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Study of the Relationship between Blood Cholecalceferol and Immunological Markers in Patients with Hoshimoto's Thyroiditis

Urunbayeva D. A.
Associate Professor, PhD, Tashkent Medical Academy, Department of Internal Diseases No. 2 and Endocrinology

Najmutdinova D. K.
Professor, DSc, Tashkent Medical Academy, Department of Internal Diseases No. 2 and Endocrinology

Annotation: This article discusses the role of vitamin D in patients with autoimmune thyroiditis (AIT). The authors found that vitamin D levels were low in patients with AIT. In the article, the authors showed an inverse correlation between thyroid-stimulating hormone, antibodies to thyroperoxidase and thyroglobulin and vitamin D content, which indicates that vitamin D deficiency is also one of the pathogenetic links in the course of AIT.

Keywords: vitamin D, autoimmune thyroiditis, hypothyroidism.

Introduction

Autoimmune thyroiditis (another name is Hashimoto's thyroiditis) is a chronic autoimmune inflammatory disease of the thyroid gland with a hereditary predisposition, accompanied by its lymphocytic infiltration with subsequent replacement by fibrous tissue, which is a common cause of primary hypothyroidism [2,11,14,16].

The prevalence of Hashimoto's thyroiditis is 800 cases per 100,000 people when assessed by review of published articles and 4600 cases per 100,000 when assessed by biochemical signs of hypothyroidism and thyroid autoantibodies [1,2,15].

The etiological factors are stress and the environmental situation, leading to surges in adrenaline and cortisol, adrenal insufficiency, with a subsequent decrease in the adaptation syndrome, resulting in an increase in autoimmune diseases, including AIT; Endogenous factors – genetic predisposition; in order to realize a predisposition to the development of an autoimmune disease, additional external factors (viruses, various infections, and others) are required; Individuals who carry histocompatibility antigens HLA DR3 (atrophic form), DR5 (hypertrophic form) are predisposed to AIT [2,4,7].

The disease is caused by a partial defect in immunological control - a deficiency of T-lymphocytes - suppressors, and therefore the survival of a prohibited phorbid clone of T-lymphocytes occurs. The interaction of the forbidden clone of T-lymphocytes with antigens triggers an immune process of the delayed-type hypersensitivity type, inflammatory mediators are released - lymphokines, tumor necrosis factor and other cytotoxic substances. Helper T lymphocytes act on B lymphocytes, which turn into plasma cells and form antibodies to thyroglobulin and the microsomal fraction (TPO). Antibodies on the surface of follicular epithelial cells, combining with killer T lymphocytes, have a cytotoxic effect, causing their destruction, reducing the secretion of T3, T4 and increasing TSH, which leads to an increase in the thyroid gland - goiter (hypertrophic form of AIT) [8,10,17].

Vitamin D is not only the main regulator of calcium-phosphorus metabolism, but also takes part in the control of various processes and functions in the body. The final active substrate, calcitriol, which is formed as a result of step-by-step synthesis from inactive precursors, is, by its mechanism of action and its characteristics, a true hormone D. Vitamin D is involved in calcium metabolism and mineralization of bone tissue [9,18,21]. In addition, vitamin D receptors are located on the surface of immune and cancer cells [11,15,17].

First of all, the role of vitamin D is determined by its effect on the immune system. In this regard, special attention is now paid to the problem of vitamin D provision for patients with autoimmune diseases [10]. Vitamin D receptors have been found on almost all immunocompetent cells: CD4+ and CD8+, lymphocytes, antigen-presenting cells, including macrophages and dendritic cells [5,6,7,17,20]. Vitamin D receptor levels change as immune system cells mature. Naive T lymphocytes contain a small number of receptors, and mature forms are characterized by a high level of expression of the vitamin D receptor. In the process of differentiation of monocytes into macrophages and dendritic cells, the number of vitamin D receptors decreases [8,20]. This pattern reflects the sensitivity of immunocompetent cells to vitamin D, which may play a role in the fine regulation of the immune response. Macrophages, being carriers of vitamin D receptors, show greater sensitivity to vitamin D. Macrophages and dendritic cells themselves synthesize the active form of vitamin D, thanks to the expression of the enzyme a 1-hydroxylase, the activity of which, unlike renal localization, is regulated not by parathyroid hormone, but by cytokines [11,12,17,19].

The purpose of the study was to study the relationship between vitamin D deficiency and immunological markers of the thyroid gland in patients with autoimmune thyroiditis.

Research methods. The study was conducted in the department of 2-therapy and endocrinology of the TMA multidisciplinary clinic. The study included 100 patients aged 18 to 45 years with autoimmune thyroiditis. Among them, 85 (85%) were women and 15 (15%) men, with an average age of 31.5±13.5 years. Laboratory tests were carried out: concentration of vitamin D - 25(OH)D in blood serum, levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), antibodies to thyropyroxidase (TPO-Ab), antibodies to thyroglobulin (TG-Ab), total calcium, as well as ultrasound data of the thyroid gland.

A clinical examination and thyroid ultrasound were performed using a SonoScape SSI-6000 device (China) with a 7.5 MHz sensor at the initial visit, then annually. The obtained values of thyroid volume were assessed according to standards calculated relative to the body surface area. Goiter was diagnosed if the upper limit of normal values was exceeded. The levels of TSH, fT4, as well as the titers of TPO-Ab and TG-Ab in the blood serum were determined by ELISA using a set of reagents from the Alkor Bio company. Normal values were TSH 0.3-4.0 mUl/l, fT4 – 8,9-17,2 ng/ml, TPO-Ab – 0-30 IU/ml, TG-Ab– 0-100 IU/ml. The degree of vitamin D supply was assessed by the level of 25(OH)D in the blood serum (enzyme immunoassay method, Rayto analyzer, China) in 100 women using the criteria of the International Society of Endocrinologists (2011) [13] and the recommendations of the Russian Association of Endocrinologists [3,13]. A value of 25(OH)D in the blood serum above 75 nmol/l (above 30 ng/ml) was taken as a normal supply of vitamin D; a insufficiency was taken as 50 to 75 nmol/l (20-30 ng/ml); deficiency 50 nmol/l (below 20 ng/ml). The combination of an elevated TSH level with normal fT4 was regarded as subclinical hypothyroidism, and with a decreased level – as manifest hypothyroidism.

Statistical processing of the results obtained was carried out using the “STATISTICA for Windows” system in accordance with the type of data and the size of the study groups. The criterion for statistical reliability of the obtained conclusions was considered to be the value $p < 0.05$, generally accepted in medicine.

Results of our own research

An analysis of thyroid hormone levels revealed: euthyroidism in 46 (46.0%) patients, with the average TSH level being 2.9±0.9 mIU/ml; hypothyroidism in 56 (56.0%) patients. Among them, patients with subclinical hypothyroidism (SH) prevailed - 37 (66.0%) compared with manifest hypothyroidism (MH) - 19 (34.0%). According to a hormonal study with SH and MH, the blood TSH content was 7.5±1.5 mIU/ml and 17.3±2.3 mIU/ml ($p<0.001$), fT4 was 10.6±1, 1pg/ml and 7.5±0.9pg/ml, respectively. The control group consisted of 20 people who did not suffer from autoimmune thyroiditis and other thyroid pathologies, with an average age of 32.3±7.9 years. In patients with autoimmune thyroiditis, the average 25(OH)D content was 17.7±3.4 ng/ml ($p<0.05$) versus the control - 26.7±7.9 ng/ml.

Among these patients, 54 (54.0%) had insufficiency, 26 (26.0%) had vitamin D deficiency, determined by the level of 25(OH)D in the blood serum. 20 (20.0%) patients had normal vitamin D levels. In the control group, it was revealed: vitamin D insufficiency in 12 subjects, normal levels of this vitamin in 8 subjects. At the same time, vitamin D deficiency was not detected in the control group. Calcium in the blood of patients ranged from 1.9 to 2.5 mmol/l, on average 2.2±0.5 mmol/l and there were no significant differences in the study group, but in patients with MH this figure was lower and amounted to 1.89±0.05 mmol/l in comparison with the SH and euthyroidism groups.

Table 1. Indicators of thyroid status and immunological markers of the thyroid gland in the examined patients

Parameter	Euthyroidism (n-46)	Subclinical hypothyroidism (n-37)	Manifest Hypothyroidism (n-19)	Control group (n-20)
fT4 (ng/ml)	11,5±3,0	10,6±1,1	7,5±0,9*	14,3±2,9
TSH (mUl/l)	2,9±0,9	7,5±1,5*	17,3±2,3<	2,3±1,1
TPO-Ab(IU/ml)	215,8±30,6*	259,8±37,1*	590±18,1<	17,1±4,5
TG-Ab (IU/ml)	98,4±7,8	104,2±9,9*	111,9±7,3*	57,7±8,5

Note: presence of reliability in relation to control, level of statistical significance *- p<0,05-< p<0,001

The fT4 level in the group with SH was within normal limits, but differed from the control group and was lower by 16%. In patients with MH, this hormone was reduced by 25% (p<0.05). A significant increase in TPO-Ab was detected in patients with MH compared with SH and euthyroidism (590±18.1 IU/ml versus 259.8±37.1 IU/ml and 215.8±30.6 IU/ml, p <0.001). TG-Ab were similarly increased, so in the SH group, this figure was 104.2±9.9 IU/ml (p<0.05), with MH 111.9±7.3 IU/ml (p<0.05) and in the group with euthyroidism 98.4±7.8 (p<0.05), (in the control group this figure was 57.7±8.5 IU/ml).

Table. 2. Vitamin D content in the blood of the examined patients

Parameter	Euthyroidism (n-46)	Subclinical hypothyroidism (n-37)	Manifest hypothyroidism (n-19)	Control group (n-20)
25(OH)D, (ng/ml)	23,5±4,2 (9-31)	19,6±3,2* (11-27)	11,5±2,2* (7-26)	26,7±5,7 (18-39)

Note: presence of reliability in relation to control, level of statistical significance *- p<0,05

The blood level of 25(OH)D in people with SH was reduced and amounted to 19±3.2 ng/ml. Whereas, in individuals with MH, 25(OH)D levels (11.5±2.2 ng/ml) were lower in comparison with the group of patients with euthyroidism by 40% (p<0.05) and by 24% (p<0 .05) with subclinical hypothyroidism. An analysis of the literature data showed that hypothyroidism is associated with immunosuppression, and 25(OH)D deficiency, in turn, has a significant impact on both thyroid function and immunity [19,22].

When conducting an ultrasound examination of the thyroid gland, the volume of the latter averaged 24.7±3.4 sm/3 (p<0.05) compared with the control group - 13.5=2.5sm/3. Comparing the average values of thyroid volume in the control group with the studied groups, it was revealed: the average thyroid volume was 13±2.5sm/3 (control), in the group with MH - 11±3.0 sm/3, SH 24.9±7.2sm/3 (P<0.05) and euthyroidism 23.3±5.9sm/3 (P<0.05). So, in the groups with SH and euthyroidism, the volume of the thyroid gland was higher 48% and 35%, respectively, in comparison with the group with MH. At the same time, hypertrophic form was detected in 45 (45%), atrophic in 9 (9%) and diffuse nodular forms of thyroid in 31 (31%) patients. The remaining patients have 15 (15%) the volume of the thyroid gland was within normal values.

To compare whether there is a relationship between the studied parameters, we conducted a correlation analysis. A study of correlation analysis showed that there are certain connections between 25(OH)D

deficiency in the blood and thyroid hormone levels - TSH and immunological markers, for example, the level of 25(OH)D in the blood negatively correlated with TSH (-60), TPO-Ab - (-0,89) (P<0.001), TG-Ab (-0.76) (P<0.001) blood. The same relationship was found between insufficiency and normal levels of 25(OH)D in the blood with TSH and immunological markers. A negative relationship was found between 25(OH)D and TSH (-0.43) (P<0.05), with TPO-Ab (-0.56) (P<0.05) and TG-Ab (-0.44) (P<0.05). A negative relationship was also found in the group with normal 25(OH)D levels with TPO-Ab (-0.34) (P<0.05) and TG-Ab (-0.31) (P<0.05). This means that 25(OH)D levels affect the course of autoimmune thyroiditis, exacerbating immunological disorders. Screening for 25(OH)D deficiency according to foreign authors is recommended for all patients with AIT, especially if there are functional impairments [11]. A positive relationship was also found between total calcium and 25(OH)D levels in the D-deficient and D- insufficiency groups.

Table 3. Correlation analysis between the level of 25(OH)D in the blood and hormonal and immunological parameters in the examined women.

	Coefficient value Spearman rank correlation (R)		
Parameter	**Normal content of 25(OH)D, 30-100 ng/ml n-54**	**25(OH)D deficiency, <20 ng/ml n-26**	**25(OH)D insufficiency, 20-30ng/ml n-20**
fT4 (ng/ml)	0,20	-0,49*	-0,41*
TSH (mUl/l)	0,22	-0,60*	-0,43*
TPO-Ab (IU/ml)	-0,34*	-0,89**	-0,56*
TG-Ab (IU/ml)	-0,31*	-0,76**	-0,44*
Total calcium, mmol/l	0,23	0,45*	0,49*

Note: Statistical significance level *- p<0,05; **-p<0,001

In conclusion, it should be noted that there is no clear answer to the question of whether 25(OH)D deficiency is the cause of the development of AIT, but it has a certain significance in the course of the disease. This is indicated by the presence of a relationship between the level of 25(OH)D in the blood and hormonal and immunological markers of the thyroid gland. It is necessary to examine the level of 25(OH)D in the blood and, if there is a deficiency, fearlessly prescribe therapeutic doses of this vitamin in order to maximize the effectiveness of therapy for autoimmune thyroiditis.

CONCLUSIONS:

1. In patients with autoimmune thyroiditis, the 25(OH)D content is probably lower (17.7±3.4 ng/ml) than in practically healthy individuals (26.7±7.9 ng/ml; p<0.05). Among the patients, 25(OH)D insufficiency prevailed, which was present in 54.0%, deficiency in 26.0%, and normal levels in 20.0% of patients.
2. A probable positive correlation was established between the content of 25(OH)D and total calcium, as well as a negative probable correlation with the level of TSH, TPO-Ab and TG-Ab. Thus, data from a correlation analysis showed that there are certain connections between 25(OH)D deficiency in the blood and thyroid hormone levels - TSH and immunological markers, while the level of 25(OH)D in the blood negatively correlated with TSH (-60), TPO-Ab (- 0.89) (P<0.001), TG-Ab (- 0.76) (P<0.001) blood. A positive relationship was also found between total calcium and 25(OH)D levels in the D-deficient and D- insufficiency groups.
3. It is necessary to examine the level of vitamin D in the blood and, if there is a deficiency, fearlessly prescribe therapeutic doses of this vitamin in order to maximize the effectiveness of therapy for autoimmune thyroiditis.

Summary

In recent years, the importance of 25(OH)D in the treatment of autoimmune thyroiditis has been highlighted in many scientific works. 25(OH)D mainly plays an important role in calcium-phosphorus metabolism. In addition, the presence of vitamin D receptors in all organs and tissues of the human body indicates that this vitamin plays an important role in the human body. Vitamin D has receptors in human immune cells and acts as an immunomodulator. Vitamin D also plays a role in the treatment of autoimmune diseases of the thyroid gland. Several studies have shown a negative correlation between this vitamin and immune markers in patients with autoimmune thyroiditis.

In this study, it was involved the patients with autoimmune thyroiditis who applied to the Multy-Specialty clinic of the Tashkent Medical Academy.

In the examined patients, the amount of 25(OH)D in the deposit (17.7±3.4 ng/ml; r<0.05) was found to be lower than in the control (26.7±7.9 ng/ml). According to the results of the correlation analysis, in patients diagnosed with vitamin D deficiency, the amount of 25(OH)D in the deposit and TTG (-60), TPO-Ab (-0.89) (R<0.001), TG-Ab (-0.76) (R<0.001) was found to have a negative reciprocal feedback. The results once again proved that the amount of vitamin D in the blood is important in the disease process in these patients.

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