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Factors Affecting Thyroid Elastography in Healthy Children and Patients with Hashimoto's Thyroiditis

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What is already known on this topic?

Thyroid elastography is used to distinguish cases with Hashimoto's thyroiditis (HT) from healthy controls in childhood. Although, the relationship between the scores obtained by the shear-wave elastography (SWE) technique and the stage of the disease was investigated, the clinical and biochemical characteristics of the cases at the time of admission were not specifically examined.

What this study adds?

Our results show that no metabolic factor other than body mass index (BMI) standard deviation score (SDS) has any effect on SWE scores, especially in healthy children. There is a positive correlation between BMI SDS and SWE in healthy children, but not in those patients with HT. Likewise, age is another factor affecting SWE only in healthy children. Since inflammation is the main factor determining thyroid elasticity in patients with HT, the effect of other factors such as age and BMI on SWE seems to be insignificant. We do not recommend routine evaluation of any laboratory parameter other than thyroid functions before thyroid elastography.

Abstract

Objective: Hashimoto's thyroiditis (HT) is the most common form of thyroiditis in childhood. In addition to thyroid ultrasonography, shear-wave elastography (SWE) can evaluate thyroid parenchyma tissue stiffness, and more detailed findings can be obtained with this method. We aimed to evaluate the relationship between SWE values and clinical, biochemical and hormonal parameters of patients with HT and in healthy individuals.

Methods: We compared 46 newly diagnosed HT cases with 46 healthy controls. We examined the effect of all metabolic parameters and thyroid-related markers on SWE values.

Results: The mean SWE values in those patients with euthyroid HT were 12.5 ± 5.1 kilopascal (kPa), whereas it was 8.2 ± 2.82 kPa in healthy controls ($p < 0.001$). Although the clinical [age, gender and body mass index (BMI)] and laboratory parameters (such as thyroid function tests, homeostasis model assessment of insulin resistance, insulin-like growth factor-1 values, which we think may affect SWE scores) of those children with HT and the healthy controls were statistically similar ($p > 0.05$), except for their thyroid autoantibodies and thyroglobulin, SWE values and thyroid volume were significantly higher in those individuals with HT ($p < 0.001$). Multiple linear regression analysis was performed to evaluate the direction and degree of the effect of the variables on thyroid elasticity scores. It was observed that age ($p = 0.002$), BMI standard deviation score (SDS) ($p = 0.04$) and anti-thyroid peroxidase ($p = 0.008$) levels were effective on the thyroid elasticity score in the regression model. We detected a SWE cut-off value of 9.68 kPa with 68% sensitivity and 72% specificity, a 70% positive predictive value, and a 69% negative predictive value in thyroid elastography when differentiating between cases with HT and healthy controls.

Conclusion: Our results show that no metabolic factor other than BMI SDS has any effect on SWE scores, especially in healthy children. There was a positive correlation between BMI SDS and SWE in healthy children ($r = 0.353$; $p = 0.02$), but not in those patients with HT ($r = 0.196$; $p = 0.19$). Likewise, age is another factor affecting SWE only in healthy children. We do not recommend routine evaluation of any laboratory parameters other than thyroid functions before thyroid elastography.

Keywords: Children, Hashimoto's thyroiditis, shear-wave elastography, thyroid

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Introduction

Hashimoto's thyroiditis (HT) is the most common form of thyroiditis in childhood and the most commonly acquired cause of childhood thyroid disease in regions without iodine deficiency of the world (1). The prevalence of HT is around 1-2% in childhood (2). It has been observed that its frequency increases with increasing age, reaching around 10-20% in adulthood. Thyroid antibody positivity can be detected up to 4 times more in women than in men (1,2). Pathologically specific findings are variable degree lymphocytic infiltration and interstitial fibrosis. Ultrasonography has been used for years in the treatment and follow-up of thyroid diseases, with evaluations such as thyroid volume and parenchyma, nodule pseudonodule discrimination, and elasticity. It is possible to evaluate findings, such as fibrosis, nodule and pseudonodule with routine B-mode ultrasonography. In recent years, thyroid parenchymal elasticity has been evaluated in more detail with the shear-wave elastography (SWE) technique (3,4). Although, heterogeneous hypoechoic echogenicity and lobulated contour are specific gray-scale findings of ultrasonography, the sensitivity of these findings is also limited. The SWE technique measures the degree of thyroid parenchymal stiffness and calculates these data as elasticity, i.e. kilopascal (kPa), and velocity, i.e. meters/second (m/s) (5). It is a real-time, non-invasive method which provides quantitative evaluation in this way. There are studies in the literature on the use of the SWE technique in children with HT. In recent years, the use of SWE in children has increased, both in the differentiation of diffuse thyroid diseases and in the differentiation of nodules from benign to malignant (6,7,8,9). In a study investigating the role of the American College of Radiology Thyroid Imaging Reporting and Data System Classification and SWE in differentiating the nature of nodules, it was observed that SWE was more diagnostically accurate in all nodule sizes. However, it was also found that the detection rate decreased as the nodule size increased (10).

Compared to healthy controls, SWE values were higher in those patients with HT. In addition, while comparing the activity and degree of the disease in patients with HT, there are also studies showing that there are significant differences in hypothyroidism, hyperthyroidism and euthyroid (8,11). In these studies, thyroid-specific parameters such as serum thyroid hormones, thyroglobulin (Tg) and thyroid autoantibodies were evaluated in terms of their relationship with SWE. However, the relationship between thyroid and systemic metabolic parameters is undeniable. For example, solid organ stiffness can be affected by serum insulin-like growth factor-1 (IGF-1), which was demonstrated in a study in cases with acromegaly (12). It is known that elasticity scores change in relation to hyperplasia and the fibrosity of the thyroid parenchyma tissue. Hyperinsulinemia and laboratory findings related to insulin resistance are observed in those individuals known to have thyroid nodules. It has also been reported that there is a positive correlation between nodule size and homeostasis model assessment of insulin resistance (HOMA-IR) levels (13). Thyroid stimulating hormone (TSH) and insulin increase the thyroid volume and the formation of hyperplastic thyroid nodules, and there are reports that local growth factors such as IGF-1 are effective independently of TSH. For example, it has been suggested that increased intrathyroid IGF-1 levels in patients with acromegaly have an effect on nodule formation (14). We hypothesized, just as thyroid hormones affect some changes in metabolism, some metabolic markers can affect some changes in thyroid tissue. The number of studies comparing individuals with HT and the healthy groups by means of thyroid elastography is insufficient in the literature. There was a study in Turkey in which shear wave velocity scores were compared. In that study, thyroid gland stiffness was observed more prominently in those patients with HT (15). However, as in the related study, a comparison of the two groups with the aim of being similar in terms of all factors which may affect elastography was not observed in the literature.

Our main purpose in this study was to reveal the underlying reasons why the elasticity cut-off results are very different from one another in the literature, and also to present a new cut-off value to the literature by comparing the elasticity scores of two groups which are very similar in clinical and laboratory terms. We aimed to investigate the relationship with SWE values and anthropometric measurements, and laboratory markers in healthy volunteers and HT cases. In the literature, we could not find any study comparing the SWE scores between the groups in terms of age, gender, puberty stage, thyroid function tests, and glucose and lipid metabolism. Therefore, we considered whether these factors could determine the differences between SWE cut-off values between healthy individuals and individuals with HT. To the best of our knowledge, this is the first study to examine all factors which may affect SWE scores. Considering these factors, we wanted to find an answer to the question of whether a new cut-off value related to SWE scores should be determined.

Methods

Participants

All individuals participating in this study were evaluated in the pediatric endocrinology outpatient clinic of University of Health Sciences Turkey, Kayseri City Hospital in 2022.

Among the patients who were referred due to abnormal thyroid function tests (mild TSH elevation, mild fT4 elevation or decrease), thyroid antibody positivity was detected and newly diagnosed patients with HT constituted the case group, and those patients who were found to be within the reference range of thyroid function tests in 2 consecutive check-ups within 3 months during the follow-up and whose thyroid antibodies were found to be negative constituted the control group. The inclusion criteria for this study were determined as not using any medication within the last 3 months, not having a concomitant systemic disease (for example, diabetes mellitus) and being younger than 18 years of age. The exclusion criteria were having any systemic or thyroid disease, and receiving treatment for any condition. The anthropometric measurements and laboratory examinations of all participants were recorded. Thyroid ultrasonography and sonoelastography evaluation were performed by a pediatric radiologist with 12 years of experience. This study was approved by University of Health Sciences Turkey, Kayseri City Hospital Clinical Research Ethics Committee with the number of 591 (date: 24.02.2022). Written informed consent forms were obtained from the legal guardians of all participants. Research ethical principles were conducted in accordance with the Declaration of Helsinki. Sample size calculation was performed using the G*Power version 3.1.9.2 (Kiel University, Kiel, Germany) software program. The sample size was calculated to be 42 patients for each group, with 95% power, 5% significance level, and an effect size value of 0.80. Ninety-two patients were included in this study due to the possibility of patients dropping out. In this way, the actual power of the study was determined to be 0.95.

Anthropometric Examinations

As an anthropometric evaluation, weight, height, body mass index (BMI) values and age and gender-specific standard deviation (SD) scores (SDSs) of these values were analyzed with an online calculation program (www.childmetrics.org) (16). Age and sex-specific reference values were evaluated according to CDC data.

Laboratory Measurements

Blood samples were obtained in the early morning after a 10-hour fasting period for biochemical and hormone measurements. Serum glucose, insulin, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TSH, free T4 (fT4), free T3, thyroglobulin (Tg), anti-thyroid peroxidase (anti-TPO), anti-Tg, IGF-1 and IGF-binding protein 3 (IGFBP3) levels were measured by the electrochemiluminescence immunological method on the Cobas 8000 e602 analyser (Roche Diagnostics, Mannheim, Germany). The HOMA-IR method [glucose (mmol/L) x insulin (mIU/mL) / 22.5] was used to assess insulin resistance (17). IGF-1 SDS and IGFBP3 SDS were calculated according to age and gender specific reference data (18).

Thyroid Ultrasonography and Elastography

An Aplio 500 ultrasound system (Toshiba Medical Systems, Tokyo, Japan) with a 14 MHz linear array was used for ultrasonography and 2D SWE examinations of the thyroid gland. Thyroid volume was calculated from the dimensions of each thyroid lobe (length × width × depth × 0.52).

A pediatric radiologists (with 12 years of experience) performed the ultrasound and 2D SWE. At least ten measurements with a round-shaped region of interest (ROI) 2 mm in diameter were obtained from three different sections (upper, middle, and lower parts) of each lobe in a transverse plane. The one-shot method was used and all measurements were recorded as kPa. The average values of the measurements were accepted as the mean stiffness value of gland. Calculations of the mean stiffness value (with SDs) of the thyroid lobes using round ROIs are shown in Figures 1A, 1B and 2A, 2B. SWE scores for each lobe were evaluated for a maximum of 2 minutes.

In both groups, thyroid volumes were evaluated according to age and gender-specific references and SDSs were calculated (19).

Statistical Analysis

Statistical analyses were calculated with the Statistical Package for the Social Sciences version 24.0 (IBM Corporation, Armonk, NY, USA) software program. The mean and SD values of the numerical variables, the frequency and percentage (%) values of the categorical variables were examined. The Shapiro-Wilk test was used to analyze the normal distribution of variables. In addition, it was accepted that the data with kurtosis and skewness values in the range of -2 to +2 showed a normal distribution. When the means of two independent variables were compared, the Student's t-test was used if the data provided the parametric assumptions, and the Mann-Whitney U test was used if they did not. The chi-squared test was used in the analysis of categorical variables. Pearson and Spearman correlation analyses were used to evaluate the degree and direction of the relationships between variables. The best cut-off value which could be used to differentiate those children with euthyroid HT and healthy controls was calculated by receiver operating characteristic curve analysis. In order to evaluate the direction and degree of the effects of independent variables on thyroid elasticity scores, SDSs were used

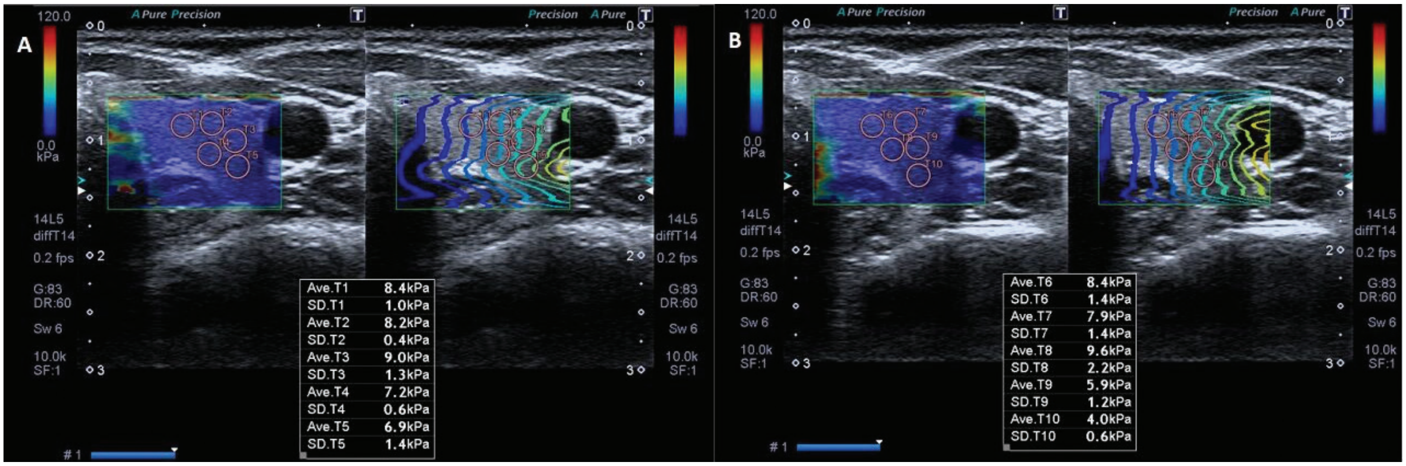

Figure 1. A, B) Calculations of the mean stiffness value (with standard deviations) of the left thyroid lobe using round region of interest in a 9-year-old female control

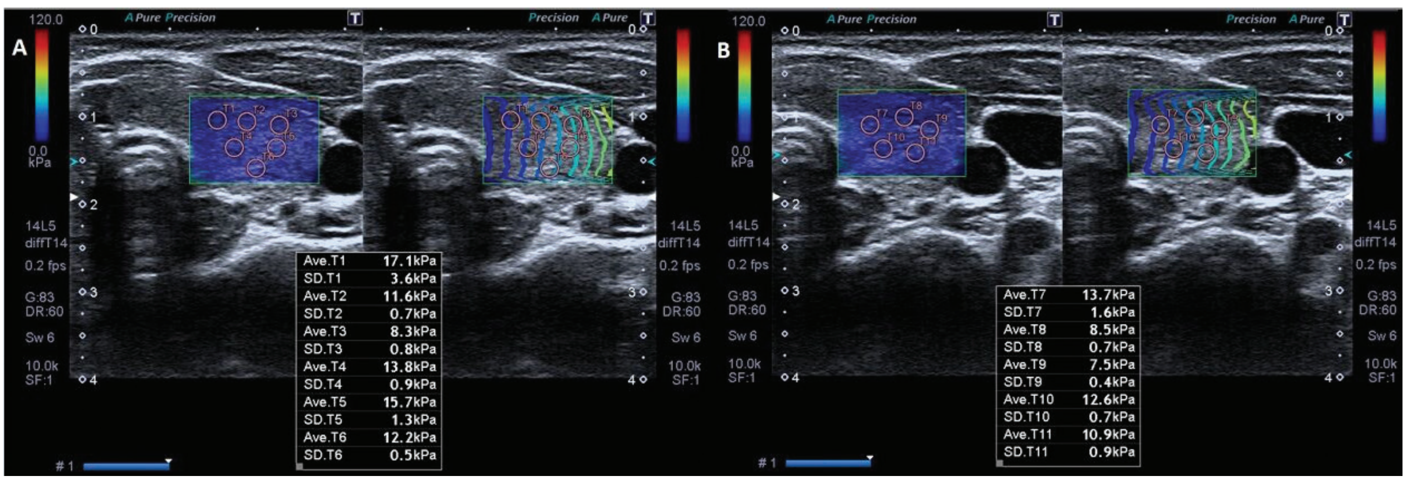

Figure 2. A, B) Calculations of the mean stiffness value (with standard deviations) of the left thyroid lobe using round region of interest in an 8-year-old male patient

instead of numerical values from those variables which change with age or sex (for example, IGF-1 SDS instead of IGF-1, BMI SDS instead of body weight and height, HOMA-IR instead of glucose and insulin) in the model and multiple linear regression analysis was performed. A p value less than 0.05 was considered statistically significant.

Results

A total of 92 children (between the ages of 5.2-17.8 years), 58 (63%) girls and 34 (37%) boys, were included in this study. Those with positive thyroid antibodies (newly diagnosed HT) constituted the case group (46 patient), and those with negative thyroid antibodies formed the healthy control group (46 healthy control). All participants came from the central Anatolian region of Turkey, mostly from the city where we conducted this research. The age, gender, anthropometric, laboratory and radiological measurements of both groups are summarized in Table 1. The average values of the SWE measurements were accepted as the mean stiffness value of the gland. Similar to previous studies, we found that the normal thyroid parenchyma appeared homogeneous. Low elasticity was mapped as blue, and autoimmune thyroiditis appeared heterogeneous with yellow and red areas scattered among the blue (6,20). We took ten measurements of each lobe, and the mean values were calculated for each lobe and for both lobes. Evaluation was carried out in a similar way to the measurement methods recommended in studies in the literature (20,21). Puberty stages were compared according to gender in both groups as they may also affect IGF-1 levels. Girls were compared in the patient and control groups according to their puberty stage. There was no statistical difference in chi-squared analysis ($p = 0.93$). Boys were also compared according to their puberty stage. No statistical difference was found in boys either ($p = 0.23$). When the group with HT and the healthy controls were compared according to their puberty stages, no significant difference was found again ($p = 0.30$).

Although the clinical (age, gender and BMI) and laboratory parameters (such as thyroid function tests, HOMA-IR, IGF-1 values, which we thought may affect SWE scores) of those children with HT and the healthy controls were statistically similar ($p > 0.05$), except for thyroid autoantibodies and Tg, SWE values and thyroid volume were significantly higher in those individuals with HT ($p < 0.001$). In addition, there were no statistically significant differences between the groups in terms of metabolic markers (such as glucose, insulin, lipids) ($p > 0.05$) (Table 1).

Those patients with HT with normal thyroid function test results (31 euthyroid patient) and healthy controls (46 controls) were also compared. The SWE scores of the patients with euthyroid HT were found to be higher than the healthy controls (12.5 ± 5.1 kPa versus 8.2 ± 2.8 kPa, $p < 0.001$).

When the presentation of the patients with HT were examined, 3 of them were hypothyroidism, 3 patient were hyperthyroidism, and 8 patient were mildly elevated TSH (TSH range 5.5-20 mIU/mL) with euthyroidism. When the mean SWE values were examined, although the number of cases were few, the mean SWE values of those cases presenting with hypothyroidism and markedly elevated TSH (TSH >40 mIU/mL) were significantly higher (24.8 ± 6.7 kPa, versus 8.2 ± 2.8 kPa, $p < 0.001$). The mean elasticity scores of those children with hyperthyroidism were high but not statistically different from those of the healthy children (12 ± 7.5 kPa, versus 8.2 ± 2.8 kPa, $p = 0.05$).

Table 1. Anthropometric, laboratory and radiological parameters of the participants

	Hashimoto's thyroiditis (mean ± SD) or (median, Q1-Q3)	Healthy controls (mean ± SD) or (median, Q1-Q3)	p value
Age (years)	13 ± 3.7	12.3 ± 3.7	0.39
Gender (girl/boy)	31 (67.4%) / 15(32.6%)	27 (58.7%) / 19 (41.3%)	0.39^{χ^2}
Weight (kg)	49.4 ± 19	49.5 ± 21	0.98
Height (cm)	151.4 ± 18	148.3 ± 18.6	0.41
BMI (kg/m^2)	20.2 ± 5.7	21.3 ± 5.5	0.33
Weight SDS	0.28 ± 1.18	0.47 ± 1.26	0.47
Height SDS	0.08 (-0.60 – 0.45)	0.04 (-0.96 – 0.81)	0.94^{α}
BMI SDS	0.59 (-0.64 – 1.26)	0.38 (-0.37 – 1.62)	0.37^{α}
FPG (mg/dL)	85.1 ± 6.2	85.2 ± 6.7	0.94
Insulin (mIU/mL)	12.2 ± 7.7	13.6 ± 7.4	0.38
HOMA-IR	2.60 ± 1.76	2.90 ± 1.64	0.40
Triglyceride (mg/dL)	88 (73 – 115)	102 (68 – 121)	0.14^{α}
Total cholesterol (mg/dL)	143.7 ± 25.7	153.1 ± 26.9	0.09
LDL-C (mg/dL)	85.3 ± 19.5	92.6 ± 23.2	0.11
HDL-C (mg/dL)	44 (39 – 57)	50 (42 – 59)	0.24^{α}
TSH (mIU/mL)	3.31 (2 – 7.08)	2.56 (1.72 – 4.63)	0.10^{α}
Free-T4 (ng/dL)	12.9 (11.8 – 14.5)	12.9 (11.7 – 14.4)	0.96^{α}
Free-T3 (ng/dL)	3.99 ± 0.80	3.98 ± 0.68	0.95
Tg (mg/dL)	1.20 (0.3 – 16.5)	13 (7.8 – 25)	**<0.001**$^{\alpha}$
Anti-TPO (U/L)	187.1 ± 182.8	8.3 ± 3.3	**<0.001**
Anti-Tg (U/L)	261 (104 – 430)	15 (13 – 17)	**<0.001**$^{\alpha}$
IGF-1 (ng/mL)	292 ± 128.6	285.7 ± 137.7	0.82
IGF-1 SDS	0.27 ± 1.24	0.56 ± 1.31	0.27
IGFBP3 (ng/mL)	5,148.7 ± 1,260.7	5,376.1 ± 1,436.7	0.43
IGFBP3 SDS	0.06 ± 0.80	0.38 ± 0.70	0.05
Thyroid volume (cm^3)	12.02 ± 6.37	6.71 ± 3.32	**<0.001**
Thyroid volume SDS	3.27 (1.43 – 5.11)	0.73 (-0.23 – 1.73)	**<0.001**$^{\alpha}$
Mean SWE value (kPa)	12.94 ± 6.01	8.23 ± 2.82	**<0.001**

Data with normal distribution evaluated with Student's t-test. $^{\alpha}$Symbol indicates the Mann-Whitney U test was used. χ^2: chi-squared test.
BMI: body mass index, SDS: standard deviation (SD) score, FPG: fasting plasma glucose, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Anti-TPO: anti-thyroid peroxidase, Anti-Tg: anti-thyroglobulin, IGF-1: insulin like growth factor-1, IGFBP3: insulin-like growth factor-binding protein 3, SWE: shear wave elastography, kPa: kilopascal, TSH: thyroid stimulating hormone

Table 2. Relationship of factors affecting SWE values

	Whole group		Hashimoto's thyroiditis group		Control group	
	r	**p value**	**r**	**p value**	**r**	**p value**
Age	0.276	**0.008**	0.156	0.30	0.555	**<0.001**
Weight	0.266	**0.01**	0.250	0.09	0.469	**0.001**
Height	0.227	**0.03**	0.141	0.35	0.402	**0.006**
BMI	0.153	0.15	0.122	0.42	0.491	**0.001**
Weight SDS	0.088	0.40	0.117	0.44	0.212	0.16
Height SDS	-0.026	0.80*	0.063	0.68*	-0.138	0.36
BMI SDS	0.228	**0.03***	0.196	0.19*	0.353	**0.02***
FPG	-0.111	0.30	-0.162	0.29	-0.069	0.66
Insulin	0.123	0.25	0.155	0.31	0.292	0.06
HOMA-IR	0.096	0.37	0.120	0.43	0.259	0.09
Triglyceride	0.181	0.09*	0.395	**0.007***	0.031	0.84
Total cholesterol	0.056	0.61	0.284	0.06	-0.067	0.67
LDL-C	0.063	0.56	0.315	**0.04**	-0.070	0.65
HDL-C	-0.230	**0.03***	-0.149	0.33	-0.086	0.58*
TSH	0.121	0.25*	0.115	0.45*	-0.084	0.58
Free-T4	-0.236	**0.02***	-0.433	**0.003***	-0.060	0.69
Free-T3	-0.202	0.06	-0.262	0.08	-0.171	0.27
Tg	-0.255	**0.01***	0.183	0.23*	-0.380	**0.009***
Anti-TPO	0.354	**0.001**	0.142	0.35	0.098	0.52*
Anti-Tg	0.427	**<0.001***	0.005	0.98*	0.220	0.14*
IGF-1	0.279	**0.008**	0.305	**0.04**	0.341	**0.02**
IGF-1 SDS	0.056	0.60	0.226	0.14	-0.052	0.74
IGFBP3	0.179	0.09	0.215	0.16	0.340	**0.02**
IGFBP3 SDS	-0.017	0.87	0.118	0.44	0.025	0.87
Thyroid volume	0.648	**<0.001**	0.542	**<0.001**	0.606	**<0.001**
Thyroid volume SDS	0.702	**<0.001***	0.572	**<0.001**	0.484	**0.001**

Pearson correlation analysis was used to examine the relationship between variables. *Indicates Spearman correlation analysis was applied.
BMI: body mass index, SDS: standard deviation score, FPG: fasting plasma glucose, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Anti-TPO: anti-thyroid peroxidase, Anti-Tg: anti-thyroglobulin, IGF-1: insulin like growth factor-1, IGFBP3: insulin-like growth factor-binding protein 3, TSH: thyroid stimulating hormone

When the relationship between the mean SWE values and other factors were examined; while age, weight, height, BMI SDS, IGF-1 level, thyroid autoantibodies, thyroid volume and thyroid volume SDS were positively correlated, HDL-C, fT4 and Tg were negatively correlated in the whole group. When only those cases with HT were evaluated, the mean SWE scores and triglyceride, LDL-C, IGF-1, thyroid volume and thyroid volume SDS were positively correlated, while fT4 was negatively correlated. The relationships between the mean SWE values and independent variables in the whole group, only in cases with HT and the healthy controls are shown in Table 2.

Multiple linear regression analysis was performed to evaluate the direction and degree of the effects of the variables on the thyroid elasticity scores, since the relationship between SWE scores and variables differed in healthy controls and patients with HT. Age and sex specific SDSs were included in the model as parameters which could change with age. When the independent factors were included in the regression model based on the multicollinearity relationship, it was observed that age, BMI SDS and anti-TPO levels were effective on the thyroid elasticity score in the regression model. The results of the multiple linear regression analysis are shown in Table 3.

We detected a SWE cut-off value of 9.68 kPa with 68% sensitivity and 72% specificity, a 70% positive predictive value, and a 69% negative predictive value in thyroid elastography in order to differentiate cases with HT from healthy controls (Figure 3). The maximum area under curves for mean kPa value was 0.754 (95% confidence interval: 0.65-0.85; $p<0.001$).

Table 3. The results of multiple linear regression analysis of variables

	Unstandardized coefficients		Standardized coefficients		95% confidence interval for B		p value
	B	Standard error	β	t	Lower limit	Upper limit	
Constant	2.213	4.244		0.521	-6.279	10.706	0.60
Age	0.037	0.011	0.413	3.318	0.015	0.059	**0.002**
BMI SDS	0.273	0.133	0.207	2.049	0.006	0.539	**0.04**
HOMA-IR	0.146	0.250	0.063	0.585	-0.354	0.646	0.56
LDL-C	0.024	0.018	0.130	1.313	-0.013	0.060	0.19
HDL-C	-0.046	0.027	-0.177	-1.711	-0.099	0.008	0.09
Triglyceride	0.004	0.009	0.046	0.429	-0.015	0.023	0.67
TSH	0.231	0.275	0.088	0.838	-0.320	0.781	0.41
Free-T4	-0.004	0.190	-0.002	-0.020	-0.384	0.377	0.98
Tg	-0.023	0.029	-0.093	-0.806	-0.080	0.034	0.42
Anti-TPO	0.009	0.003	0.289	2.741	0.002	0.015	**0.008**
Anti-Tg	0.000	0.001	0.060	0.579	-0.001	0.002	0.57
IGF-1 SDS	-0.261	0.326	-0.084	-0.800	-0.913	0.391	0.43

As a result of the analysis, it was found that a significant regression model, $F(12, 59) = 4.56$, $p < 0.001$ and 37% of the variance in the dependent variable ($R^2_{adjusted} = 0.37$) was explained by the independent variables.

BMI: body mass index, SDS: standard deviation score, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Anti-TPO: anti-thyroid peroxidase, Anti-Tg: anti-thyroglobulin, IGF-1: insulin like growth factor-1, TSH: thyroid stimulating hormone

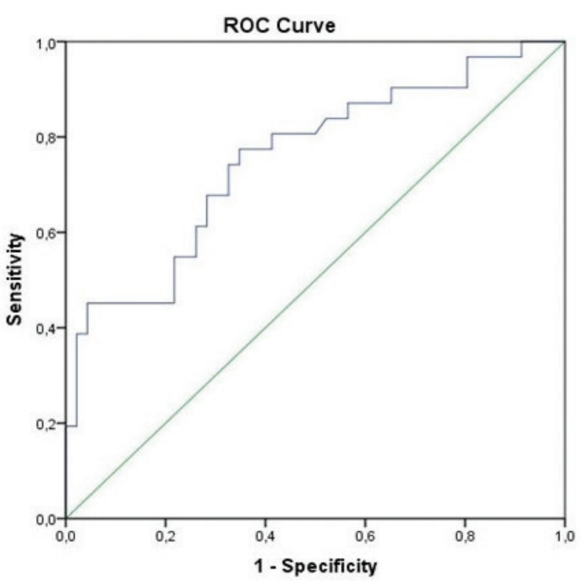

Figure 3. ROC curve analysis of the SWE values of euthyroid HT and the best cut-off value for elasticity (kPa)

ROC: receiver operating characteristic, SWE: shear-wave elastography, HT: Hashimoto's thyroiditis, kPa: kilopascal

Discussion

In this study, the degree of thyroid tissue stiffness was evaluated with SWE in both newly diagnosed and untreated patients with HT and in healthy children. In our study, we found a lower cut-off value in differentiating healthy individuals from individuals with HT in terms of SWE scores. In addition, we found that age, BMI SDS and anti-TPO had a positive and significant effect on thyroid elastography scores by means of multiple linear regression analysis.

Thyroid elastography will provide a more comprehensive evaluation of inflammation and fibrosis in the thyroid gland, and it may become more common in the future in the follow-up and treatment of those patients with HT (8). In another study in which HT was classified according to fibrosis in gray-scale ultrasound, the SWE cut-off value with the highest sensitivity was determined to be 12.3 kPa (8). Similar to previous studies, those patients with hypothyroidism had higher elasticity scores (11). SWE values increased as the stage of the disease increased on ultrasound. However, one of the limitations mentioned in that study was that the clinical and biochemical characteristics of the cases diagnosed with HT were not specified. Similarly, in our study, while the mean SWE values in those patients with HT were 12.94 ± 6.01 kPa, it was 8.23 ± 2.82 kPa in the healthy controls. In this study, we compared two groups with statistically similar clinically, metabolically and laboratory parameters and also examined the relationship of all factors on SWE values. Furthermore, a positive and significant correlation was found between anti-TPO and SWE scores when considering the whole group. Although there are studies with similar results (11), a significant relationship was found with anti-TPO in another study, and it was not found with anti-Tg (8). The positive correlation between SWE scores and age has been previously reported in the literature (11,22). Parameters such as body weight, height, and BMI increase with age. In addition, as age increases, IGF-1 levels increase with puberty. These variables can be considered in terms of their relationship with age. In the multiple linear regression analysis, we included the SDSs of those parameters which could change with age or gender, independent of the effect of the age factor. In our study, unlike the literature, we found a positive correlation between elasticity scores and BMI SDS. This is striking in terms of the effects of obesity and metabolic syndrome on thyroid elasticity. These data suggest that SWE is a significant but not robust diagnostic test for HT. For example, according to the data of this study, the SWE value of an older, obese (but otherwise healthy) child may be similar to that of a younger, lean child with new-onset HT.

The main factor affecting elasticity scores may be the stage of thyroiditis. In addition, the elasticity scores were found to be significantly higher in those individuals with hypothyroidism in the literature (11). Furthermore, it was observed that the elasticity scores of those who received levothyroxine sodium treatment did not statistically significantly differ from those who did not receive treatment, and the duration of treatment was not effective either (20). These studies show us that receiving treatment for hypothyroidism does not improve thyroiditis in terms of having any effect on SWE scores. In addition, more comprehensive results can be obtained by evaluating the effect of BMI change on SWE scores in individuals with HT in the long term.

In some previous studies in the literature, values such as 12.8 kPa and 12.3 kPa were given as kPa cut-off values for the HT discriminative SWE value. However, some of the main limitations of these studies can be expressed as the fact that the hormonal profiles at the time of application were not compared, that they were not matched for age or gender, or that there were no biochemically and hormonally similar groups (8,23).

In studies conducted with adults, the SWE cut-off values were found to be higher. This situation can be explained by the effects of other factors affecting SWE scores, as we mentioned earlier in our study (6,21,24). We detected a SWE cut-off value of 9.68 kPa with 68% sensitivity and 72% specificity. However, as we know, there are publications stating that thyroid auto-antibody positivity may not be detected in individuals with autoimmune thyroiditis who are not in the hypothyroid stage (25). This condition is referred to as seronegative autoimmune thyroiditis. In these individuals, similar imaging findings observed in chronic autoimmune thyroiditis are detected in conventional ultrasonography. In addition, in recent years, it has been reported that the rate of thyroid autoantibody positivity increases with an increase in TSH measurements together with ultra-sensitive TSH measurements (25,26,27). It has been reported that SWE may also be useful in the differential diagnosis between various types of thyroiditis (28). The fact that our study was conducted in the pediatric age group and it was conducted among similar groups in terms of metabolic factors and factors related to thyroid function tests are the distinguishing features of our study.

Study Limitations

One of the limitations of our study was the relatively small number of patients and controls in the study group, and secondly, the stages of the cases with HT were not classified according to B-mode ultrasonography.

Conclusion

SWE scores may be affected by some parameters and if an SWE cut-off value is to be determined between those patients with HT and healthy controls, it should be noted that these factors should be similar between the groups. In our study, we found a lower cut-off value in differentiating healthy individuals from those individuals with HT in terms of SWE scores. As SWE can be a helpful tool in the diagnosis, we recommend that it be used in the follow-up of patients with HT in relation to their thyroiditis stage. Our study shows that although thyroid elastography is not superior to conventional ultrasonography and thyroid auto-antibodies measurements in distinguishing between individuals with HT and healthy individuals, it can be used in the follow-up of the prognosis of the disease as it is useful in evaluating the stage of fibrosis. We think that the lower cut-off value found in our study regarding the elasticity scores in those individuals with HT is due to the evaluation of newly diagnosed individuals and the fact that the inflammation period was still in the early stage. Our results showed that no metabolic factor other than BMI SDS had an effect on SWE scores, especially in healthy children. There was a positive correlation between BMI SDS and SWE in healthy children ($r = 0.353$; $p = 0.02$), but not in those patients with HT ($r = 0.196$; $p = 0.19$). Likewise, age is another factor affecting SWE only in healthy children. Since inflammation is the main factor determining thyroid elasticity in those patients with HT, the effects of other factors such as age and BMI on SWE seems to be insignificant. We do not recommend routine evaluation of any laboratory parameters other than thyroid functions before thyroid elastography.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Kayseri City Hospital Clinical Research Ethics Committee with the number of 591 (date: 24.02.2022).

Informed Consent: Written informed consent forms were obtained from the legal guardians of all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serkan Bilge Koca, Concept: Serkan Bilge Koca, Turgut Seber, Design: Serkan Bilge Koca, Turgut Seber, Data Collection or Processing: Serkan Bilge Koca, Turgut Seber, Analysis or Interpretation: Serkan Bilge Koca, Turgut Seber, Literature Search: Serkan Bilge Koca, Writing: Serkan Bilge Koca.

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