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Shear-Wave Elastography in Diffuse Thyroid Diseases

Cristina Mihaela Cepeha, Andreea Borlea, Corina Paul, Iulian Velea and Dana Stoian

Abstract

The diagnosis and evaluation of diffuse thyroid pathologies is often a challenge for clinicians. Ultrasonography has an essential contribution in thyroid imaging, but elastography adds more accuracy. Frequently used in the evaluation of thyroid nodules, elastography has become a necessary tool in assessing the risk of malignancy. Diffuse thyroid pathologies such as Graves' disease, chronic autoimmune thyroiditis, and subacute thyroiditis, are diagnosed based on laboratory tests completed with imaging. Recently it has been shown that elastography is useful in the evaluation and differentiation of these cases due to the differences in elasticity. This chapter describes the general principles of shear-wave elastography, examination technique, features found in diffuse thyroid disease, but also the limitations of this type of investigation for a better understanding of its use in assessing diffuse thyroid pathology.

Keywords: thyroid, elastography, shear-wave elastography, ultrasonography, diffuse

1. Introduction

Optimal thyroid function is necessary for growth and development as well as for reproductive function. Iodine deficiency is the leading cause of thyroid dysfunction. In areas unaffected by iodine deficiency, thyroid dysfunction is due to autoimmunity. Thyroid pathology can be divided into nodular and diffuse pathology. One in 20 Americans will develop a thyroid disorder in their lifetime, with women being seven times more affected than men [1, 2]. In this chapter, we will address diffuse thyroid diseases (DTD) that can be divided into non-autoimmune (subacute thyroiditis, silent thyroiditis) and autoimmune diseases such as Hashimoto thyroiditis (HT) and Graves' disease (GD) [3].

Hashimoto thyroiditis is also known as chronic autoimmune thyroiditis (CAT) is considered the most common endocrine disorder, and autoimmune pathology, as well as it represents the most common cause of hypothyroidism. HT can be divided into primary and secondary based on its etiology. Primary HT includes classic form, juvenile form [4], fibrous form, painless thyroiditis, Hashitoxicosis, and IgG4-related form [5]. Secondary HT is often iatrogenic, for example, caused by interferon [6] or monoclonal antibodies [7]. The diagnosis is established by correlating the clinical manifestations with the presence of antithyroid peroxidase (ATPO) antibodies and

antithyroglobulin (ATG) antibodies correlated with the ultrasound aspect. Symptoms may vary from dysphonia, dysphagia, and dyspnea to systemic symptoms of hypothyroidism or may even be absent. The antibodies listed earlier are found in over 95% of HT cases, thus being an important diagnostic criterion [8]. The ultrasound image usually reveals hypoechogenicity and heterogeneity (**Figure 1**).

The presence of fibrous septae may explain the pseudolobulated appearance of the parenchyma. Micronodules may also be present. Increased vascularity may be observed using color Doppler. The volume of the thyroid gland is often increased, but can be normal or even decreased, atrophic in the final stages of the disease [9, 10].

Graves' disease is characterized by the presence of thyrotoxicosis, ophthalmopathy, and goiter, although not all three characteristics are always present. In iodine-sufficient areas, GD accounts for 70–80% of cases of thyrotoxicosis, being more frequent in women over 50 years old. Symptoms of hyperthyroidism include irritability, palpitations, weight loss, shortness of breath, tremor, heat intolerance, sweating, and excessive fatigue. The diagnosis is usually based on anti-TSH-receptor antibodies (TRAB) correlated with the ultrasound appearance [11–13]. The echogenicity is usually decreased, and the appearance is not homogenous. Increased volume and high blood flow may also suggest the diagnosis [10, 12, 14].

Figure 1.
US image of a patient with CAT.

Subacute thyroiditis (SA) is usually caused by a viral infection with symptoms including mild fever, swelling, and pain in the neck area, irradiating to the ear or jaw and fatigability. Thyroid stimulating hormone (TSH) is usually suppressed and inflammatory markers are elevated [15]. The presence of focal or diffuse hypoechogenicity together with diminished vascularization may suggest the diagnosis if it is associated with the mentioned symptoms [16].

Post-partum thyroiditis (PPT) occurs in the first year after giving birth and may occur after an induced or spontaneous abortion. PPT prevalence may vary from 1 to 18%, but usually is reported approximatively 5%. In general, PPT has two evolutionary stages, transient thyrotoxicosis due to tissue destruction followed by the phase of hypothyroidism with or without restauration to euthyroidism [17]. Ultrasonography (US) shows the hypoechogenic inhomogeneous texture of the thyroid with decreased vascularity [18].

The ultrasonographic examination is the most sensitive imaging method for evaluating the thyroid. The most important indications of the US are: confirmation of the presence of thyroid nodules, their measurement and characterization, evaluation of diffuse tissue changes, detection of post-operative residual tumors, screening for the patients at high-risk (multiple endocrine neoplasia, history of thyroid cancer, and neck irradiation), and the guidance of the fine needle aspiration (FNA). US is widely available, non-invasive, and reproducible [19–21].

A relatively new imaging technique is elastography, which adds value by assessing tissue elasticity. There are more types of elastography, but the two most used are strain elastography (SE) and shear-wave elastography (SWE). SE evaluates the stiffness by applying external pressure which deforms the tissue. The deformation is named strain. The pressure being exerted by the operator, SE requires longer training to obtain high-quality images. To measure the stiffness, SWE uses shock waves generated by the machine. Both methods have advantages and disadvantages [22, 23]. SWE will be further described in detail, emphasizing the principles, technique, and the value of this method as well as the peculiarities of diffuse thyroid diseases.

2. Shear-wave elastography

2.1 Principles

SWE technique relies on the production and detection of shear-waves. The wave propagation velocity depends on tissue elasticity. Tissue deformation generated by the production of waves produces changes in the echo pattern. Tissue motion is monitored among the US probe in multiple locations. Shear waves are generated at low frequencies (10–2000 Hz) and their speed (~1–50 m/s) is related to tissue density [22, 24]. SWE is used for evaluation of various tissues: liver [25–27], kidney [28, 29], breast [30, 31], thyroid [32–34], prostate [35], and muscles and tendons [36]. There are three types of dynamic elastography: transient elastography (TE), point shear-wave elastography (pSWE), and 2D-SWE [37].

Transient elastography, usually used for measuring liver stiffness, uses a mechanical push. The wave velocity is proportional to tissue fibrosis. The usefulness of TE was demonstrated in many studies [38, 39].

Compared to the previous technique, point shear-wave elastography has the advantage of image guidance so the operator can choose the best acoustic window to perform the measurements. It is an acoustic radiation force impulse (ARFI)-based

method that displays the elasticity as a numerical output (the average speed of shear wave within a region of interest [ROI], expressed in meters per second) [40, 41].

In 2D-SWE, multiple ARFI pulses generate shear waves on a larger area. The machine creates a colored map to display the stiffness. By convention, red is considered stiff and blue is considered soft. Quantitative results are expressed in meters/second (wave propagation speed) or kilo-Pascals (kPa). 2D-SWE is a reproducible, quantitative, and operator-independent technique (**Figure 2**) [42, 43].

2.2 Technique

The SWE evaluation is usually made after the conventional ultrasound examination. The method is non-invasive, completely painless. The subject is asked to stay in a supine position with the head tilted back for better exposure of the neck, without speaking or swallowing. The probe is positioned on one side of the neck, collecting images in longitudinal plane and SWE mode is initiated. The machine displays a color map from blue to red. The subject is asked to hold his/her breath for a few seconds. The image is frozen, and the tissue elasticity is measured and displayed.

2.3 SWE in diffuse thyroid diseases

2.3.1 Hashimoto thyroiditis

Being a common pathology, HT has been studied in detail. In recent years, the elastographic differences between this type of thyroid damage and other diffuse thyroid pathologies have also been studied. A group of Japanese researchers included in a study 229 subjects, healthy controls and patients diagnosed with CAT. The shear-wave velocity (SWV) was measured, and significant differences were observed between

Figure 2.
Normal thyroid tissue—2D SWE.

the two groups (2.47 ± 0.57 m/s for CAT vs. 1.59 ± 0.41 m/s for the control group; $p < 0.001$). The area under the receiver operating characteristics (AUROC) for CAT was 0.899 and the SWV cut-off value was 1.96 m/s. Statistical analysis revealed 87.4% sensitivity (Se), 78.7% specificity (Sp), 74.2% positive predictive value (PPV), 94% negative predictive value (NPV), and 85.1% diagnostic accuracy. No correlation was found between SWV and ATG antibodies (Spearman's $\rho = 0.101$), but a weak positive correlation was found between SWV and ATPO antibodies (Spearman's correlation coefficient = 0.311) [44].

Similar results were found in a study conducted in Turkey on 50 patients diagnosed with CAT and 40 control subjects. Significant differences were found between the SWV of the two groups (2.56 ± 0.3 m/s vs. 1.63 ± 0.12 ms; $p < 0.001$). A higher cut-off value was found, 2.42 m/s, but lower Se (77%) and Sp (71%). The diagnostic accuracy was 87%, 92% PPV, 81% NPV, and AUROC 0.84 [45]. Differences between thyroid stiffness in normal healthy thyroid compared with HT were also found in a study that compared the mean maximum SWV values (2.36 ± 0.22 m/s vs. 2.08 ± 0.34 m/s; $p = 0.001$). The mean minimum SWV were not statistically different (1.83 ± 0.20 m/s in HT group vs. 1.84 ± 0.3 m/s; $p = 0.884 > 0.5$) [46].

Rahatli et al. compared SWV in three groups of patients: HT, GD, and control subjects. Significant differences were found in SWV (2.5 ± 0.2 m/s for HT group, 2.71 ± 0.22 m/s for GD group and 1.92 ± 0.14 m/s for healthy subjects; $p < 0.001$) [47].

Kara et al. conducted a study on 74 HT patients and 75 healthy controls. They propose cut-off value of 2.15 m/s (Se 85.1%, Sp 78.7%, PPV 79.7%, NPV 84.2%, and diagnostic accuracy 81.8%) and 2.45 kPa (Se 82.4%, Sp 81.3%, PPV 81.3%, NV 82.4%, and diagnostic accuracy 81.8%). The mean values of the elastic index were 25.01 ± 10.53 kPa and 2.70 ± 0.53 m/s for the HT group and 12.49 ± 3.23 kPa and 1.94 ± 0.23 m/s for the control group. A positive correlation was found between SWE values and ATG antibodies. No significant correlation was found between SWE values and ATPO antibodies [48].

Other studies have also observed differences in thyroid stiffness. Ruchala et al. studied groups of patients diagnosed with CAT, SAT, GD, and healthy controls and significant differences were found. The mean values for the CAT group were 36.15 ± 18.7 kPa, higher than values for the control group (16.18 ± 5.4 kPa), $p < 0.0001$ (Figure 3) [49].

2.3.2 Graves' disease

Thyroid stiffness was evaluated in a study to compare tissue elasticity in patients diagnosed with GD compared to healthy controls. The study group consisted of 51 patients with GD and 54 volunteers for the control group. The median SWE values were significantly higher compared to those of the control group (17.34 kPa and 2.28 m/s vs. 12.05 kPa and 1.92 m/s; $p < 0.001$ in both comparisons). The cut-off values were 14.5 kPa (Se 100%, Sp 72.2%, and AUROC 0.931) and 2.15 m/s (Se 85.7%, Sp 74.1%, and AUROC 0.888). The SWE values were not correlated with the age of the subject or the duration of the disease. Also, no correlation was found between SWE values and autoantibodies levels ($p > 0.05$). A negative correlation was found between SWE values and TSH values. Between fT3, fT4 levels, and SWE values were found a strong positive correlation [50].

Another study conducted in China on 207 subjects, 45 healthy volunteers and 162 patients with GD concluded that SWE is a useful tool in diagnosing GD. The control group SWE values were significantly lower than those in the GD group. Mean,

Figure 3.
SWE in CAT.

Figure 4.
SWE in GD.

minimum, and maximum values were recorded for each subject. The mean values for the control group were 8.4 ± 2.4 kPa (min); 14.3 ± 2.7 kPa (mean), and 22.1 ± 5.4 kPa (max). GD group values were 10.7 ± 6.4 kPa (min); 17.6 ± 6.4 kPa (mean), and 25.6 ± 10.6 kPa (max); $p < 0.001$. The cut-off value was 15.45 kPa (AUROC 0.656, Se 56.8%, and Sp 71.1%). In contradiction with the previously mentioned study, Li et al. found a positive correlation between SWE values and the duration of the disease, and antibodies serum levels and no correlation between SWE values and fT3, fT4, and THS [51].

Another study published in 2019 evaluated the usefulness of SWE in differentiating thyroid autoimmune diseases. In the GD group, the mean SWV was 2.61 ± 0.32 m/s (range 2.1–3.21 m/s) while in HT group, the mean SWV was 2.85 ± 0.52 m/s (range 2.31–3.82 m/s). The mean SWV value for the control group was 1.75 ± 0.37 m/s (range 1.24–2.36 m/s). The mean values for HT and GD groups were significantly higher than the control group ($p < 0.01$). However, the mean SWV values were higher in the HT group compared to the GD group [52], contrary to the results of the study conducted by Rahatli et al. where higher stiffness was in GD compared to HT [47]. Several studies reported that SWE is not suitable for differentiating GD and CAT even though, both have significantly higher values than the normal thyroid tissue (**Figure 4**) [52–55].

Figure 5.
SWE in subacute thyroiditis.

Figure 6.
Radiation-induced thyroiditis.

2.3.3 Subacute thyroiditis

Given the difference in prevalence, studies on subacute thyroiditis are fewer. Ruchala et al. comparatively studied different types of diffuse thyroid damage, including subacute thyroiditis. This study was included two patients with acute thyroiditis, 18 with SAT, 18 with CAT, and 40 healthy controls. Patients diagnosed with SAT were evaluated three times: at baseline, at 4 weeks follow-up and 10 weeks after diagnosing and treatment initiation. There were significant differences between the three measurements: 214.26 ± 32.5 kPa at the baseline, 45.92 ± 17.4 kPa at 4 weeks and 21.65 ± 5.3 kPa at 10 weeks. The thyroid stiffness was significantly higher at baseline in SAT compared to CAT (36.15 ± 18.7 kPa) or healthy control group (16.18 ± 5.4 kPa). Undertreatment, the values were restored close to normal. The SWE values for the two patients with acute thyroiditis equaled 216.6 and 241 kPa and after treatment, it decreased to 17.93 and 85.384 kPa. All evaluated categories had higher stiffness levels than healthy thyroid ($p < 0.0001$) (Figure 5) [49].

Liu et al. also studied thyroid stiffness in SAT. The mean SWE values were 118.01 ± 51.02 kPa. However, the time of measurement is not mentioned, only the fact that all SAT patients had hyperthyroidism at the moment of evaluation. The AUROC for differentiating SAT from CAT was 0.989. The AUROC for distinguishing SAT from GD was 0.975 [54].

Both mentioned studies concluded SWE utility in diagnosing SAT and differentiating it from CAT and GD (Figure 6).

To the best of our knowledge, no specific papers have been published regarding shear-wave elastography in postpartum thyroiditis or other diffuse thyroid pathologies.

3. Conclusions

The important prevalence of diffuse thyroid diseases makes their imaging assessment essential. SWE proves to be an important tool in the diagnosis and differentiation of diffuse thyroid pathology. However, new studies on larger patient groups are needed to determine exactly whether there are significant differences in elasticity between CAT and GD, as well as have of a consensus on cut-off values.

Conflict of interest

The authors declare no conflict of interest.

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