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The Value of Ultrasound Elastography in Diffuse Thyroid Disease among a Sample of Iraqi Population

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Abstract

BACKGROUND: Early detection of many thyroid disorders is essential in the management. Ultrasound elastography (USE) is beneficial in the assessment of diffuse thyroid diseases (DTDs).

AIM: This study aims to assess the role of ultrasound (US) strain elastography in the diagnosis of diffuse non-nodular thyroid disease in comparison to healthy controls and in the characterization and differentiation of the types of DTDs.

PATIENTS AND METHODS: It is a prospective analytic study performed in the Radiology Department of Oncology Teaching Hospital/Medical city Complex in Baghdad during the period from December 1, 2019, to June 30, 2020, on convenient sample of 25 patients with DTD, in addition to a sample of 25 healthy control persons. The diagnosis of DTDs was made by combination of clinical symptoms, laboratory investigations, and thyroid US.

RESULTS: The mean elastography strain ratio (1.36) of patients with DTD was significantly higher than (0.82) mean of elastography strain ratio for healthy control persons ($p < 0.001$). The acceptable cutoff elastography strain ratio in the diagnosis of DTD was 0.89 with validity results (80% sensitivity, 70% specificity, and 75% accuracy). The mean elastography strain ratio for patients with Hashimoto's thyroiditis (HT) was significantly higher than the strain ratio of patients with Grave's disease ($p = 0.002$).

CONCLUSIONS: The USE is useful in the assessment and characterization of DTD. The USE strain ratio value is helpful in differentiation between different DTDs, especially between HT and Graves's disease.

Introduction

Diffuse thyroid disease (DTD) is a major etiology of thyroid dysfunction, and the early recognition of subclinical DTD can be useful in the proper management of the associated thyroid dysfunction [1]. DTDs include chronic autoimmune hypothyroidism (Hashimoto's thyroiditis [HT]), hyperthyroidism (Graves' disease [GD]), and subacute thyroiditis (SAT). Although the biochemical, clinical, and sonographic features of DTDs are similar, their etiopathogeneses are different and need different managements. Ultrasound (US) can distinguish DTD (thyroiditis) from normal thyroid gland but it has a limited role in the characterization of the types of thyroiditis. Hence, more advanced radiological techniques have to be developed to give important useful information that are needed when planning management [2].

US elastography (USE) is an US technique used to evaluate the biomechanical features of tissue in the medical practice. USE has different types, the first type to be introduced was strain USE and it is dependent on the principle that, when compression is applied, the softer parts of tissues deform easier than the harder parts [3]. As the histopathologic and mechanical characteristics are different, it is possible to distinguish GD from HT and SAT by USE [4]. SAT is a self-limiting disorder that generally occurs due to an autoimmune response after upper tract infection that caused by a viral etiology [5]. In the early stage of SAT, inflamed tissues lose elasticity due to fibrotic changes and revealed significant abnormality on USE [6]. HT is the most common inflammatory condition of the thyroid gland and is the main cause of hypothyroidism [7]. The degree of the fibrotic changes of thyroid parenchyma is correlated with the increased hardness and stiffness in HT that can be evaluated by elastography [8]. Chronic non-specific thyroiditis is a non-suppurative thyroiditis of unidentified cause, both men and women may be affected in any age. It is an autoimmune disorder that is not fulfilling the criteria for diagnosis of HT and GD [9]. It is characterized by the rapid change in the texture of the gland with the development of fixed hard gland without signs of hyperthyroidism or hypothyroidism, although a goiter may be present.

Aim of study

This study aims to assess the role of US strain elastography in the diagnosis of diffuse non-nodular thyroid disease in comparison to healthy controls and in the characterization and distinguishing the types of DTDs from each other.

Patients and Methods

Study design and settings

It is a prospective analytic study that performed in the Radiology Department of Oncology Teaching Hospital/Medical city in Baghdad from December 1, 2019, to June 30, 2020.

Study population

Patients referred from the surgical or endocrine outpatient clinics to the Radiology Department of Oncology Teaching Hospital with suspected thyroid gland disease and were compared with standard healthy control group with normal thyroid gland on US and normal thyroid function test.

Inclusion criteria

Patients with non-nodular DTD with or without symptoms of hypothyroidism or hyperthyroidism were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients with a previous history of thyroid surgery
2. Patients who received neck radiation therapy
3. Pregnant women
4. Patient received medication as part of management of DTD.

Sampling

The study sample included 25 patients with DTD presented to the Radiology Department of Oncology Teaching Hospital and selected according to the inclusion and exclusion criteria after their approval, in addition to a sample of 25 healthy controls for comparison.

Data collection

Clinical data were taken from patients and involved the followings.

1. Demographic characteristics of the patients: Age and gender
2. Hormonal laboratory results of patients with DTD: Euthyroid, hypothyroidism, and hyperthyroidism
3. Immunological investigation results of the patients with DTD
4. US findings of the patients (texture, echogenicity, AP diameter of thyroid gland, and vascularity)
5. Elastography findings (strain ratio).

Patients assessment

The diagnosis of DTD was made by combination of clinical symptoms, laboratory investigations, and thyroid US. The DTD was classified according to clinical symptoms, hormonal investigation (thyroid function test including T3, T4, and TSH), and immunological investigation (thyroid peroxidase antibody level) into GD, HT, and SAT. Patients with DTD that could not be classified into Graves, Hashimoto's, or SAT, according to their clinical and laboratory investigation, were considered to have non-specific thyroiditis. Fine-needle aspiration (FNA) cytology was performed for eight patients according to the physician request and to confirm the diagnosis in those patients. The FNA was done by a senior pathologist in the oncology teaching hospital, and the results were consistent with the classified type of DTD in those patients and confirmed it.

The thyroid US was performed by radiology specialist using GE healthcare machine 2019 LOGIQ S8 XDclear with linear probe (Matrix Probe ML6-15-RD). The parameters on B-mode US were included: Thyroid parenchymal echogenicity (echogenicity was classified into hypoechoic, isoechoic, or hyperechoic as compared with adjacent strap muscles), texture (homogenous or heterogeneous), vascularity of the thyroid parenchyma which was classified into normal, hypervascular and markedly hypervascular (thyroid inferno), the vascularity was classified in comparison with normal thyroid gland vascularity in control group. Thyroid size (which is calculated by the formula of thyroid lobe volume: Length × width × depth in cm × 0.5) excluding the isthmus. The volume of thyroid gland was the sum of the volume of both lobes. The size was classified into enlarged, normal and small size "atrophic" according to the normal range of thyroid volume (8–20 ml). Then, strain elastography was performed by putting the elastography square box on the thyroid gland including most of the thyroid tissue with the ipsilateral muscles within the box. Very gentle compression was applied on the thyroid tissue while asking the patients to hold breath and swallowing during elastography procedure to avoid artifact and misinterpretation. The optimal compression was achieved when the vertical bar on the upper left side of the image was filled with the green color. Method of measurement of strain ratio is demonstrated in Figure 1.

The five colors grading in elastography was not assessed in this study as it has limited role in DTD, in contrast to thyroid nodule, but the semi-quantitative measurements were obtained. Two regions of interest

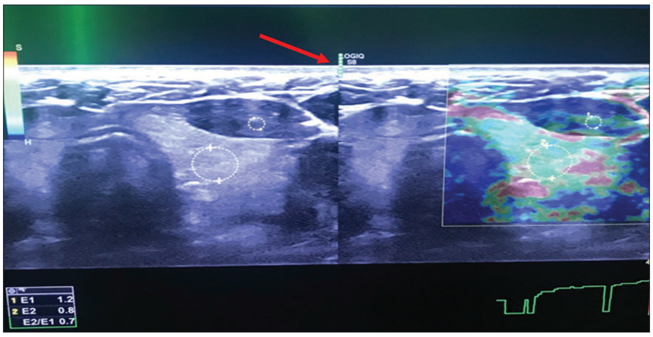

Figure 1: Method of measuring SR in control subject with normal thyroid gland in B-mode ultrasound (US) and normal thyroid function test. Two ROIs were selected to calculate the strain ratio, one circle is on the strap muscle and the 2nd circle (2nd ROI) on the ipsilateral thyroid tissue. US strain elastography ratio was 0.7. Note that the vertical bar is filled with the green color in the upper left side of the image (red arrow)

were taken; one on the adjacent strap muscle as standard reference and the other on the abnormal thyroid tissue then the US machine calculates the strain ratio automatically. The above-mentioned parameters in B-mode US and elastography were assessed and registered in both patients with DTD and control group.

Ethical considerations

1. The approval was taken from Radiology Scientific Committee of Baghdad Medical College
2. A written informed consent was taken from all patients.

Statistical analysis

All patients' data are tabulated using computerized statistical software; that is, Statistical Package for the Social Sciences version 20. Descriptive statistics obtained as mean ± standard deviation and the frequencies presented as percentages. Comparison between categorical variables was performed using Chi-square test (and Fisher's exact test was performed when the total of predictable variables being <20% of the total). Comparison between two means was done by independent sample t-test and comparison between more than 2 means was done by one-way ANOVA analysis. Receiver operating characteristic (ROC) curve was used to predict the appropriate cutoff value and the best validity of different strain ratios in prediction of DTD. The level of significance (i.e., p-value) established at ≤0.05 in all the statistical analysis, and the result was presented as tables and/or graphs. A community medicine specialist had done the statistical analysis of the study.

Results

Demographic data of the patients

This study included 25 patients with DTD presented with the mean age of 42.1 ± 12.3 years; most of the patients (32%) were in the age group of 40–49 years, other age groups are shown in Figure 2.

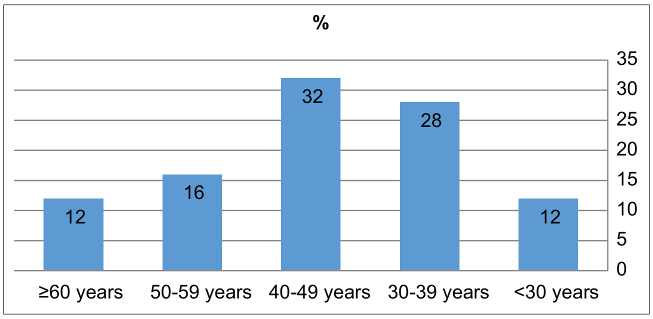

Figure 2: Distribution of patients with diffuse thyroid disease according to their age groups

Regarding gender, female gender patients with DTD were more than male gender patients with female-to-male ratio as 5.2:1. These findings are demonstrated in Figure 3.

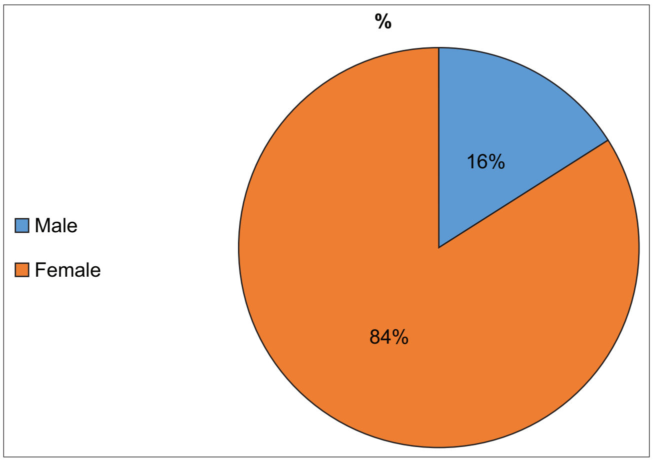

Figure 3: Gender distribution of patients with diffuse thyroid disease

The hormonal status and the types of DTD

The hormonal status of patients with DTD in this study was classified into euthyroid (12%), hypothyroidism (40%), and hyperthyroidism (48%).

The classification of patients with DTD, which was based on clinical history, hormonal and immunological investigation followed by FNA for eight patients, showed that 44% of them had HT, 44% of them had GD, 8% of them had non-specific thyroidism and 4% of them had SAT.

B-mode US characteristics of DTD

The US examination revealed that 92% of patients with DTD had heterogeneous parenchymal texture, while 8% of them had homogenous texture. Hypoechoic thyroid parenchyma was detected for 84% of patients with DTD and 16% had hyperechoic parenchyma. Regarding the size of thyroid gland, 52% of patients with DTD had enlarged gland, 36% had normal sized gland, and 12% had atrophic gland. Regarding vascularity, 16% of DTD patients had normal vascularity, 72% of them had hypervascularity, and 12% of them had marked hypervascularity (thyroid inferno). The mean elastography strain ratio of patients with DTD was 1.3 ± 0.6. All these findings are illustrated in Table 1.

Table 1: B-mode US characteristics of patients with DTD

US parameters	N	%
Texture		
Heterogeneous	23	92.0
Homogenous	2	8.0
Total	25	100.0
Echogenicity		
Hypoechoic	21	84.0
Hyperechoic	4	16.0
Total	25	100.0
Size		
Enlarged	13	52.0
Normal	9	36.0
Small	3	12.0
Total	25	100.0
Vascularity		
Normal	4	16.0
Hypervascular	18	72.0
Markedly hypervascular	3	12.0
Total	25	100.0

Elastography strain ratio mean±SD (1.3±0.6), US: Ultrasound, DTD: Diffuse thyroid disease.

Highly significant association was observed between heterogeneous thyroid texture and patients with DTD (p < 0.001); 92% of patients with DTD had heterogeneous parenchymal texture, while no healthy control had heterogeneous thyroid texture. All these findings are demonstrated in Table 2.

Table 2: Distribution of thyroid parenchymal texture on B-mode US according to study groups

Variable	DTD cases		Controls		p
	N	%	N	%	
Thyroid texture on B-mode US					
Heterogeneous	23	92.0	0	–	<0.001*S
Homogenous	2	8.0	25	100.0	

US: Ultrasound, DTD: Diffuse thyroid disease.

The elastography strain ratio

Elastography strain ratio according to the study groups

The mean elastography strain ratio (1.36) of patients with DTD was significantly higher than (0.82) mean of elastography strain ratio for healthy controls (p < 0.001). All these findings are illustrated in Table 3.

The acceptable cutoff values and the equivalent validity results for elastography strain ratio in the estimation of DTD are demonstrated in Table 4, the

Table 3: Distribution of elastography strain ratio according to study groups

Variable	DTD cases	Controls	p
	Mean ± SD	Mean ± SD	
Elastography strain ratio	1.3 ± 0.6	0.82 ± 0.13	<0.001*S

*Independent sample t-test, S: Significant, DTD: Diffuse thyroid disease.

cutoff elastography strain ratio of 0.89 had acceptable validity results (80% sensitivity, 70% specificity, 70.2% positive predictive value (PPV), 82.5% negative predictive value (NPV), and accuracy 75%).

Table 4: ROC coordinates for the prediction of DTD by elastography strain ratio

Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
0.77	90	43.3	42.8	83.4	66
0.89	80	72	70.2	82.5	75
1.01	66.7	86.7	88.8	63	70.2

DTD: Diffuse thyroid disease, NPV: Negative predictive value, PPV: Positive predictive value.

Elastography strain ratio according to the types of DTD

The mean elastography strain ratio was significantly increased among patients with SAT (increased tissue stiffness), while significantly lower among patients with non-specific thyroiditis (p < 0.001), as demonstrated in Table 5.

Table 5: Distribution of elastography strain ratio for patients with DTD according to the types of DTD

Variable	Non-specific T.	HT	GD	SAT	p
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Elastography strain ratio	0.9 ± 0.4	1.47 ± 0.4	0.98 ± 0.2	3.5 ± 0.0	<0.001*S

*One-way ANOVA analysis, S: Significant, HT: Hashimoto's thyroiditis, SAT: Subacute thyroiditis, GD: Graves' disease.

As shown in Table 6, the mean elastography strain ratio for patients with HT was significantly higher than strain ratio of patients with GD (p = 0.002) (HT reduced elasticity and increased stiffness of thyroid tissue greatly more than GD).

Table 6: Distribution of elastography strain ratio for patients with HT and GD

Variable	Hashimoto's T	GD	p
	Mean ± SD	Mean ± SD	
Elastography strain ratio	1.47 ± 0.4	0.98 ± 0.2	0.002*S

*Independent sample t-test, S: Significant, HT: Hashimoto's thyroiditis, GD: Graves' disease.

And so, differentiation between the types of the DTD was achieved using strain elastography while these types cannot be differentiated by B-mode US alone.

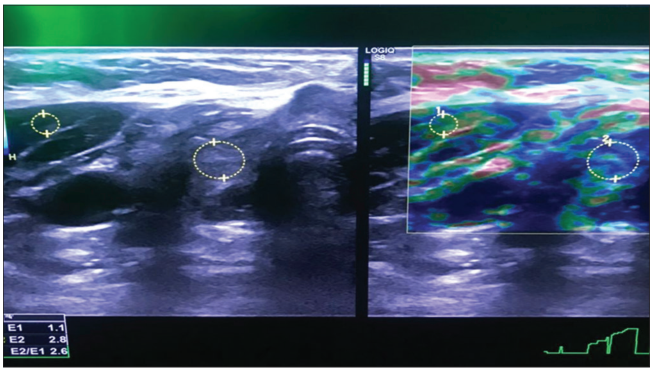

Figure 4: A 35-year-old female presented with symptoms of hypothyroidism and diagnosed with Hashimoto's thyroiditis according to hormonal and immunological investigation. B-mode ultrasound had showed heterogeneous hyperechoic thyroid parenchyma suggestive of diffuse thyroid disease. Strain elastography ratio was 2.6

Discussion

The USE is a common non-invasive imaging technique for the evaluation of thyroid dysfunction as it could be applied in the assessment of mechanical characteristics for elasticity of different tissues. Despite that, there are different pathological abnormalities that are accompanied with an appropriate elastography which are not detected till now [10]. In general, the benefits of USE in thyroid disease are proved [6].

The HT is the most common cause of goiter in Iraq [11]. This study is the first Iraqi study discussing the role of strain elastography in the evaluation and characterization of DTD. The present study revealed that mean elastography strain ratio was significantly higher in patients with DTD than the mean elastography strain ratio for healthy controls ($p < 0.001$) (i.e., all DTDs increased tissue stiffness as compared with healthy controls). These results are consistent with results of Yang *et al*. study in China which found that strain ratio of patients with diffuse thyroiditis was significantly higher than strain ratio of healthy controls [12]. Many authors reported the importance of USE in the evaluation of DTDs [13], [14].

In Turkey, Menzilcioglu *et al*. study on 31 randomized patients showed that strain elastography ratio was dependable findings and patients with HT had mean ratio of 1.39 + 0.72 while strain ratio of healthy controls was 0.76 + 0.55 [15]. The US strain elastography was shown a great role in detecting alterations in the viscoelasticity by recording the degree of stiffness of thyroid parenchyma [12]. In addition, the US of tissue textures is analyzed before and after compression of the tissues and difference between the two signals refers to the strain value [12]. The fibrosis and lymphocytic infiltration of thyroid gland of DTD increase the stiffness and hardness of the thyroid tissue [16].

Our study showed that acceptable cutoff elastography strain ratio was 0.89 with validity results (80% sensitivity, 70% specificity, and 75% accuracy) in the characterization of DTD. These results are similar to the results of Çekiç *et al*. study in Turkey which found that appropriate cutoff value for strain ratio in differentiation between patients with HT than healthy controls was 0.98 with validity findings (83% sensitivity, 93% specificity, and 84% accuracy) [17].

The present study revealed a highly significant association between heterogeneous thyroid texture and patients with diffuse thyroiditis ($p < 0.001$). This finding is similar to the results of many previous literatures which stated that heterogeneous texture of thyroid gland is accompanying mostly the DTD mainly HT and GD [18], [19], [20], [21]. However, Park *et al*. study in South Korea found that the heterogeneity of the thyroid gland is always responsible for reducing the specificity and accuracy of US in differentiation between malignant and benign thyroid nodules in DTD [22]. Despite this finding, abnormal US appearance of thyroid gland is useful in diagnosis of diffuse thyroid disorders in asymptomatic persons [23], [24] and also helpful in the early detection and diagnosis of subclinical to overt hypothyroidism in combination with thyroid antibodies [25], [26]. Moreover, the US of thyroid gland is important in the prediction of treatment outcomes for patients with subclinical hypothyroidism [26].

In the present study, the mean elastography strain ratio was significantly high among patients with SAT which is explained by the fibrotic changes that markedly increased the stiffness of the gland tissue, while the strain ratio was significantly lower among patients with non-specific thyroiditis ($p < 0.001$). These results are in agreement with the results of Korkmaz *et al*. study in Turkey on 24 patients with GD, 94 patients with HT, 20 patients with SAT, and 82 healthy controls and found that the mean elastography strain ratio was significantly higher in patients with SAT than the mean elastography strain ratio of patients with GD, HT, and healthy controls [2]. Another study carried out in Poland by Ruchala *et al*. revealed that the sonoelastography is useful in the diagnosis and monitoring of SAT in addition to the differentiation between the variable types of diffuse thyroiditis [6]. The elastography is known as an electronic palpation for thyroid gland that is required in differentiation between different types of thyroid diseases depending on strain ratio and shear wave elastography [27].

In the current study, the mean elastography strain ratio for patients with HT was significantly higher than the strain elastography ratio of patients with GD ($p = 0.002$). These results coincide with the results of many previous literatures such as Menzilcioglu *et al*. [28] study in Turkey and Yang *et al*. [12] study in China which found that the mean elastography strain ratio for HT was higher than the strain ratio of GD. In Italy, Cantisani *et al*. [29] study reported that the elastography strain ratio had an interesting role in the differentiation between HT and GD as the strain ratio was higher among patients with HT. Both HT and GD are autoimmune diseases of thyroid gland. The differentiation between both diseases might be somewhat difficult by clinical and laboratory findings [30]. The present study revealed that the B-mode US can detect DTD but cannot differentiate its types of in most patients due to the similarity in US parameters for all types of DTD. A current study conducted by Pishdad *et al*. in Iran [31] found that US examination had low sensitivity in the differentiation between HT and GD due to the marked similarity in the sonographic appearance and needed the elastography for increasing effectiveness of differentiation particularly by shear wave elastography, strain ratio, and acoustic radiation force impulse [32].

Conclusions

- The USE is a non-invasive imaging technique that is useful in the evaluation and characterization of DTD by the assessment of the changes in the tissue elasticity/stiffness caused by different types of DTD as compared with normal subjects (non-specific thyroiditis and HT reducing the tissue elasticity/increase stiffness significantly more than GD and SAT)
- The USE strain ratio value is helpful in the evaluation of DTDs with acceptable validity findings
- The USE strain ratio value is helpful in differentiation between the different DTDs, especially between HT and GD.

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