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Evaluation of Normal Thyroid Tissue and Autoimmune Thyroiditis in Children Using Shear Wave Elastography

Bakirtas Palabiyik F et al. Thyroid Elasticity in Children Using Shear Wave Elastography

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What this study adds?

The aim of this study was to measure the elasticity of thyroid tissue in children and adolescents using SWE and to investigate the role of SWE in the diagnosis of autoimmune thyroiditis in childhood. Fibrosis results in high SWV values and these values are dependent on the level of fibrosis in the thyroid tissue.

What is already known on this topic?

Shear wave elastography (SWE) provides real-time quantitative information about tissue elasticity by measuring and displaying local tissue elasticity. This noninvasive technique has the advantages of operator independence, reproducibility, high spatial resolution and quantitative evaluation without compression artifacts.

There have been many studies about the advantages of SWE; however, most were performed with adult populations. SWE is used especially in the evaluation of thyroiditis and in distinguishing malignant-benign thyroiditis from thyroid nodules in adults but there have been no studies about the evaluation of SWE of the thyroid in children. In our study, we used a standardized protocol for thyroid SWV measurements in children.

Abstract

Objectives: Shear wave elastography (SWE) is an ultrasonographic technique that evaluates tissue elasticity and is user-independent. It is used especially in the evaluation of thyroiditis and in distinguishing malignant-benign thyroiditis from thyroid nodules in adults, but so far no studies have evaluated SWE of the thyroid in children. The aim of this study was to

measure the elasticity of normal thyroid tissue in children and adolescents using SWE and to investigate the role of SWE in the diagnosis of autoimmune thyroiditis in childhood.

Methods: In total, 113 healthy children (66 girls, 47 boys) and 57 children (45 girls, 12 boys) who were being followed up for autoimmune thyroiditis were evaluated by SWE after B-mode ultrasound. The quantitative evaluation of normal thyroid tissue in healthy children and those with autoimmune thyroiditis was performed using shear wave velocity (SWV) values (m/s).

Results: The average SWV value of thyroid parenchyma in the healthy children was 1.82 ± 0.3 m/s (min: 1.32 m/s, max: 2.37 m/s). There was a significant positive correlation between age and SWV values and these values increased with age. The average SWV value of thyroid parenchyma in children with autoimmune thyroiditis was 3.7 ± 1.2 m/sn (min: 2.59 m/sn, max: 6.25 m/sn). In children with autoimmune thyroiditis, thyroid SWV values were statistically significantly higher than in healthy children ($p \leq 0.05$). The cutoff value with the highest diagnostic accuracy for elasticity value was 2.39 m/s; sensitivity and specificity were 97.4, 100 respectively. There was no correlation between elasticity values and thyroid function tests with autoantibody levels ($p > 0.05$).

Conclusions: SWE is a useful imaging method that can be used with routine US in evaluation of the thyroid in children.

Keywords: Shear wave elastography, children, thyroid, autoimmune thyroiditis

Introduction

Shear wave elastography (SWE) is a noninvasive method for measuring tissue elasticity whereby a quantitative estimate is provided of the elasticity of various soft tissues. It is real time, quantitative, repeatable and user-independent imaging technique. With this technique, a short-time high-frequency acoustic repulsive force is applied with an ultrasonic probe,

which causes small fluctuations in the tissues and the rate of advance of the formed waves to the tissue can be measured. The values of normal thyroid tissue elasticity in healthy adults is known as kilopascal (kPa) and shear wave velocity (SWV, m/s). In many studies, SWV of normal thyroid tissue of adults have been reported but few studies have been performed to evaluate the normal elasticity of thyroid tissue in children and adolescents.

Some pathologic conditions such as tumour and inflammations can change thyroid normal tissue elasticity. The elasticity measurement of thyroid tissue using SWE can be useful noninvasive test for the diagnosis of various thyroid diseases. In these days, it has been used with success in the evaluation thyroid tumours and autoimmune thyroiditis in adults (1,2,3). Autoimmune thyroiditis is the most common thyroid pathology in childhood and adolescence. It is characterized by lymphocytic infiltration and fibrosis and might affect shear wave velocities. In studies performed in adults, shear wave velocity values were reported to be significantly higher in autoimmune thyroiditis than in normal thyroid parenchyma and could be used for diagnosis. There are few studies evaluating the elasticity of thyroid tissue with SWE in children with autoimmune thyroiditis. The aim of this study was to measure the elasticity of normal thyroid tissue with SWE in children and adolescents and was investigated the role of SWE in diagnosis of autoimmune thyroiditis in childhood.

Material and methods

1. Study subjects

a. Healthy children

One hundred- thirteen healthy children and adolescents (66 girl, 37 boy) were evaluated with B-mode ultrasound and SWE. Healthy children were selected from cases of neck ultrasonography for non-thyroid pathologies. Pediatric volunteers with history of thyroid

disease or have a family history were excluded. A total of 226 thyroid lobes including right and left were evaluated in sonographic examinations, in children with no thyroid pathology.

b. Autoimmune thyroiditis cases

Fifty - seven children and adolescents (45 girls, 12 boys) who were followed up for autoimmune thyroiditis in the pediatric endocrinology department of our hospital were evaluated with B- mode ultrasound followed by SWE. The diagnosis of autoimmune thyroiditis was based on the presence of high levels of antithyroid antibodies (TPOAb and/or TGAb), normal or low thyroid function (T4, TSH), together with a heterogeneity and hypoechogenicity of thyroid parenchyma at ultrasound examination. Some of the patients were receiving antithyroid treatment during ultrasonography. A total of 114 thyroid lobes including right and left were evaluated in children with autoimmune thyroiditis.

This prospective study was approved by the local ethics committee (2016/107). Written consent was obtained from patients and/or their parents.

2. SWE technique

The SWE measurements were performed using a linear transducer probe (7.5-10 MHz) with a Toshiba Applio 500 ultrasound machine (Toshiba, Japan). The evaluation of each thyroid gland was obtained with the children in the supine position and the neck in hyperextension, eased by positioning of the pillow behind the neck. The linear probe is gently placed on the thyroid and performed slight pressure. The measurements were performed longitudinal plane with sampling deeper than 1 cm and obtained with normal breathing. Measurement of SWV was made after checked that the intensity of the signal. The region of interest (ROI) was 5×6 mm and was placed perpendicular to homogenous parenchyma that did not include vessels or surrounding structures in healthy children. The color-coded image showed soft tissue in blue and hard tissue is encoded in red. The quantitative evaluation of normal thyroid tissue in

healthy children was performed by the SWV (m/sn). An average of five measurements were performed by experienced pediatric radiologist and general radiologist from healthy children at the same time in each of the two thyroid lobes (Figure 1). In healthy children, normal SWV values by age and averages were determined. Differences interobserver variability in the measurements were evaluated.

In the patient of autoimmune thyroiditis, SWE evaluation was done in the same technique by only an experienced pediatric radiologist (Figure 2). SWV values detected during autoimmune thyroiditis cases were compared with SWV values of healthy children.

The average examination time was 5 minutes (range 4-8 minutes).

3. Statistical analyses

Statistical analyses were performed with SPSS 22.0 software. Descriptive statistics of the data included mean, standard deviation, median, minimum, maximum, frequency and ratio values. The Kolmogorov–Smirnov test was used to analyze a range of variables. The Mann–Whitney *U*-test, Wilcoxon and chi-square test were used in the analysis of quantitative data. The analysis of correlation was evaluated with the Spearman correlation test. Receiver-operating characteristic (ROC) curves were plotted for elasticity values, and the best elasticity cutoff value that represented the diagnosis of autoimmune thyroiditis was determined. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

The mean age of healthy children and adolescents was 9.7 ± 2.9 years (range:4-14 years, median: 10 years). The average SWV values of normal thyroid parenchyma was 1.8 ± 0.3

m/s (min: 1.32 m/s, max: 2.37 m/s). There was no significant difference between right and left thyroid lobes ($p>0.05$) and in girls and boys ($p>0.05$) (Figure 3). There was a significant positive correlation between age and SWV values ($r = 0.390 / p = 0.000$) (Figure 4). There was no significant difference intra-observer ($p = 0.624$) but was determined positive significant correlation ($r = 0.952 / p = 0.000$) (Figure 5).

The mean age of children with autoimmune thyroiditis was 12.6 ± 2.7 years (range: 7-17 years, median: 13 years). The average SWV values of thyroid parenchyma was 3.7 ± 1.2 m/s (min: 2.59 m/s, max: 6.25 m/s). There was no significant difference between right and left thyroid lobes ($p>0.05$) and in girls and boys ($p>0.05$). In children with autoimmune thyroiditis, thyroid SWV values were detected to be statistically higher than healthy children ($p \leq 0.05$) (Table 1).

ROC curves were plotted for elasticity values based on presence of autoimmune thyroiditis, and area under the curves (AUC) was calculated. The maximum AUC for mean elasticity value of both lobes was 0.996 (AUC, 0.996; 95% confidence interval 0.968–1.0). The cutoff value with the highest diagnostic accuracy for elasticity value was 2.39 m/s; sensitivity, specificity, PPV and NPV were 97.4, 100, 100 and 99.1 respectively (Figure 6).

There was no correlation between SWV values and thyroid function tests with autoantibody levels were analyzed in patients with autoimmune thyroiditis ($p>0.05$) (Table 2).

Seventeen of the patients were receiving antithyroid treatment during SWE. The average treatment duration was 5 months (range: 2-24 months). There was no significant correlation between SWV values and antithyroid treatment with treatment duration ($p>0.05$).

Discussion

There have been many studies about evaluation of normal thyroid tissue and its pathologies by SWE in adult populations. But there are few studies regarding of this imaging method about assessment of thyroid tissue in children. In our study we standardized protocol for normal thyroid SWV measurements with regard to frequency, measurement depth and place, size of ROI and acquisition number in pediatric populations. We used high linear frequency probes and measured the SWV at a depth of more than 1 cm below the front edge of each thyroid lobes. The capable of children were asked to hold their breath for a short time and we performed our study with free-breathing in young children. The operator applied similar amounts of transducer pressure only necessary to create gray scale image avoid preload. ROI was placed perpendicular a homogeneous parenchyma that not include vessels or surrounding structures. The thyroid tissue appears coded in a perfectly homogeneous manner with a colour code corresponding to a soft tissue (blue colour code). The ROI size was small and it allowed for more accurate measurements. The size of ROI was determined 5x6 mm similar to adults. In our study, five valid SWVs for each thyroid lobes were obtained because that most children could not tolerate a prolonged examination.

SWE measurement technique of thyroid for adults has been reported by World Federation for Ultrasound in Medicine and Biology (WFUMB) in 2017 (4). The recommended measurement technique for adults is similar to the technique we use in children. However, there were some differences during the measurement. Young children are not required to hold their breath during SWE due to the problem of cooperation. The ROI used is standardized as 5x6 mm. because of the small size of the thyroid in children. In addition, the measurement depth recommended by adults is 4-5 cm, but SWE measurement of thyroid tissue in children was evaluated any depth above 1 cm due to age depending thyroid size. The measurements of thyroid tissue in adults is reported to be from 5-6 areas for each thyroid lobes. Sporea et al. reported that SWE of the thyroid is feasible with linear and convex probes and five

measurements in every lobe are enough for an accurate assesment of thyroid tissue. Sporea et al. showed that is no significant difference between 5 or 10 measurements for thyroid stiffness in adults with ARFI elastography (5). Vlad et al. used three measurements on each thyroid lobe and calculated a mean elasticity in healthy adults (6). In our study, five SWV measurements was made in children our study and calculated the average like Bilgici et al. (7) .

We found a significant no intra-observer variability for SWV measurements of thyroid tissue. Bhatia et al. reported SWE's inter- and intra-operator reproducibility is acceptable with correlation ranging from 0.78 and 0.85 for intra-observer variability and between 0.97 to 0.98 for inter-observer variability (8). Bilgici et al. only assessed inter-observer variability and they found 0.70 for the right lobe and 0.69 for the left lobe (7).

SWV values of normal thyroid tissue have been reported in various studies in adult population. SWV values of normal thyroid tissue were obtained from healthy control groups formed during SWE evaluation of diffuse thyroid diseases and thyroid nodules. Arda et al. was reported in adults populations, the mean elasticity value was 10.97 ± 3.1 kPa (apporiximate: 1.89 m/sn) for the thyroid (9). Fukuhara et al. found that SWV value of normal thyroid was 1.60 ± 0.18 m/s in adults (10). In the study with healthy adults of Friedrich-Rust et al. the SWV value was 1.98 m/s (11). Hekimoglu et al. reported the SWV value was 1.63 ± 0.12 m/s in normal adults . .The average range of SWV is between 1.59 and 1.98 m/s in adults study (12). The average SWV values of normal thyroid parenchyma was 1.82 ± 0.3 m / s (min: 1.32 m/s, max: 2.37 m/s) in healthy children in our study. There was no significant difference in girls and boys. But unlike studies adults, there was a significant positive correlation between age and SWV values and increased with age. Studies have shown that changes in thyroid function with age and increase in size of the thyroid gland with puberty. Therefore, the increase in SWV values with age may be explained by the followed in the first

years elevation of TSH and free T4 and free T3 hormones decrease and the increase of thyroid volume with age (13,14). Unlike our study, Bilgici and et al. who are the first studies done in children, the mean SWE of the thyroid gland was found 1.22 ± 0.20 m/s (7). Besides, they did not find any correlation between age, the thyroid gland volume and body mass index compared to our study. Habibi et al. determined that SWV values of thyroid were significantly higher in the 13 to 17 years age group and there was a significant positive correlation between age and SWV values. They explained like as an function of age elasticity values of the thyroid do not show difference up to 12 years of age (15). The low SWE values may be explained by differences in the age group and thyroid hormone differences.

The number of studies on the use of SWE in diffuse thyroid pathologies in adults is limited. Most of these studies concern chronic autoimmune thyroiditis (CAT) - the subgroup of the autoimmune thyroiditis, which causes fibrosis in the thyroid gland. Autoimmune thyroiditis is the most common thyroid pathology in childhood and adolescence (16). There are few studies evaluating the elasticity of thyroid tissue with SWE in children with autoimmune thyroiditis.

The autoimmune thyroid diseases in children are usually diagnosed on the basis of clinical and laboratory findings, supported by ultrasound. The pathological of features autoimmune thyroiditis are interstitial infiltration by lymphocytes and a variable degree of fibrosis in tissue. It is thought that fibrosis results in high SWV values and depends on the level of the fibrosis in the thyroid tissue. Increased stiffness of a tissue is correlated with increased value of SWV.

Fukuhara et al. found that the SWV value in CAT (2.47 ± 0.57 m/s) was significantly higher than in healthy adults (1.59 ± 0.41 m/s) and the SWV cutoff value was 1.96 m/s (17).

Hekimoglu et al. reported the SWV value was 1.63 ± 0.12 m/s in normal adults and 2.56 ± 0.30 m/s. They found that optimal cutoff value for CAT prediction 2.42 m/s (77% sensitivity, 71% specificity, 92% PPV, 81% NPV and 87% accuracy) (12).

Sporea et al. found significant difference in SWV in autoimmune thyroid disease with a value of 2.07 ± 0.44 m/s. Graves disease compared with 2.68 ± 0.50 m/s in CAT in adults. They reported a cutoff value > 2.53 m/s for differentiation between normal thyroid tissue and diffuse thyroid diseases with positive predictive value $> 90\%$ (18). Kim et al. found a cutoff value of 27.6 kPa, with sensitivity of 40.9% and specificity of 82.9% (19). Vlad et al. said SWE may predict the presence of autoimmune thyroid disease. They found the best cutoff value for predicting the thyroid pathology by SWE was 22.3 kPa and sensitivity of 59.6% and specificity 76.9% (6). Yucel et al. was found 1.67 ± 0.63 m/s and the SWE of the thyroid gland is significantly higher than in the healthy children. They reported an optimal cutoff value of 1.41 m/s, with 73.1% sensitivity, 80.8% specificity, 79.2% PPV and 75% NPV (20). Kandemirli et al. determined 14.9 kPa and children patients with Hashimoto's thyroiditis had significantly higher elasticity values than healthy subjects. The cutoff value with the highest diagnostic accuracy for elasticity value was 12.3 kPa and 1.968 m/s; sensitivity, specificity, PPV, NPV, and diagnostic accuracy of this cutoff value were 86.4, 96.3, 98.1, 76.5, and 89.5%, respectively.

Our data is similar to published by Vlad and et al. (6), we found that normal thyroid parenchyma appears homogeneous with low elasticity colored in blue and autoimmune thyroiditis appears inhomogeneous with areas of yellow and red scattered among the blue like. The average SWV value of thyroid parenchyma was 3.7 ± 1.2 m/s (min: 2.59 m/s,, max: 6.25 m/s) in autoimmune thyroiditis in children. In our study, the mean SWV measurement was higher than that of adults and study of Yucel et al. and Kandemirli et al. (20,21).

Fukuhara et al. found that value of SWV is significantly affected by fibrosis but seldom by cellular density (17). This finding may be a sign that fibrosis is effective pathological in autoimmune thyroid diseases in children. Kandemirli et al. determined that the SWV values increased as the degree of fibrosis increased in CAT (21).

When the correlation between SWV values and autoantibody levels and thyroid function tests were analyzed in patients autoimmune thyroiditis there was no correlation between them in our study. But, Magri et al. determined a positive correlation between tissue stiffness and serum TPOAb, TPOAb values of patients could affect SWV measurements (22). Unlike, Liu and et al. found that thyroid stiffness was weakly related to TSH and TGAb and was not correlated with T3, T4 or TPOAb (23). Kandemirli et al. determined that a significant moderate correlation between elasticity values and TPOAb but no significant correlation between SWV values and TGAb levels. They explained this situation that the presence of TBOAb might be characteristic of a late adaptive immune response whereas TGAb might reflect an early immune response (21). Yucel et al. found that correlation between TPOAb values versus the SWV values in patients but no correlation TGAb and thyroid function test results. The thyroid elasticity cannot currently be used to predict thyroid functions (20).

Ruchala et al. determined that SWE might be useful in the diagnosis and differentiation between various types of thyroiditis but could not be optimal tool to differentiate between Graves disease and chronic autoimmune thyroiditis (24). Liu and et al. found that SWE aids for distinguishing Graves disease from subacute thyroiditis but SWE was unsuitable for differentiating CAT and Graves disease (23). All of the thyroiditis are characterised by increased thyroid stiffness and CAT the degree of stiffness extends with fibrosis progression. Studies have shown that medical treatment in the presence autoimmune thyroiditis has no effect on the elasticity of the thyroid tissue in adults. (25). Some of our patients were using medical treatment during SWE. There was no significant correlation between elasticity values and antithyroid treatment with treatment duration in our study.

Study limitations

The first of our limitations was that the age-average of our autoimmune thyroiditis cases was higher than our normal cases. The reason is that these pathologies are more common in late

childhood and adolescence. The second limitation was only autoimmune thyroiditis patients were evaluated in the study. There is a need for studies on how SWV measurement is affected in other diffuse thyroid pathologies in children.

Conclusion

As a result, in this study that we evaluated the elasticity values of normal thyroid tissue and present the measured values. We showed that the SWV values and increased with age. In addition, it was determined that SWV value of the autoimmune thyroiditis showed a significant increase compared to normal thyroid SWV values. There is a need to have normal values for each age group with other studies. Further studies with larger series of children and adolescents need to compare the elasticity values normal and pathologic tissues (diffuse thyroid diseases, thyroid nodule etc.) to determine the diagnostic role of thyroid diseases in children this imaging technique. SWE is useful imaging method after routine US examination in cases where autoimmune thyroid disease is suspected in children

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Figures legends

Figure 1. The evaluation of normal thyroid tissue with SWE

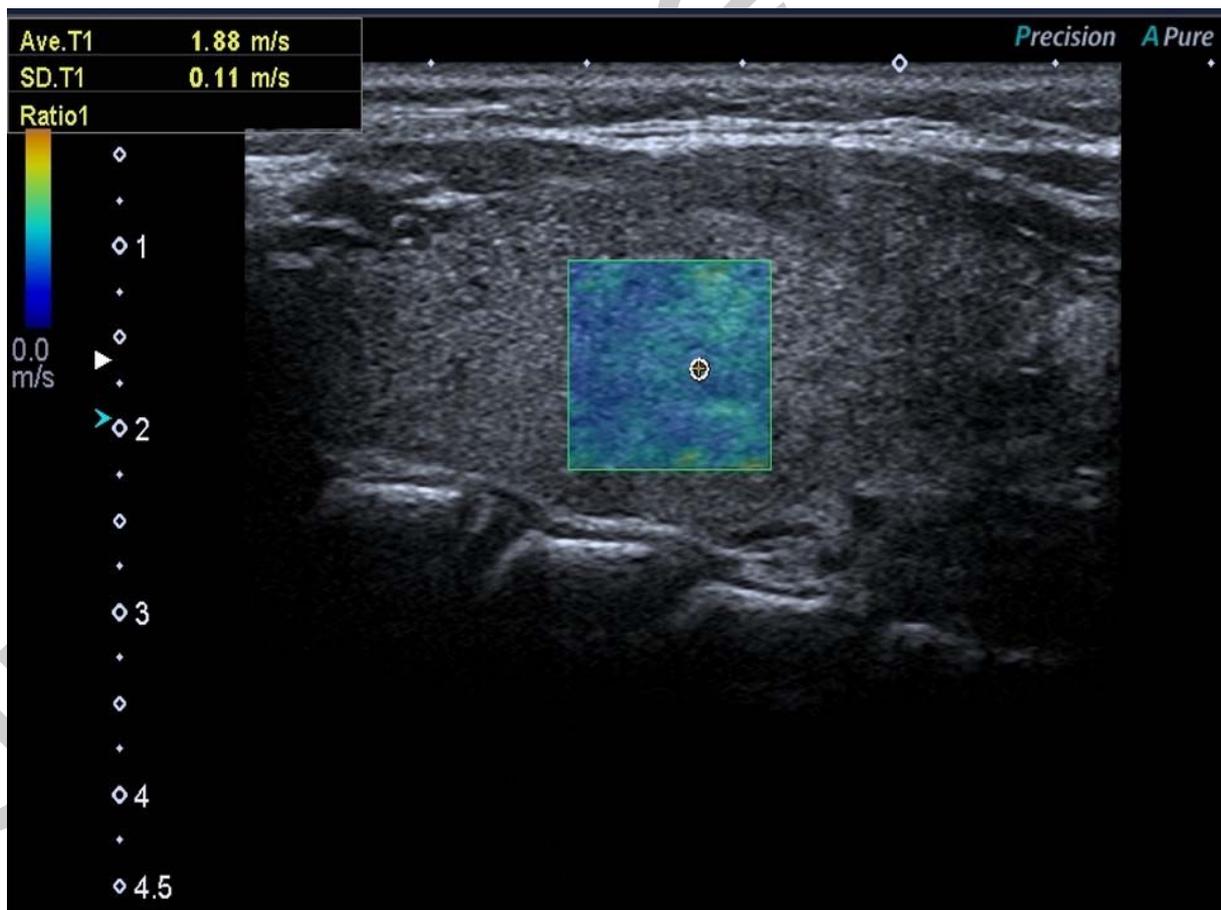


Figure 2. The evaluation of autoimmune thyroiditis with SWE

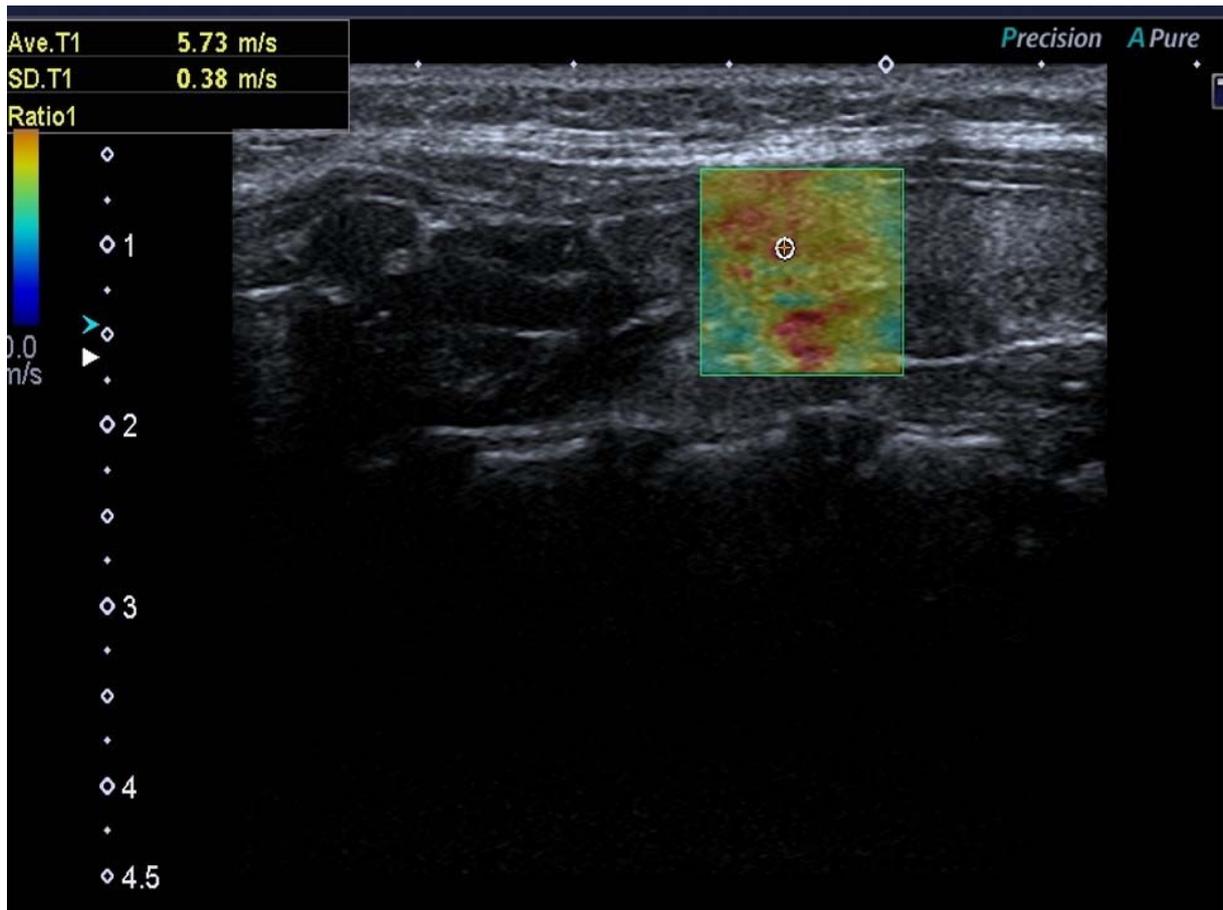
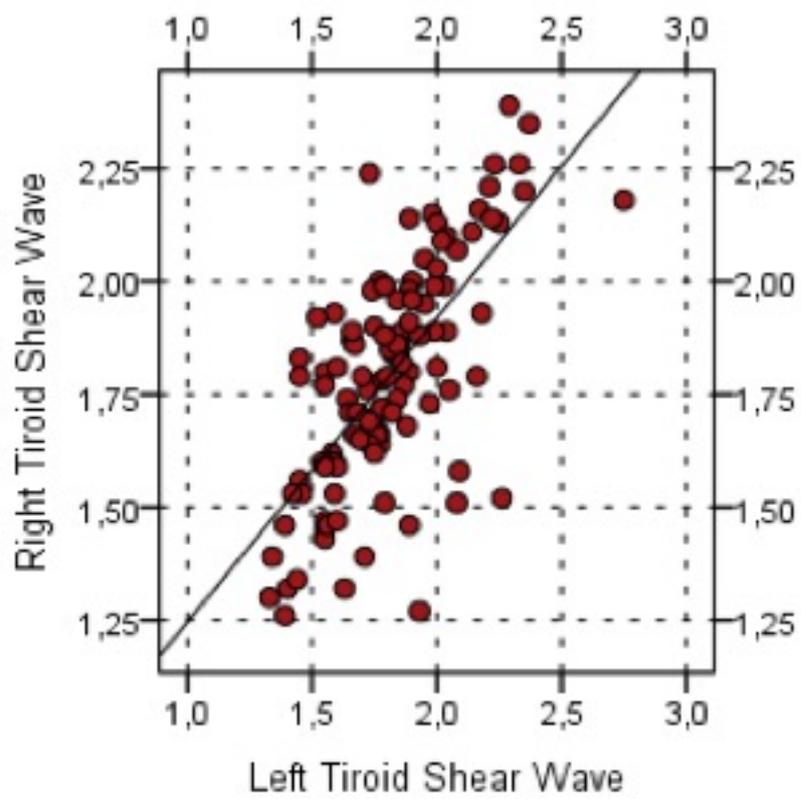


Figure 3. No significant difference between right and left thyroid lobes with SWV in healthy children



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uncorrected

Figure 4. Positive correlation between age and SWV values

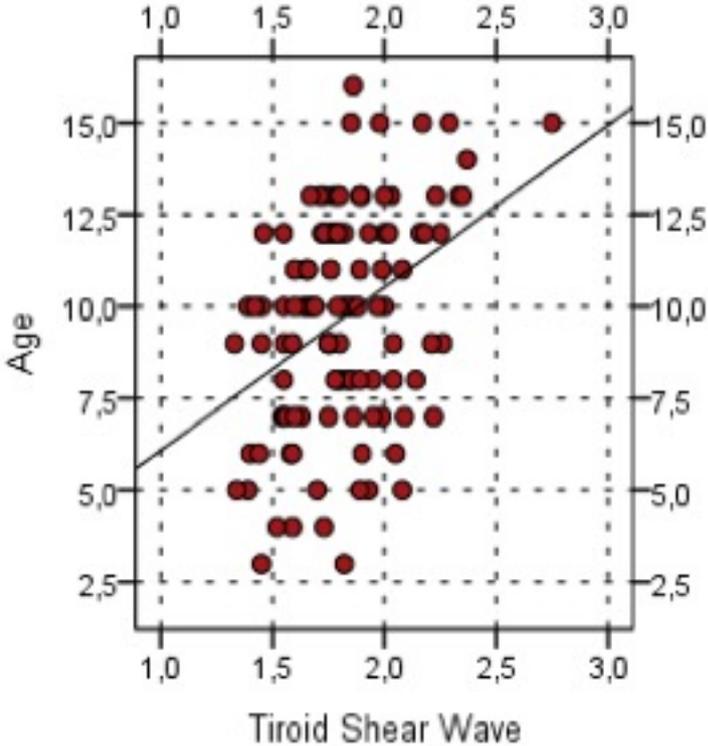


Figure 5. No significant difference intra-observer variability

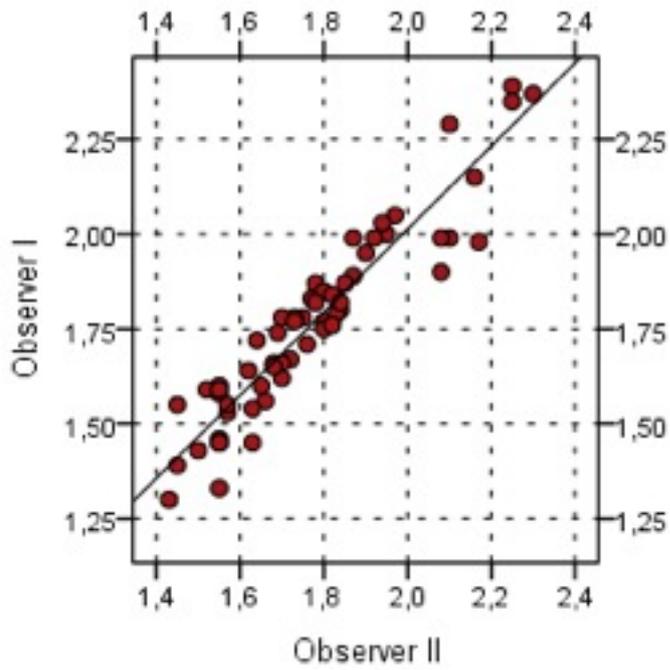


Figure 6. ROC showing the optimal SWV cutoff value for autoimmune thyroiditis.

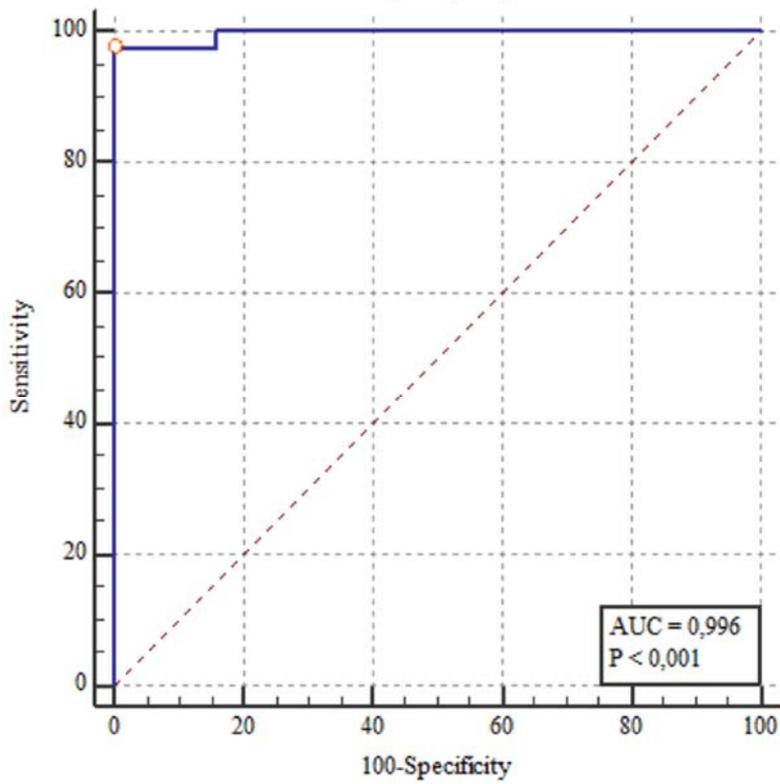


Table 1. Thyroid SWV values were higher in children with autoimmune thyroiditis than in healthy children

	Healthy children			Autoimmune thyroiditis		p
	Mean.±s.d./n-%	Median		Mean.±s.d./n-%	Median	
Age	9.7 ± 3.0	10.0		12.6 ± 2.7	13.0	0.000 ^m
Gender	Girl	66	58.4%	45	78.9%	0.008 ^{X²}
	Boy	47	41.6%	12	21.1%	
SWV						
Right m/sn	1.8 ± 0.3	1.8		3.6 ± 0.8	3.6	0.000 ^m
Left m/sn	1.8 ± 0.3	1.8		3.8 ± 1.7	3.6	0.000 ^m

^m Mann-whitney u test, ^{X²} chi-square test

Table 2. Correlation between thyroid function tests with autoantibody titers and thyroid tissue elasticity values.

	TSH	T4	TPOAb	TGAb	
Right lobe	-0.056	-0.080	0.120	0.089	r
	0.735	0.629	0.467	0.588	p
Left lobe	0.206	-0.102	-0.067	-0.047	r
	0.209	0.535	0.684	0.777	p