Effects of Hormone Replacement Therapy on Autoimmune Markers and Clinical Outcomes in Pediatric Patients with Hashimoto's Thyroiditis

Hashimoto Tiroiditli Pediatrik Hastalarda Hormon Replasman Tedavisinin Otoimmün Belirteçler ve Klinik Sonuçlar Üzerindeki Etkisi

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ABSTRACT

Objective: Hashimoto's Thyroiditis (HT), a chronic autoimmune thyroiditis, is the predominant cause of hypothyroidism in regions without iodine deficiency. HT is characterized by the loss of immunological tolerance of the thyroid gland, leading to autoimmune attacks. This study aimed to compare the autoantibody profiles, along with clinical and laboratory findings, of patients diagnosed with Hashimoto's disease who were either receiving treatment or followed without treatment.

Material and Methods: Clinical manifestations, laboratory data, and thyroid ultrasonography (USG) findings of patients diagnosed with Hashimoto's thyroiditis receiving hormone therapy and those followed without treatment were compared in our clinic.

Results: Among a total of 249 patients, 116 received hormone replacement therapy, while 133 were followed without treatment. The mean age of all patients was 13.91±3.71 years, with a mean age at diagnosis of 11.51±3.79 years. After twelve months of follow-up, the untreated group showed an increase in serum fT4 and antiTPO levels (p=0.012 and p=0.001), with no significant difference found in serum TSH, fT3, and antiTG levels. Those receiving treatment exhibited a significant decrease in serum TSH levels and a significant increase in serum fT4 levels (p=0.002 and p<0.001, respectively). Although there was an increase in serum antiTPO and antiTG levels over time, no change was detected in serum fT3 levels. Clinical improvement was significantly greater in the treatment group (p=0.044).

Conclusion: It has been concluded that early initiation of hormone replacement therapy in Hashimoto's thyroiditis can mitigate negative clinical effects during follow-up, contributing to patient comfort and alleviating clinical complaints.

Key Words: Hashimoto Thyroiditis, Hormone Replacement Therapy, Pediatrics, Thyroid Autoantibodies

ÖZ

Amaç: Hashimoto Tiroiditi (HT), (kronik otoimmün tiroidit) iyot yetersizliği görülmeyen bölgelerdeki hipotiroidizmin en sık görülen nedenidir. HT otoimmün saldırıya karşı tiroid bezinin immünolojik toleransının kaybolması olarak karşımıza çıkmaktadır. Çalışmamızda hashimoto hastalığı tanısı alan hastalar, tedavi verilen ve tedavisiz izlenen gruplar olarak

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Contribution of the Authors / Yazarların katkısı*: *ALAN TEHÇİ B: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***GÜRBÜZ F:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***BOYRAZ M:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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ayrılmıştır. Tedavi verilen ve tedavisiz izlenen grupların otoantikor seyri, hastanın klinik ve laboratuvar bulgularıyla birlikte karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Kliniğimizde hashimoto tiroiditi tanısı alan hormon tedavisi alan ve tedavisiz izlenen hastaların klinik bulguları, laboratuvar verileri ve tiroid ultrasonografi (USG) bulguları karşılaştırıldı.

Bulgular: 116'sı hormon replasman tedavisi alan, 133'ü tedavisiz izlenen toplam 249 hastanın ortalama yaşı 13.91±3.71 yıl, ortalama tanı yaşları ise 11.51±3.79 yıldı. On iki aylık izlem sonunda tedavisiz izlenen gruptaki hastaların serum sT4 ve antiTPO değerlerinde artış saptanırken (p=0.012 ve p=0.001), serum TSH, sT3 ve anti TG düzeylerinde anlamlı bir fark bulunmadı. Tedavi alanların serum TSH düzeylerinde anlamlı gerileme, serum sT4 düzeylerinde ise anlamlı bir artış olduğu görüldü (sırayla p=0.002 ve p<0.001). Ayrıca serum antiTPO ve antiTG düzeylerinde zamanla artış olmakla birlikte, serum sT3 düzeylerinde değişiklik saptanmadı. Klinik bulgularda gerileme, tedavi alan grupta anlamlı düzeyde daha fazlaydı (p=0.044).

Sonuç: Hashimoto tiroiditinde, erken dönemde başlanan hormon replasman tedavisinin izlemdeki olumsuz klinik etkileri azaltabileceği, hastanın konforu ve klinik şikayetlerini yatıştırma açısından önemli olabileceği kanısına varılmıştır.

Anahtar Sözcükler: Hashimoto Tiroiditi, Çocuklar, Hormon Replasman Tedavisi, Tiroid Otoantikorları

INTRODUCTION

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) stands as the primary cause of hypothyroidism in long-term patients. The prevalence of autoimmune hypothyroidism in childhood is approximately 1-2%, with a female predominance of 4:1. Positive family history is evident in about 50% of cases. Individuals with Hashimoto's thyroiditis face an elevated risk of other autoimmune conditions such as diabetes, alopecia, vitiligo, and celiac disease (1). The characteristic feature of Hashimoto's thyroiditis is the presence of autoantibodies against the thyroid, leading to diffuse lymphocytic infiltration of the thyroid gland by thyroid-specific B and T cells.

The pathogenesis of the disease involves autoreactivation of T and B lymphocytes, their infiltration into the thyroid gland, and the development of antibodies against three primary thyroid antigens—thyroid peroxidase (TPO), thyroglobulin (TG), and thyroid-stimulating hormone receptor (TSHR) (2, 3).

Several studies on adults have shown that prophylactic levothyroxine (LT4) treatment in euthyroid patients diagnosed with Hashimoto's thyroiditis aids in the regression of serological or cellular markers and goiter (4-6). However, there is currently no study demonstrating the impact of initiating levothyroxine treatment at TSH levels below the upper limit of 10 µU/ml on growth, development, and cognitive functions.

In our study, we aimed to assess the autoantibody levels, thyroid ultrasonographic findings, thyroid hormone levels, and clinical manifestations of patients diagnosed with Hashimoto's thyroiditis, whether they were monitored with or without levothyroxine treatment. Consequently, we sought to evaluate the influence of hormone replacement therapy on the autoimmune-induced damage to the gland and the clinical course of the disease.

MATERIAL AND METHODS

In this study, retrospective analysis was performed on the medical records of a total of 249 patients diagnosed with Hashimoto's thyroiditis. Among them, 133 were monitored without treatment, and 116 received hormone replacement therapy due to the presence of AntiTPO and/or AntiTG autoantibody positivity at Ankara Bilkent City Hospital Child Health and Diseases Clinic. The study was approved by Ankara Bilkent City Hospital, Clinical Research Committee No. 1 (14.10.2020- E1-20-1041).

Serum TSH was measured using the SIEMENS® Healthlineers Atellica IM Thyroid Stimulating Hormone 3-Ultra (TSH3-UL), fT4 with SIEMENS® Healthlineers Atellica IM Free Thyroxine FT4*A, and antiTPO and antiTG autoantibodies with SIEMENS® Healthlineers Atellica IM AntiThyroglobulin (aTgII) and SIEMENS® Healthlineers Atellica IM AntiTPO kits.

The evaluation encompassed patient demographics, including age and gender, clinical or biochemical status regarding hypothyroidism, euthyroidism, or hyperthyroidism, dosage and duration of LT4 hormone replacement therapy, clinical characteristics, and serum levels of antiTG, antiTPO, fT3, fT4, and TSH.

Patients with serum TSH levels >6.5 mU/L and normal fT4 values were classified as having subclinical hypothyroidism. Clinical, laboratory values, and ultrasonographic findings were assessed at baseline, 6th, and 12th months. Patients without regular outpatient follow-up and those with missing file data were excluded from the study.

LT4 hormone replacement therapy was initiated in patients with goiter and clinical manifestations of Hashimoto's thyroiditis (HT), or serum TSH levels >10 mIU/L with normal fT4 values. It was also initiated in cases of overt hypothyroidism with high serum TSH levels (>10 mIU/L) and low fT4 levels (<0.7 mIU/L), as well as in patients with normal serum TSH and fT4 levels but markedly elevated thyroid antibodies (antiTPO and/or antiTG) exceeding 1000 IU/ml.

Statistical Analysis

Data IBM SPSS Statistics 18© Copyright SPSS Inc. Analyzed using 1989, 2010 software. The suitability of continuous variables to normal distribution was examined with the Kolmogorov-Smirnov test. Categorical variables in the study were presented with frequency and percentage, and continuous variables were presented with mean, standard

deviation, median, minimum and maximum values. Chi-square and Fisher Chi-square significance tests, Yates and post hoc Bonferroni correction were performed in the analysis of categorical variables. Since parametric test assumptions were not met, the Mann Whitney U test was used for independent two-group mean comparisons, the Wilcoxon Signed Rank test was used for dependent two-group mean comparisons, and Friedman and post hoc pairwise comparison tests were used for repeated measurements analysis. In the study, the statistical significance level was accepted as 0.05.

RESULTS

The mean age of the total 249 patients enrolled in the study was 13.91±3.71 years, with an average age at the time of diagnosis being 11.51±3.79 years. Among these, 116 patients (46.6%) belonged to the group monitored without treatment (Mean age 13.97 ± 3.71), and 133 patients (53.4%) were in the group receiving treatment (Mean age 14.02 ± 3.41) (Table I).

At the time of diagnosis, clinical findings were present in 35.34% (88 patients) of the individuals, with the following frequency: menstrual irregularity, hair loss, constipation, weakness, palpitations, tremor, headache, loss of appetite, obesity, short stature, learning disability, edema, inguinal hernia, exophthalmus, burning on the soles of the feet, chills, and hirsutism.

Throughout the follow-up period, it was observed that clinical findings persisted in 63 patients (25.30%), improved in 11 patients (4.42%), and regressed in 10 patients (4.01%). In the group monitored without treatment, clinical findings were present in 24.14% of cases, and clinical regression was noted in 0.86% during follow-up. Among those receiving hormone replacement LT4 therapy, the average treatment dose was 1.55±4.32 mcg/kg/day, and the average treatment duration

Table I: Age analyzes by treatment groups

	Treatment (-)		Treatment (+)		p
	mean±std	Median (min-max)	mean±std	Median (min-max)	
Age (years)	13.97 ± 3.71	15.1 (3.5-19.7)	14.02 ± 3.41	14.7 (3.7-19.9)	0.823
Age at diagnosis (years)	11.6 ± 3.97	12 (3-17)	11.44 ± 3.64	12 (1-17)	0.476
Weight (kg)	51.34±20.42	50.2 (14-108.3)	49.6 ± 16.23	50.2 (16-112)	0.524
Weight (percentile)	52.95±34.22	53 (3-99)	49.86 ± 34.14	48 (3-99)	0.501
Height (cm)	152.63±20.5	159 (94-187)	152.18 ± 15.6	156.4 (95-184.5)	0.206
Height (percentile)	49.92±30.08	51 (2.7-99)	46.94 ± 30.1	45 (3-99)	0.347

Mann Whitney u test was performed and the data are shown with mean and median (min-max) values

Table II: Clinical findings characteristics according to treatment groups

Variable (n:249)	Treatment (-)*		Treatment (+)*		p
Initial clinical findings					
No	78	67.24	83	62.41	0.426
Yes	38	32.76	50	37.59	
Clinical findings during follow-ups					
No	87	75.0	89	66.92	0.044
Yes	28	24.14	35	26.32	
Regressed‡	1	0.86	9	6.76	

Chi-square test was performed and the data are shown with frequency and column percentage values. n(%), ‡The regression was significantly higher in the treatment (+) group (p=0.044). (Chi-square, post hoc Bonferroni correction made)*

Table III: Goiter stages according to treatment groups

Stages	Treatment (-)*		Treatment (+)*		p
0	94	81.03	94	70.68	0.163
1	1	0.86	4	3.01	0.163
1a	6	5.17	3	2.26	0.163
1b	8	6.90	16	12.03	0.163
2	6	5.17	12	9.02	0.163
3	1	0.86	4	3.01	0.163
Total	116	100.0	133	100.0	0.163

*****n(%), Chi-square test was performed and the data are shown with frequency and column percentage values*

Table IV: Change in laboratory values of patients over time

		0th month	6th month	12th month	p
No treatment					
TSH (n:92)	Mean ±sd	4.04±4.36	3.68±5.17	3.22±1.96	0.544
	Median (min-max)	3 (0.01-29)	2.8 (0.03-48.3)	3 (0-10.2)	
sT4 (n:90)	Mean±sd	1.26±1.60	1.30±1.04	1.38±1.61	0.012[a]
	Median (min-max)	1.12 (0.6-16)	1.17 (0.6-10)	1.19 (0.88-16.40)	
sT3 (n:21)	Mean ±sd	4.82±3.59	4.56±2.51	3.99±1.09	0.953
	Median (min-max)	4.30 (2.40-20)	4.20 (2.16-14.40)	3.80 (2.90-8.08)	
Anti TG (n:37)	Mean ±sd	708.40±2790.94	210.39±444.53	737.04±2140.01	0.936
	Median (min-max)	48.9 (0.10-16972)	50 (0.9-2130)	83 (13.5-11962)	
Anti TPO (n:44)	Mean ±sd	888.41±2741.24	915.57±1957.78	1488.46±2780.01	0.001[a]
	Median (min-max)	90.5 (0.4-17005)	173 (0.7-11529)	196 (28-11983)	
With treatment					
TSH (n:115)	Mean ±sd	97.70±829.711	11.40±24.84	6.26±14.84	0.002[a]
	Median (min-max)	7.7 (0-8908)	5.8 (0-150)	3.8 (0-150)	
sT4 (n:113)	Mean ±sd	1.12±0.77	1.23±1.20	1.27±0.34	<0.001[c]
	Median (min-max)	0.94 (0.25-4.89)	1.13 (0.3-13.5)	1.20 (0.7-3.29)	
sT3 (n:37)	Mean ±sd	6.14±4.76	4.86±3.51	4.18±1.72	0.584
	Median (min-max)	4.36 (0.62-20)	3.80 (0.65-19.70)	3.70 (1.02-11.50)	
Anti TG (n:50)	Mean ±sd	496.44±846.73	731.26±1706.25	2158.38±6214.94	0.246
	Median (min-max)	116.2 (0.5-4193)	125.7 (0.9-10000)	174.5 (3.4-39000)	
Anti TPO (n:59)	Mean ±sd	2422.69±4364.44	2942.19±4385.35	3904.47±4692.24	0.196
	Median (min-max)	708 (2.5-23108)	951 (1.4-19831)	1562 (30-13000)	

Friedman test and post hoc pairwise comparisons were performed. ***a:*** *There is a significant difference between the 0th month and the 12th month.* ***b:****The 12th month is significantly different from the others.* ***c:*** *All groups are significantly different from the others.*

was 2.21±9.41 years. Clinical findings were present in 26.32% of cases in the treatment group, with clinical regression observed in 6.76% during follow-up (p=0.044) (Table II). Additionally, during the follow-ups, it was observed that there was no significant change in goiter staging between the two groups that were monitored without treatment and those that received treatment (Table III).

When evaluating laboratory findings within each period, TSH and anti-TPO values were significantly lower (p<0.001 to p<0.001), and fT4 values were significantly higher in the untreated group at the beginning of the follow-up compared to the treated group (p=0.008). In the 6th month of follow-up, TSH, anti-TG, and anti-TPO levels in the untreated group were found to be lower than those in the treated group (p<0.001, p=0.044, and p=0.001). In the 12th month of follow-up, anti-TG and anti-TPO levels in patients without treatment were significantly lower than those in the treated group (p=0.036 and p<0.001) (Table IV). When all patients, whether untreated or treated, were evaluated, a decrease in TSH levels and an increase in anti-TPO values were observed at the 12-month follow-up (p=0.004 and p=0.001). Additionally, serum fT4 levels in all patients at the 12th month were higher than at other times (p<0.001). No significant change was observed in serum fT3 and anti-TG levels over time during follow-up (p=0.723 and p=0.379) (Table IV).

In the follow-up of patients in the untreated group, significant increases were detected in serum fT4 and anti-TPO values (p=0.012 and p=0.001). However, there was no significant difference in serum TSH, fT3, and anti-TG levels over time (p=0.544, p=0.953, and p=0.936) (Table IV).

Among the patients, those who received LT4 hormone replacement therapy showed a significant decrease in serum TSH levels and a significant increase in serum fT4 levels during their 12-month follow-up (p=0.002 and p<0.001, respectively). Additionally, although there was an increase in serum anti-TPO and anti-TG levels over time, no change was detected in serum fT3 levels (Table IV).

The changes in the initial and follow-up thyroid ultrasound findings of patients receiving and not receiving thyroid hormone replacement therapy are presented in Table V.

DISCUSSION

The aim of this study was conducted to evaluate the effect of hormone replacement therapy in patients with Hashimoto's thyroiditis, also known as chronic autoimmune thyroiditis, on autoimmunity damage in the thyroid gland. A total of 249 patients were evaluated in this study. In our study, similar to the literature. the diagnosis of Hashimoto's thyroiditis was found to be more common in female gender (78.31%) than in male gender (21.69%).

In an Italian study encompassing 715 patients and evaluating both the adult and pediatric populations, a significant reduction

Table V: Change in USG findings according to treatment groups

Group	First USG	Second USG			p
		(-)	(+)	Total	
Colloid cyst					
Treatment (-)	(-)	48 (90.56)	5 (9.43)	53 (100.0)	0.106
	(+)	3 (60.00)	2 (40.00)	5 (100.0)	
	Total	51 (87.93)	7 (12.10)	58 (100.0)	
Treatment (+)	(-)	54 (80.59)	13 (19.40)	67 (100.00)	0.132
	(+)	4 (50.00)	4 (50.00)	8 (100.00)	
	Total	58 (77.33)	17 (22.67)	75 (100.00)	
Heterogeneous parenchyma					
Treatment (-)	(-)	9 (69.23)	4 (30.77)	13 (100.00)	<0.001
	(+)	0 (0.00)	54 (100.00)	54 (100.00)	
	Total	9 (13.43)	58 (86.57)	67 (100.00)	
Treatment (+)	(-)	5 (55.56)	4 (44.44)	9 (100.00)	<0.001
	(+)	4 (5.33)	71 (94.67)	75 (100.00)	
	Total	9 (10.71)	75 (89.28)	84 (100.00)	
Nodul					
Treatment (-)	(-)	47 (87.03)	7 (12.96)	54 (100.00)	<0.001
	(+)	4 (30.77)	9 (69.23)	13 (100.00)	
	Total	51 (76.12)	16 (23.88)	67 (100.00)	
Treatment (+)	(-)	75 (97.40)	2 (2.60)	77 (100.00)	<0.001
	(+)	3 (42.86)	4 (57.14)	7 (100.00)	
	Total	78 (92.86)	6 (7.14)	84 (100.00)	
Increased blood flow					
Treatment (-)	(-)	47 (79.66)	12 (20.34)	59 (100.00)	0.001
	(+)	1 (14.29)	6 (85.71)	7 (100.00)	
	Total	48 (72.73)	18 (27.27)	66 (100.00)	
Treatment (+)	(-)	47 (73.44)	17 (26.56)	64 (100.00)	0.001
	(+)	6 (30.00)	14 (70.00)	20 (100.00)	
	Total	53 (63.09)	31 (36.91)	84 (100.00)	
Fibrous band					
Treatment (-)	(-)	53 (88.33)	7 (11.67)	60 (100.00)	0.057
	(+)	3 (50.00)	3 (50.00)	6 (100.00)	
	Total	56 (84.85)	10 (15.15)	66 (100.00)	
Treatment (+)	(-)	58 (81.69)	13 (18.31)	71 (100.00)	0.208
	(+)	8 (61.54)	5 (38.46)	13 (100.00)	
	Total	66 (78.57)	18 (21.43)	84 (100.00)	
Pseudonodul					
Treatment (-)	(-)	42 (82.35)	9 (17.65)	51 (100.00)	0.020
	(+)	3 (37.50)	5 (62.50)	8 (100.00)	
	Total	45 (76.27)	14 (23.73)	59 (100.00)	
Treatment (+)	(-)	43 (76.79)	13 (23.21)	56 (100.00)	0.002
	(+)	10 (38.46)	16 (61.54)	26 (100.00)	
	Total	53 (64.63)	29 (35.37)	82 (100.00)	

Chi square (exact) test was performed and the data are shown with frequency and line percentage values.

in serum anti-TPO levels was observed after a 12-18 month follow-up period among patients undergoing L-thyroxine treatment (7). Contrary to these findings, our study did not detect a significant change in serum anti-TPO levels within the treatment group during the follow-up period (p=0.196). However, we observed a significant increase over time in the untreated group (p=0.001). These outcomes suggest that, despite the persistent nature of the autoimmune condition, it can be partially managed with treatment.

Another study reported that, during an average follow-up of 22.5 months, 8% of 181 patients with Hashimoto's thyroiditis developed subclinical hypothyroidism, 13% developed overt hypothyroidism, and 6% exhibited nodule formation (8). Similarly, in a comparable study, it was documented that LT4 hormone replacement therapy was initiated in 13 out of 37 initially euthyroid patients who were followed without treatment, owing to the development of subclinical or overt hypothyroidism during the follow-up period (9). This underscores the notion

that, even though an individual may be euthyroid at the time of Hashimoto's thyroiditis diagnosis, hypothyroidism may evolve over time. Consequently, regular outpatient clinic follow-ups and thyroid function tests at predetermined intervals become essential.

In another study investigating patients with Hashimoto's thyroiditis (HT), both those under monitoring with or without treatment, it was observed that the group without treatment exhibited the highest serum anti-TPO levels. However, no significant correlation was identified between measured serum anti-TPO levels and serum fT4 and TSH levels (10). In our study, when we analyzed the initial, 6th, and 12th month controls separately, we observed lower antibody titers in the group without treatment.

A 2019 single-center study involving 83 cases, with 46.8% euthyroidism, 33.7% subclinical hypothyroidism, 17.7% hypothyroidism, 2.5% overt hyperthyroidism, and 2.5% subclinical hyperthyroidism, found higher serum anti-TPO and antiTG antibody levels in the treatment-initiated group, similar to our findings (p=0.01, p=0.051) (9).

In a Danish study examining retrospective data from 4649 HT-diagnosed patients, it was reported that initial thyroid autoantibodies were higher in patients who developed thyroid dysfunction during follow-up (12). These findings suggest that greater gland damage may occur when high autoantibody titers are present. Consequently, we propose that initial serum autoantibody levels may serve as a valuable predictor of the likelihood of developing hypothyroidism during follow-up.

A study aiming to elucidate the impact of prophylactic LT4 treatment on the prognosis of Hashimoto's thyroiditis reported the benefits of early replacement therapy in euthyroidic patients. While a decrease was noted in serum anti-TPO levels in cases diagnosed with HT receiving LT4 treatment, no decrease in antibody titers was observed in the untreated group (12).

Multiple studies have established a robust relationship between elevated serum TSH levels, increased serum thyroid autoantibodies, and augmented thyroid volumes (12-14). This observation reaffirms the association between high autoantibody levels and glandular damage, underscoring the importance of understanding the thyroid dysfunction that leads to clinical responses. In our study, we observed no significant changes in the ultrasound findings of patient groups diagnosed with HT, whether they received treatment or were monitored without treatment, during the first and second evaluations at the sixth month.

However, when evaluating patients undergoing treatment, this observation turned negative in 30% of those with increased blood flow in the initial ultrasound (p=0.001) (Table V). Additionally, it was noted that only 38.46% of the 13 treated patients exhibited a positive fibrous band in their initial ultrasound, and the majority of patients (61.54%) showed a negative result in the subsequent ultrasound (p=0.104) (Table V). In patients monitored without treatment, none of those with heterogeneous parenchyma observed in the initial ultrasound showed a negative result.

A study by Romaldini et al. (15), investigating the effects of LT4 treatment on autoantibody levels, lipid profile, and thyroid volume, revealed an 81% decrease in the thyroid volume of 10 patients after 6 months of levothyroxine treatment (15). The ultrasonographic changes detected in the follow-up of patients initiating treatment suggest that HT treatment may shield the gland from autoimmune damage. However, in our study, we observed no significant change in goiter staging between the two groups followed with or without treatment.

In a Korean study involving 153 patients (139 female and 14 male, ratio 9.9:1), the most common presenting complaint was thyroid gland enlargement (71.9%), followed by weight gain or fatigue (20.9%). For the remaining patients, it was detected during routine screening in the absence of thyroid dysfunction or other autoimmune diseases (16). In a study covering 102 cases diagnosed with Hashimoto's thyroiditis between 2005 and 2010 in our country, the most common complaints were neck swelling (41.1%), fatigue (12.7%), dry skin (11.7%), growth retardation (11.7%), hair loss (11.7%), and decreased academic success (10.7%), along with irritability (8.8%), cold intolerance (7.8%), and constipation (3.9%) (17).

Another study conducted in our country evaluated 41 female patients diagnosed with Hashimoto's thyroiditis, aiming to uncover the relationship between psychiatric disorders (depressive disorder, generalized anxiety disorder, ADHD, and social phobia) and Hashimoto's thyroiditis (18). In our study, the majority of patients belonged to the asymptomatic silent group, with only 35.34% (88 patients) exhibiting clinical findings.

In the follow-up of the group receiving treatment, it was observed that the clinical findings did not improve in 66.92% of the patients. the clinical complaints continued in 26.32% and the clinical findings regressed in 6.76% (p=0.044). In a study between 2012 and 2019 in our country that included patients diagnosed with Hashimoto's thyroiditis and receiving hormone replacement therapy it was reported that serum antiTPO levels decreased after LT4 treatment (19). In another study, it was observed that serum antiTG levels were high at the beginning and serum antiTPO levels increased progressively during follow-up (12,13).

In conclusion, considering the detrimental impact of autoimmunity in Hashimoto's thyroiditis (HT), regular patient follow-ups are deemed crucial. Drawing upon the findings of our study, the initiation of hormone replacement therapy, particularly in the presence of elevated autoantibody levels, especially anti-TPO, and in cases where serum TSH levels are mildly elevated, may be considered beneficial. Early commencement of hormone replacement therapy in Hashimoto's thyroiditis holds

the potential to alleviate adverse clinical effects during follow-up, enhance patient comfort, and mitigate clinical complaints.

REFERENCE

1. Aversa T, Corica D, Zirilli G, Pajno GB, Salzano G, De Luca F, et al. Phenotypic expression of autoimmunity in children with autoimmune thyroid disorders. Front Endocrinol 2019 10:476.
2. Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. J Thyroid Res 2010 2011:675703.
3. Morshed SA, Latif R, Davies TF. Delineating the autoimmune mechanisms in Graves' disease. Immunol Res 2012;54:191– 203.
4. Aksoy DY, Kerimoglu U, Okur H, Canpinar H, Karaağaoğlu E, Yetgin S, et al. Effects of prophylactic thyroid hormone replacement in euthyroid Hashimoto's thyroiditis. Endocr J 2005;52:337-43.
5. Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit? Thyroid 2001;11:249-55.
6. Dörr HG, Bettendorf M, Binder G, Karges B, Kneppo C, Schmidt H, et al. Levothyroxine Treatment of Euthyroid Children with Autoimmune Hashimoto Thyroiditis: Results of a Multicenter. Randomized. Controlled Trial Horm Res Paediatr 2015;84:266-74.
7. Yavuz K, Aylanc H. Retrospective evaluation of clinical and laboratory features of pediatric patients with Hashimoto's thyroiditis. Troia Med J 2021;2: 85-9.
8. Kara Ö. Clinical and Laboratory Characteristics of Children and Adolescents with Hashimoto Thyroiditis at Diagnosis and During Follow-upAnkara Üniversitesi Tıp Fakültesi Mecmuası 2019;72:314-9.
9. Korkmaz Ö, Özen S, Gökşen D, Darcan Ş. Clinical Characteristics and Follow-up Findings of the Cases Pediatric Hashimoto's Thyroiditis- a Single Centre Experience. Konuralp Tıp Dergisi 2019;11: 89-94.
10. Kust D, Matesa N. The impact of familial predisposition on the development of Hashimoto's thyroiditis. Acta Clin Belg 2020;75:104-108.
11. Padberg S, Heller K, Usadel KH, Schumm-Draeger PM. One-year prophylactic treatment of euthyroid Hashimoto's thyroiditis patients with levothyroxine: is there a benefit? Thyroid 2001;11:249-55.
12. Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S. Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). The natural history of euthyroid Hashimoto's thyroiditis in children. J Pediatr 2006;149:827-32.
13. Bülow Pedersen I, Laurberg P, Knudsen N, Jørgensen T, Perrild H. Ovesen L. Rasmussen LB. A population study of the association between thyroid autoantibodies in serum and abnormalities in thyroid function and structure. Clin Endocrinol (Oxf) 2005;62:713-20.
14. Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A. Antithyroid peroxidase autoantibodies in thyroid diseases. J Clin Endocrinol Metab 1990;71:661-9.
15. Romaldini JH, Biancalana MM, Figueiredo DI, Sarah CS, Mathias PC. Effect of L-thyroxine administration on antithyroid antibody levels. lipid profile. and thyroid volume in patients with Hashimoto's thyroiditis. Thyroid 1996;6:183–8.
16. Lee HS, Hwang JS. The natural course of Hashimoto's thyroiditis in children and adolescents. J Pediatr Endocrinol Metab 2014;27:807-12.
17. Yeşilkaya E, Belen B, Bideci A, Çamurdan O, Boyraz M, Cinaz P. Clinical features of children and adolescents with chronic autoimmune thyroiditis. Gülhane Tıp Dergisi 2008; 50:147-50.
18. Aydın E. Otoimmün tiroid hastası adolesan kızların psikopatolojik incelemesi. Tıpta Uzmanlık Tezi. Sakarya Üniversitesi Tıp Fakültesi Hastanesi Çocuk Endokrinoloji Bilim Dalı 2018.