Shear wave elastography in diffuse thyroid disease

Zuzana Sedlackova¹, Jan Herman², Tomas Furst³, Richard Salzman³, Jaromir Vachutka³, Miroslav Herman⁴

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

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 test because of a lower density used for calculation was 1043 kg/m3. 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 thyroiditis6,12, Hashimoto’s thyroiditis6,10,11, chronic autoimmune thyroiditis6,7, combination of Graves-Basedow disease and Hashimoto thyroiditis6, or as a combination of acute, subacute and chronic thyroiditis6. Each

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 paediatric4,11,12. 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 x density x (shear wave velocity) (ref.2) and the density used for calculation was 1043 kg/m3 (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 tissue15. 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 thyroiditis6,12, Hashimoto’s thyroiditis6,10,11, chronic autoimmune thyroiditis6,7, combination of Graves-Basedow disease and Hashimoto thyroiditis6, or as a combination of acute, subacute and chronic thyroiditis6. Each
| Author         | Country  | SWE method                                                                 | Stiffness of normal thyroid | Stiffness in DTD | P      | Ref. |
|---------------|----------|----------------------------------------------------------------------------|----------------------------|------------------|--------|------|
| Kandemirli*   | Turkey   | SuperSonic Imagine, ShearWave™ Elastography (SWE™)                           | 26                         | 10.6             | 1.84   | 59   | 14.9 | 2.18 | <0.001 | 4     |
| 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 | 5     |
| Fukuhara      | Japan    | Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)        | 145                        | 7.9±2            | 1.59±0.41 | 84   | 19.09±4.4 | 2.47±0.57 | <0.001  | 6     |
| 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  | 7     |
| Vlad          | Romania  | SuperSonic Imagine, ShearWave™ Elastography (SWE™)                           | 52                         | RL 19.6±6.6      | 2.5±0.84  | 52   | RL 26.6±10 | 2.92±1.1  | <0.001  | 8     |
| Kural         | Turkey   | Siemens Medical Solutions, Virtual Touch™ Tissue Quantification (VTQ)        | 30                         | 11.5±0.8         | 1.92±0.14 | 52   | 22.98±1.8 | 2.71±0.22 | <0.001  | 9     |
| 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  | 10    |
| 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  | 11    |
| 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   | 12    |
| Sediackova; 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  | 13    |

*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/m^3(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 ratio\(^\text{17}\). 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 group\(^\text{19}\). 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\(^\text{12,18}\). In one publication\(^4\) 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 values\(^\text{19}\).

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

The authors of one study tried to use SWE for differentiating chronic autoimmune thyroiditis from Graves’ disease and subacute thyroiditis\(^\text{20}\). 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.

**Acknowledgement:** Supported by MH CZ research grants Nr. 16-31881A (All rights reserved), DRO (FNOL, 00098892), and Internal grant of Palacky University IGA LF 2019-002.

**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.

**Conflict of interest statement:** None declared.

**REFERENCES**

1. Li H, Li J. Thyroid disorders in women. Minerva Med 2015;106(2):109-14.
2. Chaudhary V, Bano S. Thyroid ultrasound. Indian J Endocrinol Metab 2013;17(2):219-27.
3. Dudea SM, Botar-İld C. Ultrasound elastography in thyroid disease. Med Ultrason 2015;17:74-96.
4. Ruchala M, Szczepaniek-Parulska E, Zybek A, Moczko J, Czarnywojtew A, Kaminski G, Sowinski J. The role of sonoelastography in acute, subacute and chronic thyroiditis: a novel application of the method. Eur J Endocrinol 2012;166(3):425-32.
5. Fukushima T, Matsuda E, Izawa S, Fujiwara K, Kitano H. Utility of Shear Wave Elastography for Diagnosing Chronic Autoimmune Thyroiditis. J Thyroid Res 2015;2015:164548.
6. Hekimoglu L, Yildirim Donmez F, Arslan S, Ozdemir A, Demir C, Yazici C. The role of shear wave elastography in the diagnosis of chronic autoimmune thyroiditis. Med Ultrason 2015;17(3):322-6.
7. Vlad M, Golu I, Bota S, Vlad A, Timar B, Timar R, Sporea I. Real-time shear wave elastography may predict autoimmune thyroid disease. Wien Klin Wochenschr 2015;127(9-10):330-6.
8. Kandemirli SG, Bayrampoglu Z, Caliskan E, Sari ZNA, Adalenti I. Quantitative assessment of thyroid gland elasticity with shear-wave elastography in pediatric patients with Hashimoto’s thyroiditis. J Med Ultrason 2018;45(3):417-23.
9. Kural Rahali F, Tumaoglu H, Kornap NG, Turhan iyidir O, Haberal KM, Soudman A, Uslu N. Value of shear wave elastography by virtual touch tissue imaging quantification in patients with diffuse thyroid gland pathology. Turk J Med Sci 2018;48(5):993-8.
10. Lin ZM, Wang Y, Liu CM, Yan CX, Huang PT. Role of Virtual Touch Tissue Quantification in Hashimoto’s Thyroiditis. Ultrason Med Biol 2018;44(6):1164-9.
11. Yucel S, Ceyhan Bilgici M, Kara C, Can Yilmaz G, Aydin HM, Emili M, Tomak L, Saglam D. Acoustic Radiation Force Impulse Quantification in the Evaluation of Thyroid Elasticity in Pediatric Patients With Hashimoto Thyroiditis. J Ultrasound Med 2016;37(5):1143-9.
12. Palabiyik F, Inci E, Papayi Çakir ED, Haoaoglu E. Evaluation of Normal Thyroid Tissue and Autoimmune Thyroiditis in Children Using Shear Wave Elastography. J Clin Res Pediatr Endocrinol 2019;11(2):132-9.
13. Hoskins PR. Principles of ultrasound elastography. Ultrasound 2011;20(1):8-15.
14. Gao Y, Li GY, Zhang X, Liu YL. Tissue-mimicking materials for elastography phantoms: A review. Extreme Mechanics Letters 2017;17:62-70.
15. Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correas JM, D’Onofrio M, Drakonaki EE, Fink M, Friedrcich-Rust M, Gilja OH, Havre RF, Jenssen C, Klauser AS, Ohlinger R, Saftou A, Schaefer F, Sporea I, Pisacigla F. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall in der Medizin 2013;34:169-84.
16. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: A new technique for soft tissue elasticity mapping. IEEE Trans Ultrasound Ferroelectr Freq Control 2004;51:396-409.
17. Segilcioglu MS, Duyumus M, Gungor G, Citil S, Sahin T, Boysan SN, Sarica A. The value of real-time ultrasound elastography in chronic autoimmune thyroiditis. Br J Radiol 2014;87(1044):20140606.
18. Kim I, Kim EK, Yoon JH, Han KH, Son EJ, Moon HJ, Kwak JY. Diagnostic role of conventional ultrasonography and shearwave elastography in asymptomatic patients with diffuse thyroid disease: initial experience with 57 patients. Yonsei Med J 2014;55(1):247-53.
19. Herman J, Sedlackova Z, Vachutka J, Furst T, Salzman R, Vomacka J, Herman M. Differential diagnosis of parotid gland tumors: Role of shear wave elastography. Biomed Res Int 2017;2017:9234672.
20. Liu J, Zhang Y, Ji Y, Wan Q, Dun G. The value of shear wave elastography in diffuse thyroid disease. Clin Imaging 2018;49:187-92.