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HEAD AND NECK IMAGING
ORIGINAL ARTICLE

US findings in euthyroid patients with positive antithyroid autoantibody tests compared to normal and hypothyroid cases

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PURPOSE
We aimed to compare the ultrasonographic and laboratory parameters of euthyroid patients who have only positive antithyroid autoantibody test results with those of patients with a hypothyroid status of Hashimoto's thyroiditis (HT).

MATERIALS AND METHODS
Thirty-five patients with newly diagnosed HT, 35 euthyroid patients who have autoantibodies against thyroid peroxidase (TPOAb) and/or thyroglobulin (TgAb), and 40 controls were enrolled in the study. Plasma free T3, free T4, thyroid stimulating hormone, TPOAb, and TgAb levels were obtained retrospectively. For gray-scale ultrasonography, each thyroid gland of all individuals graded with gray-scale grading (GSG), which was determined according to the gland size, parenchymal structure, echogenicity, micronodulation, contour irregularity, and existence of hyperechoic septa. For Doppler analysis, the peak systolic velocity (S), resistive index (RI), and pulsatility index (PI) values were obtained from the superior thyroid artery (STA) and intrathyroidal artery (ITA). The color pixel ratio (CPR), which was computationally evaluated from a power Doppler image of all individuals, was used for quantification of the intrathyroidal vascularity.

RESULTS
Although the mean GSG values were higher in the HT and antibody-positive groups than they were in the control group, there was no significant difference between the HT and antibody-positive groups. The three study groups demonstrated no statistically significant difference with regard to the S, RI, or PI variables obtained from the STAs and ITAs. Although the CPR values were highest in the HT group, the difference between the HT and antibody-positive group did not reach statistical significance.

CONCLUSION
The euthyroid antibody-positive group revealed gray-scale and Doppler ultrasonographic findings that were similar to those of the HT group.

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Hashimoto's thyroiditis (HT), first described by Hakaru Hashimoto in 1912, is an autoimmune disease that is characterized by the lymphocytic infiltration of the thyroid gland (1). HT is the leading cause of hypothyroidism (2). Typical laboratory features detected in HT include a reduction in the blood thyroxine (FT4) and triiodothyronine (FT3) levels and the elevation of thyroid stimulating hormone (TSH), antithyroid peroxidase autoantibodies (TPOAb), and antithyroglobulin autoantibodies (TgAb). Although rarely performed for this purpose, a definite diagnosis is based on a pathological demonstration of the lymphocytic infiltration of the gland. Ultrasonography (US) is a cross-sectional imaging modality that provides valuable anatomic information in evaluating the gland size and echo structure and in assessing possible thyroid nodules in HT. The usage of Doppler US is limited in the diagnosis of thyroiditis, although it helps assessing intranodular vascularity (if any nodule is present) and the vascularity of the gland.

US has been used in HT since the 1990s. Since then, many studies have been performed using the gray-scale and Doppler US parameters. Pedersen et al. (3), Loy et al. (4), and Schiemann et al. (5) compared the parenchymal echogenicity of the thyroid gland with clinical laboratory parameters in HT patients. Schultz et al. (6) reported on the relationship between Doppler US findings and laboratory parameters in 2003. The studies in the literature generally comprise the ultrasonographic data of individuals who are in the hypothyroid stage of HT. However, tests of thyroid autoantibodies reveal another group of cases who have elevated antibody levels but are in the euthyroid state. Managing these patients is a challenging clinical issue, and whether they should be regarded as a subgroup of HT is still debated because TPOAb can be observed at up to 10% in the normal population (7). The present study focuses on the ultrasonographic features of this unique population with only elevated levels of thyroid autoantibodies and no other laboratory features suggesting HT.

Materials and methods

Patients

The detailed clinical and ultrasonographic data of 74 consecutive cases without substitution therapy who were admitted to the Endocrine and Metabolic Diseases Clinic of our hospital between January 2008 and October 2009 and were suspected to have HT were analyzed.

Four of the 64 female cases were excluded from the study because of a short neck structure and/or deeply located thyroid gland, which resulted in suboptimal ultrasonographic scanning. The remaining 70 patients, consisting of 60 females (85.7%) and 10 males (14.3%), were

enrolled into the study. According to their levels of TSH, FT4, FT3, TPOAb, and TgAb, the patients were divided into two groups: the cases with a hypothyroid status of HT and the group of euthyroids who had increased levels of antithyroid auto-antibodies. The first group comprised 35 patients (four males, 31 females; mean age, 35±12 years) who had a new diagnosis of HT and a TSH level above 2.50 μIU/mL. The second group consisted of 35 euthyroid individuals (six males, 29 females; mean age, 36±13 years) whose TPOAb and/or TgAb levels were higher than normal.

The control group data were obtained from 40 individuals (31 females, nine males; mean age, 33±12 years) who applied to the same clinic, were suffering from symptoms unrelated to the thyroid gland and were clinically proven to be free from thyroid disease in their routine endocrinologic testing.

Laboratory

TSH, FT4, and FT3 levels were measured with the use of the COBAS® (Roche, West Sussex, UK) electrochemiluminescence immunological test kit. TSH levels higher than 2.50 μIU/mL were accepted as elevated (8). The normal ranges of FT4 and FT3 were 0.93–1.7 ng/dL and 1.8–4.6 pg/mL, respectively. The measurement of TPOAb and TgAb were performed with the use of the IMMULITE® 2000 (Siemens Healthcare Diagnostics Inc., Tarrytown, New York, USA) solid phase, enzyme-labeled chemiluminescence sequential immunometric test kit. The normal ranges of TPOAb and TgAb were accepted as 0–35 IU/mL and 0–40 IU/mL, respectively.

US

During the patients' routine thyroid gray-scale and Doppler US examinations, which had been requested by their endocrinologist, detailed Doppler data were collected. The patients were informed about the extra data, and their oral approvals were obtained. The gray-scale and Doppler US examinations of all of the study cases were performed by a radiologist who was experienced in US and who had no information about the laboratory results. During the US examinations, a color Doppler US unit (Siemens Sonoline Antares, Siemens Healthcare Diagnostics Inc., Mountain View, California, USA) with linear VFX 9-4 MHz and VFX 13-5 MHz transducers was used. The US images were acquired and stored digitally for future analysis.

All US parameters, including the thyroid gland volume (craniocaudal×anterior-posterior×transverse dimensions×0.52), parenchymal structure, parenchymal echogenicity, presence of micronodulation, contour irregularity, and intraparenchymal hyperechoic septa were noted. After using these gray-scale data, the thyroid glands were qualitatively graded using gray-scale grading (GSG), which we developed from a comparison of different morphologic ultrasonographic patterns of HT (Table 1).

During the Doppler US examination, three different spectral waveforms were obtained from each lobe's superior thyroidal artery (STA). After appropriate angle correction, the waveforms were quantitatively analyzed, and the peak systolic velocity (S), resistive index (RI), and pulsatility index (PI) values were measured. Six S values were averaged to calculate the representative S value for each patient. Similarly, the representative RI and PI mean values were also calculated. Later, we searched and the visualized linear segments of three intrathyroid arteries (ITA) in each lobe. After precise angle correction, the S, RI, and PI values were obtained for each ITA. The means of the six measurements were later calculated to find the representative ITA-S, RI, and PI value for each patient in a similar fashion as that described for the STA parameters. During the STA and ITA sampling and Doppler measurements, the insonation of an artery at a Doppler angle above 60° was strictly avoided.

Apart from the Doppler parameters derived from the ITAs and STAs, power Doppler US was performed in a standardized fashion to assess the vascularization of the thyroid parenchyma. Using the same probe and sound frequency (7.3 MHz), scanning parameters (gray-scale gain, 40 dB; dynamic range, 55 dB; pulse repetition frequency, 488 Hz) and a color box with dimensions of 15×10 mm, we obtained and digitally archived three separate, sagittal power Doppler images from each lobe. After obtaining data from all patients, we quantitatively assessed the degree of parenchymal vascularization in each patient using digital techniques. For this purpose, we calculated the percentage of colored pixels in the color box using the Canny edge detection operator (9) and Hough transformation (10). Each pixel's distance to the gray-scale was calculated by these two methods. The pixels whose colors were close to the gray-scale spectrum counted as gray pixels, while the others were counted as color pixels. The colored pixels were then subtracted from the 15×10 mm standard power Doppler color box for each power Doppler image. By dividing the number of colored pixels by the total number of pixels in the box with standardized dimensions, we calculated the color pixel ratio (CPR) for each power Doppler image (Fig. 1). The mean of six CPR values from each study subject was accepted as the representative CPR value.

Table 1. Gray-scale US grading used in the analysis of thyroid gland parenchyma

Grade	Size	Parenchymal structure	Echogenicity	Micronodularity	Contour irregularity	Hyperechoic septa
0	N	N	N	-	-	-
1	N or ↑	Mildly Irregular	N	-	-	-
2	N or ↑	Irregular	Minimally ↓	+ or -	- or +	-
3	N or ↑	Irregular	Patchy ↓	+	+	- or +
4	N or ↑	Very irregular	Diffusely ↓	+	+	+
5	↓	Very irregular	Diffusely ↓	+	+	+

N, normal; ↑, increased; ↓, decreased; +, positive; - negative.

Statistical analysis

The study data were mostly expressed as the means and standard deviations. The GSG values were given as the mean, median, and range because these data did not conform to a normal distribution. The analyses among three groups were performed with the Kruskal-Wallis test, and with two groups, the Mann-Whitney U test was used. A receiver operating characteristic (ROC) analysis was performed to determine the cut-off point between the two groups. The linear relationship between the variables was evaluated with Spearman's correlation analysis. The level of significance was set at $P < 0.05$. Statistical analyses were performed using a computer software (Statistical Package for Social Sciences, Version 17.0, SPSS Inc., Chicago, Illinois, USA).

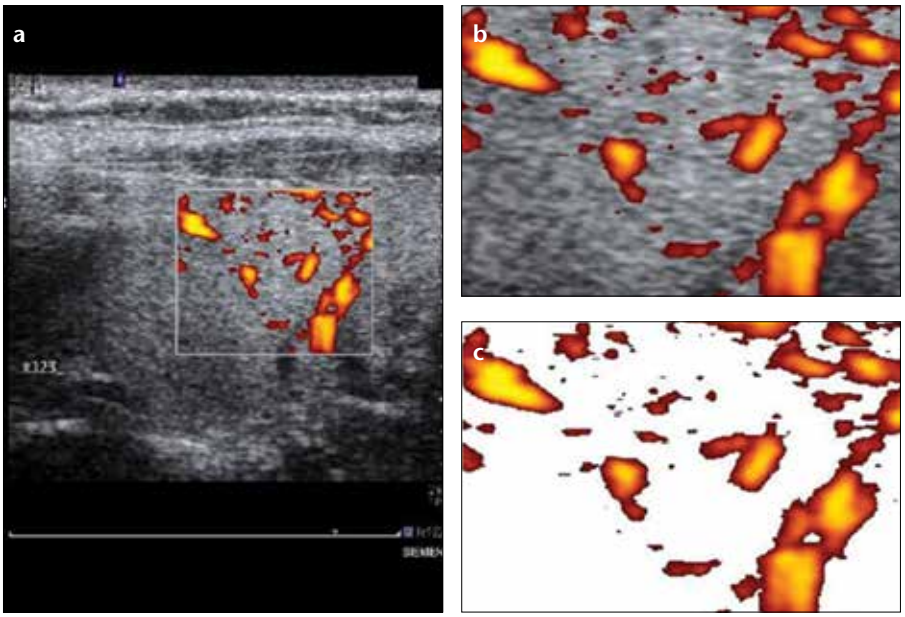

Figure 1. a–c. Standard size color image of the longitudinal US of the thyroid gland **(a)**, 15×10 mm standard color box taken into the analysis **(b)**, and computational subtraction of gray-scale pixels **(c)** are seen.

Results

All three study groups exhibited similar features in terms of their age ranges and genders. There was no significant difference between the groups with regard to their age and gender distribution ($P > 0.05$).

The hypothyroid group, as expected, had higher mean TSH levels and lower mean FT4 levels ($P < 0.001$) (Table 2). The mean autoantibody levels in the control group were normal, whereas both the hypothyroid and antibody-positive groups had elevated levels. There was no significant difference between the hypothyroid and antibody-positive groups in terms of their autoantibody levels (for both TPOAb and TgAb, $P > 0.05$). The antibody-positive group had higher thyroid volumes than did the hypothyroid and control groups ($P = 0.02$), whereas there was no significant difference between the hypothyroid and the control group (Table 3). While the average GSG (Figs. 2 and 3) values were significantly higher in both the hypothyroid and antibody-positive groups ($P < 0.001$) than they were in the control group, there was no statistically significant difference between the hypothyroid and antibody-positive group (Table 3). Micronodulation was more frequent in the hypothyroid and antibody-positive group as compared to the control group (Fig. 4). However, the hypothyroid and antibody-positive group had no statistically significant difference in terms of these variables. The GSG values correlated significantly with the TSH (r=0.374, $P < 0.001$), TgAb (r=0.402, $P < 0.001$) and TPOAb (r=0.586, $P < 0.001$) levels.

Table 2. Laboratory parameters of study groups

Study groups	TSH (μIU/mL)	FT3 (pg/mL)	FT4 (ng/dL)
Control (n=40)	2.02±1.04	3.26±0.42	1.23±0.26
Hypothyroid (n=35)	6.14±7.54[a]	3.05±0.39	0.76±0.18[a]
Antibody positive (n=35)	1.67±0.60[b]	3.17±0.39	0.82±0.19[a]

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.
[a]$P < 0.001$ for comparison to control group; [b]$P < 0.001$ for comparison to hypothyroid group.
Data are given as mean±standard deviation.

Table 3. US findings of study groups

Study groups	Gray-scale grading	Thyroid volume (mL)
Control (n=40)	0.05 (0, 0–1)	14.07±5.41
Hypothyroid (n=35)	1.51 (1, 0–4)[a]	15.11±11.37
Antibody positive (n=35)	0.94 (1, 0–3)[a]	20.30±15.82[c]

[a]$P < 0.001$ for comparison to control group; [b]$P < 0.001$ for comparison to hypothyroid group; [c]$P = 0.02$ for comparison to both control and hypothyroid groups.
Data are given as mean (median, range) or mean±standard deviation.

The three study groups demonstrated no statistically significant difference with regard to the S, RI, and PI variables obtained from the STAs and ITAs (Tables 4 and 5). According to the correlation analysis, the peak systolic velocity obtained from the ITAs correlated with both the TPOAb (r=0.300, $P = 0.001$) and the TgAb (r=0.242, $P < 0.001$).

The CPR values (control group, 0.10±0.07; hypothyroid group, 0.20±0.17; antibody-positive group, 0.13±0.08) showed statistically significant differences among the three study groups ($P < 0.01$). However, a dual comparison analysis demonstrat-

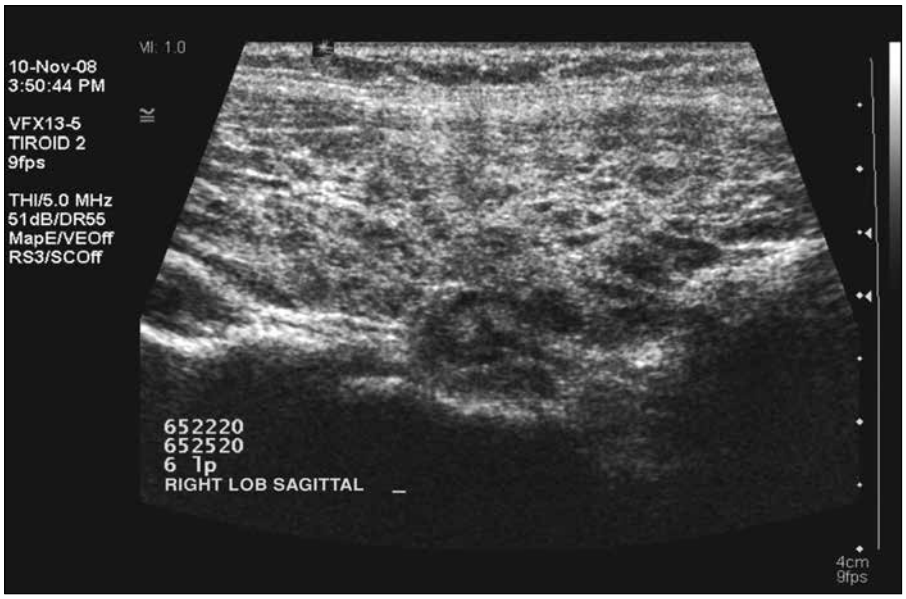

Figure 2. Right thyroid lobe longitudinal US of a 27-year-old woman. The parenchymal gray-scale grade was 2. The contours of the gland are slightly irregular, and the echogenicity of the thyroid gland is minimally reduced.

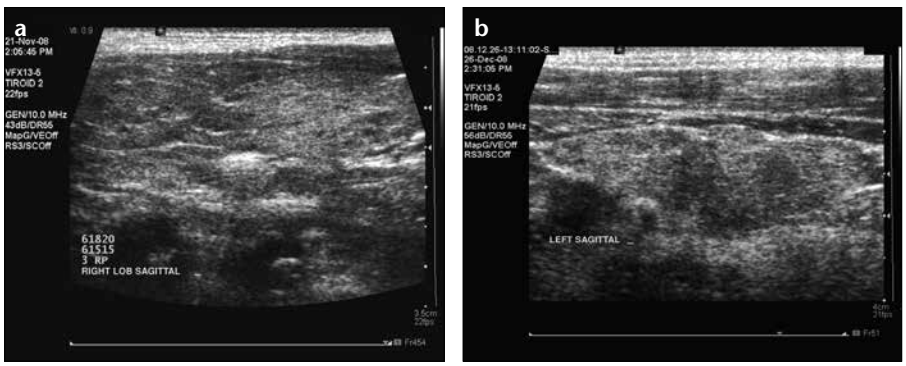

Figure 3. a, b. In the right thyroid lobe longitudinal US of a 25-year-old woman **(a)**, the parenchymal gray-scale grade was 3. The contour irregularity is more evident, and the echogenicity of the thyroid gland is reduced in a patchy fashion. In the left thyroid lobe longitudinal US of 38-year-old man **(b)**, the parenchymal gray-scale grade was 4. The contour of the thyroid gland is very irregular, and it is almost impossible to detect normal parenchyma.

Table 4. Superior thyroid artery parameters of study groups

Study groups	STA-S (cm/s)	STA-RI	STA-PI
Control (n=40)	27.73±8.16	0.61±0.05	1.02±0.23
Hypothyroid (n=35)	29.99±10.72	0.59±0.06	0.94±0.23
Antibody positive (n=35)	28.98±8.23	0.60±0.06	0.93±0.24

PI, pulsatility index; RI, resistive index; S, peak systolic velocity; STA, superior thyroid artery.
Data are given as mean±standard deviation.

Table 5. Intrathyroid artery parameters of study groups

Groups	ITA-S (cm/s)	ITA-RI	ITA-PI
Control (n=40)	19.14±4.75	0.54±0.04	0.54±0.04
Hypothyroid (n=35)	21.68±8.85	0.54±0.05	0.53±0.05
Antibody positive (n=35)	21.73±6.30	0.56±0.05	0.56±0.05

ITA, intrathyroid artery; PI, pulsatility index; RI, resistive index; S, peak systolic velocity.
Data are given as mean±standard deviation.

ed that only the difference between the control and hypothyroid groups was significant. A ROC analysis demonstrated that a CPR value of 0.12 can differentiate between the control and hypothyroid group with sensitivity and specificity rates of 65% and 67%, respectively. Correlation analyses indicated that the CPR was significantly correlated with the GSG (r=0.257, $P < 0.01$), TPOAb (r=0.262, $P = 0.005$) and TgAb (r=0.265, $P < 0.005$) values. The correlation between the CPR and FT3 values was also significant, but in the negative direction (r=-0.290, $P < 0.005$).

Discussion

The TPOAb can be observed at up to 10% in the normal population (7). Whether this subpopulation without any symptoms or laboratory disorders will develop hypothyroidism or should receive any form of hormonal replacement is a challenging question for clinicians. It was interesting to find out that this apparently healthy subgroup of our study demonstrated a gray-scale and hemodynamic ultrasonographic features that were similar to those of patients with a hypothyroid status of HT.

An overall size increase, hypoechogenicity, heterogeneity, and contour lobulation were the US findings that have been reported in HT in the past (11, 12). Another ultrasonographic feature, parenchymal micronodularity, was observed in HT, and it was thought to represent an infiltration of the lobules by the lymphocytes and plasmocytes (13). In our study, micronodulation was never observed in the control group, while 26% of the hypothyroid patients and 43% of the antibody-positive cases were found to have some form of micronodulation.

Hypoechogenicity in the thyroid parenchyma is a commonly reported phenomenon in HT (14, 15). Pedersen et al. in 2000 (3), Loy et al. in 2004 (4), and Schiemann et al. in 2003 (5) found a significant relationship between gland echogenicity reduction and HT. According to these studies, hypoechogenicity is an index showing the degree of the autoimmune involvement of the gland. In these articles, thyroid glands have only been evaluated in terms of their hypoechogenicity, without any analysis with other gray-scale

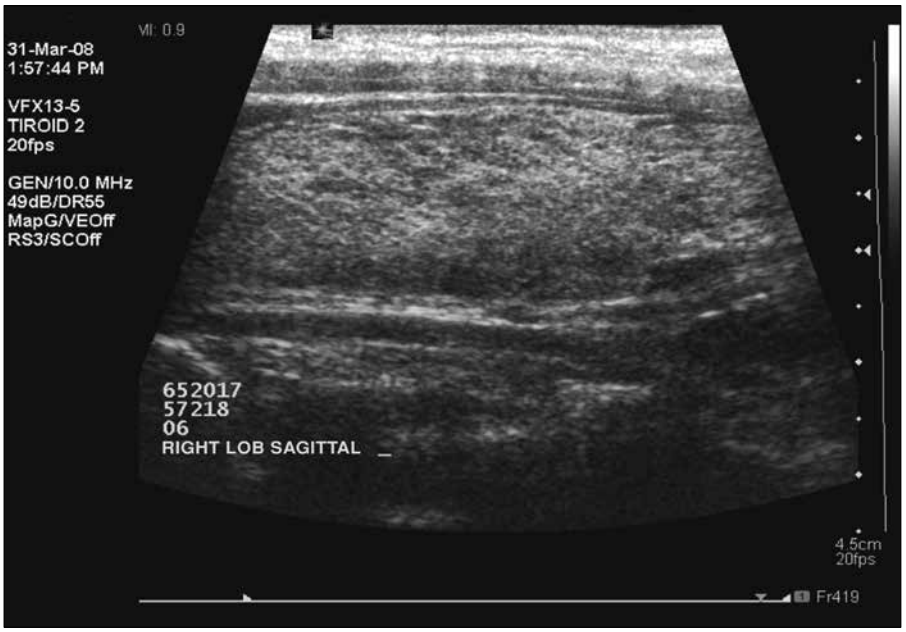

Figure 4. Right thyroid lobe longitudinal US of a 27-year-old woman shows parenchymal micronodularity.

ultrasonographic parameters. Apart from parenchymal echogenicity, we included all other parameters in our morphologic assessment of thyroid gland, and we compared the study groups as a whole using the gray-scale grading score. This analysis indicated that the GSG values correlated significantly with the thyroid autoantibodies and TSH levels, which are accepted as indicators of autoimmune activity.

The Doppler US examination as a noninvasive tool to evaluate the degree of vascularization of different organs, especially the highly vascularized thyroid gland, has long been the subject of various studies. Andrade et al. (16) demonstrated the relationship between the velocities of the thyroid arteries and the ultrasonographic parenchymal changes in the gland.

In the study group, apart from the Doppler analyses of the thyroidal artery velocities and indices, we also calculated the CPR values for each gland to obtain a quantitative value for the parenchymal vascularity level. Although a statistically significant difference was found between the CPR values of the normal and hypothyroid cases, the discriminatory power of this parameter is too low to be used in clinical practice. In fact, the hormonal tests of the patients provide enough evidence to differentiate between these two groups.

The effect of thyroid hormone level on thyroid gland vascularity and blood in different thyroid pathologies was investigated using Doppler US by Bogazzi et al. (17). In this study, thyroid vascularity was assessed with the use of both qualitative Doppler assessment and quantitative measurement of the systolic velocities in the intrathyroidal arteries (without angle correction). The thyroid vascularity was found to be higher in patients who had spontaneous hyperthyroidism and in the patients in the hypothyroid state of HT. The authors concluded that thyroid vascularity was not associated with a serum increase in the thyroid hormone levels, but rather with thyroid stimulation due to high TSH receptor antibody or TSH levels. Their conclusions were partially supported by our results, which were obtained with the use of a more quantified methodology and state-of-the-art ultrasonographic equipment. Similar to their results, we found a significant and positive correlation between the TSH levels and the CPR, but we were unable to demonstrate any correlation between the TSH levels and the intrathyroidal arterial velocities.

One of the most comprehensive articles on Doppler US findings in hypothyroidism is the one written by Schulz et al. (6). Eighty-nine cases diagnosed as having HT (26% among newly diagnosed cases without therapy; 74% among cases under levothyroxine substitution therapy) were investigated in terms of the relationship between the systolic velocities, color intensity, and clinical parameters, such as TSH, FT3, FT4, TPOAb, TgAb. According to the results of the study, the color intensity and maximum systolic velocities obtained from the thyroid parenchyma displayed positive correlations with TSH, TPOAb, and TgAb levels. The color intensity was inversely correlated with the duration of hypothyroidism. The authors speculated that hypervascularization in the thyroid gland was not related to the stimulation of thyroid hormone production, but it may be related to the autoimmune activity. The last speculation was supported by the results of our study, in which we found that the peak systolic velocities obtained from the intrathyroidal arteries and CPR values correlated significantly with the antibody levels. We believe that the methodology of the present study, with a more objective quantification of the thyroid perfusion and measurement of the systolic velocities of the intrathyroidal arteries using angle correction, provided more solid proof for this explanation.

A relatively limited number of patients was one of the limitations of this study. This limitation was due to the difficulty of finding untreated patients with HT and cases with isolated elevated levels of antithyroid autoantibodies. An interesting adjunct to the methodology would be an analysis of the vascular endothelial growth factor levels in the study groups, which may further contribute to the discussion (18). Another limitation was the subjective assessment of gray-scale parameters such as micronodulation, contour irregularity, and parenchymal structure, from which the gray-scale grades were produced. Establishing an objective scoring system regarding the gray-scale features of the organs is inherently not possible, and it would be beneficial for intra- and interobserver agreement analyses of the GSG to be performed in a larger group of cases.

In conclusion, despite the clinical belief that it is not appropriate to diagnose asymptomatic individuals with only high levels of antithyroid au-

to-antibodies as HT, our study results demonstrated that they have similar structural and hemodynamic ultrasonographic features as do HT patients with a hypothyroid status. Our findings suggest that the structural and hemodynamic changes may start long before the symptoms and hormonal imbalances, which are secondary to HT, manifest clinically. This information, which should be supported by larger-scale studies with more precise controls, may change the clinical management of euthyroid cases with only high levels of antithyroid autoantibodies.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Hashimoto H. ZurKenntniss der lymphomatösen Vernderung der Shilddrüse: Struma lymphomatosa. Arch Klin Chir 1912; 97:219–248.
2. Koloğlu S, Erdoğan G. Koloğlu endokrinoloji temel ve klinik. 2nd ed. Ankara: Nobel Tıp Kitabevi, 2005; 270–271.
3. Pedersen OM, Aardal NP, Larssen TB, Varhang JE, Myking O, Vik-Mo H. The value of ultrasonography in predicting autoimmune thyroid disease. Eur Thyroid J 2000; 10:251–259. [CrossRef]
4. Loy M, Cianchetti ME, Cardia F, Melis A, Boi F, Mariotti S. Correlation of computerized gray-scale sonographic findings with thyroid function and thyroid autoimmune activity in patients with Hashimoto's thyroiditis. J Clin Ultrasound 2004; 32:136–140. [CrossRef]
5. Schiemann U, Avenhaus W, Konturek JW, Gellner R, Hengst K, Gross M. Relationship of clinical features and laboratory parameters to thyroid echogenicity measured by standardized grey scale ultrasonography in patients with Hashimoto's thyroiditis. Med Sci Monit 2003; 9:13–17.
6. Schulz SL, Seeberger U, Hengstmann JH. Color Doppler sonography in hypothyroidism. Eur J Ultrasound 2003; 16:183–189. [CrossRef]
7. Singer PA. Clinical approach to thyroid function testing. In: Falk SA, ed. Thyroid disease. Endocrinology, surgery, nuclear medicine and radiotherapy. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1997; 41–52.
8. Wartofsky L, Dickey RA. Controversy in clinical endocrinology. J Clin Endocrinol Metab 2005; 90:5483–5488. [CrossRef]
9. Canny J. A computational approach to edge detection. IEEE Trans Pattern Anal Mach Intell 1986; 6:679–698. [CrossRef]
10. Princen J, Illingworth J, Kittler J. A formal definition of the Hough transform: properties and relationships. J Math Imaging Vis 1992; 1:153–168. [CrossRef]
11. Gutenkust R, Hafermann W, Mansky T, Scriba PC. Ultrasonography related to clinical and laboratory findings in lymphocitic thyroiditis. Acta Endocrinol 1989; 121:129–135.
12. Hayashi N, Tamaki N, Konishi J, et al. Sonography of Hashimoto's thyroiditis. J Clin Ultrasound 1986; 14:123–126. [CrossRef]
13. Solbiati L, Charboneau JW, Osti V, et al. The thyroid gland, In: Rumarck CM, Wilson SR, Sharboneau JW, Johnson JM, eds. Diagnostic ultrasound. 3rd ed. St. Louis: Elsevier Mosby, 2005; 735–770.
14. Espinasse P, Espinasse D, Estour B, et al. Echography in thyroiditis. Ultrason Sonochem 1980; 1:345–352.
15. Marcocci C, Vitti P, Cetani F, et al. Thyroid ultrasonography helps to identify patients with diffuse lymphocytic thyroiditis who are prone to develop hypothyroidism. J Clin Endocrinol Metab 1991; 72:209–213. [CrossRef]
16. Andrade L, Andrade M, Cruz T, et al. Color flow Doppler ultrasonography in Hashimoto's thyroiditis. R Ci Md Biol Salvador 2011; 10:14–18.
17. Bogazzi F, Bartalena L, Brogioni S, et al. Thyroid vascularity and blood flow are not dependent on serum thyroid hormone levels: studies invivo by color flow Doppler sonography. Eur J Endocrinol 1999; 140:452–456. [CrossRef]
18. Itaka M, Miura S, Yamanaka K, et al. Increased serum vascular endothelial growth factor levels and intrathyroidal vascular area in patients with Graves disease and Hashimoto's thyroiditis. J Clin Endocrinol Metab 1998; 83:3908–3912. [CrossRef]