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Original Article

Acoustic Radiation Force Impulse Elastography Findings of Achilles Tendon in Patients with Hypothyroidism

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ABSTRACT

Background The aim of our study was to investigate the effect of thyroid dysfunction on tendons and the contribution of Acoustic Radiation Force Impulse (ARFI) elastography to the diagnosis of tendinopathy.

Material and Methods Eighty Achilles tendons of 40 patients under levothyroxine treatment, who had previously known hypothyroidism but high serum thyroid stimulating hormone levels, and 80 Achilles tendons of 40 healthy individuals were evaluated with ARFI (Virtual Touch Quantification®). 19 of 40 of the patients with hypothyroidism' Achilles tendons were re-evaluated after thyroid stimulating hormone levels reached to normal limits following the adjustments in thyroid hormone replacement therapy. The middle portion of the each Achilles tendon was chosen for the examination. Every examination consisted of three to five independent measurements (shear wave velocity - meters per second). The mean shear wave velocity value was calculated for each tendon, and used for statistical analysis.

Results The stiffness values of both left and right Achilles tendons, represented as shear wave velocity, were similar in patients with hypothyroidism and control group. There was no significant difference between the Achilles tendon shear wave velocity measurements of 19 of 40 hypothyroidism patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy.

Conclusions The lack of significant difference in Achilles tendon stiffness between non-naive hypothyroid patients and the control group may be explained as a positive clinical effect of thyroid hormone replacement therapy.

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Introduction

Thyroid hormones triiodothyronine (T3) and thyroxine (T4) play an important role in the development and regulation of many tissues and organs. As shown in in vitro studies on animals and both in vitro and in vivo studies on humans, thyroid hormones also structurally affect tendons.[1] However, there are very limited number of clinical studies and data on the effect of thyroid dysfunction in hypothyroidism on connective tissue.[1,2,3] Tendinitis can be the first complaint in hypothyroidism and symptomatic relief can be provided with the appropriate treatment of primary thyroid deficiency.[2,3]

Achilles tendon, which comprises the tendinous components of gastrocnemius and soleus muscles, is the strongest, largest and thickest tendon in the human body.[4] Achilles tendon injuries are common among both athletes and general population due to sports-related trauma and excessive use.[5] In order to prevent achilles tendon rupture and tendon injury from becoming chronic, early diagnosis and treatment of tendinopathy is important. While conventional B-mode ultrasonography (US) detects tendon rupture with a high rate of accuracy, its value in the diagnosis of tendinopathy is controversial.[5-7] Unlike classical US, elastography, which has come to use in the recent years, enables the assessment of tissue stiffness. There are studies with the ultrasonographic and elastographic findings of achilles tendon in normal population, the elderly, professional athletes, end-stage renal disease patients, long-term hemodialysis patients, secondary hyperparathyroidism, and smokers.[5,8,9]

With the initial elastographic methods, tissue stiffness was evaluated subjectively using a color scale. Acoustic radiation force impulse (ARFI) imaging is an elastography technique that provides an objective numerical assessment of tissue stiffness differently from the other elastography techniques. It provides an estimate of tissue elasticity by measuring the propagation of shear waves emitted during induced tissue displacements. The speed of the shear waves can be measured as shear wave velocity (SWH) and it is expressed quantitatively in meters per second (m/s). Stiffer tissues are associated with a higher SWV.[10] The benefits and usefulness of ARFI imaging has been shown in many clinical conditions. There have been a small number of studies on the evaluation of achilles tendon in different patient groups using ARFI elastography. In these studies, it has been shown that there is softening in Achilles tendon with age, in patients with intermittent claudication, diabetes patients, and chronic kidney disease patients.[8,11-13] To our knowledge, there are no studies in the literature on ARFI elastography findings of the Achilles tendon in hypothyroidism patients.

The aim of this study was to investigate the effect of thyroid dysfunction on tendons and the contribution of ARFI elastography to the diagnosis of tendinopathy by comparing ARFI elastography findings of the Achilles tendon in hypothyroidism patients and normal individuals.

Material and Methods

Study Population

This prospective study was conducted in the Radiology and Endocrinology department of Baskent University Ankara Hospital, and approved by the medical ethics committee. Informed consent was obtained from all subjects, according to the Edinburgh (2000) revision of the World Medical Association Declaration of Helsinki.

The participants of the patient group were selected from Endocrinology outpatient clinics. Forty patients under levothyroxine treatment, who had previously known hypothyroidism but high serum thyroid stimulating hormone (TSH) levels, were included in this study. Eighty Achilles tendons of 40 patients with non-naive hypothyroidism were evaluated with ARFI. Nineteen of these patients' Achilles tendons were re-evaluated after TSH values reached to normal limits following the adjustments in thyroid hormone replacement therapy. For the control group, 40 age- and gender-matched healthy individuals from the check-up outpatient clinics were included, and 80 Achilles tendons of the volunteers were evaluated. All participants were asymptomatic, and none had any past operations or history of trauma affecting the Achilles tendons or cruris muscles. None of the individuals had a history of systemic or another endocrinological disease, surgery, intensive exercise, peripheral artery disease or chronic drug use that could be associated with tendinopathy. All patients' clinical records, including their age, sex, TSH ve free T4 (fT4) levels were recorded.

Imaging technique

Ultrasonographic studies were performed using a 9–14-MHz linear transducer (Acuson S2000, Siemens Healthcare, Erlangen, Germany) and adequate software for performing elastographic examinations in quantitative ARFI mode (Virtual Touch Quantification®, VTQ). All examinations were performed by the same radiologist with 14 years of experience in US and 6 years of experience in elastography. Each Achilles tendon was examined in axial and longitudinal planes in the prone position with the foot hanging over the examination bed in a relaxed position.[9] The middle portion of the Achilles tendon, which is nearly 2 to 6 cm proximal to the calcaneus insertion, was chosen for the examination. ARFI (VTQ) mode was performed on the longitudinal plane of Achilles tendon, and the probe was held perpendicular to the tendon to avoid anisotropy. The transducer was gently applied without pressure, together with a sufficient amount of contact gel. Because of the superficial localization of the Achilles tendon, more ultrasonic coupling gel was used. A fixed size of 5×6 mm region of interest (ROI) was used. Every examination consisted of three to five independent ARFI measurements (SWV - meters per second). The mean SWV value of the three to five SWV measurements was calculated for each tendon, and used for statistical analysis.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, Version 23.0 (SPSS, Chicago, IL, USA). Continuous data were presented as mean±standard deviation or median (minimum–maximum) as appropriate. The level of significance was determined using t-test for values with normal distribution and the Mann–Whitney test for values with non-normal distribution. Categorical variables were compared using Chi-squared test. One-way repeated measures ANOVA was conducted to determine whether there were any statistically significant differences between ARFI measurements of patients in hypothyroid and euthyroid states. P value of <0.05 was considered statistically significant.

Results

Forty hypothyroidism patients and 40 age- and gender-matched healthy controls were included. Table 1 demonstrates the demographic and biochemical characteristics of hypothyroidism group and control group. There was no significant difference between the groups in terms of age and gender. As expected, TSH and sT4 levels were significantly high and low, respectively, in the patient group compared with control group.

Table 1. The demographic and biochemical characteristics of hypothyroidism group and control group

	Patient Group* (n=40)	Control Group (n=40)	P value
Age (year)	47.2±14.0	48.5±9.9	0.053
Sex (F/M)	33 / 7	32 / 8	0.075
TSH levels (mU/L) ¥	21.0 (6.5-372.0)	1.6 (0.6-3.1)	<0.0001
fT4 levels (ng/dL)	0.7±0.3	0.9±0.2	0.005

*Group of patients with hypothyroidism, ¥ median (minimum-maximum)
Normal range fT4: 0.7-1.48 ng/dL, TSH: 0.35-4.94 mU/L

Table 2. The shear wave velocity (SWV) measurements of Achilles tendon in patients with hypothyroidism and control group

	Patient group * (n=40)	Control group (n=40)	P value
Right Achilles tendon (m/s)	5.07±1.14	5.36±1.11	0.245
Left Achilles tendon (m/s)	5.09±1.16	5.21±1.11	0.662

*Group of patients with hypothyroidism

Table 3. Achilles tendon shear wave velocity (SWV) measurements of 19 of 40 patients with hypothyroidism, which were obtained before- and after- the adjustments in thyroid hormone replacement therapy

	Before*	After**	P value
Right Achilles tendon (m/s)	5.14±1.45	4.7±1.37	0.269
Left Achilles tendon (m/s)	5.34±1.36	4.7±1.17	0.097

*before-, and **after- the adjustments in thyroid hormone replacement therapy

Table 2 shows the SWV measurements of both left and right Achilles tendon in the groups. The stiffness values of both left and right Achilles tendons, represented as SWV, were similar in patients with hypothyroidism and control group *(Table 2)*.

There was no significant difference between the Achilles tendon SWV measurements of 19 of 40 hypothyroidism patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy *(Table 3, Figure 1)*. The mean duration of re-evaluation of these patients after therapy adjustment was a mean of 2.6±1.2 months. TSH levels of these 19 patients before- and after- the adjustments in thyroid hormone replacement therapy were 58.7±1.32 mU/L, and 1.5±1.23 mU/L, respectively.

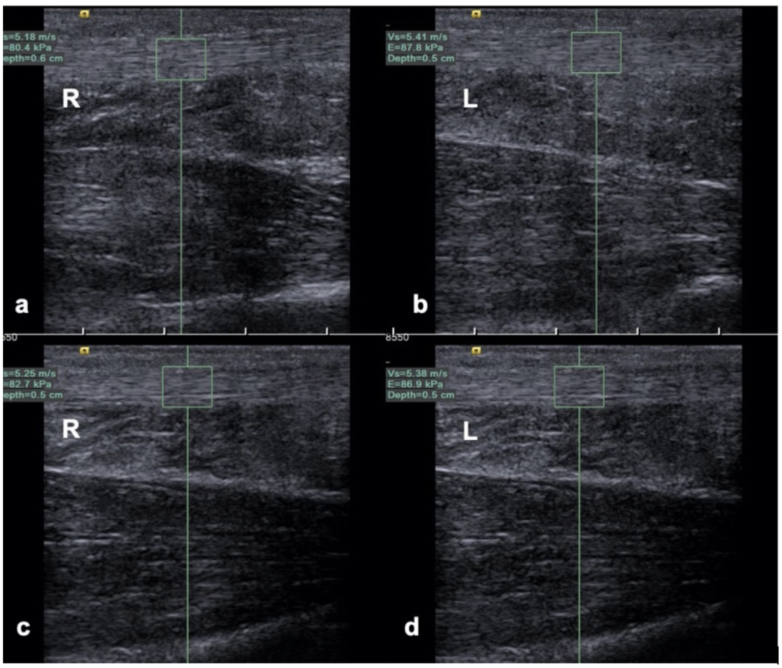

Figure 1. Shear wave velocity (SWV) measurements in the right (a, c) and left (b, d) Achilles tendon of a 42 years old female with hypothyroidism, before (a, b) and after (c, d) the thyroid hormone replacement. The SWV of the tendons were measured with fixed measurement sample dimensions of 5x6 mm. In this patient, the mean SWV of the right and left Achilles tendons were calculated 5.94 m/sn, 5.14 m/sn before the theraphy, and 5.32 m/sn, 5.24 m/sn after the theraphy, respectively. R: right; L: left

Discussion

Our data indicate that there was no significant difference between non-naive hypothyroidism patients and healty individuals in terms of Achilles tendon stiffness. Moreover, there was no significant difference between patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy in terms of Achilles tendon stiffness. To the best of our knowledge, this is the first study that evaluates Achilles tendon stiffness using ARFI elastography in patients with and without hypothyroidism.

Elastography is a recently developed noninvasive method that allows for the assessment of tendon elasticity. Several studies confirmed that a normal Achilles tendon was more stiff than an abnormal tendon, as well as a tendon with tendinopathy and a ruptured tendon.[9,14] Klauser et al.[15] compared the elastography of cadaveric Achilles tendons to histological data and confirmed that elastography could predict signs of histopathologic degeneration in Achilles tendon disorders. Turan et al.[16] demonstrated that elastography was useful for evaluating tendon abnormalities in patients with ankylosing spondylitis. These and similar studies revealed that the elastic properties of the Achilles tendon might improve the diagnosis of early stages of tendon abnormalities. ARFI elastography is an elastography technique that allows for the attainment of numerical results, therefore enabling more clear and objective interpretation of the level of tissue stiffness. This technique has also been used to evaluate tendons, especially the Achilles tendon, which is the largest and thickest tendon in the human body. To our knowledge, there were only a few small scale studies on the elasticity of Achilles tendon using ARFI elastography. Iyidir et al.[13] demostrated that diabetic patients with neuropathy had a softer Achilles tendon while the elasticity of Achilles tendon measured using ARFI was similar in diabetic patients without neuropathy and healthy controls. Yılmaz et al.[11] showed that the elasticity of Achilles tendons decreased in patients with intermittent claudication. Karatekin et al.[17] demonstrated that there was a decrease in the elasticity value measured using ARFI of the repaired Achilles tendon compared to the non-injured side. Kural Rahatli et al.[12] reported that Achilles tendons in patients with chronic renal failure and patients receiving hemodialysis were softer than renal transplant patients and control group.

Different soft tissues and bone diseases have been associated with hormone imbalance due to the alteration of biological pathways and the loss of control of cellular homeostasis.[18] In addition, various biomechanical properties of the musculoskeletal system seem to be affected by hormonal diseases.[19] Thyroid hormones play an important role in cell growth and proliferation in a dose-dependent manner, and affect the structural setting of the tendons.[20,21] In vivo studies underlined that hypothyroidism leads to hypoxia and apoptosis, contributing to musculoskeletal problems in humans.[22,23] Thyroid symptomatology differs significantly across hypothyroidism spectrum. Restoration of euthyroidism is associated with the reversal of majority of thyroid symptomatology, improves the quality of life and reverses the impairments of cardiovascular, respiratory, and muscle functions at rest and during exercise.[24,25] Tendinitis can be the presenting complaint in hypothyroidism and symptomatic relief can be obtained by appropriate management of the primary thyroid deficiency.[2] Several authors have reported complete disappearance, while others have reported only a decrease in symptoms and signs.[3] Some studies indicated that the patient's symptoms commonly improved rapidly after levothyroxine was started, and the relief of the musculoskeletal complaints occurs 2 to 8 weeks after the initiation of replacement therapy.[2,22,26-29] Knopp et al.[2] concluded that, the dramatic improvement and complete resolution of the symptoms with thyroid replacement therapy after failure with all other medical treatments suggest that normal tendon healing is impaired in hypothyroidism. Unfortunately, to the best of our knowledge, there were no studies in the literature that evaluated tendinitis symptomatology and biochemical parameters of the patients with high serum TSH levels during thyroid hormone replacement therapy. In our study population, all patients had previously known hypothyroidism and all were under levothyroxine treatment. Positive clinical effect of levothyroxine treatment may explain the fact that there was no significant difference between the Achilles tendon stiffness of non-naive hypothyroidism patients and healthy individuals, and the absence of a significant difference in Achilles tendon stiffness between patients who were re-evaluated after adjustment of thyroid hormone replacement therapy in our study. Furthermore, the duration of hypothyroidism in our patients is not known. Hypothyroidism level and duration is important for the chronic connective tissue changes.[30] So as we do not know the duration of hypothyroidism state of these patients, it is hard to make a judgement that hypothyroidism do not effect tissue elasticity measured by ARFI elastography. The short duration of hypothyroidism in our patients may also explain these findings.

The major limitation of this study was the small sample size. In addition, while the study included patients with previously known hypothyroidism under levothyroxine treatment but with high serum TSH levels, patients with naive hypothyroidism were not included. Also, the duration of hypothyroidism of the non-naive patients which may be important for the chronic connective tissue changes, were not known. Another limitation was that a histological analysis was not performed. Since all our patients were asymptomatic, an invasive procedure like biopsy could not be performed. In addition, Achilles tendon was evaluated with ARFI, just the middle portion of the tendon was selected. Thus, the values did not represent the entire tendon. However, most abnormalities of the tendon occur in the middle third or proximal two-thirds.[14,31] The tendon has a highly anisotropic nature, which requires positioning the ultrasonic beam in a perfectly parallel or perpendicular direction with respect to the fibers. The anatomic position and angle in the proximal third of the Achilles tendon is complex, as it consists of interpenetration and rotation of fibers from the gastrocnemius and soleus muscles. It is relatively easy to achieve the requirements only in the middle portion of the tendon.[5]

In conclusion, there were no significant differences between non-naive hypothyroidism patients, healthy individuals and patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy in terms of the stiffness of Achilles tendon. These findings may be explained as a positive clinical effect of thyroid hormone replacement therapy. ARFI is a simple, non-invasive and objective method for the assesment of changes in Achilles tendon. This study is important in terms of being a pilot study on a subject that can be considered new for the literature. Further prospective studies with larger sample size, which also include naive clinically overt hypothyroidism patients, are needed to identify the causal relationship between the sonoelastographic changes in Achilles tendon and hypothyroidism. Besides prospective follow-up studies evaluating the effect of thyroid hormone replacements on sonoelastographic measurements in hypothyroid patients can be conducted to clarify the treatment effects on thyroid hormone levels and Achilles tendon elasticity measured by ARFI.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

All authors have contributed the conception and design, or analysis and interpretation of data, the drafting of the article or its critical review for important intellectual content. All authors read the final version of the manuscript. All authors have agreed with the content of the manuscript and approved the submission to the 'Turkish Journal of Internal Medicine'.

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