CLINICAL SCIENCE

The role of the resistive index in Hashimoto's thyroiditis: a Sonographic pilot study in children

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OBJECTIVE: The role of Doppler ultrasonography in the diagnosis of diffuse thyroid diseases is not well established. In particular, Doppler ultrasonography findings in children with Hashimoto's thyroiditis are very limited. We examined gray-scale and Doppler ultrasound findings in Hashimoto's thyroiditis in children in an attempt to understand the feasibility of future prospective controlled studies.

MATERIALS AND METHODS: Twenty-one children with newly diagnosed Hashimoto's thyroiditis were recruited in the study. The patients were euthyroid or had subclinical hypothyroidism at the time of the ultrasonography examination. According to the color Doppler scale developed by Schulz et al., thyroid glands were classified into four patterns based on visual scoring and the mean resistive index (RI), which was calculated via measurements from both lobes, and these results were compared with gray-scale findings.

RESULTS: The mean RI value, calculated as the mean of the RI values of both lobes obtained from each patient, was found to be 0.57 ± 0.05 (range 0.48-0.67) cm/sn. The distribution of thyroid classifications was as follows: Pattern 0, n = 7; Pattern I, n = 6; Pattern II, n = 4; and Pattern III (''thyroid inferno''), n = 4. The mean RI values in patients with normal or near-normal gray-scale findings (n = 10) and patients with more substantial gray-scale changes (n = 11) were not significantly different and were lower than the values in normal children previously presented in the literature.

CONCLUSION: The results indicated that the RI may be more sensitive than other ultrasound parameters for the diagnosis of Hashimoto's thyroiditis.

KEYWORDS: Doppler Ultrasound; Hashimoto's Thyroiditis.

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INTRODUCTION

Ultrasonography has been used in the diagnosis of diffuse thyroid diseases for many years (1-10). The diagnostic role of Doppler ultrasonography (US) in diseases of the thyroid was evaluated in studies on thyroid nodules during the 1980s and 1990s (11,12). However, the use of color Doppler US in thyroid disease is a relatively new and promising concept. Previously published studies mainly focused on the detection of adenomas and the differentiation of adenomas from carcinomas in cases of cold nodules with different points of view (13,14).

Limited information on the role of color Doppler US in diagnosing diffuse thyroid diseases, such as Hashimoto's disease, exists in the literature. Ralls et al. initially described a color Doppler US pattern in Graves' disease that was not observed in normal individuals or in patients with other thyroid diseases and named it the ''thyroid inferno''. This pattern results from continuous multiple intrathyroidal flows during systole and diastole (15).

However, to the best of our knowledge, no previous study has described Doppler US findings in children with Hashimoto's disease. In this preliminary study, we aimed to compare conventional ultrasonography (gray scale) with color Doppler US findings in newly diagnosed patients with Hashimoto's disease.

MATERIALS AND METHODS

This study was conducted by a retrospective review of digitally stored US images of newly diagnosed Hashimoto's thyroiditis patients. The subject population consisted of a small portion of a larger cohort of patients referred to the Ultrasound Unit from the Pediatric Endocrinology Unit of Hacettepe University Medical Center, Ankara, Turkey (16). Twenty-one patients were included over an 18-month period, including 19 females and two males, with ages

No potential conflict of interest was reported.

Table 1 - Grading system created by Sostre and Reyes (4).

Grade 1 (G1)	Diffusely enlarged gland with a normoechoic (similar to normal tissue) pattern
Grade 2 (G2)	Multiple hypoechoic foci or patches scattered throughout an otherwise normoechoic gland; a pattern suggestive of focal rather than diffuse involvement
Grade 3 (G3)	Enlarged gland with diffuse but mild hypoechogenicity
Grade 4 (G4)	Enlarged gland with diffuse and marked hypoechogenicity

ranging from 6-12 years (median age = 10 years). The study was approved by the Hacettepe University Medical School Institutional Review Board, and informed consent was waived. Inclusion criteria included a new diagnosis of the disease with no history of treatment and euthyroid or subclinical hypothyroidism. Doppler US was performed as an adjunct to routine clinical sonographic evaluation of the patients.

Each subject underwent ultrasound examination using a Sonoline Elegra (Siemens, Erlangen, Germany) sonographic machine with a 7.5-MHz transducer. Ultrasound examinations were performed by the same researcher for all patients. Gray-scale ultrasonography parameters included echogenicity and size of the thyroid gland. The total thyroid volume in each patient was compared with upper level values determined for specific age groups by the World Health Organization (WHO), and patients with thyroids larger than the reference values were classified as having thyromegaly (17). The echogenicity of each individual thyroid gland was noted and used in the classification of gray-scale findings based on a classification system originally created by Sostre and Reyes (Table 1) (4). However, a modification to the original classification was required to account for patients with completely normal gray-scale findings (Grade 0).

Color Doppler US examination was performed by setting the pulse repetition frequency (PRF) and color Doppler gain to appropriate levels (the maximum gain and minimum PRF at which no aliasing in the carotid artery or internal jugular vein was observed) in all patients. The vascularity of both lobes was determined based on a visual scale according to the classification previously created by Schulz et al. (Table 2) (18).

RI measurements were performed within each lobe of the thyroid at a location close to the center, where vascularity could still be observed. The values obtained for each lobe were averaged for each patient, and a mean RI value for the entire patient group was calculated. Mean RI values were also calculated for each Doppler pattern. The RI values of patients with normal gray-scale findings or minimal changes (Grade 0 or 1) were compared with those of patients with strongly positive gray-scale findings (n = 11).

Table 2 - Color Doppler classification in hypothyroidism, by Schulz et al.

Pattern 0	Blood flow limited to the peripheral thyroid arteries, while parenchymal flow is absent
Pattern I	Presence of mildly increased parenchymal flow
Pattern II	Clearly increased color flow with a diffuse homogenous distribution
Pattern III	Markedly increased color flow with a homogenous distribution, including the so-called ''thyroid inferno''

RESULTS

The patients' laboratory findings were as follows. Nineteen patients had positive thyroid antibodies (one or more of the following antibodies: antithyroglobuline (ATA), anti-thyroid peroxidase (anti-TPO), and anti-microsomal (AMA) antibodies). Two patients had negative values at the time of US examination but had previously tested positive for thyroid antibodies. Sixteen patients were euthyroid during US examination, and five patients had subclinical hypothyroidism.

The thyroid gland volume was within normal limits (according to the WHO reference) in 13 patients, and eight patients had thyromegaly. According to the modified Sostre and Reyes gray-scale classification, thyroid glands were scored as Grade 0 in seven patients, Grade 1 in three patients, Grade 2 in seven patients, Grade 3 in two patients and Grade 4 in two patients (Table 3; also see Figure 1).

According to the color Doppler scale of Schulz et al. (17), seven patients had Pattern 0, six patients had Pattern I, five patients had Pattern II, and four patients had Pattern III (''thyroid inferno'') thyroid glands (Figure 2 and Table 4). The mean RI value, calculated as the mean of the mean RI values of both lobes in all patients, was 0.57 ± 0.05 (range 0.48-0.67) cm/sn.

Thyroid glands that were classified as having normal or near-normal gray-scale findings (n = 10) and those with substantial gray-scale changes (n = 11) demonstrated no statistically significant difference in the RI. Patients with minimal or no US gray-scale findings were found to have a mean RI value of 0.58 ± 0.056 cm/sn, and patients with substantial gray-scale changes had a mean RI value of 0.56 ± 0.059 cm/sn.

In addition, the mean RIs calculated for each Doppler pattern were found to range from 0.56 to 0.58 (Table 5).

DISCUSSION

Hashimoto's thyroiditis is the most common cause of goiter and hypothyroidism in children (19-21). Nearly all cases of thyroiditis seen in children are cases of Hashimoto's disease (21). In the diagnosis of Hashimoto's thyroiditis, two different diagnostic criteria exist, namely one developed by

Table 3 - Grading of the gray-scale findings and distribution of patients within the grades. (Note: we have added Grade 0 to the original grading system created by Sostre and Reyes).

US GRADE	Percentage of Patients
Grade 0	33.3% (7/21)
Grade 1	14.3% (3/21)
Grade 2	33.3% (7/21)
Grade 3	9.5% (2/21)
Grade 4	9.5% (2/21)

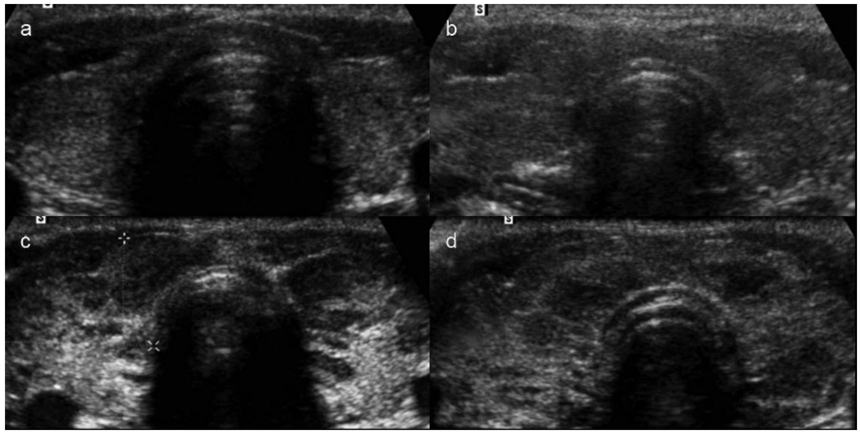

Figure 1 - Gray-scale grading. Grades 1-4 are shown in a-d, respectively. Grade 0, representing a completely normal thyroid gland, is not shown in this figure.

Fischer et al. and the other developed by the Japan Thyroid Association. These two criteria, while different, are both based on clinical and laboratory findings (22). Imaging of the thyroid gland (ultrasonography and scintigraphy) is not included in the diagnostic criteria because of its low specificity. The most objective finding in thyroid ultrasonography is the quantitative measurement of thyroid volume. The WHO has defined the standard normal upper limits of ultrasonographically measured thyroid volumes according to age and gender because only 50% of goiter classifications can be accurately made by palpation. In an article published in 1999, the authors evaluated intraobserver and interobserver differences and found no significant differences, therefore concluding that thyroid ultrasonography was reliable for evaluating thyroid dimensions and volume (23).

US is valuable for determining the presence of nodular goiter in patients with Hashimoto's disease and can enable the characterization and surveillance of these nodules. Furthermore, US also helps to position and guide fine-needle aspiration biopsy (24,25).

Hayashi et al. investigated ultrasound findings in 53 histologically confirmed patients with diffuse thyroid diseases and classified the thyroid echogenity into groups A and B, as iso-, hypo-, or hyperechoic compared with adjacent muscles. Because the thyroid gland is expected to be more echogenic than adjacent muscles in normal individuals, the authors emphasized that a hypoechoic gland may be suggestive of hypothyroidism and that ultrasonography may be an important easy and noninvasive method for diagnosing Hashimoto's disease (2).

In the absence of an ideal test for Hashimoto's thyroiditis, Sostre and Reyes proposed that thyroid US could be an appropriate diagnostic test. They used a grading system to classify ultrasonographic patterns into four groups, with the sternomastoid muscle chosen as a reference (4). However, because Sostre and Reyes' classification is based solely on the presence of ultrasonographic changes, there is no group in the classification that corresponds to clinical and laboratory findings of Hashimoto's disease or to findings of completely normal ultrasonographic examinations. Therefore, in this study, it was deemed appropriate to add Grade 0 to their original grading system. In the present study, we found that a high grade was correlated with thyroid gland destruction and hypothyroidism. Five patients with subclinical hypothyroidism were found to have Grade 3 or Grade 4 disease.

Bogazzi et al. investigated the cause of the increase in thyroid blood flow in untreated Graves' disease patients,

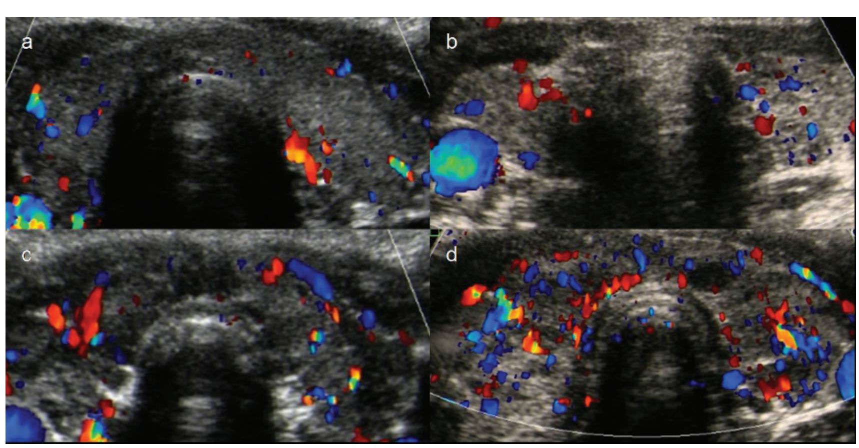

Figure 2 - Color Doppler patterns. **a.** Pattern 0 (normal thyroid vascularity); **b.** color Doppler Pattern I (minimally increased thyroid vascularity); **c.** color Doppler Pattern II (increased blood flow with a diffuse homogenous distribution); and **d.** color Doppler Pattern III (''thyroid inferno'').

Table 4 - Distribution of Color Doppler patterns based on the classification initially created by Schulz et al. for hypothyroidism.

PATTERN	Percentage of Patients
Pattern 0	33.3% (7/21)
Pattern I	28.6% (6/21)
Pattern II	19% (4/21)
Pattern III	19% (4/21)

and they observed thyroid vascularity in different subgroups corresponding to different thyroid disease types (26). These authors stated that thyroid hormones were not the cause of increased thyroid vascularity but that TSH-receptor antibodies or TSH may be the cause. This hypothesis was based on the fact that intrathyroidal vascularity and flow velocity increase in spontaneous hyperthyroidism but not in hyperthyroidism secondary to thyroid hormone intake or thyroid gland destruction. In addition, an increase in vascularity and flow velocity is also seen in Hashimoto's disease patients with hypothyroidism (26). In the same study, intrathyroidal peak systolic flow velocity was thought to be a better index of thyroid disease because it demonstrated a more significant increase in patients with Graves' disease than in those with Hashimoto's disease. Iitaca et al. examined vascular endothelial growth factor (VEGF), which is an antigenic growth factor, and concluded that a significant relationship existed between intrathyroidal flows and VEGF levels (27).

Once it was realized that hypervascularity was not unique to hyperthyroidism, Caruso et al. evaluated flow velocity in autoimmune thyroid diseases and concluded that the inferior thyroid arterial peak systolic flow velocity exceeded 150 cm/sec in patients with these diseases. However, the velocity remained within normal limits in patients with other thyroid diseases and did not exceed 65 cm/sec. These authors emphasized the importance of inferior thyroid artery peak systolic flow velocity in the differential diagnosis of diffuse thyroid disease and follow-up care of patients with Graves' disease (28).

Schulz et al. investigated the role of color Doppler US in hypothyroidism and, in reference to previous studies, classified the vascularity (Table 2) (18). In their study, it was reported that the hypervascularity found in patients with Graves' disease was also present in patients with hypothyroidism to some extent.

There is no consensus regarding normal values for Doppler parameters measured in the thyroid gland or inferior thyroid artery, namely the resistivity index (RI), pulsatility index (PI) and peak systolic flow velocities. In addition, no common guidelines exist on how to obtain these parameters (29-31). Mahmutyazicioglu and Turgut compared 20 children with normal thyroids, with 20 children with endemic goiter and found that RI values were significantly lower in the disease group (32). The mean RI was 0.58 ± 0.05 in the disease group and 0.70 ± 0.05 in the control group. Although the measurements were taken from thyroid arteries, rather than from the gland itself, the RI value in the disease group was in accordance with the mean RI value in our study (0.57 ± 0.05).

Table 5 - Mean RI values in patients with different Doppler patterns.

DOPPLER US PATTERN	Mean RI value
Pattern 0	0.58
Pattern I	0.56
Pattern II	0.58
Pattern III	0.57
All patients	0.57

The major conclusion of our study is that, despite variations in color Doppler patterns, there was no statistically significant difference in the mean RI values between patients with normal or near-normal gray-scale findings and patients with marked gray-scale changes. Both RI values were below normal limits. This finding indicates that it is important to evaluate the RI even in subjects with sonographically normal thyroid glands.

Conversely, subjective color Doppler grading of the thyroid gland did not yield the expected results. Specifically, a small group of patients (38%, 8/21) was found to have markedly increased vascularity of the thyroid.

This study has several limitations. The major limitation is the lack of a control group. In future studies designed to test the efficacy of RI, the presence of a control group of age- and gender-matched subjects free of thyroid disease is crucial. Another limitation is the small size of the patient group, which limited our ability to perform any statistical analysis. Of the different spectral Doppler US parameters, only the RI was tested in this study. Other parameters, such as the peak systolic velocity, end diastolic velocity and pulsatility index, could be examined in future studies. The lack of assessment of the interobserver and intraobserver variability, due to the retrospective nature of the study, is another important limitation. This particular issue is extremely important for studies based on US imaging, a method known to result in significant interobserver and intraobserver variability.

Color Doppler imaging in Hashimoto's disease appears to be a promising diagnostic imaging modality. In particular, the changes in RI values in patients with relatively normal gray-scale findings prompt us to suggest adding Color Doppler imaging to routine ultrasound examination of those patients. Further blinded, controlled studies with a sufficient number of patients are required to determine measures of test performance of RI in Hashimoto's disease and would aid in determining the cut-off point for a normal RI value.

AUTHOR CONTRIBUTIONS

Sarikaya B participated in the radiological evaluations, data collection and analysis, literature review, and manuscript preparation. Demirbilek H participated in the patient selection, clinical assessment, data collection and analysis, and manuscript preparation. Akata D contributed to the radiological evaluations, manuscript preparation, and proofreading. Kandemir N contributed to the clinical assessment, manuscript preparation, and proofreading.

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