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Research Article

Relationship Between Vitamin D and Autoimmune Condition and Thyroid Function with Newly Onset Grave's Disease

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Abstract

Vitamin due to the presence of the receptor (VDR), which is found in almost all nuclear cells is an important regulator in the pathogenesis of many diseases. The question of the causal relationship between vitamin D deficiency and Graves 'disease and the importance of this vitamin for thyroid function in the treatment of Graves' disease deserves special attention. The aim of the study was to investigate the level of 25- (OH) D in the body in Graves' disease and its relationship with thyroid function. We examined 143 patients who were first diagnosed with moderate Graves' disease (GD). All patients studied by us, residents of Ukraine, 67% of them live in Kyiv, 19% in Kyiv region, 14% in other regions of Ukraine. The average age of the subjects was 43.8 ± 0.95, among whom were men 22.4%, women - 77.6%. The analysis of immune parameters and thyroid function depending on the age of patients, the content of vitamin D in the serum, and its quartile distribution before treatment. Subsequently, all patients were divided into two groups depending on the therapy. The first group included 73 subjects, whose average age was 44.69 ± 1.39, patients in this group received tyrosol at a dose of 5 - 10 mg per day. The second group consisted of 70 patients. whose average age was 42.93 ± 1.29, they took tyrosol at a dose of 5-10 mg per day and vitamin D preparations - 2000 MO/day. In patients with Graves' disease. the highest content of 25- (OH) D in serum was observed in the age group of 19-30 years -59.1 nmol/l and a low level of antibodies to the TSH receptor - 9.0 mUi/l. A significant decrease in the immune index was observed only in the 3rd and 4th quartiles, when the content of 25- (OH) D in the serum reached 47.5 nmol/l and above, i.e. approached a moderate deficit. At a slight increase to 34 nmol/l, such changes were insignificant. After 3 months of treatment, the level of AbrTSH in the serum during treatment with vitamin D was twice lower than when treated with tyrosol alone. After 6 months, compared with the treatment with tyrosol, the effect of treatment was 2 times better. In contrast to TPOAbs in Graves' disease without treatment with vitamin D, where it did not differ depending on the level of 25 (OH) D, in the second group after 6 months of treatment there was a significant decrease in this indicator (p = 0.009). Compared to tyrosol treatment alone, there was a significant increase in TSH levels and a decrease in thyroid volume after 6 months. Data on the dependence of thyroid function on the level of 25 (OH) D were indicative. In each of the quartiles, the level of TSH after treatment with vitamin D was 4-5 times higher than in the group of patients treated only with tyrosol. Convincing data on the positive effect of vitamin D on autoimmune parameters, thyroid function and the need for its inclusion in the treatment of Graves' disease.

Keywords: Thyroid, Graves' Disease, Tyrosol, Vitamin D, TSH, TSH Receptor, Antibodies to Thyroxine Peroxidase, Free Thyroxine, Free Triiodothyronine, Thyroid Volume, Risk Factors

Abbreviations

1,25(OH)2D: 1,25-dihydroxyvitamin D; 25(OH)D: 25-Hydroxyvitamin D; VDR: Vitamin D Receptor; FT3: Free Triiodothyronine; FT4: Free Thyroxine; TSH: Thyroid Stimulating Hormone; AMP: Adenosine Monophosphate; GD: Grave's Disease; TPOAb: Thyroid-Peroxidase Antibody; TRAb: Thyrotropin-Receptor Antibody; rTSH: TSH Receptor; AbrTSH: TSH Antibody Receptor

Introduction

In the pathogenesis of many diseases, much attention is paid to vitamin D, which is an important regulatory factor in the human body. For many years, vitamin D has been considered an important regulator of calcium metabolism in the body and in the pathogenesis of renal osteodystrophy. Deficiency of this nutrient is the cause of most cases of rickets and can cause bone loss and osteoporosis in the elderly [1]. Subsequent studies have shown that vitamin D is a necessary factor in regulating cell growth and differentiation, plays the role of a steroid hormone, has effects in many organs, and is an important factor in the pathogenesis of many diseases [2]. Vitamin D has been shown to exert its effect by binding to the vitamin D receptor (VDR). Vitamin receptors are found in all cells that have a nucleus, their genomic activation will regulate a large number of genes, so it can affect different organs [3]. Vitamin D exists in several forms, but its metabolite 25 is hydroxy calciferol (25- (OH) D). Importantly, the concentrations of 25- (OH) D in the body are under genetic control, using mononucleotide polymorphisms (SNRs) around the genes involved in the synthesis, metabolism and transport of vitamin D [4,5]. Recently, there have been increasing reports that the metabolic enzymes VDR and vitamin D are involved in various parts of innate and adaptive immunity, which is of great clinical importance [6]. The link between the endocrine system and vitamin D intake is completely logical, but the specific question arises as to what the real relationship is between vitamin D levels and disease. Consideration of scientific research over the past 20 years regarding the role of cellular and humoral immunity in the occurrence of autoimmune thyroid diseases shows their important participation in adaptive and innate immunity [7]. The most common of these are autoimmune thyroiditis (Hashimoto's disease) and autoimmune thyrotoxicosis (Graves' disease). The prevalence of hyperthyroidism is 1.2 - 1.6% of them 0.5 - 0.6 overt and 0.7 - 1% subclinical [8]. The most common manifestation of this disease is Graves' disease.

Graves' disease is an organ-specific autoimmune disease, the main manifestation of which is the formation of circulating autoantibodies to the thyroid-stimulating hormone receptor. Binding of antibodies to the TSH receptor increases the production of intracellular AMP, resulting in the release of thyroid hormones and hyperplasia of thyrocytes. The importance of vitamin D in the pathogenesis of Graves' disease has been the subject of research in recent years in various countries [9-12]. Due to Graves' disease, specialists are studying the supply of this vitamin to the population and its effect on immune parameters and thyroid function. In Ukraine, this issue is being studied [13].

Aim of the Study

The aim of this study was to investigate the effect of vitamin D on autoimmune parameters and thyroid function in Graves' disease.

Materials and Methods

In order to perform the tasks in the open controlled study included 143 patients who applied to the consultative clinic of the VP Komissarenko State Institution "Institute of Endocrinology and Metabolism Natl. Acad. Of Med.Sci. of Ukraine" in the period 2017-2020. Patients were first diagnosed with moderate Graves' disease (GD). All patients studied by us, residents of Ukraine, 67% of them live in Kyiv, 19% in Kyiv region, 14% in other regions of Ukraine. The study involved patients of both gender with clinical manifestations of GD verified according to international diagnostic standards and able to meet the requirements of the study protocol. The average age of the subjects was 43.8 ± 0.95 years, men were 22.4%, women - 77.6%. Exclusion criteria were: age of patients younger than 19 years and older than 65; severe dysfunction of internal organs, kidneys and liver; disorders of the hematopoietic system; pregnancy; patients taking other antithyroid drugs for previously diagnosed severe and mild GD; patients with the presence of nodules of the thyroid gland; patients with moderate and severe orbitopathy; patients taking drugs that contain vitamin D and mineral supplements with selenium; chemotherapy or radiotherapy for malignant tumors the previous 5 months; patient incompatibility. All patients in our study were divided into two groups depending on the therapy. Thus, the first group included 73 subjects, aged 44.69 ± 1.39, the second group consisted of 70 patients, aged 42.93 ± 1.29, patients in both study groups received tyrosol in the initial dose of 20-30 mg per day with the subsequent transition to

maintenance doses of 5-10 mg per day as the disease compensates. Patients of the second group, in addition to thyrostatic therapy, depending on the indicators of 25- (OH) D serum received vitamin D preparations, in a daily dose of 1000 to 4000 IU, followed by switching to maintenance doses of 2000 IU per day. Ultrasound examinations of the thyroid gland were performed with the device "Toshiba" SSA-580A and "Ultima" RA GRIS.941217.01343. The size of the thyroid gland was determined according to the recommendations of Brunn [14]. Ultrasound was performed before therapy and 3 and 6 months after treatment. When assessing thyroid volumes in adults: the level of free fractions of thyroid hormones (FT4, FT3) and thyroid-stimulating hormone (TSH) in venous blood serum was determined by radioimmunoassay using standard kits from Immunotech (Czech Republic) designed to quantify these hormones. Normal values for FT4 were 11.5 - 23.0 pmol/l and FT3 2.5 - 5.8 pmol/l, the reference values of TSH were in the range of 0.17 - 4.05 mUi/ml. To determine the presence of autoimmune processes in the thyroid gland, the levels of circulating antibodies to the TSH receptor (AbrTSH) and antibodies to thyroid peroxidase (TPOAbs) were examined. When determining the level of AbrTSH in the serum used automatic immunochemiluminescent system IMMULITE 2000 which uses recombinant human TSH receptors (rTSH), so by determining the stimulating autoimmune antibodies, the differential diagnosis of Graves' disease is reliable (sensitivity 98.3%, specificity 99.7%). Normal values of AbrTSH were considered to be not exceeding 0.5 mUi/l. Antibodies to thyroid peroxidase were determined by enzyme-linked immunosorbent assay with chemiluminescent detection using Hema-Medica test kits (Switzerland). The concentration of antibodies from 0 to 35 mUi/l was considered normal. When determining the level of 25- (OH) D in the serum used an automatic immunochemiluminescent system IMMULITE 2000. The unit of measurement is nmol/l. The content of 25- (OH) D in the serum below 25 was considered as a clear deficiency, below 50 nmol/l - is considered a deficiency of vitamin D, at its level from 50 to 75 nmol/l - inadequate intake of vitamin D, and at values above 75 nmol/l - normal supply of vitamin D. Levels of free fractions of thyroid hormones (FT4, FT3), TSH, AbrTSH, TPOAbs, and 25- (OH) D serum were determined in patients before treatment and after 3, 6 months after starting therapy with tyrosol and vitamin D drugs. Before starting therapy, all patients underwent a complete biochemical blood test, general urine test to exclude the presence of acute infectious processes, severe liver and kidney dysfunction. In order to identify possible cellular disorders in the hematopoietic system on the background of tyrosol, a clinical blood test was performed once every 10 days, and in the transition to maintenance doses of the drug once a month. Criteria for the effectiveness of therapy in addition to the elimination of the clinical picture of thyrotoxicosis was the normalization of laboratory parameters: FT4, FT3, TSH, AbrTSH. In addition to antithyroid therapy, patients received beta-blockers, potassium supplements and, if necessary, sedatives.

Statistical data processing was performed in accordance with the requirements of evidence-based medicine and biostatistics, using the approaches of modern non-infectious epidemiology [15,16]. The statistical package used the software package SPSS 16.0. and MedStat [17]. Mann-Whitney criteria were used for odd comparisons, and Wilcoxon criteria were used for related samples, and $p < 0.05$ values were considered to be significantly significant.

Ethical approval for the study was obtained from the V.P. Komissarenko Institute of Endocrinology and Metabolism Ethics Committee (protocol no. 7; 29.11.2018). All participants were briefed about the study and gave informed written consent to participate.

Results

Its metabolite of vitamin D-25-(OH) D is physiologically active in the body. To study the dependence of immune status and thyroid function on sex, age of patients, and the level of 25-(OH) D, the analysis of indicators in the combined group of patients - 143 patients before treatment. It was found that among the patients there were 32 men and 111 women, i.e. the number of women with Graves was 4 times greater than men. The minimum age of patients was 19 years, the maximum -65. Accordingly, the age categories of 19 - 30 years were 21 (14.68%), 30 - 49.9 years-76 (53.15%), 50 years and older - 46 (32.17%). Most patients were aged 30 - 49.9 years. Existing publications indicate the dependence of serum vitamin D on the age of patients. In this study, in patients with Graves' disease, the highest content of 25-(OH) D in serum was observed in the age group 19 - 30 (Table 1). This group had the lowest antibody titer to the TSH receptor. With age, the content of 25- (OH) D in the serum decreased, so in the age group 30 - 49.9 years compared with the age group up to 30 years, it was lower by 21%, and in the group 50 years and older twice less. Accordingly, the reverse nature of serum AbrTSH levels was observed depending on age. In the age group of 50 years and older, the content of AbrTSH was 2.5 times

higher than in the group under 30 years. Among other indicators, a significantly increased thyroid volume in the group of 50 years and older compared to the indicator in the group up to 30 years.

Because of these data, it was important to examine other indicators depending on the level of vitamin supply. Existing supply criteria for Central Europe distinguish levels: significant insufficiency < 25 nmol/l, obvious insufficiency -25 - 50 nmol/l, moderate insufficiency 50 - 75 nmol/l, satisfactory supply of more than 75 nmol/l vitamin D [18,19]. The distribution of data on the content of 25-(OH) D showed that in the first group there were 25 patients, in the second group 71 patients, in the third - 41, in the area of normal support only 2 cases (1.4%) (Table 2). These data indicate that almost all patients with Graves' disease are deficient in vitamin D. Due to the small number of cases, the level of satisfaction is not included in the table for analysis. When analyzing the data, there were differences only in the level of AbrTSH in the 2nd and 3rd groups compared to the first.

Parameters	Up to 30 years	30-49,9 years	50 years and older	p1	p2	p3
25-(OH)Д nmol/L	59.1 [45.6-64.2]	46.0 [34.0-54.27]	25.6 [18.47-36.80]	0.001	0.000	0.000
AbrTSH mUi/L	9.0 [4.42-17.60]	17.1 [12.33-25.88]	21.9 [11.15-31.17]	0.005	0.002	0.246
TSH mUi/ml	0.01 [0.005-0.020]	0.00815 [0.001-0.030]	0.01 [0.0012-0.030]	0.930	0.823	0.754
TPOAbs mUi/L	500.0 [325.1-600.0]	400.0 [246.25-555.75]	400.0 [218.72-599.5]	0.145	0.128	0.737
FT4 pmol/L	28.30 [26-30.1]	28.89 [26.1-37.2]	31.30 [27.43-38.525]	0.310	0.016	0.118
FT3 pmol/L	9.9 [7.80-14.45]	12.0 [10.202-18.09]	11.9 [10.07-18.50]	0.049	0.075	0.952
Thyroid volume, cm^3	29.06 [24.12-47.83]	41.99 [31.11-58.39]	50.02 [29.23-76.64]	0.078	0.011	0.267

Table 1: Immunological parameters and thyroid function depending on the age of patients with Grave's disease.
Note. p1 - 30-49.9 against up to 30 years; p2 -50 years and older against the group up to 30 years;
p3 - group 30-49.9 years against 50 years and older.

The abnormal data distribution of the number of observations in different groups did not allow for a detailed analysis of the dependence of immune status and thyroid function depending on the level of 25- (OH) D. With this in mind, we divided the data on the content of 25- (OH) D in the serum into 4 uniform quartiles and performed the corresponding calculations (Table 3). The number of surveyed in each quartile was the same - 36 cases, except for the first quartile where there were 35 cases, which was not of fundamental importance for calculations. In each subsequent quartile, the content of 25- (OH) D increased uniformly almost linearly. Accordingly, in each subsequent group, the content of vitamin D was significantly higher than in the previous group. The most important indicator of Graves' disease is the content of AbrTSH in the serum.

A significant decrease in the immune index was observed only in the 3rd and 4th quartiles, when the content of 25- (OH) D in the serum reached 47.5 and above nmol/l, i.e. approached a moderate deficit. At a slight increase to 34 nmol/l, such changes were insignificant. With this quartile distribution of data, among other indicators, the increased level of TSH in the 4th quartile compared to the second and the decrease in the level of T4, which indicates the possibility of changes in thyroid function during treatment with vitamin D.

Parameters	Up to 25 nmol/L	25-49,9 nmol/L	50-75 nmol/L	p1	p2	p3
	n = 29 (20.28%)	n = 71 (49.65%)	n = 41 (28.67%)			
25-(OH)Д nmol/L	17.7 [11.90-21.0]	37.2 [31.85-45.80]	57.4 [55.10-62.20]	0.000	0.000	0.000
AbrTSH mUi/L	26.0 [13.1-37.4]	17.2 [11.6-28.42]	12.8 [6.5-19]	0.154	0.001	0.007
TSH mUi/мl	0.008 [0.001-0.03]	0.008 [0.001-0.027]	0.01 [0.002-0.04]	1.000	0.430	0.257
TPOAbs mUi/L	400.0 [238.9-671.]	358.0 [209.0-599.0]	490.0 [312.0-598.0]	0.568	0.522	0.081
FT4 pmol/L	29.0 [26.40-34.4]	30.1 [27.20-38.50]	28.0 [25.76-35.0]	0.414	0.311	0.049
FT3 pmol/L	12.1 [10.36-19.7]	12.2 [10.10-18.75]	11.54 [9.11-14.45]	0.779	0.156	0.101
Thyroid volume, cm^3	49.14 [29.18-86.4]	43.62 [28.55-59.42]	41.73 [29.06-49.09]	0.217	0.081	0.403

Table 2: Immunological parameters and thyroid function depending on the provision of vitamin D in patients with Graves' disease.

Note. p1 - up to 25 nmol/l vs 25-49.9; p2 - up to 25 vs 50-75; p3 - 25-49.9 vs 50-75 nmol/l.

Parameters	Q1	Q2	Q3	Q4	p1	p2	p3	p4	p5
	n = 35 (24.48%)	n = 36 (25.17%)	n = 36 (25.17%)	n = 36 (25.17%)					
	Up to 27	27.0-42.2	42.3-52.4	52.5 and higher					
	Q1	Q1-Me	Me-Q3	Q3					
25-(OH)Д nmol/L	18.2 [12.6-24.2]	34.0 [30.40-36.75]	47.5 [45.0-49.17]	59.0 [56.60-64.9]	0.000	0.000	0.000	0.000	0.000
AbrTSH mUi/L	22.9 [12.85-36.90]	17.6 [12.22-28.70]	17.45 [11.35-25.42]	11.9 [6.42-19.10]	0.398	0.223	0.002	0.006	0.036
TSH mUi/мl	0.008 [0.002-0.035]	0.005 [0.001-0.02]	0.007 [0.001-0.032]	0.01 [0.004-0.040]	0.304	0.991	0.522	0.045	0.561
TPOAbs mUi/L	400.0 [264.45-686.0]	352.0 [200-555.25]	355.0 [256-525]	494.0 [340.775-590.5]	0.303	0.394	0.616	0.092	0.095
FT4 pmol/L	29.0 [26.5-35.4]	32.1 [27.27-38.37]	30.15 [27.71-38.90]	27.8 [25.51-30.68]	0.311	0.641	0.072	0.006	0.024
FT3 pmol/L	12.1 [10.29-20.55]	12.15 [9.52-18.01]	11.5 [10.12-17.02]	11.6 [9.16-14.51]	0.704	0.565	0.236	0.359	0.386
Thyroid volume, cm^3	48.06 [28.15-86.43]	44.9 [33.49-58.48]	45.2 [28.82-55.63]	38.2 [28.92-48.33]	0.581	0.414	0.151	0.180	0.401

Table 3: Analysis of immune parameters and thyroid function depending on the quartile distribution of vitamin D (median, Q1 - Q4) in serum before treatment.

Notes. p1 -Q1 vs Q2; p2 -Q1 vs Q3; p3 -Q1 vs Q4; p4 -Q2 vs Q4; p5 -Q3 vs Q4.

Tyrosol treatment has an important positive effect on thyroid function. To determine the additional effect of vitamin D, the effects of tyrosol treatment were compared with tyrosol combined with vitamin D after 3 and 6 months of treatment (Table 4).

Parameters	3 months of treatment		6 months of treatment		P1	P2
	Group 1	Group 2	Group 1	Group 2		
	ME [Q1 - Q3]	ME [Q1 - Q3]	ME [Q1 - Q3]	ME [Q1 - Q3]	.000	.000
25-(OH)D nmol/L	44.2 [28.0-51.89]	50.55 [40.55-62.45]	45.0 [32.8-52.1]	69.9 [60-75.12]	.001	.000
AbrTSH mUi/L	8.99 [4.10-12.60]	4.38 [1.56-9.20]	2.17 [0.90-4.20]	1.2 [0.62-2.02]	.000	.000
TSH mUi/ml	0.34 [0.17-0.76]	1.38 [0.92-2.23]	1.12 [0.92-1.54]	2.11 [1.60-2.65]	.215	.020
TPOAbs mUi/L	344.0 [260-500]	320.0 [187.7-52.0]	359.0 [288-515]	299.0 [175-500]	.009	.067
FT4 pmol/L	16.1 [12.5-18.3]	13.7 [11.7-15.9]	13.8 [12.2-16.5]	14.8 [13.3-16.1]	.003	.392
FT3 pmol/L	3.95 [2.88-4.49]	3.12 [2.70-3.92]	3.11 [2.66-3.76]	3.12 [2.88-3.93]	.446	.159
Thyroid volume, cm3	41.22 [26.54-58.08]	32.1 [25.14-55.80	41.6 [26.45-55.1]	30.4 [23.44-53.57]	.000	.000

Table 4: Comparison of groups of patients on therapy with tyrosol (group 1) and tyrosol + vitD (group 2) after 3 and 6 months from the start of treatment.

Note. P1 - in comparison with group 1 after 3 months of treatment; P2 - compared with group 1 after 6 months of treatment according to the Mann-Whitney test.

Due to the appointment of vitamin D in the second group compared to the first level of 25 (OH) D was significantly higher after 3 and 6 months of treatment. Vitamin D treatment had a positive effect on the normalization of serum AbrTSH levels.

After 3 months of treatment, the level of AbrTSH in the serum during treatment with vitamin D was twice lower than when treated with tyrosol alone. After 6 months, compared with treatment with tyrosol, the effect of treatment was 2 times better. It is important that in contrast to the indicators of TPOAbs in Grave's disease without treatment with vitamin D, where it did not differ depending on the level of 25 (OH) D, after 6 months of treatment there was a significant decrease in this indicator (p = 0.009). It is impossible not to note another positive effect of vitamin D. Compared to tyrosol treatment alone, there was a significant increase in TSH levels and a decrease in thyroid volume after 6 months.

Taking into account these data and the results of the quartile analysis shown in table 3, we also divided the data obtained during treatment with tyrosol and tyrosol with vitamin D into 4 quartiles and performed the analysis in each quartile.

Quarters of 25 (OH) D after 3 months in the control group were almost the same as in the group examined in table 3. After 3 months where the difference between the level of 25 (OH) D in the groups was quite significant, the level of AbrTSH after vitamin

D in 3-th quartile was twice lower than in the treatment of tyrosol alone. In the 4th, this effect of vitamin D treatment was almost 9 times better (Figure 1).

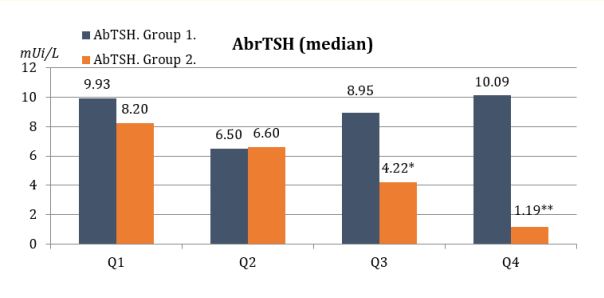

Figure 1: The content of AbrTSH (mUi/L) (median) in the serum depending on the quartile distribution of 25 (OH) (nmol/l) after 3 months of treatment.

Note. *p = 0,02, **p = 0,0001.

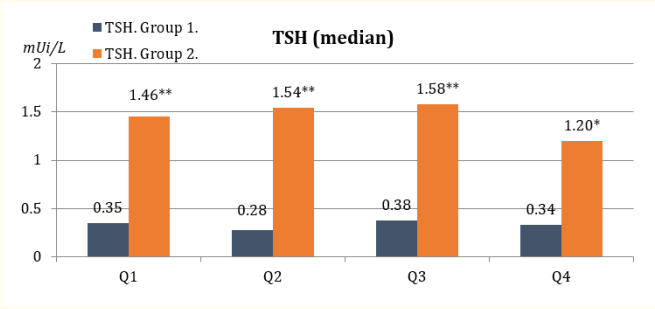

Figure 2: The level of TSH (mUi/L) (median) in the serum depending on the quartile distribution of 25 (OH) (nmol/l) after 3 months of treatment.

Note. *p < 0,05, **p < 0,001.

Data on the dependence of thyroid function on the level of 25 (OH) D were indicative. The positive effect of increasing TSH levels after vitamin D administration was observed in all quartile groups. In each of the quartiles, the TSH level after vitamin D treatment was 4-5 times higher than in the group of patients treated with tyrosol alone.

Almost the same positive, statistically significant effect with a decrease in FT4 levels was observed in the first, second and fourth quartile groups. The level of FT3 in the first and 3rd quartiles was significantly reduced.

Thus, convincing data on the positive effect of vitamin D on autoimmune parameters, thyroid function and the need for its inclusion in the treatment of Graves' disease.

An important criterion for the reliability of changes is the ROC analysis. Figure 3 shows the results of the ROC analysis of the effect of vitamin D on AbrTSH.

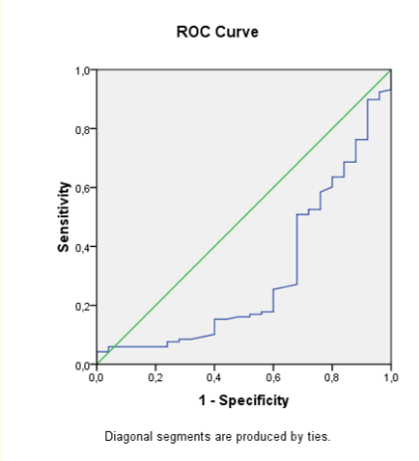

Figure 3: ROC analysis of the effect of vitamin D on AbrTSH after 6 months of treatment.

Area Under the Curve				
Test Result Variable(s):Vit_D_dec				
			Asymptotic 95% Confidence Interval	
Area	Std. Error	Asymptotic Sig.	Lower Bound	Upper Bound
0,303	0,062	0,002	0,182	0,424

Table a

ROC analysis of the chances of having elevated AbrTSH levels before treatment and 6 months after the start of vitamin D treatment showed a significant reduction in the results curve compared to the midline of no change. The area under the curve was significantly less than 0.5, which confirms the reduction of risks. Similar reliability was found for 3 months of vitamin D treatment relative to the median AbrTSH.

Discussion and Conclusion

In newly diagnosed 143 Graves patients, vitamin D deficiency and high titers of antibodies to TSN receptors were found. At low levels of vitamin D the titer of antibodies to AbrTSH was significantly higher than at high levels. This trend was observed in patients of different age groups, where with age the content of vitamin D in the serum decreased, and the titer of AbrTSH increased. When analyzing the data of the level of vitamin D in the serum and the content of TSN, free T3 and free T4, no significant changes were revealed before treatment. A more thorough analysis using the quartile uniform distribution of serum vitamin D results also found no effect of vitamin D deficiency on thyroid function prior to treatment. In this regard, our results confirm the previously published studies [20]. After treatment with tyrosol, we found a decrease in the titer of antibodies to the TSH receptor, improved thyroid function. Adherence to the vitamin D treatment regimen significantly reduced the titer of antibodies to TSH compared with treatment with tyrosol alone. At the same time, 3 months after the start of treatment, the titer of antibodies to TPO, the level of free thyroxine and the volume of the thyroid gland also decreased. Six months after the start of treatment, there was an even greater decrease in the titer of antibodies to TSH receptors and a significant increase in the level of TSH in the blood. Uniform quartile distribution of the results of vitamin D in the groups and analysis of thyroid function confirmed a significant increase in TSH levels in each of the quartiles in the group of patients receiving additional vitamin D after 3 months of treatment. The effect of vitamin D on the titer of AbrTSH will be explained by the immunomodulatory effect of vitamin D on different parts of innate and adaptive immunity [21].

The active form of vitamin D 1.25 $(OH)_2D_3$, has anti-inflammatory action, inhibits chemotaxis and antigen presentation of dendritic cells (DCs), regulates the decrease in the expression of costimulating molecules CD40, CD80 and CD86, as well as the main complex of compatibility II molecules (MHC II), which reduces antigen uptake, activation of naive T cells and inhibition of autoimmunity. 1.25 $(OH)_2D_3$ can affect the maturation and migration of DCs, performing an immunoregulatory role, and affects the production of cytokines and chemokines [22]. It is necessary to take into account the effects of vitamin on innate immunity. Experiments on mice show an increase in the activity of NK cells under the influence of dietary supplements of vitamin D [23].

Particularly positive effect of vitamin D is observed on acquired immunity Under the influence 1.25 $(OH)_2D_3$ significantly reduces proinflammatory cytokines TNF-α, IFN-γ and IL-1β, as well as the chemokine IL-8 after stimulation with bacterial ligands HK19F and LPS (in 3 - 53 times) and increases anti-inflammatory IL-10 (twice, $p = 0.016$) after stimulation of HK19F monocytes isolated from peripheral blood (PC) of healthy individuals [24]. Vitamin D inhibits T-lymphocyte proliferation and modulates cytokine production and differentiation with different effects on different T-lymphocyte subpopulations. 1.25 $(OH)_2D_3$ plays an important role in the regulation of Th1, Th2 and Th17 cells, as well as the secretion of IFN-γ, IL-4 and IL-17. However, 1.25 $(OH)_2D_3$ induces cell differentiation and increases the activity of Treg cells, which leads to increased anti-inflammatory action mediated by TGF-β and IL-10. Vitamin D can regulate Th17/Treg imbalance by increasing Treg and inhibiting Th17 cell differentiation [25]. Stimulation of Treg cell activity may be one explanation for how vitamin D may have a protective effect against autoimmune diseases.

This means that the lower the levels of vitamin D in the blood of patients with Grave's disease, the higher the activity of the disease. Using vitamin D in optimal doses, in our opinion, it is possible to prevent autoimmune diseases or alleviate their clinical manifestations. The research we are planning to conduct in the near future is designed not only to deeply investigate the exact mechanism of the link between vitamin D deficiency and Grave's disease, but also to answer a number of practical questions: patients with GD, whether the inclusion of vitamin D in the complex treatment scheme can have a significant positive effect on the activity and rate of disease progression in persons with an established diagnosis. Thus, a deep understanding of the role of vitamin D deficiency in the etiopathogenesis of GD will contribute to the development of new approaches to the prevention and comprehensive treatment of this pathology.

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