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Shear wave elastography as a quantitative method for thyroid gland elasticity assessment in pediatrics patients with autoimmune-related thyroid disease, diagnostic utility and laboratory correlation

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Abstract

Background: Autoimmune thyroiditis (AIT) is the most common thyroid pathology in pediatric patients among which Hashimoto's thyroiditis has the highest prevalence. Along with size, measuring mechano-acoustic tissue elasticity is evolving as an important parameter in the evaluation of diffuse thyroid pathology. This study aims to investigate the role of shear wave elastography (SWE) in the diagnosis of autoimmune thyroid disease (AITD) in the pediatric population and also compare the elasticity between them and healthy individuals.

Results: This case–control analytical study was carried out on 64 pediatric subjects ranging in age from 7 to 17 years. All the cases were diagnosed as AIT by anti-thyroid antibodies, and their thyroid function was evaluated by thyroid hormones. We performed thyroid Ultrasonography and Shear wave elastography. Patients with AIT had significantly higher elasticity values (35.6 kPa, IQR 8.43–103.7 kPa) than the control group (9.35 kPa, IQR 5.73–13.21 kPa). There was no correlation of elasticity values of thyroid gland in patients with AIT with autoantibodies and thyroid function test, respectively. The cutoff value for elasticity was 12.317 kPa with sensitivity and specificity of 96.9% and 100%, respectively.

Conclusions: SWE is a highly sensitive imaging method integrating routine ultrasonography in the diagnosis of AITD which estimates the extent of fibrosis in numerical value.

Keywords: Shear wave elastography, Autoimmune thyroid disease, Hashimoto's thyroiditis, Elasticity

Background

Autoimmune thyroiditis (AIT) is the commonest pediatric thyroid pathology. It entails glandular lymphocytic infiltration and consequently fibrosis which may alter tissue elasticity [1] There are many autoimmune diseases that are associated with autoimmune thyroiditis other

than Hashimoto's thyroiditis (HT) and Graves' disease including; pernicious anemia, systemic or ocular myasthenia, immune thrombocytopenia, Addison's disease, type 1 insulin-dependent diabetes mellitus and vitiligo [2].

Elastography is an evolving imaging tool quantitatively evaluating the elasticity of the tissues, with additive diagnostic value to the routine ultrasound assessments for thyroid pathologies being focal or diffuse [3].

Shear wave elastography through measuring the propagation speed of its waves within certain tissues can

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reflect their stiffness [4] and represent it in unit measurements as kilopascals or meters per second [5]. Operator dependability, when compared with strain Elastography, is lower ensuring more accurate information on tissue elasticity [6].

Methods

Study population

Over a 6 months period, we prospectively evaluated 64 patients, 32 with autoimmune thyroiditis (AIT) (5 males and 27 females) and 32 healthy volunteers (9 males and 23 females), ranging in age from 7 to 17 years. Patients were diagnosed by the treating endocrinologist as well as the patient's clinical and laboratory records. This was done after approval from the institutional review board. Written consent was taken before performing sonoelastography. Our control group subjects were recruited from patients performing radiological examinations for various complaints other than thyroid-related diseases. We excluded patients who underwent thyroid surgery or fine needle biopsy in the previous 6 months for possible alterations in the parenchyma of the thyroid gland.

Clinical examination

Detailed history of chief complaints, the onset of symptoms, associated autoimmune diseases and family history of any thyroid diseases were taken.

Laboratory investigations

Results of anti-thyroid peroxidase (TPOAb) and/or antithyroglobulin (TGAb), and other specific antibodies according to autoimmune diseases, along with Thyroxine (T4), Tri-iodothyronine (T3), thyroid-stimulating hormone (TSH) are obtained.

Imaging

The examination was performed with the patients in a supine position having their necks extended by a pillow. The subjects were advised not to move and swallow during the examination. Ultrasound Sonography system (Toshiba APLIO 400) was used to perform thyroid ultrasonography and shear wave elastography using linear wave transducer (frequency 7–14 MHz).

Ultrasound

During dedicated ultrasound examination of the thyroid gland, dimensions and volumes of the gland were calculated by using the formula width $(cm) \times length$ $(cm) \times depth$ $(cm) \times 0.523$. The assessment of parenchymal pathologies altering gland's echogenicity was decided upon by comparing the gland's echogenicity to that of strap muscles, and we also reported the degree of heterogeneity, thyroiditis foci, and pseudo-nodular appearance.

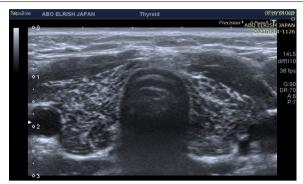


Fig. 1 Thyroid ultra-sound of a 9 years female with history of neck swelling since 4 years with positive TPOAb and TGAb, T4 1.1 and TSH 0.07 diagnosed as Hashimoto's thyroiditis under medication with tab eltroxin showing heterogeneous texture of both thyroid lobes with multiple scattered hypoechoic micronodules and hyperechoic septations

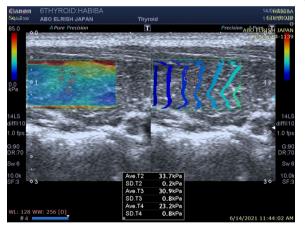


Fig. 2 Elastography of right thyroid gland measuring elasticity (33.7, 30.9 and 23.2 kPa

Shear wave elastography (SWE)

SWE software was activated. In split-screen mode, the 2-dimensional SWE map of both thyroid lobes was examined. We obtained three measurements in the longitudinal plane for each lobe using a 3 mm rounded ROI, measurements were represented in kPa. The mean stiffness values in each lobe were calculated as the average of the three measurements. We were keen to exclude the main carotid artery from the 2-dimensional SWE map to avoid pulsation artifact.

Detailed sonographic and elastographic evaluation of thyroid gland was interpreted on basis of the following findings (Figs. 1, 2,3,4,5 and 6):

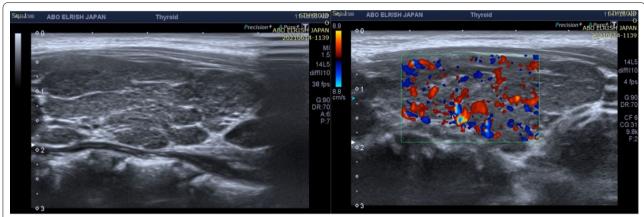


Fig. 3 Thyroid Ultrasound of a 13 years old female with history of neck swelling since 4 years, positive TPOAb and TGAb, T4 1.6, T3 3.1 and TSH 6.8 under medication with tab. Carbimazole and diagnosed as Grave's disease. The gland shows increased size of right lobe with coarse echotexture, hyperechoic septations giving pseudonodular appearance with few scattered micro hypoechoic nodules and increased vascularity

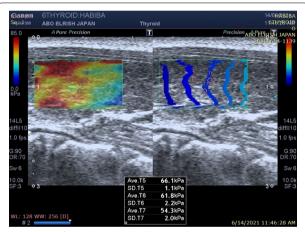


Fig. 4 SWE of right thyroid lobe showing three measurements of elasticity 66.1, 61.8 and 54.3 kPa

- Dimensions of both thyroid lobes: length, width and depth
- Echotexture: Homogeneous or heterogeneous parenchymal interface
- Nodules present or absent
- Vascularity of the thyroid gland: whether normal or increased or decreased.
- Elasticity of both thyroid lobes.

Statistical analysis

Descriptive statistical analysis was carried out in the present study using SPSS version 22. Descriptive data statistics which included the mean, median, SD and

range were calculated. Kolmogorov–Smirnov test was used to analyze a range of variables. The Mann–Whitney U test was used for comparison between patients with autoimmune-related thyroid disease and control. The analysis of correlation was evaluated with the spearman correlation test. ROC curve was plotted for elasticity values and the optimum elasticity cutoff value was determined. Sensitivity, Specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

This case–control analytical study included a total of 64 patients (32 patients with autoimmune thyroiditis (AIT) and 32 healthy volunteers without any known thyroid pathologies).

Healthy control group

The mean and median age of the healthy control group were 10.56 ± 2.39 years and 10 years (range 7–16 years), respectively. The number of male and female was 9 and 23, respectively. Table 1 presents a descriptive analysis of age, volume, and elasticity in healthy control.

Autoimmune thyroiditis (AIT) patient group

The mean and median age of the Autoimmune thyroiditis (AIT) group were 11.31 ± 2.77 years and 11 years (range 7–17 years), respectively. The number of male and female was 5 and 27, respectively. Descriptive analysis of age, volume and elasticity in AIT Table 2 presents descriptive analysis of age, volume, and elasticity in AIT.

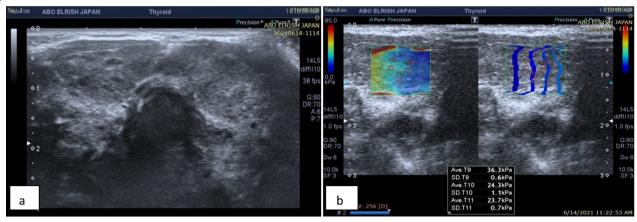


Fig. 5 a Gray scale findings in an 8-year-old female with positive anti-thyroglobulin and anti-microsomal antibodies, showing inhomogeneous increased echogenicity with hyperechoic septations of both thyroid lobes. **b** SWE showing three measurements of elasticity (36.3, 24.3 and 23.47 kPa) of right thyroid lobe in longitudinal plane

Correlation between elasticity, autoimmune antibodies, and thyroid hormones:

The correlation between elasticity values and autoantibodies [anti thyroid peroxidase (TPOAb) and anti-thyroglobulin (TGAb) levels] in AIT groups were non-significant (p > 0.05), as given in Table 3. Also, there was no significant correlation between elasticity values and thyroid function test (T4 & TSH) in children with AIT, i.e., their p-value > 0.05, as given in Table 4.

Comparison of elasticity values between healthy and AIT groups:

In children with autoimmune thyroiditis, thyroid SWE (Fig. 2) values were significantly greater than those of healthy children (p-value < 0.05, n1 = n2 = 32, Ustat = 12, Ucritical = > 172, Ustat < Ucritical), as given in Table 5

ROC curves analysis:

ROC curve analysis of the SWE values of AIT was calculated; kPa is given in Fig. 7.The maximum area under the curve(AUC) for the mean elasticity value of both lobes in AIT was 0.978(95% confidence interval). The cutoff value with the highest diagnostic accuracy for elasticity value was 13.217 kPa; Sensitivity, Specificity, positive predictive value (PPV), and negative predictive value (NPV) were 96.9%, 100%, 100% and 96.9%, respectively with diagnostic accuracy of 98%, as given in Table 6

Discussion

Diffuse thyroid disease in the pediatric population can lead to gross metabolic abnormalities affecting development and growth rendering early accurate diagnosis mandatory [7]. Traditionally the diagnosis is achieved by clinical examination, thyroid hormones levels, and

thyroid ultrasonography [8]. Thyroid ultrasound is pivotal to the assessment of the gland's echogenicity, volume, and vasculature as well as any related or surrounding abnormality [9]. SWE is a recent ultra-sound-based elastography method with the ability to quantitatively evaluate thyroid gland stiffness using the concept of strain elastography [10]. Any diffuse thyroid disease with its disease-related histological changes, e.g., follicular cell hyperplasia, lymphocytic infiltration, and colloid accumulation will change the glandular elastic properties, and if these histological changes proceed for a longer time, fibrosis, septations, and focal nodularity may evolve [11].

In the present study, we attempted to perform conventional thyroid Ultrasound to patients with autoimmune thyroiditis and normal participants calculating the gland's volume and examining its parenchyma for echogenicity, the extent of heterogeneity, and pseudo-nodular appearance. Regarding the volume of the thyroid gland, we observed patients with AIT had significantly higher total thyroid volume (10.88 ml; IQR 0.6–22.47 ml) than control subjects (5 ml; IQR 2.87–7.87 ml). This matched the results of a previous retrospective study done by Kandemirli et al. [12] whose study population's total thyroid volume with AIT was significantly higher than that of the healthy control group (HT group:9.73 ml; IQR 5.31–16.73 ml, control subjects: 4.11 ml; IQR 2.42–5.72 ml).

Ultrasonography is a widely used imaging tool in the diagnosis and follow-up of AIT. Its reported common findings of glandular heterogeneity, hypoechogenicity, and lobulated outline though specific are hardly sensitive [13]. The AIT disease-related histological changes including lymphocytic infiltration and interstitial fibrosis [14] consequently lead to parenchymal stiffness when compared to healthy thyroid tissue which will be invariably

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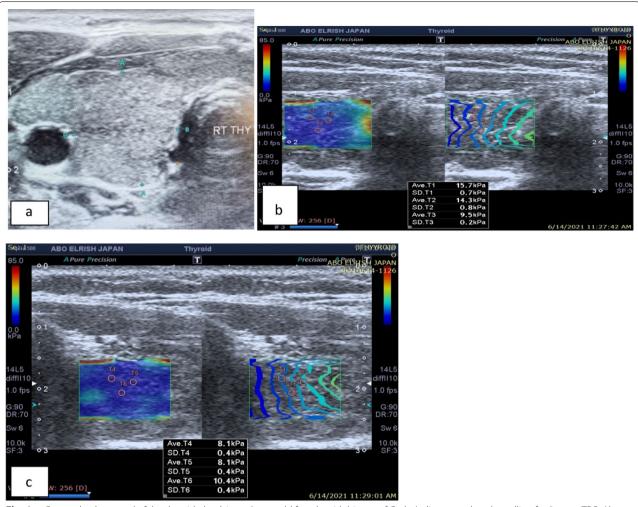


Fig. 6 a Gray scale ultrasound of the thyroid gland, in an 8-year-old female with history of Crohn's disease and neck swelling for 2 years. TPO-Ab positive and TG-Ab borderline, diagnosed as Hashimoto's thyroiditis. The gland is of homogeneous hyperechoic echotexture with normal dimensions of both glands and vascularity. **b**, **c** SWE of thyroid glands measuring elasticity of both thyroid glands (b) right thyroid lobe (15.7, 14.3 and 9.5 kPa) **c** left thyroid lobe (8.1,8.1 and 10.4 kPa)

Table 1 Descriptive analysis of age, volume and elasticity in healthy control

n=32	Mean	SD	Median	Range	Minimum	Maximum
Age	10.56	2.39	10	9	7	16
Rt. thyroid lobe						
Volume (ml)	2.40	0.64	2.32	2.46	1.42	3.8
SWE (kPa)	10.12	3.98	9.76	21.33	5.86	27.2
Lt. thyroid lobe						
Volume (ml)	2.23	0.66	2.06	2.70	1.27	3.98
SWE(kPa)	9.41	1.74	9.25	8.3	5.6	13.9
Both lobes						
Volume (ml)	5	1.23	4.25	4.99	2.87	7.87
SWE (kPa)	9.35	1.63	9.74	7.48	5.73	13.21

SD standard deviation; Rt right; Lt left; SWE shear wave elasticity; kPa kilopascals; ml milliliter

Table 2 Descriptive analysis of age, volume and elasticity in AIT

Mean	SD	Median	Range	Minimum	Maximum
11.31	2.77	11	10	7	17
5.49	2.21	5.18	11.81	0.29	12.11
35.31	20.70	30.13	104.7	9.96	114.66
5.38	2.34	5.35	10	0.35	10.36
35.96	20.97	30.33	85.83	6.9	92.73
10.88	4.11	10.77	21.82	0.64	22.47
35.63	20.30	31.27	95.26	8.43	103.7
	11.31 5.49 35.31 5.38 35.96 10.88	11.31 2.77 5.49 2.21 35.31 20.70 5.38 2.34 35.96 20.97 10.88 4.11	11.31 2.77 11 5.49 2.21 5.18 35.31 20.70 30.13 5.38 2.34 5.35 35.96 20.97 30.33 10.88 4.11 10.77	11.31 2.77 11 10 5.49 2.21 5.18 11.81 35.31 20.70 30.13 104.7 5.38 2.34 5.35 10 35.96 20.97 30.33 85.83 10.88 4.11 10.77 21.82	11.31 2.77 11 10 7 5.49 2.21 5.18 11.81 0.29 35.31 20.70 30.13 104.7 9.96 5.38 2.34 5.35 10 0.35 35.96 20.97 30.33 85.83 6.9 10.88 4.11 10.77 21.82 0.64

SD standard deviation; Rt right; Lt left; SWE shear wave elasticity; kPa kilopascals; ml milliliter; AIT autoimmune thyroiditis

Table 3 Correlation of SWE with TPOAb and TGAb in AIT

Parameters	Value
TPOAb	
Pearson (r)	-0.127
T statistics	0.642
<i>p</i> value	0.526
TGAb	
Pearson (r)	0.204
T statistics	1.022
<i>p</i> value	0.841

SWE shear wave elasticity; TPOAb anti thyroid peroxidase; TGAb anti thyroidobulin: AIT autoimmune thyroiditis

Table 4 Correlation of SWE with TSH and T4 in AIT

Parameters	Value
TSH	
Pearson (r)	0.192
T statistics	1.076
<i>p</i> value	0.290
T4	
Pearson (r)	0.093
T statistics	0.514
<i>p</i> value	0.610

TSH thyroid stimulating hormone; T4 thyroxine

reflected in elasticity values [15]. In our study, elasticity mean values are higher in patients with autoimmune thyroiditis as compared to normal subjects in the same age group. Our reported mean elasticity value of the healthy control group was 9.35 ± 1.63 kPa (5.7-13.21 kPa) and the AIT group was 35.63 ± 20.30 kPa (8.43-103.7 kPa) which was close to the elasticity values of Kara et al. [16] who studied 149 participants ranging from 8 to 60 years showing the result of mean elasticity value in patient with AIT to be 25.01 ± 10.53 kPa (10.72-68.27 kPa). The elasticity values were also close to many other studies [17-21].

Kandemirli et al. [12] studied 59 patients diagnosed with HT and 26 healthy volunteers without any thyroid-related disorders, they used a scoring system based on gray-scale ultrasonographic findings subdividing patients with Hashimoto thyroiditis into three categories as follows: focal thyroiditis (grade 1), diffuse thyroiditis (grade2), and fibrotic thyroid gland (grade 3). Based on elasticity values, grade 3 patients had the highest and the most significant elasticity values (19.7 kPa; IQR 17.8–21.5 kPa) when compared to the patients with grade 2 (15.5 kPa; IQR 14.5-17.8 kPa) and grade 1 thyroiditis (12.8 kPa; IQR 11.9-13.1 kPa). Vlad et al. [21] also studied 104 patients the mean elasticity value in patients with AIT was found to be 26.2 ± 10.8 kPa with SWE_{max} 52.4 ± 24.6 Kpa. In our study, the SWE of thyroid gland in children with AIT was found to be 35.63 ± 20.3 ; IQR

Table 5 Showing demographic data of SWE in healthy control and AIT

N=64	Mean	SD	Median	Range	Minimum	Maximum
Control						
SWE(kPa)	9.35	1.63	9.74	7.48	5.73	13.21
AIT						
SWE(kPa)	35.63	20.30	31.27	95.26	8.43	103.7

 $\textit{SWE} \ \text{shear wave elasticity}; \textit{AIT} \ \text{autoimmune thyroiditis}; \textit{SD} \ \text{standard deviation}; \textit{kPa} \ \text{kilopascals}$

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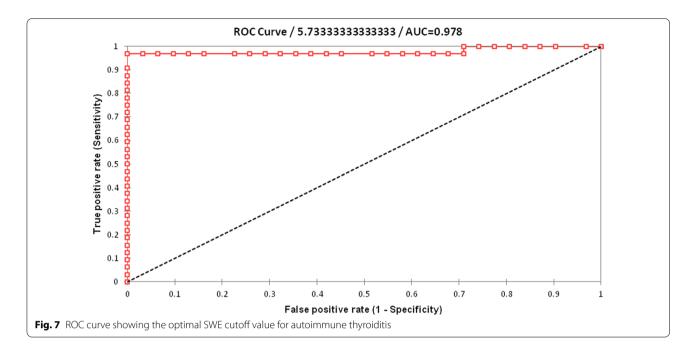


Table 6 Cutoff values of SWE (kPa) for AIT and Sensitivity, Specificity, PPV, NPV and diagnostic accuracy of these cutoff value

Cutoff value (kPa)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
13.217	96.9	100	100	96.9	98

PPV positive predictive value; *NPV* negative predictive value; *kPa* kilopascals; *SWE* shear wave elasticity; *AIT* autoimmune thyroiditis

8.43-103.7 kPa which is consistent with the values of Ruchala et al. [17] which had reported having baseline thyroid stiffness in chronic autoimmune thyroiditis(CAT) to be 36.15 ± 18.7 kPa.

In healthy children our mean SWE was found to be 9.35 ± 1.63 kPa; IQR 5.73-13.21 kPa which is the approximate SWE postulated by Bhatia et al. [22] $(9.0\pm4.0 \text{ kPa})$.

In the study conducted by Kandemirli et al. [12] they reported no significant correlation between SWE and TGOAb in patients with HT. Our study also showed a negative correlation between SWE, TPOAb and TGAb. In concordance with Kara et al. [16], our study showed no positive correlation between SWE and TFT(TSH & T4) as well.

The cutoff value of elasticity in our study was 12.317 kPa with sensitivity, specificity, and accuracy rates of 96.9%, 100% and 98%, respectively. The cutoff value with the highest diagnostic accuracy for elasticity value in the study conducted by Fukuhara [19] was 12.3 kPa with reported sensitivity, specificity, and accuracy rates of 87.4%, 78.7% and 85.1%, respectively.

In our study, we were dependent on clinical examination, ultrasound findings, and laboratory tests, to diagnose AIT rather than tissue biopsy which we consider a limitation, this being rather controversial as any fine needle biopsy or surgery would have altered the gland parenchyma. In addition, most of our patients were under medication with Eltroxin and some of them were on the carbimazole medication. We considered this irrelevant guided by previous studies which reported no significant elasticity changes when comparing treated and nontreated patients [18, 23]. We also ignored age-related changes having a rather narrow age group; this was decided upon because previous studies documented statistically insignificant changes with narrow age gaps [24].

Conclusions

SWE is a useful and highly sensitive imaging method that complements routine ultrasonography examination in children with autoimmune thyroid disease by providing objective numerical values and estimating the degree of fibrosis. However, further studies are recommended to seek out the conventional reference values per age groups in the pediatric population. Larger cohorts in the Egyptian population are needed to compare the elasticity values of normal and pathologic tissues.

Abbreviations

AIT: Autoimmune thyroiditis; SWE: Shear wave elastography; AITD: Autoimmune thyroid disease; TPOAb: Anti-thyroid peroxidase; TGAb: Antithyroglobulin.

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Author contributions

SM and WA have designed this study together. SB and KM contributed to the data collection, SB and SM contributed to data analysis. SB contributed to data processing. SM and WA shared together in writing the manuscript. ALL authors read and approved the final manuscript.

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Availability of data and materials

Data available within the article or its supplementary materials.

Declarations

Ethical approval and consent to participate

This study was approved by the Ethical Research Committee of Faculty of Medicine Cairo University in Egypt. The ethics committee reference number is not available. A written consent was taken from the legal guardians of all patients accepting to participate in our research work.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

The authors declared that they have no conflicts of interest.

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