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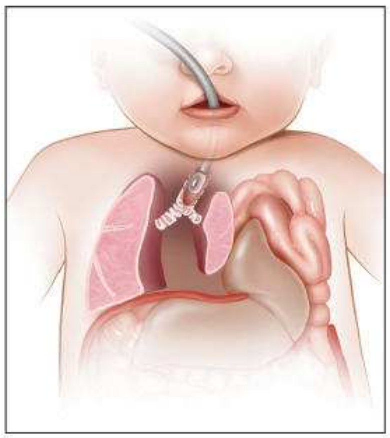

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Correlation Between Sonography and Antibody Activity in Patients With Hashimoto Thyroiditis

Arnulf Willms, MD, Dan Bieler, MD, Helmut Wieler, MD, Diana Willms, MD, Klaus P. Kaiser, MD, Robert Schwab, MD

Objectives—Patients with Hashimoto thyroiditis show structural changes of the thyroid that can be identified by a variety of sonographic criteria. We conducted this study to investigate whether there is a correlation between sonography and antibody activity and to assess the role of sonography in the diagnosis and follow-up of Hashimoto thyroiditis. In addition, we present a new classification system (termed the VESINC system [volume, echogenicity, sonographic texture, pseudonodular hypoechoic infiltration, nodules, and cysts]), which helps improve the clarity of sonographic findings.

Methods—The study included 223 consecutive patients with previously diagnosed Hashimoto autoimmune thyroiditis who attended the thyroid clinic of the German Armed Forces Central Hospital in Koblenz for follow-up examinations between 2006 and 2008. Laboratory tests were performed to measure the levels of free triiodothyronine, free thyroxine, thyrotropin, anti-thyroglobulin antibodies (TgAbs), and anti-thyroid peroxidase antibodies (TPOAbs). Sonography was performed according to a strict protocol. We then assessed whether a correlation existed between antibody activity and the 6 sonographic variables of the VESINC system.

Results—Hypoechogenicity, heterogeneity, and pseudonodular hypoechoic infiltration were associated with significantly higher TPOAb activity ($P < .001$). There were no significant correlations between the other sonographic variables examined (cysts, nodules, and volume) or the biometric data with the TPOAb and TgAb levels. In addition, an assessment of TgAb levels did not show significant differences in correlations with any of the sonographic variables.

Conclusions—Sonography is a noninvasive diagnostic imaging modality that provides information about the level of inflammatory activity. Markedly decreased echogenicity, heterogeneity, and multifocal pseudoinodular hypoechoic infiltration are indicative of a high level of inflammatory activity. The sonographic classification system presented here (VESINC system) can be a useful tool for comparing sonographic findings in a rapid and objective manner during follow-up of Hashimoto thyroiditis.

Key Words—anti-thyroglobulin; anti-thyroid peroxidase; Hashimoto thyroiditis; sonographic patterns; sonography

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Abbreviations

RIA, radioimmunoassay; T_4, thyroxine; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyrotropin; T_3, triiodothyronine

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Hashimoto thyroiditis is the most common inflammatory disease of the thyroid gland.[1] This autoimmune disease, which is also known as chronic lymphocytic thyroiditis, is the major cause of spontaneous hypothyroidism in adults.[2] In meta-analyses, the reported incidence ranged between 2 and 498 per 100,000 per year.[3] Women are far more often affected than men (7:1).

Diagnosis is usually based on laboratory tests, clinical signs and symptoms, and typical hypoechogenicity on sonography. Typical laboratory findings are low levels of free triiodothyronine (T_3) and free thyroxine (T_4) and elevated levels of thyrotropin (TSH).[4,5] High levels of anti-thyroid peroxidase antibodies (TPOAbs) are detected in 95% of patients with Hashimoto thyroiditis. In addition, elevated levels of anti-thyroglobulin antibodies (TgAbs) are found in 70% of patients.[2,4,6,7] It should be noted, however, that TgAbs are also present in approximately 5% of the general population.[2]

In the recent past, sonography of the thyroid gland has benefited from considerable technical advances and substantially higher resolution. Today, this noninvasive procedure is able to provide typical characteristics of the gland during diagnosis and follow-up examinations of Hashimoto thyroiditis. A typical sonogram shows generalized hypoechogenicity, usually of the entire thyroid gland.[2,8–11] Marked heterogeneity of the internal structure is seen in 70% of patients.[12] A proportion of patients show hypoechoic pseudonodular and multifocal lesions representing areas of high inflammatory activity (ie, lymphocytic infiltration).[13] Asymmetry of the thyroid is seen in many patients. At an initial stage, color duplex sonography may reveal increased vascularity,[14] which, however, generally develops into hypovasularity in the medium to long term, especially in patients with atrophic forms of thyroiditis (eg, subtypes 1B and 2B and Ord thyroiditis).

Against this background, the objective of this study was to assess whether there are correlations between sonographic variables of the thyroid and autoantibody activity in patients with Hashimoto thyroiditis. A further objective was to present a simple descriptive classification system that describes follow-up sonographic scans on the basis of 6 parameters using a universal and comparable code (VESINC system). The purpose of this tool is to enhance the comparison of sonographic findings by improving their clarity.

Materials and Methods

Study Design and Patients

This prospective single-center study included 223 consecutive patients with previously diagnosed Hashimoto autoimmune thyroiditis who attended the thyroid clinic of the German Armed Forces Central Hospital in Koblenz for follow-up examinations between 2006 and 2008. Originally, the diagnosis was made on the basis of laboratory tests and clinical signs and symptoms. In addition, sonography was performed in every examination so that typical sonographic characteristics could contribute to the diagnosis and follow-up. Especially for differentiating Hashimoto thyroiditis from morbus Basedow in the presence of hyperthyroidism, scintigraphy was conducted. If a case was still inconclusive, a fine-needle aspiration cytologic examination was performed as well. Irrespective of the disease stage, all patients undergoing follow-up examinations with previously diagnosed Hashimoto disease who had not undergone previous thyroid surgery were included. Patient evaluations included a physical examination, laboratory tests, including measurements of free T_3, free T_4, TSH, TPOAb, and TgAb, and sonography of the thyroid gland. Biometric data such as age, sex, height, weight, blood pressure, and pulse rate were collected as well.

Laboratory Tests

Thyrotropin and free T_3 levels were measured by radioimmunoassay (RIA) using TSH1 RIA and Brahms free T_3 SPART RIA kits (Brahms GmbH, Hennigsdorf, Germany). Free T_4 levels were assessed by RIA using a SELco FT4 kit (Medipan GmbH, Dahlewitz, Germany). Serum TPOAb and TgAb levels were measured by RIA using RIAZENco TPOAb and RIAZENco TgAb kits (ZenTech SA, Angleur, Belgium). Table 1 provides a list of serum levels that are considered normal in our laboratory.

Sonography

During sonography, the patients were positioned with their upper body elevated and their neck hyperextended in accordance with a standard sonographic protocol. First, an axial scan of the entire organ was obtained. Then each thyroid lobe was separately scanned in the longitudinal and transverse planes. Using a Nemio scanner (SSA-550A, version F; Toshiba Medical Systems Co, Ltd, Tokyo, Japan), 2 sonographers performed the examinations in accordance with the protocol presented below. Both examiners have many years of experience in nuclear medicine and perform several hundred sonographic examinations of the thyroid per year. A 6–12-MHz linear transducer was used. B-mode sonography was used and combined with color

Table 1. Normal Serum Levels in Our Laboratory

Parameter	Level
TSH	0.1–4.0 μIU/mL
Free T_3	2.3–5.3 pg/mL
Free T_4	11.0–23.0 pmol/L
TPOAb	0.0–50.0 U/mL
TgAb	0.0–70.0 IU/mL

Doppler sonography to evaluate vascularity. In theory, the transducer can image to a depth of 24 cm. All data were made anonymous and entered into an Excel spreadsheet (Microsoft Corporation, Redmond, WA).

The following parameters were assessed by the study's protocol:

1. Volume in cubic centimeters (according to Brunn et al[15]: length × width × depth × 0.52 for both thyroid lobes);
2. Echogenicity—semiquantitative criteria with 3 possible expressions: isoechoic, mildly hypoechoic, and hypoechoic (compared to the sternocleidomastoid muscle);
3. Sonographic texture—qualitative criteria with 2 possible expressions:
   a. Homogeneous means a regular echo pattern within the entire thyroid parenchyma with a uniform distribution of reflections;
   b. Heterogeneous means an irregular echo pattern within the entire thyroid parenchyma with an uneven distribution of reflections;
4. Pseudonodular hypoechoic infiltration—qualitative criteria representing the presence of multiple multifocal hypoechoic lesions within the thyroid parenchyma with a round, oval, or irregular shape without a sharp margin to the parenchyma, representing areas of high inflammatory activity (ie, lymphocytic infiltration[13]);
5. Nodules—yes or no; and
6. Cysts—yes or no.

These 6 variables can be summarized in the descriptive VESINC system in a code of 6 letters and 6 numbers. The letters V, E, S, I, N, and C represent the variables volume (V), echogenicity (E), sonographic texture (S), pseudonodular hypoechoic infiltration (I), the presence of nodules (N), and the presence of cysts (C). The numbers represent the expression of the variables:

1. Volume (V) in cubic centimeters;
2. Echogenicity—E1, isoechoic (Figure 1); E2, mildly hypoechoic (Figure 2); E3, hypoechoic (Figure 3);
3. Sonographic texture—S1, homogeneous (Figure 1); S2, heterogeneous (Figures 2 and 3);
4. Pseudonodular hypoechoic infiltration—I0, no; I1, yes (Figure 4);
5. Nodules—N0, no; N1, yes; and
6. Cysts—C0, no; C1, yes.

This classification provides a universal description of a sonographic scan of the thyroid and establishes the basis for rapid intraindividual or interindividual comparisons between 2 examinations. As an example, a thyroid with a volume of 25 cm^3, hypoechoic echogenicity, a heterogeneous echo texture, the presence of lymphocytic infiltration, and the absence of nodules and cysts is classified as V25, E3, S2, I1, N0, C0.

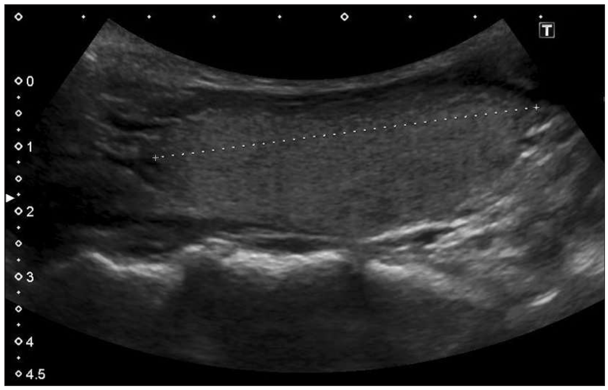


Figure 1. Isoechoic (E1) homogeneous (S1) gland (TPOAb, 16.8 U/mL; TgAb, 14.1 IU/mL).

Statistical Analysis

Data were analyzed by SPSS version 13.0 software (SPSS Inc, Chicago, IL) and tested for correlation and statistical significance. Sonographic variables (independent variables) were correlated with serum levels of TPOAb and TgAb (dependent variables). If a sonographic variable had more than 2 possible values, the Kruskal-Wallis test was used. If an independent variable had 2 possible values, the Mann-Whitney *U* test was used. Pearson and Spearman coefficients were calculated to test volumes for bivariate correlation with autoantibody activity. The level of significance was set at $P < .05$.

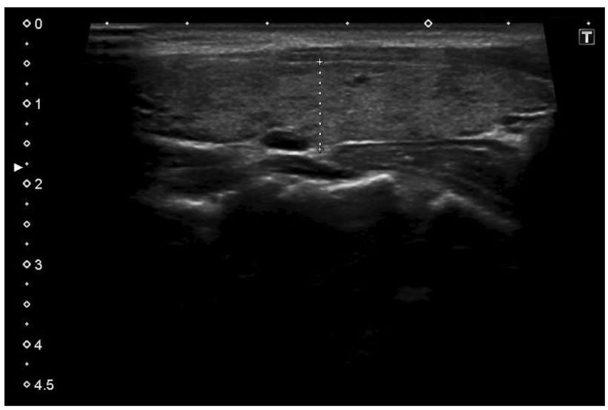


Figure 2. Mildly hypoechoic (E2) heterogeneous (S2) gland (TPOAb, 306 U/mL; TgAb, 21.8 IU/mL).

Figure 3. Hypoechoic (E3) heterogeneous (S2) gland (TPOAb, 424 U/mL; TgAb, 48.1 IU/mL).

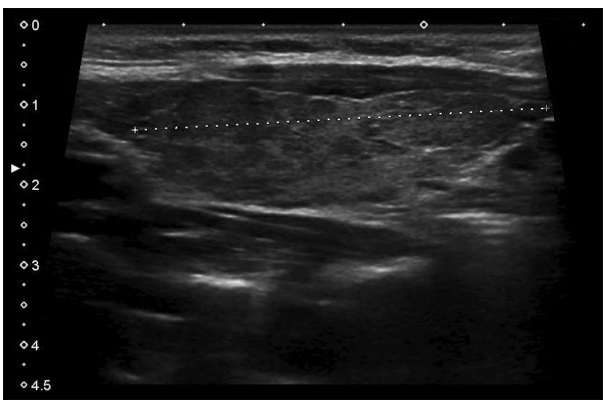
Results

A total of 223 patients with previously diagnosed Hashimoto thyroiditis were examined during follow-ups at our thyroid clinic between 2006 and 2008. Of these, 57 were women, and 166 were men. The mean patient age ± SD was 43.5 ± 12.4 years. The oldest patient was 76 years, and the youngest was 18 years. Further biometric data are shown in Table 2.

Descriptive Statistics

A descriptive analysis of biometric, laboratory, and sonographic data from our patients is given in Table 2. The mean thyroid volume was 15.8 ± cm^3. Cysts were present in 6.7% of the patients. Nodular structures were detected in 21.9%. Focal lymphocytic infiltrates were found in 56% of the thyroids. The echo texture was homogeneous in 32.3% and heterogeneous in 67.7%. Echogenicity was recorded as isoechoic in 21.5%, mildly hypoechoic in 32.7%, and hypoechoic in 45.7%. The sonographic variables (ie, thyroid volume, presence of cysts, presence of nodules, lymphocytic infiltration, echo texture, and echogenicity) were correlated with serum autoantibody levels (TPOAb and TgAb).

Figure 4. Hypoechoic (E3) gland with lymphocytic infiltration (I1; TPOAb, 805 U/mL; TgAb, 132 IU/mL).



Echo Texture Versus TPOAb and TgAb Levels

When we correlated these variables, we found that a heterogeneous echo texture was associated with significantly higher TPOAb concentrations than a homogeneous echo texture ($P < .001$). Patients with a heterogeneous echo texture also showed higher TgAb levels (mean level, 374.5 IU/mL) than patients with a homogeneous echo texture (mean level, 224.8 IU/mL). This difference, however, was not significant ($P = .66$; Table 3 and Figure 5).

Table 2. Biometric and Laboratory Data

Parameter	Value
Patients, n	223
Age, y	43.5 ± 12.4 (18–76)
Height, cm	178.4 ± 8.9 (155–204)
Weight, kg	85.4 ± 17.2 (45–147)
Male/female, n (%)	166/57 (74.4/25.6)
Thyroid volume, cm^3	15.8 ± 8.4 (2–50)
Free T_3, pg/mL	3.9 ± 4.1 (0.98–44.6)
Free T_4, pmol/L	15.3 ± 3.3 (1–27.5)
TSH, μIU/mL	3.5 ± 8.3 (0–77.2)
TPOAb, U/L	1492.4 ± 1779.9 (1.2–8839.9)
TgAb, IU/mL	326.1 ± 518.4 (1–2235.1)

Values are mean ± SD (range) where applicable.

Table 3. Echo Texture Versus TPOAb and TgAb Levels

Parameter	TPOAb, U/mL	TgAb, IU/mL
Homogeneous		
Mean	4717.111	224.777
n	72	72
SD	596.6	353.7
Maximum	4288	2000
Minimum	17.8	1
Heterogeneous		
Mean	1979	374.5
n	151	151
SD	1944.6	575.5
Maximum	8839.9	2235.1
Minimum	1.2	1
Total		
Mean	1492.4	326.1
n	223	223
SD	1779.9	518.4
Maximum	8839.9	2235.1
Minimum	1.2	1

Echogenicity Versus TPOAb and TgAb Levels

Hypoechoic echogenicity was associated with significantly higher TPOAb levels than mildly hypoechoic or isoechoic echogenicity ($P < .001$). An assessment of TgAb levels did not show significant differences between the 3 echogenicity groups ($P = .63$; Table 4 and Figure 6).

Pseudonudolar Hypoechoic Infiltration Versus TPOAb and TgAb Levels

Patients with sonographically detected lymphocytic infiltration showed significantly higher TPOAb concentrations than patients without lymphocytic infiltration ($P = .017$). An assessment of TgAb levels did not show significant differences between the 2 groups ($P = .21$; Table 5 and Figure 7).

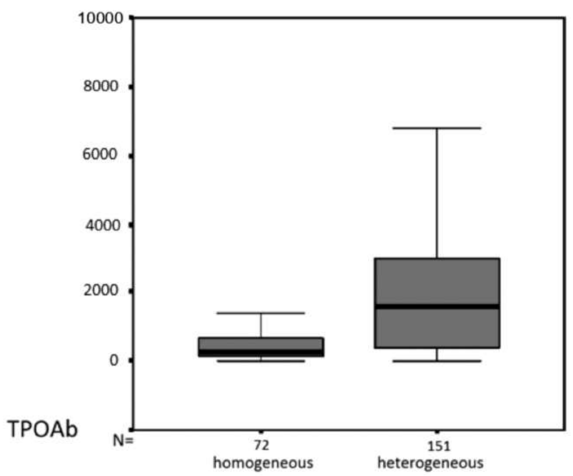
Nodules, Cysts, and Volume Versus TPOAb and TgAb Levels

There were no significant correlations between the presence of nodules or cysts on sonography and antibody activity. There were also no significant correlations between thyroid volume and TPOAb and TgAb levels. In addition, we compared the various groups with a view to detecting significant differences in terms of thyroid volume, age, weight, height, TSH, free T_4, free T_3, and sex. There were no significant differences.

VESINC Classification System

The sonographic variables examined in this study were transferred to the VESINC system, which allows us to express sonographic variables (ie, volume, echogenicity, echo texture, lymphocytic infiltration, nodules, and cysts) as a combination of 6 letters and 6 numbers. It was found to be an effective tool for summarizing sonographic follow-up examinations of patients with Hashimoto thyroiditis and thus eases intraindividual and interindividual comparisons between 2 examinations.

Figure 5. Echo texture versus TPOAb levels.



Discussion

The diagnosis and follow-up of Hashimoto thyroiditis cannot rely solely on a single diagnostic procedure. Several diagnostic tools are required for this purpose. When a patient presents with an undiagnosed pathologic condition, a diagnostic procedure should ideally be able to suggest the presence of Hashimoto thyroiditis, to distinguish it from other conditions, to measure the organ size, to detect changes in size during follow-up examinations, and to provide information about disease activity. Its ease of use and noninvasiveness could make sonography a key procedure in the diagnosis and follow-up of Hashimoto thyroiditis.

Sonography is used for monitoring treatment and helps avoid complications such as malignant transformation.[16] In addition, Marcocci et al[9] found that sonography was useful for identifying patients at risk for developing hypothyroidism. This noninvasive procedure thus appears to be able to predict functional disorders on the basis of morphologic criteria. The purpose of this study was to eval-

Table 4. Echogenicity Versus TPOAb and TgAb Levels

Parameter	TPOAb, U/mL	TgAb, IU/mL
Isoechoic		
Mean	656.6	185.7
n	48	48
SD	837.4	266.8
Maximum	3755	1708
Minimum	1.2	1
Mildly hypoechoic		
Mean	1343	362.6
n	73	73
SD	1636.2	574.6
Maximum	7500	2235.1
Minimum	4.8	1
Hypoechoic		
Mean	1992.6	366.1
n	102	102
SD	2031.6	557
Maximum	8839.9	2000
Minimum	2	1
Total		
Mean	1492.4	326.1
n	223	223
SD	1779.9	518.4
Maximum	8839.9	2235.1
Minimum	1.2	1

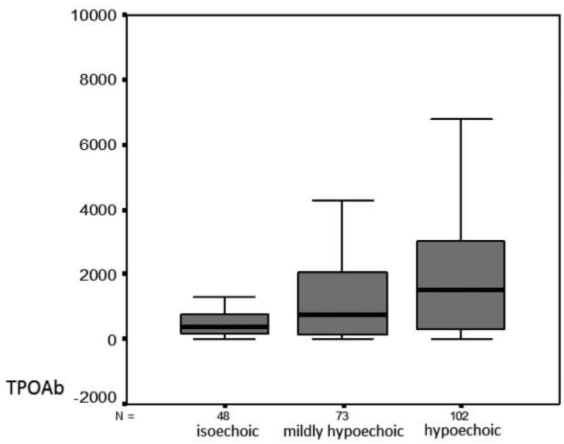


Figure 6. Echogenicity versus TPOAb levels.

uate the role of sonography in assessing inflammatory activity during the follow-up of a suitable group of patients with Hashimoto thyroiditis. A further purpose of this study was to introduce the descriptive VESINC classification system, which could facilitate comparisons of sonographic examinations. Sonography thus has the potential to become an ideal tool for the diagnosis of Hashimoto thyroiditis. We postulate that sonographic patterns that demonstrate the type and extent of structural changes of the thyroid reflect different courses of the disease.

Many authors have reported the thyroid to be diffusely hypoechoic in patients with Hashimoto thyroiditis.[8,9,17,18] Hypoechoic pseudonodular and multifocal lesions representing areas of high inflammatory activity (ie, lymphocytic infiltration), have also been described in a proportion of patients.[13]

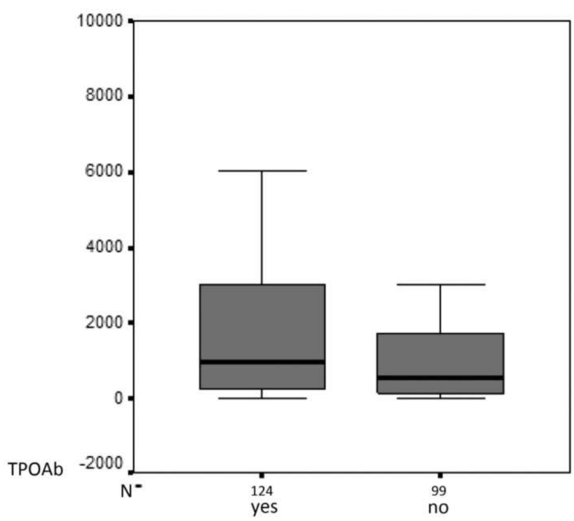
Reduced echogenicity is caused by a decrease in colloid content,[19] an increase in thyroid blood flow,[20] or an increase in lymphocytic infiltration.[13,21] Classifying echogenicity in 3 categories is a modification of the classification system published by Sostre and Reyes.[22] In our opinion, a classification system with only 2 values for the variable "echogenicity," such as that presented by Hayashi et al,[8] is too strict. For this reason, this variable has 3 values in our system. Since the sonographic pattern of Hashimoto thyroiditis can be described not only by the degree of echogenicity, we used further sonographic variables for characterization of the disease. It should be noted that echogenicity varies with gain. For this reason, care must be taken to ensure that the same scanner settings are always used to ensure the comparability of initial and follow-up examinations.[19,20,23–25] Although the classification system does not include absolute echogenicity, it is easy to use and provides the basis for qualitative and reproducible comparisons similar to those advocated by Sostre and Reyes.[22] The results can also be expressed in 3 grayscale levels, whenever this is considered more practicable in a hospital setting.

Apart from echogenicity, we assessed 5 further sonographic variables in a standardized manner. The results can be transferred to the VESINC system as a combination of 6 letters and 6 numbers, which provide the basis for intraindividual and interindividual comparisons between 2 examinations and which, in particular, facilitate the follow-up of

Table 5. Lymphocytic Infiltration Versus TPOAb and TgAb Levels

Parameter	TPOAb, U/mL	TgAb, IU/mL
Infiltration		
Mean	1718.2	321.1
n	124	124
SD	1904.7	478.2
Maximum	8839.9	2000
Minimum	1.2	0
No infiltration		
Mean	1239.3	304.9
n	99	99
SD	1581.8	533.2
Maximum	7500	2235.1
Minimum	2	0
Total		
Mean	1505.6	314
n	223	223
SD	1780.8	502
Maximum	8839.9	2235.1
Minimum	1.2	0

Figure 7. Lymphocytic infiltration versus TPOAb levels.



patients with Hashimoto thyroiditis. Similar to laboratory parameters, sonographic data can be coded (VESINC system) and entered into a table, which allows the results to be easily compared.

Our study shows that significant correlations exist between certain sonographic variables and disease activity measured by TPOAb levels. Three of the 6 variables were found to be correlated with disease activity: hypoechogenicity, heterogeneity, and the presence of lymphocytic infiltration.

Similar to other publications, this study shows that hypoechogenicity is associated with higher TPOAb concentrations.[22,26,27] There were no significant correlations between sonographic variables and TgAb levels. This result also confirms findings reported elsewhere in the literature.[25,26] Studies that were based on grayscale analysis and not on a quantitative analysis reported the same results.[26,27] In a study that was published as early as 1986, Hayashi et al[8] studied 53 patients with untreated Hashimoto thyroiditis and showed that patients with lower echogenicity had lower free T_4 levels as a result of increased antibody activity and showed histologic evidence of a greater degree of follicular degeneration.

Apart from the relationship between thyroid echogenicity and antibody titers, which was investigated in other studies too, this study also evaluated other sonographic variables. Positive correlations were demonstrated between TPOAb titers and a heterogeneous echo texture and the presence of lymphatic infiltration.

Increased lymphocytic infiltration is believed to be one of the factors causing hypoechogenicity. Apart from diffuse lymphocytic infiltration, patients also show localized pseudonuclear hypoechoic structures,[13] which can be interpreted as local accumulations of lymphocytes and were seen in 56% of our patients. These patients showed significantly higher TPOAb titers.

In our study, we assessed a further sonographic variable, echo texture, which was classified as homogeneous or heterogeneous. A heterogeneous internal structure was seen in 67.7% of the thyroids. This value is almost exactly the same percentage as that reported in the literature.[12] Patients with an inhomogeneous internal structure showed significantly higher TPOAb titers than patients with a homogeneous internal structure (32.3%). An inhomogeneous echo texture thus appears to be indicative of increased inflammatory activity. By contrast, Sostre and Reyes[22] measured the highest level of antibody activity in their G4 group (enlarged gland with marked but homogeneous hypoechogenicity). The level of significance, however, was not reached for TPOAb titers in their study on 47 patients.[22]

It would now be important to assess whether a combination of our sonographic variables can provide the basis for identifying and classifying sonographic patterns that are associated with higher antibody concentrations. Together with the significantly different levels of antibody activity, the sonographic variables show that different autoimmune entities with different courses are currently subsumed under the term Hashimoto thyroiditis.[28] Further studies should be conducted to substantiate this conclusion and to investigate correlations between sonographic, histologic, and immunohistochemical findings.

The VESINC classification system that we presented in this study is a novel tool that accommodates various sonographic parameters, summarizes sonographic findings, and thus could be able to facilitate comparisons between 2 examinations. Our study emphasizes that sonography is a noninvasive procedure that can predict functional disorders on the basis of morphologic criteria. No other single procedure can provide such comprehensive information on patients with Hashimoto thyroiditis. The classification system increases the potential of sonography to become an ideal diagnostic tool. It has proven its effectiveness in our thyroid clinic by standardizing and facilitating follow-up examinations of patients with Hashimoto thyroiditis.

This study had some limitations. The interpretation of the VESINC system was not evaluated by multiple examiners; therefore, it is unproven whether other interpreters would see the same and find out exactly the same classification. It also has to be stated that this work was a preliminary study and needs to be evaluated in a population of all thyroid patients to determine its value.

In conclusion, sonography of the thyroid is a useful, simple, and noninvasive modality for following patients with Hashimoto thyroiditis and provides useful information on the level of inflammatory activity. A marked decrease in echogenicity, a heterogeneous echo texture, and the presence of localized lymphocytic infiltration are indicative of a high level of inflammatory activity. The VESINC classification system presented here can be a useful tool for comparing sonographic findings in a rapid and objective manner during follow-up.

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