

The relationship between Hashimoto's thyroiditis and vitamin D and the inflammatory marker platelet-to-lymphocyte ratio

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ABSTRACT

Aim: Hashimoto's thyroiditis (HT) is a chronic autoimmune-mediated disease that leads to overt hypothyroidism. Vitamin D is essential for immunity. This study examines possible impacts of vitamin D on the progression of HT and evaluates the use of platelet-lymphocyte ratio (PLR) as an indicator of its relationship with the inflammatory process.

Material and Method: This is a retrospective case-control study, consisting of 60 individuals with HT and 40 healthy controls. Thyroid function tests, thyroid antibodies, vitamin D levels, erythrocyte sedimentation rate (ESR), parameters of complete blood count and C-reactive protein (CRP) levels were scanned retrospectively using participants' medical files between September 2018 and March 2019. Platelet count was divided by lymphocyte count to determine PLR.

Results: HT patients had both considerably lower median vitamin D levels and higher percentages of vitamin D deficiency than the controls [12.08 (8.79–17.00) vs. 20.09 (20.00–34.00) and 80% vs. 22.5%, respectively, $p < 0.001$). Vitamin D deficiency was also higher within the hypothyroid HT group than in the euthyroid HT group ($p < 0.001$). The vitamin D levels of HT patients with subclinical hypothyroidism were lower than those with euthyroidism ($p < 0.004$). The study groups showed no differences regarding CRP levels, higher levels of ESR were reported only in the overt hypothyroid patients ($p = 0.001$), and higher PLRs were found in those euthyroid HT patients. Vitamin D was negatively correlated with TSH and anti-thyroid peroxidase (anti-TPO) levels ($r = -0.294$, $p = 0.023$; $r = -0.281$, $p = 0.030$, respectively). A positive correlation existed between TSH and anti-TPO ($r = 0.411$, $p = 0.001$) and ESR ($r = 0.365$, $p = 0.002$), but TSH and PLR were negatively correlated ($r = -0.390$, $p = 0.002$).

Conclusion: According to these findings, vitamin D may play a role in the transition to the hypothyroid phase in HT patients, and thus, vitamin D replacement may inhibit this progression. Moreover, our results indicate that PLR may not be a good inflammatory indicator for vitamin D-deficient HT patients.

Keywords: Hashimoto's thyroiditis, vitamin D, platelet lymphocyte ratio, autoimmune thyroiditis, hypothyroidism, inflammation

INTRODUCTION

Hashimoto's thyroiditis (HT) may lead to overt hypothyroidism at a rate of approximately 5% every year (1,2). Environmental and genetic factors are thought to play a vital role in this chronic autoimmune-mediated disease, but the etiology is unclear. A better explanation of the underlying causes and factors that influence the progression to the hypothyroid stage can significantly benefit efforts to prevent and control the disease.

Vitamin D is essentially formed in the skin. It performs regulatory functions for the expression of more than 200 genes directly or indirectly (3). Vitamin D primarily maintains the homeostasis in calcium and phosphorus and regulates the metabolism of bone. However, the widespread existence of vitamin D receptors (VDR) in

various cells and tissues throughout the body indicates that vitamin D might carry out additional functions beyond bone tissue (4). It has been shown that this type of vitamin has a chief role in adaptive and innate immunity (5). Vitamin D-deficient individuals are inclined to have a higher incidence and greater severity of autoimmune disorders (6). While several studies suggest that autoimmune thyroid diseases and deficiency of vitamin D are associated, how low vitamin D levels affect HT remains unclear (7,8).

Neutrophil, lymphocyte, and platelet measurements are inexpensive and easily measurable indicators for inflammation in various diseases. While neutrophil numbers increase and lymphocytes decrease in stress

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states, thrombocytosis is observed in inflammation (9). The neutrophil-to-lymphocyte ratio (NLR) increases in autoimmune thyroid diseases (AITD) (10). Similarly, some studies detected high platelet-to-lymphocyte ratios (PLR) among patients with AITD (11-14).

The study examines the probable influence of vitamin D on the clinical progression of HT patients and explores the use of PLR as an indicator of its relationship with the inflammatory process.

MATERIAL AND METHOD

This retrospective case-control study was conducted in the internal medicine and endocrine outpatient clinics of a tertiary referral hospital. The study protocol was in accordance with the Declaration of Helsinki. The researchers received ethics committee approval of the Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 30.05.2019, Decision No: 32/2019). The data on patient and control groups were collected through retrospective scanning of the medical records of the cases from September 2018 through March 2019. The study included one hundred participants, consisting of 60 individuals with HT (20 with euthyroidism, 20 with subclinical hypothyroidism, and 20 with overt hypothyroidism) and 40 healthy controls. The participants were matched for body mass index (BMI), age, and gender. HT was diagnosed based on the findings of high titers of anti-thyroglobulin (anti-TG) antibodies or anti-thyroid peroxidase (anti-TPO), followed by confirmation of thyroiditis by thyroid ultrasound examination. HT patients were classified according to thyroid function tests. While thyroid function tests were normal and only those with high thyroid antibodies were classified as euthyroid, patients with increased thyroid stimulating hormone (TSH) levels and normal levels of free triiodothyronine (fT3) and free thyroxine were diagnosed with subclinical hypothyroidism. Overt hypothyroidism was defined as having both low fT3 and/or fT4 levels as well as high TSH levels. The study included individuals between the ages of 18 and 65. Pregnant women, individuals with acute or chronic infections, chronic illnesses such as hypertension, diabetes mellitus, kidney disease, cardiovascular disease, liver disease, parathyroid gland disorders, smokers, and those who consume alcohol were excluded from the study. Individuals who have taken vitamin D medications or supplements which influence the metabolism of vitamin D and those who use any thyroid hormone replacement, immunosuppressive agents, anti-inflammatory drugs, or antibiotics were also not included in the study.

Age, gender, and BMI of each participant, 25(OH) vitamin D3, thyroid function tests, thyroid antibody levels, leukocyte, lymphocyte, neutrophil, and platelet counts, C-reactive protein (CRP) values, and erythrocyte sedimentation

rate (ESR) were recorded from the medical files. Vitamin D levels were categorized based on the following criteria: levels of ≥ 30 ng/mL were considered sufficient, levels between 20 ng/mL and 30 ng/mL as insufficient, and levels below 20 ng/mL as vitamin D-deficient.

Complete blood count parameters (leukocytes, neutrophils, lymphocytes, and platelets) were analyzed by the auto analysis method on the Coulter LH 780 Analyzer device from the blood taken into the tube with ethylenediamine tetraacetic acid (EDTA) anticoagulant. The platelet count was divided by the lymphocyte count to calculate PLR. Anti-TG and Anti-TPO antibodies, fT3, fT4, and TSH were quantified by means of the electrochemiluminescence method on a Roche Cobas 8000 chemistry analyzer (Rotkreuz, Switzerland). Tandem gold liquid chromatography-tandem mass spectrometry (Zivak Technologies, Turkey) was used for 25 (OH)D3 measurements and evaluated using the Dvit-Dia Source kits through the radioimmunoassay method.

Statistical Analyses

The data analyses were fulfilled through the SPSS version 23.0 (IBM Corp., Armonk, NY). The descriptive statistics examined within the scope of the study consisted of mean, median (interquartile range), standard deviation, percentiles, and number of cases. For study group comparisons, the Mann-Whitney U test and Student's t-test were utilized. Furthermore, ANOVA and the Kruskal-Wallis test were utilized to compare more than two groups according to the Kolmogorov-Smirnov normality test. Fisher's exact chi-square and Pearson's chi-square tests were employed to analyze categorical data. Pearson and Spearman correlation analyses were performed for correlations. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The sample consisted of 60 HT patients (20 euthyroid, 20 subclinical, and 20 overt hypothyroid) and 40 healthy controls. The groups showed similarities in gender, age, and BMI. Significantly lower median levels of vitamin D were detected in the HT group [12.08 (8.79–17.00) vs. 20.09 (20.00–34.00), $p < 0.001$]. Although the percentages of vitamin D sufficiency and insufficiency were higher in the control participants than those with HT (50%, 27.5% vs. 6.7%, 13.3%, $p < 0.001$), the percentage of vitamin D deficiency was higher among participants with HT (22.5% vs. 80%, $p < 0.001$). While the two groups did not display any statistical differences in leukocytes, neutrophils, lymphocytes, platelets, MPV, PLR, or CRP levels (all $p > 0.05$), ESR values in the HT group were detected to be significantly higher than in the control group ($p = 0.01$) (Table 1).

According to the subgroup analysis, the comparison of the HT subgroups and the control patients did not reveal any statistical difference in age, gender, or BMI (Table 2). Vitamin D levels were statistically lower among the participants in all the subgroups of HT compared to the controls ($p < 0.001$) (Figure 1a). Despite lower vitamin D levels in the hypothyroid HT groups than in the euthyroid HT groups, a significant difference was only uncovered between subclinical hypothyroid HT and euthyroid HT groups ($p = 0.004$). The patients with euthyroid, subclinical, and hypothyroid HT were observed to be vitamin D-deficient more frequently than the control patients (90%, 90.0%, 60.0% vs. 22.5% respectively, $p < 0.001$) (Figure 1b). Vitamin D deficiency was also higher within the hypothyroid HT groups than in the euthyroid HT group ($p < 0.001$). Although the euthyroid HT patients had a higher level of PLR than the overt ($p = 0.002$) and subclinical hypothyroid HT groups ($p < 0.001$), no difference was found between this group and the controls (Figure 2). The CRP levels did not vary between the study groups; ESR was higher only in the overt hypothyroid HT group ($p = 0.001$). The study groups displayed no differences in leukocytes, neutrophils, lymphocytes, platelet counts, and MPV (Table 2).

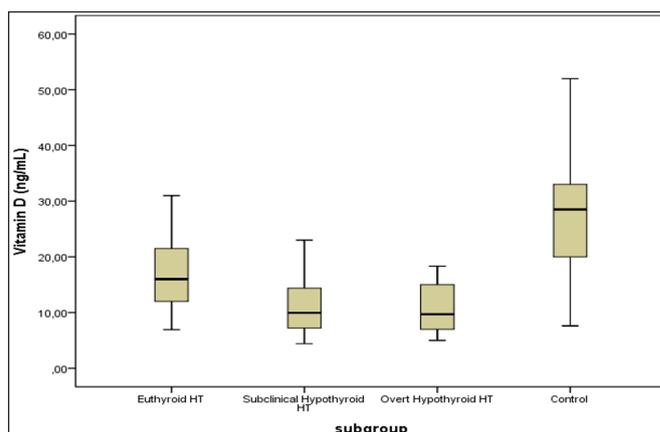


Figure 1a. Vitamin D levels in groups

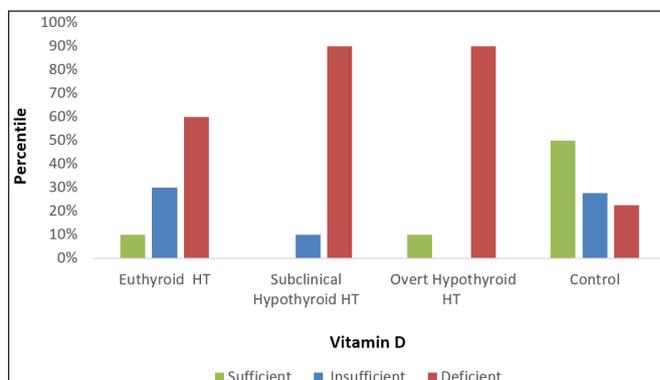


Figure 1b. Vitamin D deficiency rates in groups

Table 1. Comparison of clinical and laboratory characteristics between Hashimoto's thyroiditis and control groups			
	HT (n:60)	Control (n:40)	P
Age(years)	45.50 (32.00-57.25)	47.61 (37.25-57.50)	0.394
Female/Male (n)	42/12	32/8	0.604
BMI (kg/m ²)	28.22±1.83	28.21±1.74	0.742
TSH (μU/L)	5.00 (3.00-10.88)	1.85 (1.28 -3.17)	<0.001
fT3 (ng/L)	2.97±0.53	3.23±0.45	0.416
fT4 (ng/dL)	1.01±0.32	1.26±0.13	<0.001
Anti-TPO (IU/mL)	194 (63 - 447)	12.5 (10-13)	<0.001
Anti-TG (IU/mL)	238 (31-476)	10(10-14)	<0.001
25(OH)D3 (ng/mL)	12.00 (8.79-17.00)	29.09 (20.00-34.00)	<0.001
Calcium (mg/dL)	8.85 (8.67-9.33)	9.14 (8.84-9.37)	0.064
Phosphorus (mg/dL)	3.20 (2.97-3.51)	3.69 (3.33-4.00)	0.001
Leukocyte (10 ³ /μL)	6.57 (5.62-7.69)	6.65 (5.32-8.22)	0.961
Neutrophil (10 ³ /μL)	3.56 (2.70-4.49)	3.96 (2.83-4.69)	0.497
Lymphocyte (10 ³ / μL)	2.20 (1.88-2.54)	2.27 (1.81-2.81)	0.869
Platelet (10 ⁶ / μL)	296.50 (227.00-334.25)	266.00 (235.50-339.00)	0.655
MPV	10.64±0.75	10.71±0.95	0.281
PLR	123.57 (99.39-147.73)	129.52 (91.93-161.73)	0.688
ESR (mm/s)	6.00 (4.00-16.00)	4.00 (2.25-7.50)	0.01
CRP (mg/dL)	1.35 (0.60-2.55)	1.65 (0.60-4.19)	0.358
Sufficient (n, %)	4 (6.7%)	20 (50%)	
Vitamin D Insufficient (n, %)	8 (13.3%)	11 (27.5%)	<0.001
Deficient (n, %)	48 (80%)	9 (22.5%)	

HT, Hashimoto's thyroiditis; BMI, body mass index; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamin D; PLR, platelet-to- lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Data were expressed as mean±standard deviation and median (interquartile range). P <0.05 was considered significant.

Table 2. Comparison of laboratory parameters in patients with euthyroid, subclinical hypothyroid, and overt hypothyroid Hashimoto's thyroiditis

	Euthyroid HT (n:20)	Subclinical Hypothyroid HT (n:20)	Overt Hypothyroid HT (n:20)	P
TSH (µU/L)	2.06 (1.61-3.01) ^{b,c}	5.0 (4.38-7.10) ^{a,d}	17.21 (8.96-54.00) ^{a,d}	<0.001
fT3 (ng/L)	3.15±0.58 ^c	3.03±0.40	2.72±0.52 ^{a,d}	0.003
fT4 (ng/dL)	1.14±0.19 ^c	1.16±0.15 ^c	0.66±0.23 ^{a,b,d}	<0.001
Anti-TPO (IU/mL)	125 (34-248)	177 (62-553) ^d	349 (165-570) ^d	<0.001
Anti-TG (IU/mL)	198 (29-341) ^d	278 (31-832)	213 (22-932) ^d	<0.001
25(OH)D3 (ng/mL)	16.00 (12.00-21.75) ^{b,d}	9.95 (6.90-14.55) ^{a,d}	10.00 (7.29-15.90) ^d	<0.001
PLR	148.90 (126.90-164.74) ^{b,c}	114.55 (98.23-125.81) ^a	110.77 (87.08-133.52) ^a	0.006
ESR (mm/s)	4.00 (3.00-7.75)	6.50 (4.00-16.25)	12.00 (4.00-18.00) ^d	0.003
CRP (mg/dL)	1.40 (0.45-1.77)	1.15 (0.50-2.75)	1.55 (0.80-4.45)	0.380

HT, Hashimoto's thyroiditis; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamin D3; PLR, platelet-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Data were expressed as mean ± standard deviation and median (interquartile range). Letter a denotes a statistically significant difference with euthyroid HT; b denotes a significant difference with subclinical hypothyroid HT; c denotes a significant difference with overt hypothyroid HT; and d denotes a difference with the control group. P <0.008 was considered significant according to the Bonferroni correction.

Table 3. Correlation analysis of parameters in the HT group

	Vitamin D		PLR		ESR		CRP	
	r	p	r	p	r	p	r	p
TSH	-0.294	0.023	-0.390	0.002	0.365	0.004	0.231	0.076
fT3	-0.164	0.211	0.709	0.547	-0.240	0.065	-0.129	0.325
fT4	0.054	0.684	0.171	0.192	-0.179	0.170	-0.261	0.044
Anti-TPO	-0.281	0.030	-0.054	0.683	0.191	0.145	0.237	0.068
Anti-TG	-0.201	0.124	-0.074	0.576	0.144	0.273	0.104	0.431
Vitamin D	1.0		0.068	0.605	-0.190	0.146	-0.175	0.180
PLR	0.068	0.605	1.0		0.045	0.734	0.175	0.180
ESR	-0.190	0.146	0.045	0.734	1.0		0.570	<0.001

TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamin D3; PLR, platelet-to-lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

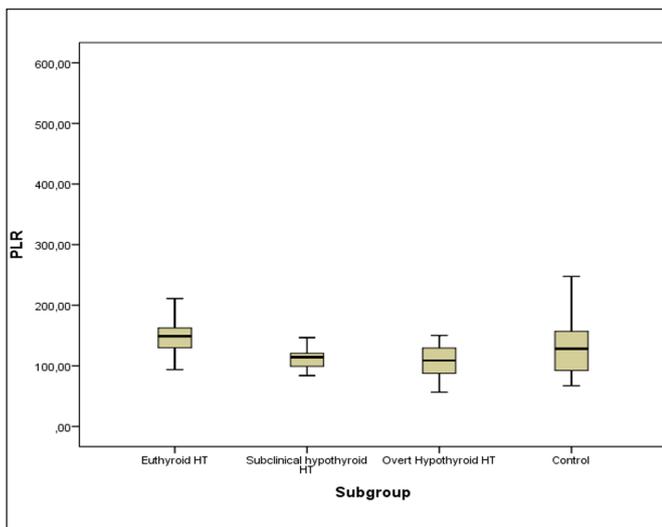


Figure 2. Platelet-to-lymphocyte ratios in groups

According to the correlation analysis, vitamin D levels were correlated with TSH and Anti-TPO levels in a negative direction ($r=-0.294$, $p=0.023$; $r=-0.281$, $p=0.030$, respectively). A positive correlation existed between TSH and anti-TPO ($r=0.411$, $p=0.001$) and ESR ($r=0.365$, $p=0.002$), but TSH and PLR were negatively correlated ($r=-0.390$, $p=0.002$) (Table 3).

DISCUSSION

The HT group had significantly lower amounts of vitamin D and higher prevalence of vitamin D deficiency than the controls in this study. Additionally, vitamin D deficiency was also found more frequently among the hypothyroid groups. HT patients with subclinical hypothyroidism displayed the lowest vitamin D levels. The study groups showed no differences regarding CRP levels, higher levels of ESR were observed only in the overtly hypothyroid HT group, and higher PLRs were found in those euthyroid HT patients. Vitamin D levels were negatively correlated with TSH and Anti-TPO. A positive correlation existed between TSH and anti-TPO and ESR, but TSH and PLR were negatively correlated.

It has recently been suggested that autoimmune diseases might be affected by vitamin D due to its essential role as an immune regulator (15). Studies have shown that vitamin D induces regulatory T lymphocytes, it decreases pro-inflammatory Th-1, Th-9, and Th-17 lymphocytes, and also suppresses the secretion of immunoglobulins from B lymphocytes (15,16). Most immune system cells harbor vitamin D receptors and express 1-alpha hydroxylase (CYP27B1). Active vitamin D synthesized

by this enzyme reduces the expression of the major histocompatibility complex class II on the surfaces of antigen-presenting cells, thereby making these cells more tolerant (15).

The pathophysiology of HT is mainly explained by an imbalance between T helper cells (CD4) and suppressor T cells (17,18). In this way, these cells can cooperate and activate B lymphocytes. Moreover, the production of various cytokines, such as interferon-gamma, by T helpers leads to the expression of MHC class II surface HLA-DR antigens not previously present in thyrocytes. This sensitizes the thyrocytes to immunological attack. Additionally, the production of thyroid antibodies by activated B lymphocytes further contributes to the autoimmune response. As we mentioned earlier, individuals with autoimmune thyroid disease are more likely to have lower levels of vitamin D and a higher prevalence of vitamin D deficiency (6). Furthermore, VDR gene polymorphisms are related to a raised risk of autoimmune thyroid disease (19,20). However, some studies detected no differences between the HT patients and the controls with respect to vitamin D levels (7,8). While Tamer et al. (21) observed lower vitamin D and a higher rate of vitamin D insufficiency among HT patients, there were no differences concerning vitamin D in euthyroid, subclinical hypothyroid, or overt hypothyroid HT groups. Likewise, another study revealed that lower vitamin D in the HT groups, and active vitamin D levels were similar to the control group (22). Consistent with most of the literature, our study showed that HT patients had lower vitamin D levels and more frequently suffered from vitamin D deficiency. Patients with subclinical hypothyroidism had significantly lower vitamin D than those with euthyroid HT. Moreover, vitamin D deficiency was more common in our patients with subclinical or overt hypothyroidism than in euthyroid HT patients. Vitamin D levels also had negative correlations with both TSH and anti-TPO levels. This made us think that vitamin D deficiency might influence the progression to the hypothyroid stage, and thus, the replacement of vitamin D may prevent this clinical course. The lack of expected differences in the levels of vitamin D between subclinical and overt hypothyroid groups may be due to variances in VDR gene polymorphism and individual 1-alpha hydroxylase activity.

Platelets significantly affect the regulation of immunity, inflammation, and hemostatic function (23). Although immune thrombocytopenia may be observed in some autoimmune thyroid patients, reactive thrombocytosis was found in the HT population (24,25). After the activation of platelets, various platelet-derived prothrombotic and pro-inflammatory factors,

especially P-selectin, are synthesized and released from their granules. Platelets can bind to the inflamed endothelium and collect circulating leukocytes through these factors, enhancing platelet-leukocyte aggregation and thereby initiating an inflammatory reaction in the injured location (26). Inflammatory factors, including TNF-alfa, can also activate thrombopoietin secretion, which increases platelet production (27). Additionally, the stimulation of platelet activation and adhesion by these factors leads to the formation of a greater number of platelet-leukocyte aggregates, further promoting the progression of immune inflammation and creating a vicious circle. In the current study, PLR was similar to the controls but higher only in euthyroid HT patients than those with hypothyroid HT. Moreover, no differences existed between the groups in MPV, one of the platelet activation indicators. Even though the groups did not show any differences with regard to the CRP levels, ESR was only higher in the overtly hypothyroid HT patients. The levels of TSH were correlated with PLR in a negative direction and with anti-TPO and ESR in a positive direction. However, since different inflammatory parameters were increased in euthyroid and overt hypothyroid HT patients, we thought that PLR was not a good inflammatory indicator for our HT patients with vitamin D deficiency. We think other asymptomatic or unknown infectious or inflammatory processes accompanying the participants may contribute to the lack of expected differences in PLR.

The present study has certain limitations. Although the inclusion of only newly diagnosed patients in the same season is advantageous for the study, relying on retrospective data from medical records reduces the explanatory power of the study. Additionally, it may not be possible to identify all inflammatory conditions that could influence PLR values in participants.

CONCLUSION

Our study revealed that HT patients had lower vitamin D and higher vitamin D deficiency than the controls. Lower amounts of vitamin D were found in subclinical hypothyroid HT patients than the euthyroid HT patients. It can be concluded based on the study results that vitamin D may play a role on the transition from the euthyroid phase to the hypothyroid phase, and the replacement of vitamin D could inhibit the progression to hypothyroidism. Moreover, our results indicate that PLR might not be a good inflammatory marker for vitamin D-deficient HT patients. In order to improve our understanding of how significant vitamin D is in the onset and progression of HT, randomized controlled trials with extended follow-up periods are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Clinical Researches Ethics Committee of Ankara Training and Research Hospital (Date: 30.05.2019, Decision No: 32/2019).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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