Shear wave elastography in diffuse thyroid disease

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Aim. Our aim was to examine the contribution of shear wave elastography to ultrasonographic assessment in diffuse thyroid disease, specifically to evaluate the stiffness of the thyroid gland in diffuse thyroid disease and compare it with healthy controls.

Methods. A total of 46 patients with diffuse thyroid disease were examined clinically, by conventional ultrasound, and shear wave elastography. The conventional ultrasound parameters followed were: volume, margin quality, presence of nodules, and vascularisation. We measured the mean, minimum, and maximum stiffnesses by shear wave elastography. Results were correlated with values in 128 healthy subjects.

Results. Patients with diffuse thyroid disease had significantly higher mean and maximal stiffnesses of the thyroid gland: 12.5 ± 5 kPa and 35.3 ± 12.8 kPa, respectively, and lower minimal stiffness: 0.5 ± 0.6 kPa than the healthy control group with mean, maximal, and minimal values of 9.5 ± 3.6 kPa, 22.5 ± 7.3 kPa, and 2.2 ± 2.1 kPa ($P < 0.001$). Stiffness values were positively correlated with BMI and volume of the thyroid; they did not correlate with margin quality, presence of nodules nor vascularisation. Compared with healthy volunteers, thyroid glands of patients with diffuse thyroid disease had a blurred margin more frequently and the amount of nodules and vascularisation were higher. Patients with Graves-Basedow disease did not have significantly different mean, maximal, nor minimal stiffnesses than those with thyroiditis.

Conclusion. Both mean and maximal stiffness of the thyroid gland are significantly higher in diffuse thyroid disease than in the healthy population, while minimal stiffness is lower.

Key words: diffuse thyroid disease, elastography, shear wave, ultrasound

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INTRODUCTION

Diffuse thyroid diseases include Graves-Basedow disease and various types of thyroiditis. Graves-Basedow disease is an autoimmune condition also associated with goitre, hyperthyroidism, and orbitopathy. Thyroiditis can be divided according to the aetiology. Acute thyroiditis is caused by bacteria, subacute thyroiditis (De Quervain's) has viral aetiology. Chronic thyroiditis is an autoimmune disease, with the most common subtype being Hashimoto's thyroiditis. Thyroiditis is generally more frequent in women¹. Although chronic thyroiditis can cause temporary hyperthyroidism, it leads to gradual destruction of the thyroid and hypothyroidism, usually with the formation of goitre.

Ultrasound is a useful tool for evaluation and management of thyroid disorders². Apart from differences from normal thyroid in B-mode and Doppler ultrasound, changes may result in an increase in stiffness of the thyroid gland due to fibrosis³.

Ultrasound shear wave elastography (SWE) is a method for measuring tissue stiffness. It is a real-time, non-invasive imaging technique that, as opposed to strain

elastography, provides quantitative measurements. It is also easier to perform than elastography requiring manual compression, and results of the examination are more repeatable.

Most studies on the role of SWE in the thyroid disease have been focused on nodules so far. There is only a limited number of studies concerning SWE in diffuse thyroid disease⁴⁻¹².

MATERIALS AND METHODS

This prospective observational study was approved by the Ethics Committee of Palacky University Olomouc under the reference number 153/13 and all patients have given their written informed consent. A total of 46 consecutive patients with a diagnosis of diffuse thyroid disease had been examined by ultrasound, and the stiffness of both thyroid lobes was measured by shear wave elastography. The patients were sorted according to the diagnosis – either Graves-Basedow disease (which was confirmed by histology after total thyroidectomy) or thyroiditis. Ultrasound findings were correlated with the

diagnosis, demographic parameters, and thyroid stiffness measured by SWE. Stiffness was also compared with the values found previously in 128 healthy volunteers that were measured on the same ultrasound (US) machine by the same radiologist – these results were published earlier, with volunteers signing the written informed consent.

The standard demographic data were obtained from each patient: age, sex, and body mass index (BMI). The cohort comprised 41 women and 5 men, aged 50.8 ± 16.2 years, range 21–80.

All patients were examined in supine position by an experienced radiologist performing elastography routinely using the Aixplorer US system (SuperSonic Imagine, Aix-en-Provence, France) with a 4–15 MHz compact linear array transducer. The examination consisted of a conventional US, Doppler US, and shear wave elastography (SWE) with a quantitative assessment of tissue stiffness measured in kilopascals.

The recorded conventional US features of the thyroid gland included volume, margin quality (clearly delineated or blurred), presence of nodules (yes/no), and vascularisation (normal/higher). We measured the mean, minimum, and maximum of a selected region of interest (ROI) with shear wave elastography – for our purpose, each lobe in the axial plane with the largest possible diameter not extending beyond the border of the thyroid gland and not covering nodules (when present), with each side measured twice at different levels (Fig. 1). While the mean value was calculated as the average of four measurements, maximal and minimal values were the highest or the lowest number out of four measurements. All the images were stored digitally.

To assess the difference in continuous parameters (e.g. tissue stiffness or age) between two or more groups of patients, the Kruskal-Wallis test was used. Kruskal-Wallis test is a non-parametric version of ANOVA, i.e. it does not assume that the parameters are normally distributed. To test the difference between categorical parameters (e.g. presence of nodules) between two or more groups, the exact Fisher's factorial test was used. (The Fisher's test was used instead of the more standard asymptotic chi-square test in contingency tables because of a lower number of patients.) All the tests were performed in STATISTICA, version 10.0, Statsoft Inc, Tulsa, CA, and MatLab R2013b, The MathWorks Inc., Natick, MA. The level of significance was set at 0.05.

RESULTS

The mean, maximal, and minimal values of thyroid gland stiffness measured in healthy volunteers on the same machine by the same radiologist were 9.5 ± 3.6 kPa, 22.5 ± 7.3 kPa, and 2.2 ± 2.1 kPa, respectively. Fig. 2 shows the comparison of mean, maximal, and minimal stiffnesses of the thyroid gland in patients with diffuse thyroid disease and healthy volunteers. In the thyroid affected by diffuse thyroid disease, the mean stiffness was 12.5 ± 5 kPa and it was significantly higher than in healthy subjects ($P < 0.001$). The average maximal value

was 35.3 ± 12.8 kPa and was also significantly higher in patients with diffuse thyroid disease ($P < 0.001$), and the average minimal value was 0.5 ± 0.6 kPa – it was significantly lower in diffuse thyroid disease than in healthy volunteers ($P < 0.001$), often with values reaching the machine's technical minimum (0.1 kPa).

There was no correlation between age and sex and elasticity of the thyroid gland in patients with diffuse thyroid disease. BMI and volume of the thyroid were positively correlated. BMI increased by 1 unit resulted in the elevation of maximal stiffness by 1 kPa ($P = 0.006$) and the increase in volume by 1 ml by approximately 0.5 kPa.

The thyroid lobe margins were clearly delineated (in 78% of cases) and vascularisation was higher (also in 78%) in the patients with diffuse thyroid disease, with the majority of patients being women (89%). When compared with the healthy population, the presence of blurred margin was statistically significant higher in patients with diffuse thyroid disease as was the presence of nodules and higher vascularisation ($P < 0.0001$ in all the cases).

Out of 46 patients, there were 36 patients with thyroiditis and 8 with Graves-Basedow disease in our study. Patients with Graves-Basedow disease did not have significantly different mean, maximal, nor minimal stiffnesses than those with thyroiditis. Age and sex differences were not statistically significant in patients with Graves-Basedow disease and thyroiditis.

DISCUSSION

Table 1 summarizes the results of nine studies that measured the mean stiffness of the thyroid gland in patients with diffuse thyroid disease and healthy control groups, with three of them being paediatric^{4,11,12}. Since several studies presented stiffness in m/s and some in kPa, we used a simplified formula to at least approximately compare the results. The formula used was: Young's modulus = $3 \times \text{density} \times (\text{shear wave velocity})^2$ (ref.²) and the density used for calculation was 1043 kg/m^3 (ref.^{13,14}). As can be seen in Table 1, the authors of the previous studies used three different methods of shear wave elastography depending on the manufacturer of the ultrasound system. However, all these methods are based on the same principle – acoustic radiation force impulse is used to create transient shear waves in measured tissue and the velocity of the shear waves propagation is measured by the ultrasound system¹⁵. One of the manufacturers then uses the formula mentioned above to calculate the Young's modulus of the tissue¹⁶. As we do not have the detailed information about the measurement procedure and signal processing in different manufacturers, we present the calculated values only as estimation of actual values (shown in gray in the Table 1). However, this approximation enables direct comparison of the results obtained in previous studies. Diffuse thyroid disease was classified either as autoimmune thyroiditis^{8,12}, Hashimoto's thyroiditis^{4,10,11}, chronic autoimmune thyroiditis^{6,7}, combination of Graves-Basedow disease and Hashimoto thyroiditis⁹, or as a combination of acute, subacute and chronic thyroiditis⁵. Each

Table 1. List of publications comparing mean stiffnesses of normal thyroid and in diffuse thyroid disease^{4,12}.

Author	Country	SWE method	Stiffness of normal thyroid		Stiffness in DTD		P	Ref.
			N°	kPa	m/s	N°	kPa	m/s
Kandemirli*	Turkey	SuperSonic Imagine, ShearWave™ Elastography (SWE™)	26	10.6	1.84	59	14.9	2.18
								<0.001
Ruchala	Poland	SuperSonic Imagine, ShearWave™ Elastography (SWE™)	40	16.18±5.4	2.27±0.94	38	36.15±18.7	3.4±1.76
								<0.0001
Fukuhara	Japan	Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)	145	7.91±2	1.59±0.41	84	19.09±4.4	2.47±0.57
								<0.001
Hekimoglu	Turkey	Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)	40	8.31±0.6	1.63±0.12	50	20.45±2.4	2.56±0.3
								<0.001
Vlad	Romania	SuperSonic Imagine, ShearWave™ Elastography (SWE™)	52	RL 19.6±6.6 LL 19.5±6.8	2.5±0.84 2.49±0.87	52	RL 26.6±10 LL 25.8±11.7	2.92±1.1 2.87±1.3
								<0.001
Kural	Turkey	Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)	30	11.5±0.8	1.92±0.14	52	22.98±1.87	2.71±0.22
								<0.001
Lin	China	Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)	100	11.66±2	1.93±0.33	200	16.84±3.56	2.32±0.49
								<0.001
Yucel*	Turkey	Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)	26	5.29±0.5	1.3±0.13	26	8.73±3.3	1.67±0.63
								<0.001
Palabiyik*	Turkey	Toshiba, ShearWave Velocity (SWV)	113	10.36±1.7	1.82±0.3	75	42.8±13.9	3.7±1.2
								≤0.05
Sedlackova; 2019	Czech R.	SuperSonic Imagine, ShearWave™ Elastography (SWE™)	128	9.5±3.6	1.74±0.66	42	12.5±5	2±0.8
								<0.001

* paediatric study; DTD diffuse thyroid disease; N° number of healthy volunteers/number of patients, RL right lobe, LL left lobe; grey numbers are approximate values calculated with the formula Young's modulus = 3 x density x (shear wave velocity)² and the density used was 1043 kg/m³ (ref.^{13,14})

Fig. 1. Thyroid gland with the ROI (region of interest) placed in the left lobe; patient with Hashimoto's thyroiditis.

Fig. 2. Mean, maximal, and minimal stiffnesses of the thyroid gland in patients with diffuse thyroid disease and in healthy volunteers.

of these listed studies found statistically higher values in patients with diffuse thyroid disease than in control group, which corresponds with our findings.

The authors of one publication evaluated the thyroid gland in 31 patients with chronic autoimmune thyroiditis and 21 healthy controls with strain index ratio¹⁷. The results were significantly higher in patients with diffuse thyroid disease as well.

We found only one publication in our search where the stiffness of the thyroid gland between patients with and without diffuse thyroid disease was not significantly different ($P=0.802$), even though it was still higher in the former group¹⁹. However, the design of this study

was not optimal, because it was a retrospective study using only patients that underwent fine-needle aspiration biopsy.

There have only been few publications analysing maximal and minimal stiffnesses^{12,18}. In one publication⁴ the authors reported that the measurements were taken in the stiffest area in the thyroid), however, they worked only with the mean values. Maximal and minimal values can be affected by certain focal changes in the thyroid (such as small cysts or calcifications), and the ROI should be placed with awareness of this issue. However, since our results show that patients with diffuse thyroid disease have higher maximal values alongside with lower mini-

mal values, the mean values may not be best to evaluate the process.

The difference between maximal and minimal stiffness may be further potentiated by calculating the coefficient of stiffness variability (CSV) as the ratio of the maximum and minimum stiffness values¹⁹.

$$\text{CSV} = \frac{\text{maximum of stiffness over the ROI}}{\text{minimum of stiffness over the ROI}}$$

The authors of one study tried to use SWE for differentiating chronic autoimmune thyroiditis from Graves' disease and subacute thyroiditis²⁰. Although SWE was capable of distinguishing Graves-Basedow disease from subacute thyroiditis, it was unsuitable for differentiating Graves-Basedow disease from chronic autoimmune thyroiditis. In our study, patients with Graves-Basedow and thyroiditis did not have significantly different mean, maximal, nor minimal stiffnesses.

Possible limitation of the use of maximal and minimal values is that they may be affected by the occurrence of a small number of extreme values within the ROI. A possible solution could be evaluation of a histogram which could better show the degree of tissue heterogeneity. However, histogram was not available in our equipment.

Other main limitations of our study were the relatively small number of patients with diffuse thyroid disease and a high female predilection.

CONCLUSION

Stiffness of the thyroid gland is significantly higher in diffuse thyroid disease than in healthy population. We found maximal and minimal stiffness to differ more than mean stiffness values (which was used in the majority of previous studies). Patients with Graves-Basedow disease had higher maximal and mean values alongside with lower minimal values of stiffness than patients with thyroiditis.

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Author contributions: ZS: measurements, manuscript writing; JH: manuscript writing, recruitment of subjects; TF: statistical analysis; RS: study design, manuscript revisions; JV: study design, technical counselling; MH: study design, manuscript revisions.

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