strong, negative correlation between TSH and vit-D levels in all the study groups. Moreover, there was also a weak, negative correlation between anti-TPO and vit-D levels in females with HT regardless of vit-D status: < 20 ng/mL, 20–30 ng/mL, and > 30 ng/mL. There was also a weak, negative correlation between anti-TG and vit-D levels in females with HT regardless of vit-D status: < 20 ng/mL, 20–30 ng/mL, and > 30 ng/mL (Tab. 3).

Discussion

One billion people worldwide have vit-D deficiency or insufficiency [6]. Although the biological activities of vit-D are mainly manifested in the regulation of calcium-phosphorus metabolism, studies in the past 30 years indicate that vit-D may play an important role in the immune system. In the past 2 decades, VDRs have

Table 2. *The level of vitamin D (vit-D) in each subgroup.*

Vit-D [ng/mL]	N	Laboratory parameters	Healthy individuals (n = 125)	Hypothyreosis (n = 111)	HT (n = 134)	p
< 20	83		24 (19.2%)	27 (24.3%)	32 (23.8%)	
		TSH [μIU/mL]	2.24 ± 1.2	4.07 ± 2.1	7.17 ± 2.4	< 0.001
		fT4 [pmol/L]	17.02 ± 3.4	14.66 ± 2.8	12.95 ± 2.6	< 0.001
		Ca [mmol/L]	2.24 ± 0.12	2.25 ± 0.09	2.26 ± 0.11	NS
20–30	145		38 (30.4%)	48 (43.2%)	59 (44.1%)	
		TSH [μIU/mL]	1.99 ± 0.9	3.87 ± 1.2	4.27 ± 1.6	< 0.001
		fT4 [pmol/L]	17.26 ± 2.4	15.94 ± 2.2	13.21 ± 2.1	< 0.001
		Ca [mmol/L]	2.35 ± 0.11	2.38 ± 0.07	2.32 ± 0.09	NS
> 30	142		63 (50.4%)	36 (32.5%)	43 (32.1%)	
		TSH [μIU/mL]	1.92 ± 0.7	3.98 ± 1.2	2.72 ± 1.2	< 0.001
		fT4 [pmol/L]	17.89 ± 2.7	17.02 ± 3.2	16.05 ± 3.4	< 0.001
		Ca [mmol/L]	2.39 ± 0.11	2.29 ± 0.12	2.37 ± 0.08	NS

Vit-D — vitamin D; HT — Hashimoto's thyroiditis; TSH — thyroid-stimulating hormone; fT4 — free thyroxine; Ca — calcium; NS — non-significant

Table 3. *Correlation between vitamin D (vit-D) and thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (anti-TPO), and antithyroglobulin antibody (anti-TG) levels*

Parameters	TSH		Anti-TPO		Anti-TG	
Vit-D	r	p	R	p	r	p
Total	–3.235	0.002	–0.3638	0.034	–1.3749	0.026
< 20 [ng/mL]	–4.713	0.001	–0.6764	0.004	–1.6533	0.004
20–30 [ng/mL]	–1.874	0.003	–0.3523	0.045	–1.3568	0.037
> 30 [ng/mL]	–1.356	0.002	–0.3126	0.049	–1.2355	0.022

R — Spearman rho correlation coefficient

been found not only in bone, kidney, and intestine, but also in the immune system (T and B cells, macrophages, and monocytes) [7]. Vit-D determines suppression of T-cell proliferation [8], the final effect of which is a reduction in the number of antigen-presenting cells. It plays a significant role in the modulation of the immune system, enhancing the innate immune response while exerting an inhibitory action on the adaptive immune system [9–11]. The ability of vit-D to suppress the adaptive immune system promotes immune tolerance and appears to be beneficial for a number of autoimmune diseases [9, 12].

A decreased level of vit-D is associated with many autoimmune health disorders such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus [13]. There is also an association between low vit-D status and autoimmune thyroid diseases such as HT [14]. AITD has been thought to be related to unbalanced ratio of T helper cell type 1 (Th1) and Th2 cells. Vit-D plays an important role in regulating Th1, Th2, and Th17 cells, as well as the immunologic mediators [15, 16]. These findings may explain why lower levels of vit-D contribute to thyroid gland immune disorder.

The prevalence of insufficient level of vit-D is very high. According to the Endocrine Society Guidelines, a sufficiency of vit-D is considered when serum 25(OH)D is equal to or greater than 30 ng/mL. Insufficiency is considered when vit-D levels are between 20 and 29.9 ng/mL, while vit-D deficiency is considered when serum 25(OH)D is below 20 ng/mL [17]. In our study vit-D insufficiency or deficiency was observed in 61% of the examined patients. About 70% of the group with vit-D deficiency were patients with hypothyreosis or HT.

In our research, we observed a significantly lower concentration of vit-D levels in patients with hypothyroidism, especially with HT, compared to healthy subjects. The vit-D levels were lower in patients with hypothyroidism and HT compared to healthy individuals (31.15 *vs*. 27.01 *vs*. 34.38, respectively; $p < 0.001$). Kivity et al. reported that the prevalence of vit-D deficiency (25[OH]D level < 25 nmol/L) was higher in people with autoimmune thyroid disease [18]. However, there are

studies which do not confirm such findings. Cvek et al. showed no significant differences in vit-D levels, or proportions of vit-D deficiency between HT patients of all disease stages and healthy controls [19].

In our study there was a strong, negative correlation between vit-D and TSH levels. The higher the TSH level, the lower the observed vit-D concentration. Kim also showed that serum 25(OH)D levels are significantly negatively correlated with serum TSH levels [20]. A recent Chinese meta-analysis of 20 case-control studies showed that AITD patients had lower 25(OH)D levels and were more likely to be vit-D deficient compared to controls [21]. Tamer et al. demonstrated that patients with HT had lower vit-D levels when compared to age- and sex-matched controls. Moreover, vit-D insufficiency (< 30 ng/mL) occurred more frequently in patients with HT rather than in a healthy population [22]. Nevertheless, the authors were not able to demonstrate a significant difference among the degree of vit-D insufficiency between hypothyroid, euthyroid, or hyperthyroid patients with HT, suggesting that vit-D levels do not correlate with the progress of damage to thyrocyte. Kivity et al. reported that the prevalence of vit-D deficiency (25[OH]D level, 25 nmol/L) was significantly higher in 50 patients with AITD compared with 98 healthy individuals (72% *vs*. 30.6%, $p < 0.001$) as well as in 28 patients with HT compared to 42 patients with non-AITD (79% *vs*. 52%, $p < 0.05$). Vit-D deficiency was also found to be correlated with the presence of anti-thyroid antibodies ($p = 0.01$), suggesting the involvement of vit-D in the pathogenesis of AITD [18].

In contrast, a potential role of vit-D in the development or progression of HT has been suggested by Bozkurt et al., demonstrating a correlation between severity of vit-D deficiency and duration of HT, antibody levels, and thyroid volume [23].

In our study, we also observed the relationship between the level of anti-thyroid antibodies and the level of vit-D. There was a weak, negative correlation between anti-TPO and anti-TG and vit-D levels in females with HT regardless of vit-D status: < 20 ng/mL, 20-30 ng/mL, and > 30 ng/mL. Shin et al. reported that 111 patients with elevated anti-thyroid antibodies had lower levels of serum 25(OH)D than 193 patients with no elevation ($p < 0.001$). Moreover, after adjusting for age, a negative correlation ($r = –0.252$; $p<0.001$) was found between 25(OH)D and anti-TPO levels [24]. Ural et al. also reported that serum 25(OH)D levels were inversely correlated with anti-TG ($r = –0.136$; $p = 0.025$) and anti-TPO ($r = –0.176$; $p = 0.003$) antibodies [25]. Wang et al. also showed a negative correlation ($r = –0.121$; $p = 0.014$) between 25(OH)D anti-TG levels, but only in female subjects [26]. Choi et al. analysed 6685 subjects and found significantly lower serum 25(OH)D levels in pre-menopausal women with AITD, but not in postmenopausal women, suggesting a possible link between vit-D and oestrogen in the development of AITD [27]. Moreover, preliminary results of a small randomized controlled trial also showed that vit-D treatment significantly decreased anti-TPO and anti-TG compared with placebo treatment in AITD patients [28].

Limitations of the study: The diet in patients and doses of L-thyroxine were not taken into account. The treatment period with L-thyroxine was also not taken into account.

Conclusions: To our knowledge, the current study is the first in Poland to compare vit-D status in healthy patients and patients with hypothyroidism, taking into account the **level of** antibodies (anti-TPO and anti-TG). The results of our study support vit-D supplementation in patients with hypothyroidism, especially in the course of AITD, although determining its optimal, safe dose requires further research.

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