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The Effectiveness of Thyroid Elastography in Evaluating Thyroiditis in Children with Type 1 Diabetes

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What is already known on this topic?

- *Shear wave elastography technique can evaluate inflammation and fibrosis in thyroid tissue. It is used as an auxiliary evaluation tool in the early diagnosis of thyroiditis conditions such as Hashimoto's thyroiditis and in the staging of thyroiditis. Elasticity scores of thyroiditis patients are higher than that of healthy children.*

What this study adds on this topic?

- *In children with type 1 diabetes mellitus (T1DM) who did not have Hashimoto's thyroiditis (HT), shear wave elastography (SWE) scores were found to be similar compared to the healthy control group. The SWE scores of children with T1DM accompanying HT were found to be significantly higher.*

ABSTRACT

Objective: Shear wave elastography can detect inflammation and fibrosis in the thyroid tissue. It can be used to evaluate Hashimoto's thyroiditis or in the assessment of thyroid diseases accompanying type 1 diabetes mellitus. Our aim was to examine whether there is a difference between the shear wave elastography scores as kilopascals of individuals with type 1 diabetes mellitus and healthy children, and the relationship between diabetes-related parameters and shear wave elastography scores.

Materials and Methods: A total of 77 type 1 diabetes mellitus children and 53 healthy controls were compared. Serum thyroid-stimulating hormone, free thyroxine, free tri-iodothyronine, antibodies against thyroid peroxidase and thyroglobulin, average of the last 2 control plasma glycosylated hemoglobin A1c, duration of diabetes and daily insulin dose in diabetic individuals, thyroiditis staging by ultrasound, and shear wave elastography scores were also recorded.

Results: In terms of shear wave elastography scores, no significant difference was found between the healthy control group and the group with type 1 diabetes mellitus without Hashimoto's thyroiditis (7.9 ± 2.8 kPa vs. 8.4 ± 3.3 kPa, $P = .772$). The score of the group with type 1 diabetes mellitus accompanied by Hashimoto's thyroiditis (15.1 ± 6.6 kPa) was found to be higher than the group with type 1 diabetes mellitus without Hashimoto's thyroiditis and the healthy control group ($P = .022$ and $P = .015$, respectively).

Conclusions: This is the first study to compare children with type 1 diabetes mellitus and healthy controls in terms of shear wave elastography scores. We found that there was no significant difference between the shear wave elastography scores of children with type 1 diabetes mellitus without Hashimoto's thyroiditis compared to healthy controls.

Keywords: Children, elasticity, shear wave elastography, thyroid, type 1 diabetes mellitus

INTRODUCTION

Thyroid elastography techniques have become a routine method to evaluate inflammation in the thyroid tissue, to show elasticity or fibrosis, alongside ultrasound examination. With the shear wave elastography (SWE) technique, both ultrasound and elastography can be evaluated together in a single session. Especially in cases with Hashimoto's thyroiditis (HT), the degree of stiffness in the thyroid gland measured by the SWE technique is used to classify the patients in the grading of inflammation in the thyroid gland (fibrosis staging).[1-3]

It has been reported that there is an entity defined as seronegative chronic autoimmune thyroiditis (SN-CAT), thyroid autoantibodies were found to be negative in some cases of autoimmune thyroiditis, but ultrasound examinations showed similar images to cases with HT.[4] In fact, it has been stated that SN-CAT may be a subform of chronic autoimmune thyroiditis due to findings similar to ultrasound images observed in individuals with HT.[5] By ultrasound

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of these cases, a decrease in the echogenicity of the thyroid parenchyma was observed, and some of them were reported to accompany type 1 diabetes mellitus (T1DM).[6]

In a study conducted in Turkey, it was reported that shear wave velocity was lower in children with T1DM who were negative thyroid autoantibodies.[7] In that study, the groups were compared in terms of age and gender, but other factors that could affect the groups' elasticity scores, such as body mass index (BMI) or standard deviation score (SDS) of other anthropometric data, were not determined homogeneously.[7]

In this study, we aimed to examine the SWE scores of groups (type 1 diabetic children with negative and positive thyroid autoantibodies and healthy control group with negative thyroid autoantibodies) similar to each other in terms of age, gender, and anthropometric data. To the best of our knowledge, this is the first study to compare children with T1DM and healthy controls in terms of SWE scores.

MATERIALS AND METHODS

This case-control study was approved by the clinical research ethics committee of Kayseri City Education and Research Hospital with its decision dated 22.11.2022 and numbered 741. Informed consent forms were obtained from the legal guardians of all children included in the study and also from children over the age of 12. Our research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Subjects

After the approval of the ethics committee, children with T1DM (195 patients) who were followed up regularly in our department were invited to our clinic for our research. Among the children who were referred to our pediatric endocrinology outpatient clinic with abnormal serum thyroid function tests (low or high thyroid-stimulating hormone [TSH] hormone, low or high free thyroxine [fT4] hormone) were evaluated. Those who have negative thyroid autoantibodies and detected normal thyroid function test results in 2 consecutive controls within the last 3 months were invited to our clinic for our research.

Inclusion criteria of the study group were as follows:

- Individuals between the ages of 4 and 18,
- Normal thyroid hormone level,
- Having T1DM, whose diagnosis date was over 1 year and who were not on their honeymoon period,
- Children with T1DM, who have had at least 3 plasma glycosylated hemoglobin A1c (HbA_{1c}) measurements in the last 1 year.

Inclusion criteria of the control group were as follows:

- Individuals between the ages of 4 and 18,
- Normal thyroid hormone level,
- Having negative thyroid autoantibodies.

Exclusion criteria of the study group were as follows:

- Children with T1DM, having any systemic disease (such as celiac disease) other than thyroid autoantibody positivity,
- Taking any medication (including those administering treatment for hypothyroidism or hyperthyroidism) other than insulin (specific for individuals with T1DM),
- Those under the age of 4 and over the age of 18.

Exclusion criteria of the control group were as follows:

- Having any systemic disease,
- Those under the age of 4 and over the age of 18.

A total of 77 children with T1DM who met the criteria were included. A total of 53 children constituted the control group.

Anthropometric measurements (body weight, height, BMI) and age- and sex-specific SDSs of these values were calculated with an online calculation program (www.childmetricscs.org).[8] Age and gender-specific Centers for Disease Control and Prevention (CDC) reference cards were used for assessment. The brand name ADE, model M320600-01 (GmbH & Co) Hamburg-Germany, was used as the scale and measuring device.

Diabetes duration and total daily insulin dose of children with T1DM were recorded.

While determining the sample size, more cases than the number of controls were included in the study, considering that some of the children with T1DM might have positive thyroid autoantibodies and some of them might have thyroiditis findings on ultrasound even if they were negative for thyroid autoantibodies.

Laboratory Measurements

Blood samples were taken for biochemical and hormonal measurements in the early morning after 10 hours of night fasting. Serum TSH, fT4, free tri-iodothyronine (fT3) levels, antibodies against thyroid peroxidase (TPOAb) and thyroglobulin, and HbA_{1c} were measured by electrochemiluminescence immunological method (ECLIA) using an automated analyzer (Cobas 8000 c502-c702 and Cobas 6000 c501-e601, Roche Diagnostics, Mannheim, Germany). The mean of 2 HbA_{1c} measurements in the last 6 months of children with T1DM was calculated and this value was used in the analyses.

Thyroid Ultrasonography and Elastography

Ultrasound and 2-dimensional SWE of the thyroid gland were performed via an Aplio 500 ultrasound system (Toshiba Medical Systems, Tokyo, Japan) with a 14 MHz linear array transducer by a pediatric radiologist (T.S.; with 14 years of experience).

The total volume of the thyroid gland was obtained by calculating and summing the volume of each lobe separately (length × width × depth × 0.52). We evaluated HT in 3 categories according to ultrasound findings (Figure 1A, 1B, and 1C). If parenchymal infiltration of thyroiditis involved less than 50% of the gland, grade 1; if they involved more than 50%, grade 2; and if echogenic fibrotic septa were observed, was accepted as grade 3.[3]

In SWE, measurements were made via a round-shaped region of interest 2 mm in diameter from the hardest coded regions on the color map of the each lobe (from the upper, middle, and lower parts, in the transverse plane) (Figure 2A and 2B). At least 10 measurements were made from each lobe. The one-shot

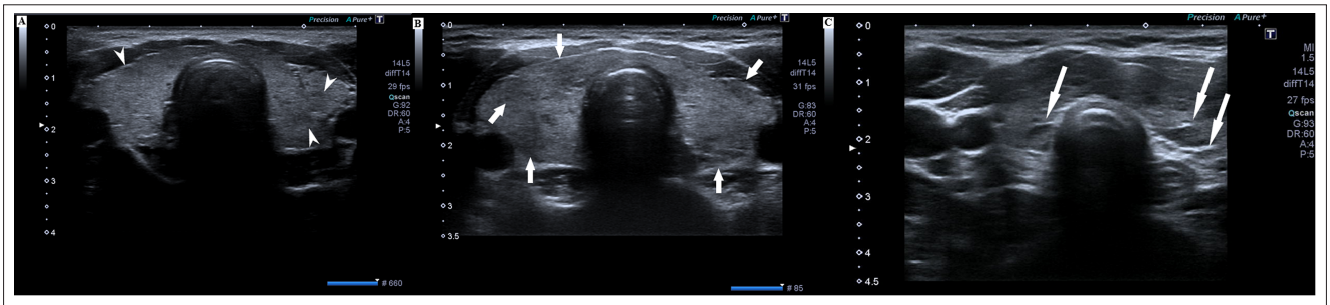

Figure 1. (A) B-mode ultrasound staging of Hashimoto's thyroiditis. Grade 1, (B) hypoechoic parenchymal infiltration of thyroiditis (arrowheads) affecting less than 50% of the thyroid gland; grade 2, (C) affected area is more than 50% (white short arrows); grade 3, fibrous septas (white long arrows) are also added to parenchymal findings.

method was used for measurement and recorded as kilopascal (kPa). The average of all measurements was accepted as the stiffness value of the thyroid gland. The examination time took approximately 10 minutes for each patient.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp.; Armonk, NY, USA) software program. The mean, standard deviation, median, and first and third quartiles (Q1-Q3) of numerical variables were calculated. Categorical variables were shown as numbers and percentages (%). Shapiro–Wilk test was used to evaluate the assumption of normal distribution of the variables. In addition, the variables with kurtosis and skewness values in the range of −2, +2 were considered to have a normal distribution. Student's *t*-test and Mann–Whitney U-test were used to compare 2 independent groups. The chi-square test was used for the analysis of categorical variables. Fisher's exact test was used when comparing children with T1DM without HT and healthy control groups according to the presence of thyroiditis by ultrasound. Kruskal–Wallis test was used when comparing healthy controls and children with T1DM with and without HT in terms of SWE scores. Tamhane test was used as post hoc analysis. The relationship between the variables was analyzed with the Pearson and Spearman correlation coefficient. In terms of statistical significance, *P* value less than .05 was accepted.

RESULTS

A total of 130 children aged 4-17.9 years, 77 with T1DM and 53 healthy controls, were included in the study. When evaluated according to thyroid autoantibody positivity, 11 (14.3%) of the children with T1DM had HT, while autoimmune thyroiditis was not accompanied in 66 (85.7%) of them. There was no significant difference between the T1DM without HT group and the control group according to age distribution (11.7 ± 3.6 years and 11.6 ± 3.7 years, respectively; $P = .925$). Of the children with T1DM without HT, 33 (50%) were girls and 33 (50%) were boys. There was no difference between the groups (T1DM without HT vs. healthy controls) in terms of distribution by gender ($\chi 2$: $P = .473$). According to ultrasound findings of children with T1DM, stage 1 thyroiditis was detected in 5 (6.5%) patients and stage 2 thyroiditis was detected in 9 (11.7%) patients, while no signs of thyroiditis were observed in 63 (81.8%) children.

The baseline clinical and laboratory characteristics of children with T1DM without HT and healthy control group are shown in Table 1. Although TSH and fT3 were statistically different between the groups, they were found within the normal reference ranges in both groups ($P = .001$, $P = .009$, respectively).

Stage 1 thyroiditis was detected in 3 children and stage 2 thyroiditis was found in 1 child among children with T1DM who did

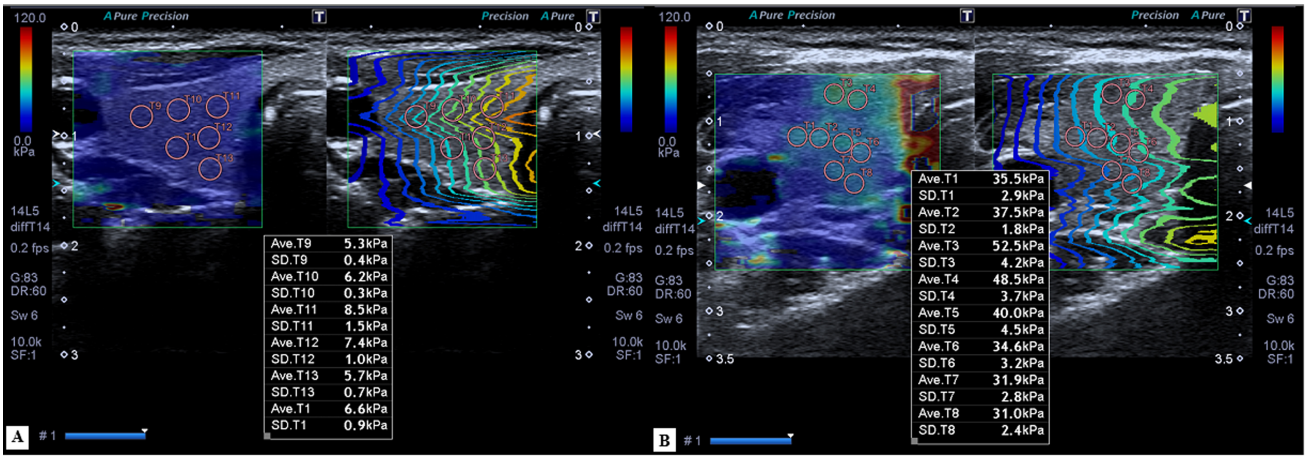

Figure 2. The SWE images of the thyroid glands of 2 patients with T1DM. An 8-year-old boy (A) without Hashimoto's thyroiditis and a 15-year-old boy (B) with Hashimoto's thyroiditis. The mean stiffness value (with standard deviations) of the thyroid gland is calculated using standard round ROIs. It is seen that the stiffness value of the thyroid gland is more in the patient with Hashimoto's disease. ROI, region of interest; SWE, shear wave elastography; T1DM, type 1 diabetes mellitus)

Table 1. Baseline Clinical and Laboratory Characteristics of Individuals with Type 1 Diabetes Mellitus Without Hashimoto's Thyroiditis and Healthy Control Group

	T1DM Without Hashimoto's Thyroiditis Group		Healthy Control Group		
	Mean ± SD	Median (Q1-Q3)	Mean ± SD	Median (Q1-Q3)	*P*
Age (years)	11.7 ± 3.6	11.9 (10.1-14.1)	11.6 ± 3.7	11.5 (8.4-14.6)	.925
Weight (kg)	40.7 ± 14.6	39 (30.6-50.3)	46.3 ± 21.4	44 (26.1-62.5)	.257
Height (cm)	144.6 ± 18.2	147.8 (137.3-158)	145.2 ± 19.6	145 (127.9-160.4)	.981
BMI (kg/m²)	18.7 ± 3.7	17.8 (16.3-19.9)	20.6 ± 5.5	19.3 (15.4-24.7)	.14*
Weight SDS	−0.12 ± 0.99	−0.14 (−0.68-0.53)	0.32 ± 1.29	0.23 (−0.52 to 1.63)	.065
Height SDS	−0.25 ± 0.98	−0.28 (−1.11 to 0.32)	−0.13 ± 1	−0.09 (−0.98 to 0.72)	.506
BMI SDS	0.27 ± 2.22	0.02 (−0.47 to 0.59)	0.43 ± 1.23	0.35 (−0.4 to 1.41)	.098
TSH (mIU/mL)	2.02 ± 1.08	1.76 (1.28-2.55)	3.01 ± 1.65	2.6 (1.7-4.6)	**.001***
Free T4 (ng/L)	13.2 ± 2.2	13.1 (12-14.6)	13.3 ± 1.8	13.3 (11.9-14.7)	.972*
Free T3 (ng/dL)	3.6 ± 0.7	3.7 (3.3-4.1)	4 ± 0.7	4.1 (3.5-4.4)	**.009**
TPOAb (U/L)	9.2 ± 3.8	8 (7-10)	8.4 ± 3.1	8 (6-10)	.262*
TgAb (U/L)	15.3 ± 4.5	15 (12-17)	16.5 ± 5.7	15 (13-17)	.193*
TV (mL)	6.7 ± 2.9	6.3 (4.8-8.4)	6.4 ± 3.2	6 (4.2-8.7)	.497*
TV SDS	1.19 ± 1.15	0.95 (0.49-1.72)	0.95 ± 1.39	0.75 (−0.21 to 1.96)	.207*
SWE value (kPa)	8.4 ± 3.3	7.7 (6-9.3)	7.9 ± 2.8	7.2 (6-9.8)	.465*

BMI, body mass index; kPa, kilopascal; SDS, standard deviation score; SWE, shear wave elastography; T1DM, type 1 diabetes mellitus; T3, tri-iodothyronine; T4, thyroxine; TgAb, anti-thyroglobulin; TPOAb, anti-thyroid peroxidase; TSH, thyroid-stimulating hormone; TV, thyroid volume.
Data with normal distribution was calculated with Student's *t*-test. *P* values less than .05 are shown in bold and statistically significant.
*Mann–Whitney U-test was used for those who did not have a normal distribution.

not have HT. No signs of thyroiditis were observed by ultrasound in any child in the healthy control group. Four patients with T1DM who had thyroiditis findings by ultrasound but negative thyroid autoantibodies were evaluated within themselves. The age ranged from 10.1 to 17.8 years. The mean SWE score of the group with T1DM with thyroiditis findings by ultrasound was 11.6 ± 4.9 kPa, the mean SWE score of the group with T1DM without thyroiditis findings by ultrasound was 8.2 ± 3.1 kPa, and there was no statistical difference between the groups ($P = .264$).

When children with T1DM with HT were also included in the analysis, a significant difference was observed between groups in terms of thyroid autoantibodies, thyroid volume, thyroid volume SDS, and SWE scores ($P < .001$). Children with T1DM with and without HT were compared with the healthy control group in terms of SWE scores in post hoc analysis. While no significant difference was found between the healthy control group and the group with T1DM without HT (7.9 ± 2.8 kPa vs. 8.4 ± 3.3 kPa, $P = .772$), a significant difference was found between the healthy control group and the group with T1DM accompanied by HT (7.9 ± 2.8 kPa vs. 15.1 ± 6.6 kPa, $P = .015$), and between the group with T1DM without HT and the group with T1DM accompanied by HT (8.4 ± 3.3 kPa vs. 15.1 ± 6.6 kPa, $P = .022$).

The relationship of factors affecting SWE scores is shown in Table 2.

DISCUSSION

In our study, we found that there was no significant difference between the SWE scores of children with T1DM without HT compared to healthy controls. In a previously reported study from Turkey, shear wave velocity of the thyroid gland with acoustic radiation force impulse elastography in children with T1DM was found to be lower than in healthy controls. Based on this result, the authors suggested that T1DM affects thyroid gland tissue stiffness.[7] However, in this study, it was not clear whether the groups were similar in terms of factors affecting thyroid elastography. In another study in which factors affecting thyroid elastography by comparing children with HT with healthy controls, a positive correlation has been found with age, BMI SDS, and TPOAb.[9] There are other studies in the literature regarding a positive correlation between SWE scores with age and TPOAb.[3,10,11] In our current study, we observed a

Table 2. Relationship of Factors Affecting Shear Wave Elastography (SWE) Scores

	Correlation Coefficient	*P*
Age	0.509	**<.001**
Weight	0.499	**<.001**
Height	0.392	**<.001**
BMI	0.471	**<.001**
Weight SDS	0.14	.112
Height SDS	−0.162	.066
BMI SDS	0.225	**.01**
TSH	−0.028	.754
Free T4	−0.07	.382
Free T3	−0.16	.096*
TPOAb	0.296	**.001**
TgAb	0.19	**.03**
TV	0.606	**<.001**
TV SDS	0.468	**<.001**
Daily insulin dosage	0.145	.215
Diabetes duration	0.116	.317
Mean HbA_{1c}	0.154	.18*

BMI, body mass index; HbA_{1c}, glycosylated hemoglobin A1c; SDS, standard deviation score; T3, tri-iodothyronine; T4, thyroxine; TgAb, anti-thyroglobulin; TPOAb, anti-thyroid peroxidase; TSH, thyroid-stimulating hormone; TV, thyroid volume.
Spearman correlation analysis was used to examine the relationship between variables. *P* values less than .05 are shown in bold and statistically significant.
*Indicates that Pearson correlation analysis has been applied.

positive correlation between thyroid autoantibodies, age or other parameters that increase with age (body weight, height, BMI, thyroid volume), BMI SDS, and SWE scores. We did not find any positive or negative correlation between daily insulin dose, duration of diabetes or mean HbA_{1c} level, and SWE scores in children with T1DM.

In a study comparing obese children aged 6-18 years with and without subclinical hypothyroidism, serum insulin and homeostatic model assessment for insulin resistance (HOMA-IR) were found to be higher in the subclinical hypothyroidism group, and a positive correlation was observed between serum TSH level and insulin, and HOMA-IR.[12]

In a study comparing children with celiac disease and healthy control groups, with similar age, gender, BMI values, and negative thyroid autoantibodies, SWE scores were found to be higher in children with celiac disease.[13] In that study, it was seen that there was a statistical difference between the groups in terms of thyroiditis findings by ultrasound, but such a difference was not observed in our study.

In some studies, the correlation of SWE scores and the parameters examined in the studies was evaluated together in the case and control group and in others only in the case group. Moreover, in some of the sample groups, the age range is 8-60 years, and some are in the pediatric age range.[3,14,15] In 1 study, the factors affecting SWE scores in individuals with HT, in the control group, and in the whole group were evaluated separately.[9] Influencing factors were also examined by multivariate regression analysis, and it was observed that only age, BMI SDS, and anti-TPO had an effect on the thyroid elasticity score in the regression model.[9]

In our study, T1DM cases (4 patients) with thyroiditis findings by ultrasound and T1DM cases without thyroiditis findings by ultrasound were compared in terms of SWE scores. Although the SWE scores of T1DM patients with negative thyroid autoantibodies and thyroiditis findings by ultrasound were higher, this difference was not statistically significant. In addition, the SWE scores of T1DM patients with accompanying HT were found to be higher than those with T1DM without HT. Therefore, we suggest that thyroid elastography may be an evaluation method that can guide the clinician in terms of follow-up in children with T1DM who are negative for thyroid autoantibodies but have thyroiditis findings on thyroid ultrasound. It should also be noted that new studies involving more children with T1DM are needed for this hypothesis.

The limitations of this study were that it was a case-control study and the study population was relatively small. Also, the low number of patients with T1DM with HT and the low number of patients especially with stage 2 thyroiditis make the statistical comparison of stages inappropriate.

CONCLUSION

To the best of our knowledge, this is the first study to compare children with T1DM and healthy controls in terms of SWE scores. The remarkable aspects of our study are that the clinical and laboratory characteristics of both groups were evaluated in detail, and 2 similar groups were compared in terms of factors affecting the results of thyroid elastography.

Ethics Committee Approval: This case-control study was approved by the clinical research ethics committee of Kayseri City Education and Research Hospital with its decision dated 22.11.2022 and numbered 741.

Informed Consent: Informed consent forms were obtained from the legal guardians of all children included in the study and also from children over the age of 12.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.B.K., T.S.; Design – S.B.K., T.S.; Literature Search – S.B.K.; Writing Manuscript – S.B.K., T.S.; Critical Review – S.B.K., T.S.

Declaration of Interests: The authors have no conflict of interest to declare.

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