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*Original Article*

# Application of real-time elastography in evaluation of hashimoto thyroiditis progression

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**Abstract:** This study aimed to assessment of Hashimoto thyroiditis (HT) progression by real-time elastography (RTE). RTE showed that eight out of 12 parameters had a significant difference between healthy controls and HT patients (all $P<0.05$). HT in hyperthyroidism, euthyroidism, or hypothyroidism group had a significantly increase in the ratio of the blue area (% Area) and elastic index (EI) compared with those of the control group (all $P<0.05$). Besides, the % Area and the EI positively correlated with the thyroid function of HT patients ($r=0.851$, $P<0.05$ for % Area and $r=0.865$, $P<0.05$ for elastic index). The cut-off point of the diagnostic accuracy of EI in determining the stage of hyperthyroidism, hypothyroidism was 1.37, 1.62, respectively, and the area under ROC (AUC) was 0.859 with a sensitivity of 80.8% and specificity of 81.0%, 0.871 with a sensitivity of 82.0% and specificity of 83.0%, respectively.

**Keywords:** Hashimoto thyroiditis, chronic lymphocytic thyroiditis, real-time elastography

## Introduction

Hashimoto thyroiditis (HT) is one of the most common autoimmune diseases characterized as high titers of circulating antibodies to thyroid peroxidase and thyroglobulin [1]. The typical microscopic changes of Hashimoto thyroiditis include lymphoplasmacytic infiltration and fibrosis [1]. The gland undergoes progressive loss of thyroid follicular cells, which gradually progresses to the stage of hypothyroidism [2]. Growing evidence has suggested that unrecognized hypothyroidism is deleterious, and early diagnosis of HT could be advantageous in predicting thyroid failure due to massive thyroid tissue damage [3].

Under traditional sonography, the thyroid gland of HT patients usually shows diffusely enlarged gland with inhomogeneous echogenicity and a general decrease in echogenicity [4, 5]. Such examination is not capable in picking up the subtle signs of the disease [4, 5]. Therefore, fine-needle aspiration and cytology examination currently is recommended as the gold standard in determining the progression of HT. Studies have proposed several non-invasive methods in assessing the HT progression such as serum thyroid stimulating hormone (TSH) and real-time elastography (RTE) [5, 6]. Compared with traditional transient elastography, RTE is a relatively new method of in tissue elasticity measurement [6]. Many clinical researches have suggested that RTE could reach a high accuracy in the diagnosis of superficial and focal solid tissue lesion such as breast tumors, thyroid tumors and prostate tumors [6, 7]. Recently, Kanamoto et al. [8] and Wang J et al. [9] examined the application value of RTE in the evaluation of liver fibrosis recognized as a diffused liver pathological change, and concluded that RTE is a newly-developed but promising sonography-based noninvasive method in evaluating diffused liver fibrosis. Since HT is another diseases with diffused pathological lesions once HT progresses, the application of RTE in the assessment of HT progression could be valuable. However, this has been rarely studied and reported by others. The purpose of this study is to investigate the clinical application of the RTE as a novel quantitative technology in assessing the progression of HT.

## Materials and methods

### *Patients*

A total of HT 118 patients (12 males and 106 females with an average age of 39.5±11.5 years old) were recruited as HT group in the current study. Patients received diagnosis and treatment from October 2012 to July 2013 in the Affiliated Hospital of Qingdao University. These patients were diagnosed as HT based on their clinical symptoms, laboratory data and sonographic image. Fifty healthy controls including 5 males and 45 females with an average age of 36.7±10.5 years old were also enrolled. These controls had no reported thyroid diseases when they were recruited in the current study. According to the thyroid function tests, these 118 HT patients were further divided into three groups: (1) hyperthyroidism group (n=29), (2) euthyroidism group (n=38) and (3) hypothyroidism group (n=51).

The research protocol was approved by the ethics committee of the Affiliated Hospital of Qingdao University. Written informed consent was obtained from each patient.

### *Real-time elastography (RTE)*

RTE was performed using Hivision Preirus system (Hitachi Medical Corporation 4-14-1, Sotokanda, Chiyoda-ku, Tokyo, 101-0021, Japan) with a linear probe (EUP-L52; central frequency 5.5 MHz). The US pattern of the thyroid parenchyma was recorded for each scan. All scans were performed by an operator with more than 5 years of experience in thyroid imaging. After the examination in B-mode, the mode was switched to elastography. The probe was placed on the neck and scanned vertically from the thyroid to observe a longitudinal section of the right thyroid lobe. An identical area where the thyroid tissue was free of large blood vessels was set as the region of interest (ROI) for all subjects. The colors in the ROI include red (soft tissue), blue (hard tissue) and green (intermediate, normal tissue). The device automatically captured the internal compressions transmitted to the thyroid parenchyma by the carotid pulsation. Numerical strain values for the pixels were converted into a color image within the rectangle ranging from 0 (shown as red) at the minimal degree of stiffness to 255 (shown as blue) at the maximal degree of stiffness, and a histogram was then generated based on the data.

The model applying to the quantitative analysis of diffuse disease was chosen as a method of image measurement and analysis. Nine image features were extracted from each RTE scanning, including the mean of relative strain value (MEAN), standard deviation of the relative strain value (SD), ratio of the blue area in the analyzed region (% Area), complexity of the blue area (COMP), kurtosis of the strain histogram (KURT), skewness of the strain histogram (SKEW), entropy (ENT), inverse difference moment (IDM) and angular second moment (ASM). These above parameters reflect the tissue stiffness using RTE. Multiple regression analysis was then performed with these nine image features to quantify the elastic index (LF Index), according to the following formula: elastic index (LF Index) = -0.00897 × MEAN - 0.00502 × SD + 0.0232 × % AREA + 0.0253 × COMP + 0.775 × SKEW - 0.281 × KURT + 2.08 × ENT + 3.04 × IDM + 40.0 × ASM - 5.54 as reported before.

### *Blood test*

Blood biochemistry was performed at the enrollment including thyroid stimulating hormone (TSH), free triodothyronine (FT3), free thyroxine (FT4), antithyroid peroxidase (anti-TPO), antithyroglobulin (anti-Tg). The present study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional ethics board of the Affiliated Hospital of Qingdao University.

### *Statistical analysis*

All results were shown as mean ± SD. Spearman's test was used to analyze the correlation between elasticity parameters from RTE and different thyroid functional parameters. Statistical significance was defined as $P<0.05$. The diagnostic performance of the elasticity index was evaluated by receiver operating characteristic curves (ROC). The ROC curve represents sensitivity versus 1 minus the specificity for all possible cut off values. The areas under the ROC curve (AUCs) and 95% CIs of AUC were calculated by SPSS (16.0 version).

## Results

### *Clinical characteristics of HT patients and controls in this study*

HT patients of this study had an age ranged from 11 to 64 years old (39.5±11.5 years). 12

**Table 1.** Clinical characteristics of HT patients and controls in this study

| | Control group | Hyperthyroidism group | Euthyroidism group | Hypothyroidism group |
|---|---|---|---|---|
| Age (years) | 36.7±10.5 | 37.32±13.57 | 40.87±13.07 | 38.07±12.85 |
| Gender (male/female) | 5/45 | 3/26 | 4/34 | 5/51 |
| T4 (pmol/L) | 12.09±3.51 | 40.45±27.23** | 13.03±3.67 | 6.78±3.87** |
| TSH (uIU/Ml) | 5.35±10.06 | 0.55±1.57** | 6.13±16.64 | 27.26±39.91** |

**P<0.01 vs. control group.

**Table 2.** Twelve parameters used to evaluate the thyroid tissue stiffness and elasticity from RTE

| | Control group | Hyperthyroidism group | Euthyroidism group | Hypothyroidism group |
|---|---|---|---|---|
| AREA% | 3.23±1.07 | 7.23±3.92* | 11.87±2.53* | 18.78±4.12* |
| MEAN | 134.56±6.63 | 122.20±5.50* | 116.11±5.98* | 110.29±7.68* |
| SD | 38.02±3.63 | 41.68±5.93* | 45.48±3.84* | 50.37±5.41* |
| COMP | 23.73±8.31 | 20.72±3.63 | 23.61±4.22 | 25.25±4.29 |
| KUET | 2.91±0.27 | 2.62±0.19* | 2.61±0.18* | 2.54±0.25* |
| SKEW | 0.09±0.16 | 0.11±0.16* | 0.21±0.19* | 0.35±0.19* |
| CONT | 38.72±0.06 | 43.95±10.19* | 50.27±10.93* | 63.94±13.66* |
| ENT | 3.46±0.06 | 3.51±0.08* | 3.55±0.6* | 3.59±0.07* |
| IDM | 0.19±0.01 | 0.19±0.02 | 0.19±0.02 | 0.19±0.02 |
| ASM | 0.00±0.00 | 0.00±0.00 | 0.00±0.00 | 0.00±0.00 |
| CORR | 0.98 | 0.98 | 0.98 | 0.98 |
| Elastic index | 0.64±0.19 | 1.11±0.34* | 1.48±0.25* | 1.89±0.26* |

*P<0.05 vs. control group.

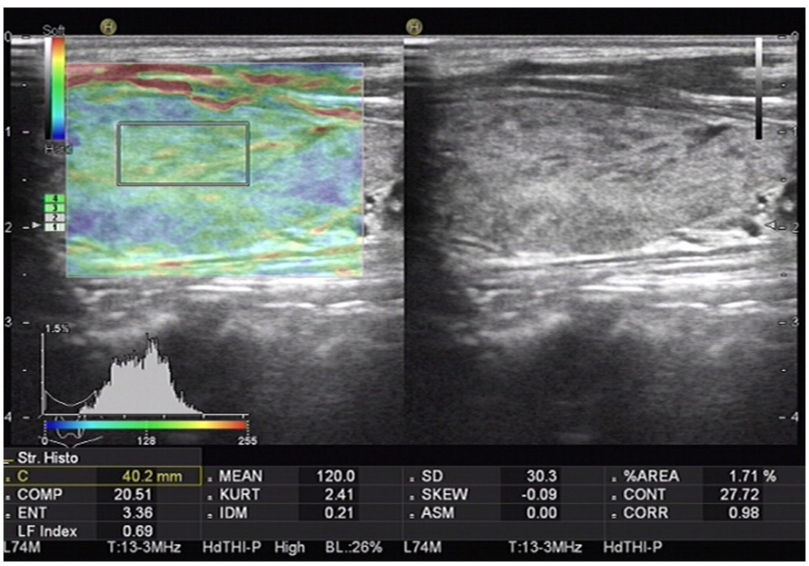


**Figure 1.** Eleven parameters and tissue elasticity distribution represented as color-coded images over conventional B-mode image.

of them are males and the remaining 106 are females. Symptoms of patients with HT were vague and non-specific. Detailed clinical characteristics of HT patients and controls are shown in **Table 1**.

*RTE analysis of thyroid elasticity in four groups*

Twelve parameters reflecting the thyroid tissue stiffness from B-mode images were analyzed and summarized in **Table 2**, with a representative image from one HT patients shown in **Figure 1**. The uniform green from B-mode images indicated a normal level of elasticity, while blue area suggested a gradually increase in elasticity. % Area was defined as the percentage of blue area in the analyzed thyroid tissue from a B-mode image. RTE showed that the blue area in the analyzed region (% AREA) were 3.23±1.07%, 7.23±3.92%, 11.87±2.53% and 18.78±4.12% in control, hyperthyroidism group, euthyroidism group and hypothyroidism group. The % Area in the latter three groups (HT groups) were significantly higher than that of the control group (all P<0.05) (**Table 2**). Besides, there was a significant correlation between the thyroid dysfunction (hypothyroidism) and % Area of decreased elasticity (r=0.851, P=0.001). Further, except the 4 out of the remaining 11 elasticity parameters including COMP, IDM, ASM and CORR, HT

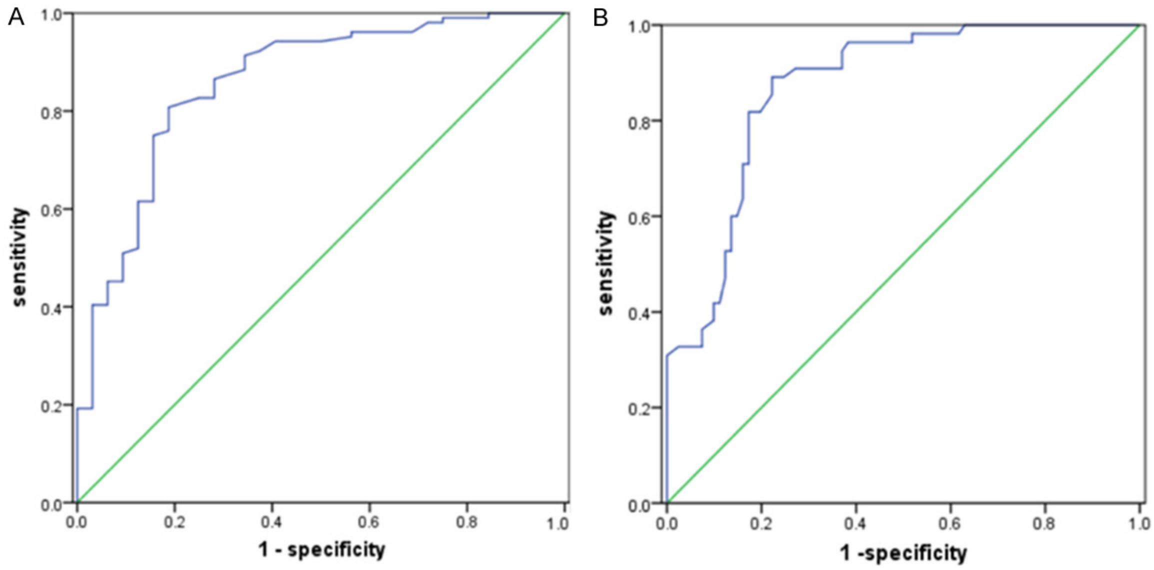


**Figure 2.** Receiver operating characteristic curves (ROC) and area under the ROC curve (AUC) of the curve for real-time elastography (RTE) in assessment of hyperthyroidism (A) and hypothyroidism (B).

patients had a significantly different levels of elasticity compared with those of healthy controls (all P<0.05 in all three HT groups vs. controls for the 7 parameters shown in **Table 2**). The decreased elasticity of thyroid tissue was associated with a gradual deterioration of thyroid function (**Table 2**).

In addition, elasticity index calculated based on the 12 elasticity parameters were 0.64±0.19, 1.11±0.34, 1.48±0.25 and 1.89±0.26 in control, hyperthyroidism, euthyroidism and hypothyroidism group (**Table 2**). Further, the elasticity also showed a significant correlation between elasticity indexes and clinical progression of thyroid function (r=0.865, P=0.001).

*Accuracy evaluation of RTE in the assessment of thyroid function of HT patients*

The cut-off point of elasticity index in accurately assess the phase of hyperthyroidism in HT patients was 1.37 and the area under ROC (AUC) was 0.859 with a sensitivity of 80.8% and a specificity of 81.0% (**Figure 2A**). The cut-off point of elasticity index in accurately assess the phase of hypothyroidism was 1.62 and the AUC was 0.871 with a sensitivity of 82.0% and a specificity of 83.0% (**Figure 2B**).

## Discussion

HT is an autoimmune thyroid disease that can induce goiter and/or thyroid dysfunction. HT usually progresses from euthyroid to hypothyroid in both children and adult patients [2, 10]. HT patients usually have diffuse goiter with hard consistency at palpation. As HT progresses, thyroid tissue of HT patients has diffusely decreased echogenicity, coupled with a varying extent of fibrosis on ultrasound [11]. Fine-needle aspiration and cytology examination are currently recommended as the golden standard to determine the clinical progression of Hashimoto thyroiditis. Thus, an invasive method has been needed for the HT severity evaluation and disease progression.

RTE combines the advantages of high frequency ultrasound have been used in evaluating the stiffness and elasticity of tissues other than thyroid [12]. Recently, elastography has been mainly applied in the differential diagnostics of thyroid nodular disease rather than HT which is characterized as a disease with diffused lesion [13-15]. So far, little has been known about the value of sonoelastographic image in the assessment of diffuse thyroid diseases.

Transient elastography was recently developed for the noninvasive evaluation of liver elasticity, and was further reported as a useful, new and promising sonography-based noninvasive method for the assessment of liver fibrosis in patients with chronic viral hepatitis [8, 16]. Wang et al. reported that a new quantitative technology for diffuse histological lesion (HI VISION Preirus) had been successfully applied in the evaluation of liver tissue stiffness degree with 11 different parameters [9]. Further, they reported that there was a significant correlation between the elasticity index and the histological fibrosis degree with high accuracy.

In our study, we applied this new quantitative technology to the evaluation of clinical progression of HT, another disease with diffused lesion. We found a significantly increased area with less elasticity of thyroid tissue in HT patients which further correlated with the thyroid function. As the disease progresses, thyroid tissue has an increased lymphoplasmacytic infiltration and stromal fibrosis, which ultimately leads to the increased stiffness of thyroid and then thyroid failure. In the study carried out by Ruchala et al. [17], they applied this new quantitative technology sonoelastography in acute thyroiditis, sub-acute thyroiditis, and chronic autoimmune thyroiditis, and further proposed such technology as a useful way in differentiating various types of thyroiditis.

There were some limitations in this study. First, the number of patients recruited in this study was relatively small. A larger scale study was needed. Secondly, this study demonstrated a general difference of thyroid function of HT patients using elastographic images. Hence, a further detailed description of RTE images and its correlation with drug treatment would be an interesting topic to be studied.

## Conclusion

Data from current study showed that RTE with a new quantitative methodology for diffused pathological lesion of thyroid is a useful way to evaluate thyroid elasticity. Elastic indexes from RTE also associated with thyroid function. Therefore, RTE could be a useful method in differentiating thyroid functional stage and monitoring thyroid function in HT patients.

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## Disclosure of conflict of interest

None.

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