EJONS International Journal on Mathematic, Engineering and Natural Sciences ISSN 2602 - 4136

Article Arrival Date 27.07.2020 | Article Type Research Article | Article Published Date 15.09.2020

Doi Number: http://dx.doi.org/10.38063/ejons.299

THE RELATIONSHIP BETWEEN ANTI-TPO AND VIT D IN DIFFERENT AGE GROUP PATIENTS WITH OTOIMMUN THYROIDITIS DISORDER

Ünsal GÜNDOĞDU

University of Health Sciences Izmir Bozyaka Education and Research Hospital, Medical Biochemistry, Izmir, Turkey

ORCİD: 0000 0002 6442 6671

ABSTRACT

Objective: The results of studies conducted to investigate the relationship between autoimmune thyroid diseases (AITD) and vitamin D are different. The aim of our study is to investigate the relationship between anti-TPO and vitamin D in patients divided into different age groups with autoimmuntyroid disorder.

Methods: Between January 2019 and July 2019, test data of 625 patients who came to our laboratory with the diagnosis of autoimmuntyroid disorder were retrospectively examined.447 patients were divided into four groups (0-25), (25-65, (66-90), (20-84). 178 patients with low and normal Vit-D levels were examined in two separate groups (Group A, Group B) (Table 2). Patients with a vitamin D level less than <20 ng / mL constituted Group A, and patients with a Vit D level higher than ≥20 ng / mL constituted Group B.

Results: The proportion of patients with vitamin D deficiency was approximately 56%. In our study, 625 patients with positive autoimmune antibody test were divided into six groups and examined. No significant relationship was found between Vit D levels and Anti-TPO in all six groups (P> 0.05).

Conclusion: We could not find a significant relationship between the pathogenesis of AITD disease according to the specific age groups and Vit D levels of the patients. More research is needed to fully understand the role of vitamin D levels in autoimmuntyroid disorder.

Keywords: Autoimmun Hypothyroidism, Vit-D,Antithyroid Peroxidase Antibodies(anti-TPO).

1.INTRODUCTION

Thyroid disorders are a group of disease that are common in Turkey and in the world. Chronic autoimmune thyroiditis (KrOT), which consists of a group of diseases such as Hashimoto thyroiditis, chronic lymphocytic thyroiditis, chronic goiter thyroiditis and chronic atrophic thyroiditis, develops due to impaired person's tolerance to thyroid autoantigens (Table1). KrOT is the most common cause of primary hypothyroidism and the most common among thyroid diseases, except in areas with iodine deficiency. It occurs in approximately 2% of the society (1,2). Chronic autoimmune thyroiditis (KrOT) is an autoimmune disease with anti-TPO or anti-TG positivity. Cellular immune response plays more role in its pathogenesis. These patients have autoantibodies that are developed against high concentrations of thyroid antigens in their serum. 95% of patients are women. Hypothyroidism develops at a rate of 5% per year in women which have both anti-TPO and anti-TG antibodies are positive and TSH is high. (3,4)

Autoantibodies formed by the thyroid gland against its own antigen were first described at Hashimoto thyroiditis in 1956. High levels of anti-TPO or anti-TG levels in the patient serum enables the diagnosis of KrOT(Chronic autoimmune thyroiditis). Anti-TPO positivity in 90-100% in KrOT and 65-80% in Basedow-Graves disease. Anti-TG positivity is 60-70% in KrOT and 20-40% in Graves disease. Anti-TPO positivity is used in the diagnosis of Hashimoto's disease. Various autoimmune mechanisms, including CD8 + T cells, cytokines and antithyroid antibody mediated cytotoxicity, have been proposed in the pathogenesis of the disease. (5,6). Vitamin D, unlike conventional vitamins, is synthesized in the body, therefore it is called hormone.The effects of vitamin D on calcium homeostasis and bone metabolism have been investigated for many years. However, studies in the last 20-25 years have shown us that vitamin D has many more functions than these known functions. Today, it is known that vitamin D deficiency plays a role in the formation of autoimmune diseases, inflammatory bowel diseases, rheumatoid arthritis, multiple sclerosis, diabetes, many types of cancer and heart diseases (7,8,9,10).

Table.1 Types of autoimmune thyroiditis (11)

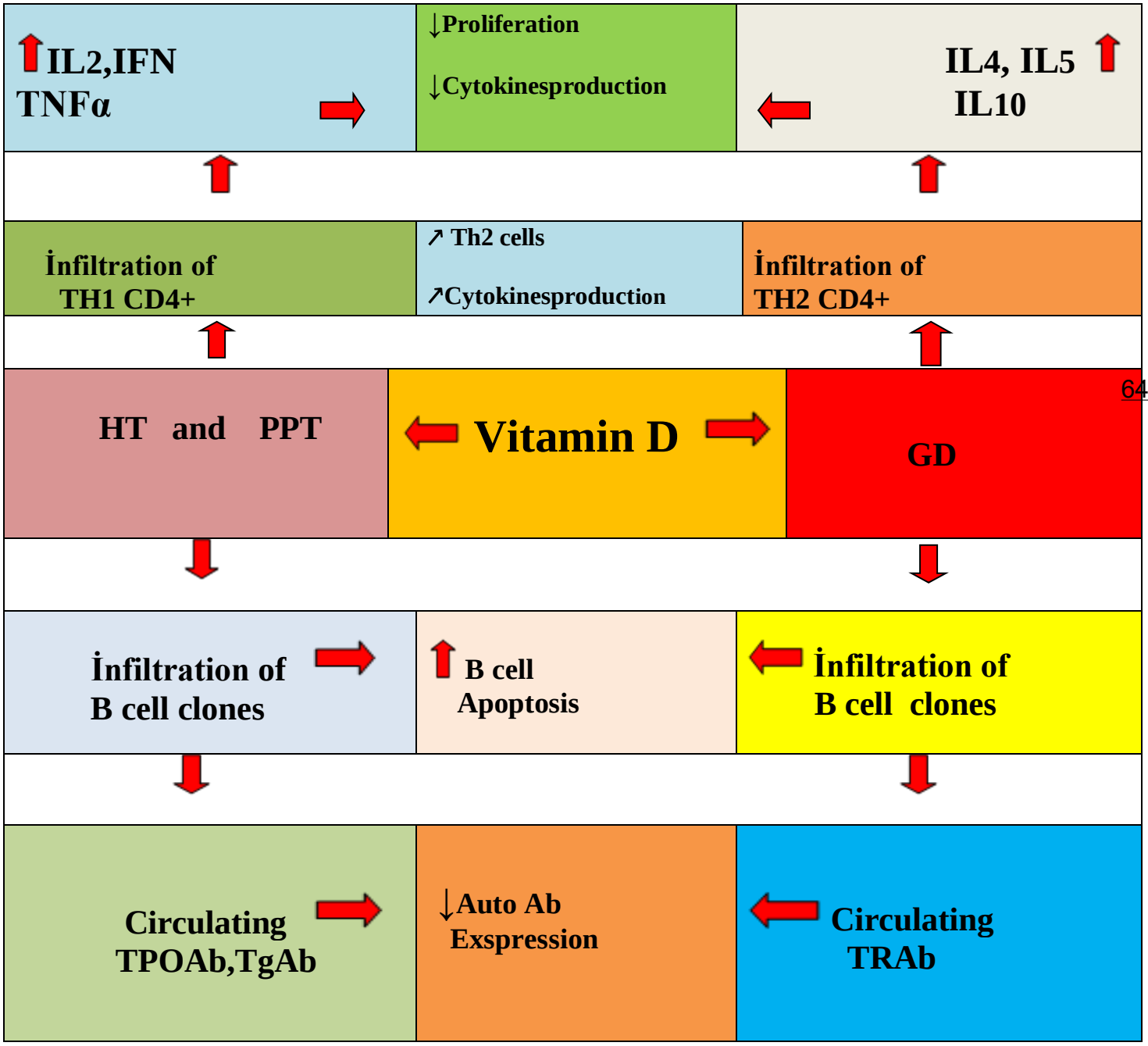
Types of autoimmune thyroiditis	The course of the disease	Appearance of the disease
Goiter (Hashimoto) thyroiditis	**Chronic**	**Enlarged goiter Lymphocytic infiltration Thyroid cell hyperplasia**
Atrophic thyroiditis (Pr. Miksödem)	**Chronic**	**Atrophy Fibrosis**
Juvenile thyroiditis	**Chronic**	**Lymphocytic Infiltration**
Postpartum thyroiditis	**Temporary May turn into chronic thyroiditis**	**Small Goiter Lymphocytic Infiltration**
Subakut lymphocytic thyroiditis	**Temporary**	**Small Goiter Lymphocytic Infiltration**
Focal thyroiditis	**May progress**	**At autopsy 20%**

The discovery of vitamin D receptors (VDR) in many tissues led to these studies. The presence of vitamin D receptors (VDR) in many immune system cells, especially active T and B lymphocytes, active macrophages and antritic cells such as dentritic cells (12), drew attention to the role of vitamin D in immune regulation. In 1993, S. Yang et al. Found that high-dose vitamin D had an immunosuppressive effect. This feature of vitamin D suggests that there may be new possibilities to control autoimmune diseases.Vitamin D has strong immunomodulatory effects (Figure 2). The active form of vitamin D, 1,25 dihydroxy vitamin D3 (1.25 (OH) 2D3) suppresses the proliferation of T helper (Th) 1 cells and reduces producing of cytokine (interferon (IFN) and interleukin (IL -2) from these cells. (13).Vitamin D increases production of transforming growthfactor, which suppresses IL-4 and inflammatory T cell activity from Th2 cells. Chen and her friends suggested that vitamin D may also play a role in regulating antibody production. She showed that 1,25(OH)2D3 not only suppresses the proliferation of B cells but also induces the apoptosis of B

cells. Epidemiological studies have shown a relationship between vitamin D deficiency and autoimmune diseases such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus and autoimmune thyroiditis. [14-15]

Figure 2.Scheme of theimmuno modulating role of vitamin D

Abbreviations :autoAb, autoantibodies; **GD**, Graves' disease; **HT**, Hashimoto'sthyroiditis; **IFN**, Interferon**; IL**, Interleukin; **PPT**, Post-partumthyroiditis; **Th**, T helper; **TNF**, TumorNecrosisFactor; **TPOAb**, anti-thyroidperoxidaseantibodies; **TgAb**, anti-thyroglobulinantibodies; **TRAb**, TSH receptorautoantibodies.



Hashimoto Thyroiditis is the most common auto immune thyroiditis in society.In this disease, the thyroid gland is targeted by lymphocytes, and hormone production is disrupted as a result of subsequent damage (16).Based on the effects of vitamin D on the immune system, it has been suggested that vitamin D may play a role in the pathogenesis of Hashimoto thyroiditis. Indeed, studies have found that vitamin D receptor (VDR) polymorphism increases the frequency of Hashimoto thyroiditis (17)

2.MATERİALS AND METHODS

Test data belonging to 625 patients who applied to our hospital laboratory between January 2019 and July 2019, diagnosed with Autoimmuntiroid disorder, and who had Anti-TPO, Anti-TG, Vit-D, TSH, FT4 and FT3 tests simultaneously studied were retrospectively evaluated. To investigate the relationship between Anti-TPO and Vitamin D level, patients were examined in four different groups according to age ranges and Vitamin D levels: Group 1 (mean age,21.8±2.5, age range, 0-25), %93 female, %7 male), Group 2 (mean age, 45 ± 11.3, age range, 25-65, %96 female, %4 male), Group 3(mean age, 73.7 ± 5,3, age range, 66-90, %87 female, %13 male), Group 4(mean age, 46.2 ±14.9, age range 20-84, %92 female, %8 male)(Table 1).In addition, in order to investigate the effect of Vitamin D deficiency directly on Anti-TPO and thyroid function tests, patients with Vit-D deficiency and patients with normal Vit-D level were collected in two groups. Group of patients with Vit-D <20 ng /ml (Group A). Patient group with Vit-D ≥20 ng / ml (Group B). Group A(mean age, 32.5±18,3, mean Vitamin D, 12.4 ±4.0 ng/ml, %96 female, %4 male), Group B(mean age, 43 ± 20.3 ng/ml, mean Vitamin D, 29.3± 8.3 ng/ml, %91 female, %9 male)(Table 2).These tests were studied in UniCelDxI 800 (BeckmanCoulterDiagnostics, USA) immunoassay device by chemiluminescence method using 3 different level control serum (low, normal, high).Statistical analyzes were performed in IBM SPPP 25 statistical program.Since our data did not show normal distribution, it was decided to use nonparametric tests.

Nonparametric Spearman correlation test was used to calculate the correlations between Anti-TPO and other tests(Vit-D, Anti-TG, FT4,FT3 and TSH) in different four age groups.Kruskal-Wallis variance analysis test was used to compare the Anti-TPO test between four different age groups.Nonparametric Mann Whitney U test was used to calculate the difference between two independent groups (Group A, Group B).

3.RESULTS

In our study, 415 of 447 patients in four different age groups who were diagnosed with Autoimmune Thyroiditis, who have positive anti-TPO and Anti-TG tests, are female and the remaining 32 are male. The rate of male patients are 7.7% and the rate of female patients are 92.3%.The patients were divided into four groups according to different age ranges, Group1 ((0-25 years), Group2 (25-65 years), Group 3 (66-90 years) and Group 4 (20-84 years) (Table 1).Two other patient groups (Group A, Group B)were created to reveal the relationship between Vitamin D and Anti-TPO.Patients with vit-D levels below 20 ng / ml were collected in Group A and patients with Vitamin D levels above 20 ng / ml were collected in Group B (Table 2).There were a total of 178 patients in both groups (Group A(n=101, Group B (n=77) (Table 2).The proportion of patients with vitamin D deficiency was found to be about 56%.Vit-D levels were below <20 ng / ml in all groups except Group 3 with the highest average age (73.7 ± 5.3).The average of Group1 was 18.9 ± 9.6 ng / ml, the average of Group2 was 18.1 ± 8.5 ng / ml, and the average of Group 4 was 17.0 ±

8.0 ng / ml. In Group 3, the mean Vit-D level was calculated as 22.3 ± 15.4 ng / ml.Group A's Vit-D level average (12.4 ± 4.0) ng / ml, Anti-TPO level average (320.9 ± 304.3), Group B's Vit-D level average (29.3 ± 8.3) ng, / ml, Anti -TPO level average was calculated as (274.4 ± 279.9).Anti-TPO average of Group B was about 17% lower than Group A.While the mean of Vit-D level (22.3 ± 15.4ng / ml) of Group 3 is higher than the average of the other 3 groups (Group 1, Group 2, Group 4), the average of Anti-TPO level (185.0 ± 203.6) is lower than the other three groups. found) (Table 1).Four groups with different age ranges (Group 1, Group 2, Group 3, Group 4) were compared using Nonparametric Kruskall-Wallis test in terms of Anti-TPO, Anti-Tg, FT4, FT3 and TSH test parameters.According to the test result, a significant difference was found between the groups ($p < 0.05$).However, according to Mann-Whitney U test results in the other two groups (Group A, Group B), no significant difference was found between the Anti-TPO tests of the two groups. ($P > 0.05$).However, no significant correlation was found between Anti-TPO and Vit-D test levels in any group ($r = -0.05$, $p > 0.05$).Demographic data and parameters of the patients are given below (Table 2, 3).

Table 2. Demographic data and Biochemical parameters (Group1, Group2, Group3, Group4)

Variables	(0-25)Age n= 102 Group1	(25-65)Age n=140 Group2	(66-90)Age n=60 Group3	(20-84)Age n=145 Group4
Age(Years)	21.8±2.5	45 ± 11.3	73.7 ± 5,3	46.2 ±14.9
Sex(F/M %	102(95/7) % 93/7	140(135/5) % 96/4	60(52/8) % 87/13	145(133/12) % 92/8
Anti-TPO	317.1±312.7	268.3 ± 265.6	185.0 ±203.6	294.4 ±276.8
Anti-TG	99.3±308.1	63.6 ± 269.1	107.3 ±250.8	104.6 ±334.2
Vitamin D	18.9±9.6	18.1 ± 8.5	22.3 ±15.4	17.0 ±8.0
FT4	0.81±0.1	0.8 ± 0,4	0.8 ±0.1	0.9 ±0.5
FT3	3.5±0.5	3,4 ± 1,4	3.1 ±0.4	3.6 ±1.1
TSH	3.5±	3,8 ± 1,4	2.9 ±2.2	4.0 ±6.5

Table 3. Biochemical parameters of Group A and Group B

Variables	GrupA (Vit-D<20 ng/ml)	GrupB (Vit-D≥20 ng/ml)
Age(Years)	32.5±18,3	43 ± 20.3
Sex(F/M) %	101(97/4) %96/4	77(70/7) %91/9
Anti-TPO	320.9±304.3	274.4± 279.9
Anti-TG	121.0±337.3	67.6 ± 219.9
Vitamin D	12.4 ±4.0	29.3± 8.3

FT4	0.8±0.3	0.8 ± 0,1
FT3	3.5 ±1.0	3,2±0.4
TSH	3.3 ±3.3	4.0±5.4

Correlation coefficients and significance levels calculated for each group of patients between Anti-TPO and Age, Anti-TG, Vit D, FT4, FT3 and TSH tests are given below.

Table 3. Correlations and significance levels in Group 1

Anti -TPO	**r [a]**	**P**
Yaş	-0,01	>0,05
Anti-TG	0,08	>0,05
Vit D	-0,15	>0,05
FT4	-0,21	<0,05×
FT3	-0,01	>0,05
TSH	0,29	<0,05
Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.		

Significant correlations were found between Anti-TPO levels and FT4, TSH levels in Group 1 respectively, r= -0.21; P <0,05, r:=0.29; P <0.05)(Table 3). Correlation between anti-TPO and vit-D was insignificant (r=-0,15;P>0,05) Group 1 (Table 3).

Table 4.Correlations and significance levels in Group 2

Anti -TPO	**r [a]**	**P**
Yaş	0,01	>0,05
Anti-TG	0,20	<0,05×
Vit D	-0,02	>0,05
FT4	0,03	>0,05
FT3	0,07	>0,05
TSH	0,10	>0,05
Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.		

Correlation between anti-TPO and anti-TG was significant(r=0,20;P<0,05) in Group2.Correlation between anti-TPO andvit-D was insignificant (r=--0,02;P>0,05) in Group2 (Table 4).

Table 5. Correlations and significance levels in Group 3

Anti -TPO	r [a]	P
Yaş	-0,15	>0,05
Anti-TG	0,29	<0,05×
Vit D	0,19	>0,05
FT4	-0,19	>0,05
FT3	0,04	>0,05
TSH	0,14	>0,05

Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.

Correlation between anti-TPO and anti-TG was significant(r=0,29; P<0,05) in Group3.Correlation between anti-TPO and vit-D was insignificant (r=-0,19;P>0,05) in Group3 (Table 5).

Table 6. Correlations and significance levels in Group 4

Anti -TPO	r [a]	P
Yaş	-0,10	>0,05
Anti-TG	0,09	>0,05
Vit D	-0,05	>0,05
FT4	-0,13	>0,05
FT3	-0,04	>0,05
TSH	0,20	<0,05×

Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.

Correlationbetween anti-TPO and TSH was significant(r=0,20;P<0,05) in Group4. Correlationbetween anti-TPO andvit-D was insignificant (r=--0,05;P>0,05) in Group4 (Table 6).

Table 7. Correlations and significance levels in Group A

Anti -TPO	r [a]	P
Yaş	-0,15	>0,05
Anti-TG	0,14	>0,05
Vit D	-0,12	>0,05
FT4	-0,28	<0,01×
FT3	0,05	>0,05
TSH	0,16	>0,05

Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.

Correlation between anti-TPO and FT4 was significant(r=0,20;P<0,01) in GroupA (Table7). Correlation between anti-TPO and Vit D wasinsignificant (r=- 0,12;P>0,05) in Group A (Table 7).

Table 8.Correlations and significance levels in Group B

Anti-TPO	r [a]	P
Yaş	-0,13	>0,05
Anti-TG	0,31	<0,01×
Vit D	0.14	>0,05
FT4	-0,10	>0,05
FT3	0,01	>0,05
TSH	0,16	>0,05

Correlations is significant (p<0,05)×, [a] Spearman rho correlation coefficient.

Correlation between anti-TPO and anti-TG was significant(r= 0,31;P<0,01) in Group B (Table8).

4.DISCUSSION:

Many scientific studies have been conducted on autoimmune thyroids and Vit-D. In a study conducted in Korea, Shin and colleagues investigated the relationship between vitamin D and TPO-Ab in patients with and without autoimmune thyroid (AITD(18)). They showed a significant negative correlation between vitamin D level and TPO-Ab in patients with AITD(20). In a study conducted in Turkey, Bozkurt and colleagues examined the relationship between vitamin D deficiency is with Hashimoto's thyroiditis(19). They showed a correlation between increased vitamin D deficiency and thyroid volume, thyroid autoantibody(Anti-TPO) level, and Hashimoto's thyroiditis duration. They concluded that vitamin D may play a potential role in the development and progression of hypothyroidism in Hashimato thyroiditis (20). They also showed that the risk of occurrence of Hashimoto's thyroiditis will decrease by 19% with increases in vitamin D levels of 5 ng / mL (21,22).

On the other hand, some studies did not support the relationship between vitamin D and thyroid autoimmunity(23,24,25,26,27,28).In a study by Effraimidis et al., They compared the vitamin D level of euthyroid individuals with a genetic predisposition to AITD and those who had positive anti-TPO-Ab test.Their findings showed that the vitamin D level of euthyroid participants with a genetic predisposition to AITD's was higher than the control group, but there was no significant difference between the newly diagnosed autoimmune thyroid patient group and the control group (29).D'Aurizio et al. Also found no association between low vitamin D levels and AITD's (30).Our result is similar to them.

In our study, 447 patients with positive autoimmune antibody tests were divided into four different age groups (Group 1,2,3,4) and 178 patients were divided into two groups (Group A, B) that were low and normal compared to Vit-D level. No significant relationship was found between Vit D levels and Anti-TPO in all six groups (P> 0.05).

In addition, according to the results of Mann-Whitney U test applied to 178 patients collected in two groups (Group A, Group B) according to Vit-D test levels, there was no significant difference between the two groups according to Anti-TPO(P> 0.05).The average of Vit-D level in the patient group (, Group 3) with the oldest patients (66-90 years) is normal compared to other age groups.We think that patients in this age group gain experience over time, pay attention to their treatment and control, and take regular vitamin D.Anti-TPO level was also the lowest in this group (185.0 ± 203.6 IU / ml) (Table 1).

In this retrospective study, we could not find a relationship between vitamin D levels and thyroid antibody levels in patients with autoimmune thyroiditis.

5.CONCLUSION:

We investigated the relationship between Vit-D levels and A-TPO levels in patients diagnosed with autoimmuntiroid disorder and positive anti-TPO test, and its effect on thyroid function.Our results showed that Vit-D has no significant effect on thyroid function and autoimmunity.Further clinical trials are needed to better understand and fully illuminate the role of vitamin D levels and autoimmune mechanisms in autoimmune thyroiditis.

References:

1.Kumar V, Abbas A, Aster J. Robbins "Temel Patoloji". 9.baskı. İstanbul, Nobel Tıp Kitabevleri. 2013;723-4.

2.Wang C, Crapo LM. Theepidemiology of thyroiddis ease and implications for screening. Endocrinol Metab Clin North A 1997;26:18.

3.Tunbridge WM, Vanderpump MP. Populationscreeningforautoimmunethyroiddisease. EndocrinolMetabClin North Am 2000;29:2

4.Bravermann LE, Utiger RD. "WernerandIngbar'sTheThyroid". 9th ed. Philadelphia, JB Lippincott. 2005.

5.Chistiakov DA. Immunogenetics of Hashimoto'sthyroiditis. J AutoimmuneDis 2005;2:1.

6.Li D, Cai W, Gu R, et al. Th17 cellplays a role in thepathogenesis of Hashimoto'sthyroiditis in patients. ClinImmuno 2013;149(3):411-20.

7. Hollick MF. Sunlightand vitamin D for bone healthandprevention of autoimmune

diseases, cancerand cardiovasculardisease. Am J ClinNutr 2004; 80 (6suppl): S1678- 88.

8. Ward LM. Vitamin D deficiency in the 21st century: a persistent problem among

Canadianinfantsandmothers. CMAJ 2005; 172:769- 70.

9. Holick MF. The Vitamin D epidemicanditshealthconsequences. J Nutr 2005; 135:2739- 48.

10. Heaney RP. Long-latencydeficiencydisease: insightsfromcalciumand vitamin D. AmJ ClinNutr 2003; 78: 912- 9.

11.Weetman PA, Section B: Causes of hypothyroidism, chronic autoimmune thyroiditis, In: Lewis E.B, Robert D.U,eds, Werner's & Ingbar's, The Thyroid, Philadelphia, Baltimore, New York. Lippincott Williams& Wilkins, 8.edition 2000; S. 731- 732.

12. Mathieu C, Van Etten E, Decallonne B, Guilietti A, Gyseman C, Bouillon R et al.Vitamin D and 1,25 dihydroxyvitamin D3 as modulators in immunsystem. J SteroidBiochem MolBiol 2004; 89- 90: 449- 52.

13. Mathieu C. Adorini L. Thecomingage of 1,25 dihydroxyvitamin D3 analogs asİmmunomodulatory agents. TrendsMolMed 2002; 8: 174- 9.

14. Holick MF. Vitamin D: importantforprevention of osteoporosis, cardiovascularheartdisease, type 1 diabetes, autoimmunediseases, andsomecancers. South Med J 2005; 98: 1024- 7.

15.Cutolo M, Otsa K, Uprus M, vd. (2007): Rheu'da D Vitamini -matoidartrit. AutoimmunRev 7: 59-6

16. N Bozkurt, B Karbek, B Ucan, M Sahin, E Cakal, M Ozbek, T Delibasi. Endocrine Practice 19 (3), 479-484, 2013 .

17. Lin WY, Wan L, Tsai CH, Chen RH, Lee CC, Tsai FC. Vitamin D receptor gene polymorphismsareassociatedwith risk of Hashimoto'sthyroiditis in Chinesepatients in Taiwan. J ClinLab Anal 2006; 20: 109- 12.

18..Shin DY, Kim KJ, Kim D, Hwang S, Lee EJ. Low serum Vitamin D is associated with anti-thyroid peroxidase antibody in autoimmune thyroiditis. Yonsei Med J 2014;55:476-81.

19..Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of Vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract 2013;19:479-84.

20..Mackawy AM, Al-Ayed BM, Al-Rashidi BM. Vitamin D deficiency and its association with thyroid disease. Int J Health Sci (Qassim) 2013;7:267-75

21.Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of Vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract 2013;19:479-84.

22.Cardoso-Sánchez LI, Gómez-Díaz RA, Wacher NH. Vitamin D intake associates with insulin resistance in type 2 diabetes, but not in latent autoimmune diabetes in adults. Nutr Res 2015;35:689-99

23.Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, et al. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol 2011;8:243-7.

24.Mansournia N, Mansournia MA, Saeedi S, Dehghan J. The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis. J Endocrinol Invest 2014;37:473-6.

25.Tamer G, Arik S, Tamer I, Coksert D. Relative Vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid 2011;21:891-6.

26.Arslan MS, Topaloglu O, Ucan B, Karakose M, Karbek B, Tutal E, et al. Isolated Vitamin D deficiency is not associated with nonthyroidal illness syndrome, but with thyroid autoimmunity. ScientificWorldJournal 2015;2015:239815.

27.Unal AD, Tarcin O, Parildar H, Cigerli O, Eroglu H, Demirag NG. Vitamin D deficiency is related to thyroid antibodies in autoimmune thyroiditis. Cent Eur J Immunol 2014;39:493-7

28..Jie May, Di Wu, Chengyang Li Nannan Chao, Jing Lui. Lower Serum 25-Hydroxyvitamin D Level is Associated With 3 Types of Autoimmune Thyroid Diseases.Baltimoure 2015:96-3

29.Effraimidis G, Badenhoop K, Tijssen JG, Wiersinga WM. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. Eur J Endocrinol 2012;167:43-8.

30.Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is Vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? Autoimmun Rev 2015;14:363-9.