Original Article

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The role of ARFI elastography to evaluate microstructrual changes of patients with testicular microlithiasis

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Abstract

Background: Testicular microlithiasis (TML) is thought to cause microstructural changes in the parenchyma of the testis, but it is difficult to demonstrate this by ultrasonography. It may be possible to evaluate microstructural changes in the testis by Acoustic Radiation Force Impulse (ARFI) elastography, which measures tissue stiffness.

Purpose: To assess the tissue stiffness of testicles of children with TML and to compare them with the healthy control group.

Material and Methods: Between November 2015 and May 2016, 25 pediatric patients with TML and 24 healthy children were enrolled in the study (mean age for TML and control group 6.7 ± 3.17 and 7.9 ± 4.18 years, respectively). Testicular volumes and mean shear wave velocity (SWV) values were calculated and compared with each other in both groups.

Results: There was no significant difference in average testicular volumes between the TML group and the control group (1.14 cm^3, 1.21 cm^3, respectively; $P = 0.986$). Mean SWV of the testicles with TML and normal testicles with control group was 1.18 ± 0.22 cm/s and 0.88 ± 0.11 cm/s, respectively. The SWV of the testicles with TML was higher than the normal testicles and this was statistically significant ($P < 0.001$).

Conclusion: This study has shown that tissue stiffness in patients with TML is increased compared to the normal population. ARFI elastography helps the early detection of microstructural changes in TML and can be used for screening and follow-up.

Keywords
Acoustic Radiation Force Impulse (ARFI) elastography, children, testicular microlithiasis (TML)

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Introduction

Testicular microlithiasis (TML) is a rare, asymptomatic clinical condition that is first described by Doherty et al. as the presence of 1–3-mm uniform calcifications within the testis parenchyma (1). Its etiology remains unknown and it is diagnosed incidentally while performing scrotal ultrasonography (US) for any other reason.

Elastography is an US-based imaging modality used to evaluate tissue stiffness. There are many studies in the literature investigating how the normal elasticity range of different tissue types varies in different organs such as the liver (2), breast (3), rectum (4), lymph nodes (5), prostate (6), testis (7), thyroid (8), and kidney (9). Those studies have shown that elastography provides valuable information regarding the microstructural changes of those tissues by evaluating tissue stiffness (10). The liver and thyroid have also

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been shown to be effective for shear wave elastography (SWE) predicting the degree of fibrosis after damage (11). Two known elastography techniques are SWE and strain elastography. Strain elastography relies on mechanical compression of the examined tissue by the operator. Two methods of SWE are Acoustic Radiation Force Impulse (ARFI) and Supersonic Shear Imaging (SSI). ARFI elastography is a kind of SWE and evaluates the tissue elasticity quantitatively. ARFI elastography is a safe, fast, operator-independent method that is easy to apply. The ARFI method measures tissue stiffness in meters per second (m/s) and the SSI method measures tissue stiffness in kPa. With the use of ARFI, a vertical pressure is applied to the tissue through a short-duration, high-powered acoustic repulsive radiation force from the probe which makes it an operator-independent technique. This vertical pressure causes horizontal displacements in tissue that are called "shear waves." The Virtual Touch Quantification (VTQ) technique is based on measurement of these shear waves. It is superior to conventional strain elastography as the vertical pressure is acquired from the probe which makes it an operator-independent technique (12,13).

ARFI elastography is a new method of measuring tissue stiffness in testes. The extra-abdominal location of the testicles and the thinness of the surrounding tissues make it more ideal for ARFI elastography use (7). The aim of this study was to assess the tissue stiffness of testicles of children with TML and to compare them with the healthy control group.

Material and Methods

This prospective study was approved by our institutional ethics committee. We informed all the patients' parents and obtained written consent. All healthy children were informed about their families and participated voluntarily.

Twenty-eight pediatric patients with TML and 26 healthy children who applied to our clinic between November 2015 and May 2016 had ARFI elastography performed. The inclusion criteria for the patient group were followed up for TML; for this reason, the US was requested and the TML was detected incidentally in the US. Inclusion criteria for the control group were any diseases related to the testicles and no known systemic diseases. Exclusion criteria were similar for both groups: the presence of any heterogeneous appearance or mass in the testis, undescended testis, or presence of varicocele. The inclusion and exclusion criteria for both groups are shown on flow diagrams (Figs. 1 and 2). Three patients in the TML group and two healthy children were not included in the study because of undescended testes. Finally, 25 pediatric patients with TML (patient group) and 24 healthy children (control group) were included in the study. The mean age of the patient group was 6.7 ± 3.17 years (age range = 1–13 years) and the mean age of the control group was 7.9 ± 4.18 years (age range = 6 months–17 years). The demographic data of the study population are given in Table 1. Multiple and diffuse microlithiasis was present in all patients in the patient group (Fig. 3).

Gray-scale US and ARFI elastography were performed by a radiology resident with five years of US and ARFI elastography experience. During the

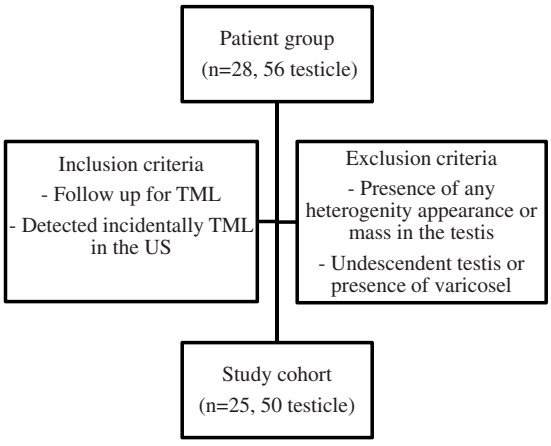

Fig. 1. Flow diagram in patient group.

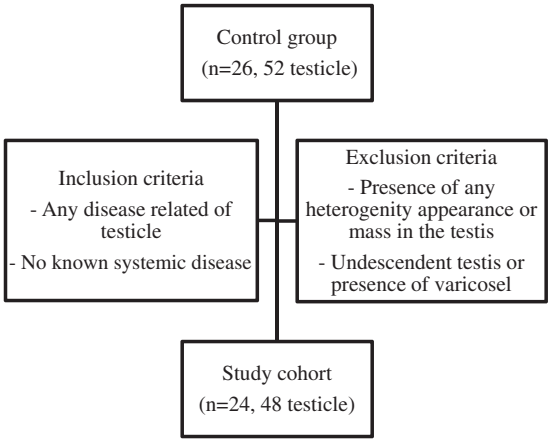

Fig. 2. Flow diagram in control group.

Table 1. Demographic data on the study population.

Group	Mean age ± SD (years)	Range
Patient group	7.9 ± 4.18	6 months–17 years
Control group	6.7 ± 3.17	1–13 years

SD, standard deviation.

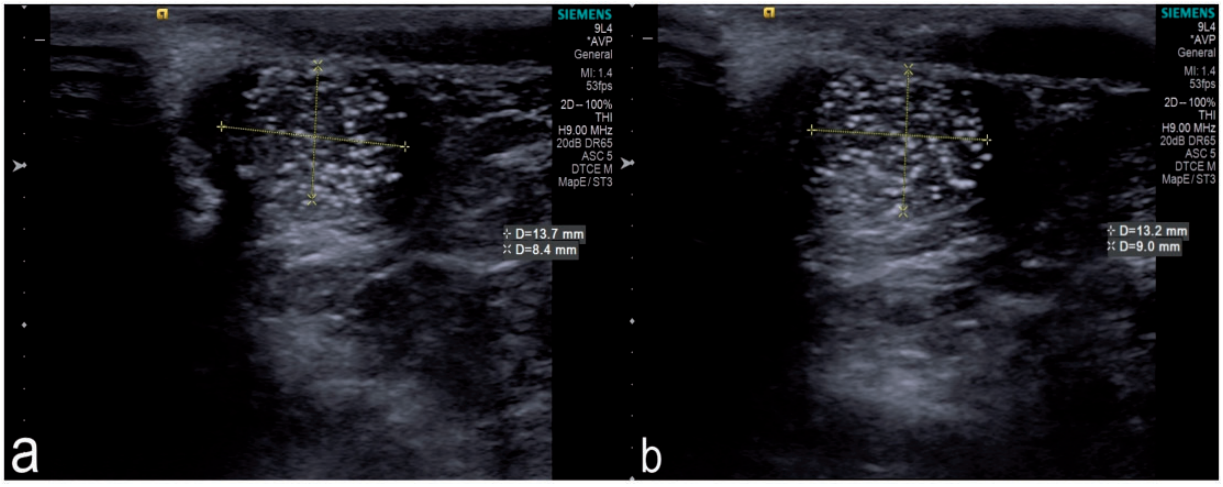

Fig. 3. Gray-scale US examination ((a) right, (b) left) shows that diffuse microlithiasis. All cases had diffuse microlithiasis.

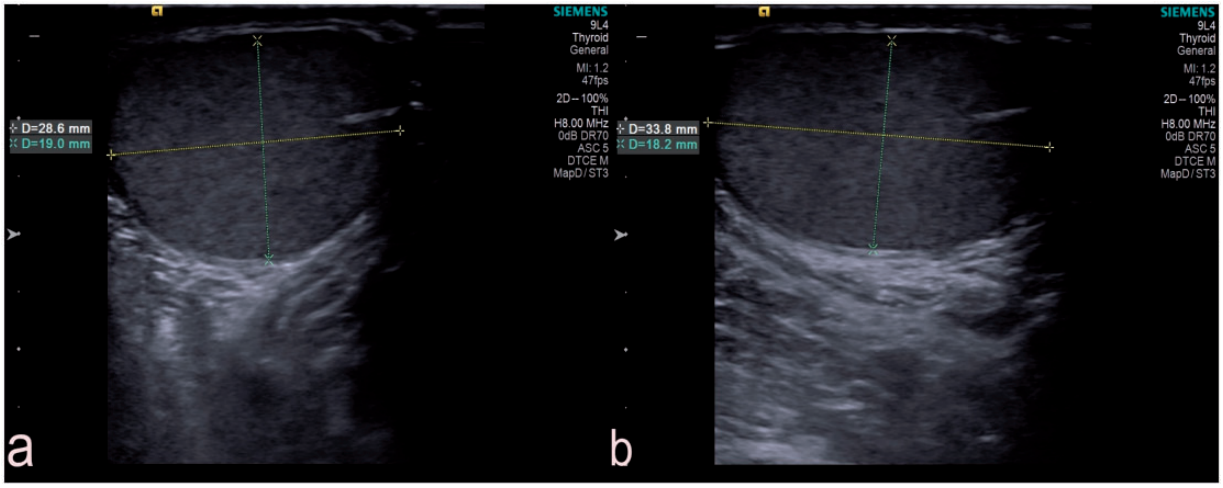

Fig. 4. Gray-scale US examination in case of the control group both testes ((a) right, (b) left) was normally observed.

gray-scale US and ARFI elastography, a pediatric radiologist with 13 years of US and five years of ARFI elastography experience monitored the examinations, thereby eliminating inter-observer variability. A Siemens Acuson S2000 (Mountain View, CA, USA) with a linear transducer (4–9 MHz) was used. All procedures were carried out with the patient in the supine position. First, B-mode examination of the testicles was performed (Figs. 3 and 4). Testis volumes were calculated using the length (cm) × width (cm) × depth (cm) × 0.523 formula. ARFI elastography measurements were performed with VTQ, a point SWE technique in which an acoustic force pulse is generated and detection pulses focused with ARFI VTQ are used for the calculation of shear wave speed. An adequate amount of gel was used during the SWE examination to avoid compression effect. A 6 × 5 mm ROI box was placed on the area where TML was seen (Fig. 5). For the healthy control group, the ROI box was placed randomly on the testis by carefully avoiding the vas deferens (Fig. 6). Five consecutive measurements were performed and tissue stiffness was expressed as shear wave velocity (SWV) in m/s (Figs. 5 and 6).

Previous studies with the pediatric group on this subject are not available in the literature. For this reason, the sampling interval was determined based on the study performed by Pedersen et al. (14). At 95% accuracy, the number of cases required to demonstrate the difference between the patient and control groups was calculated as at least 11 patients. Statistical analyses were performed with SPSS software, version 21 (IBM Corporation, Armonk, NY, USA). The data are expressed as the mean ± standard deviation (SD)

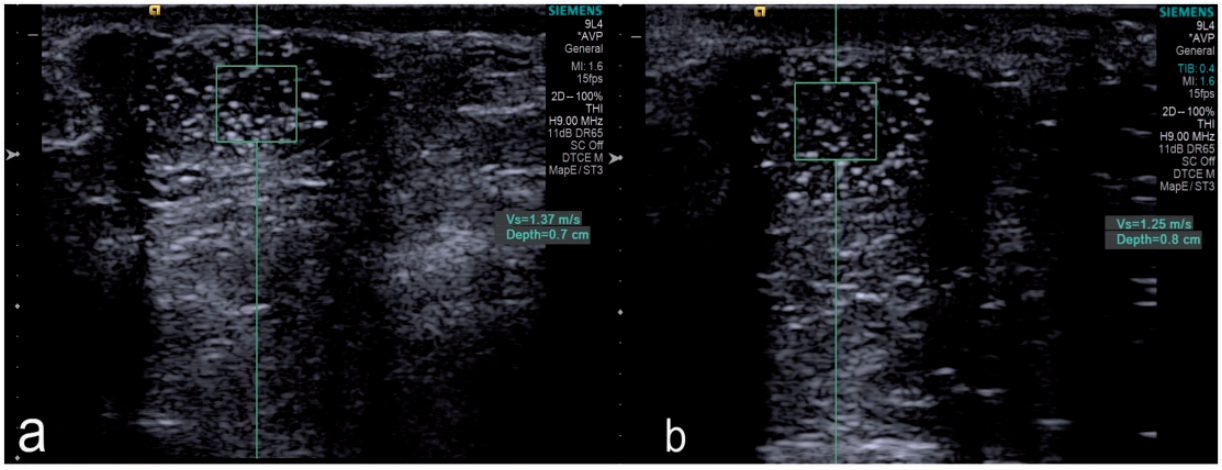

Fig. 5. ARFI elastography examination shows that measurement of the SWV of the testicles from the right (a) and left (b) in the axial section in a ten-year-old boy. ROI box was placed in the area where microlithiasis is most intense.

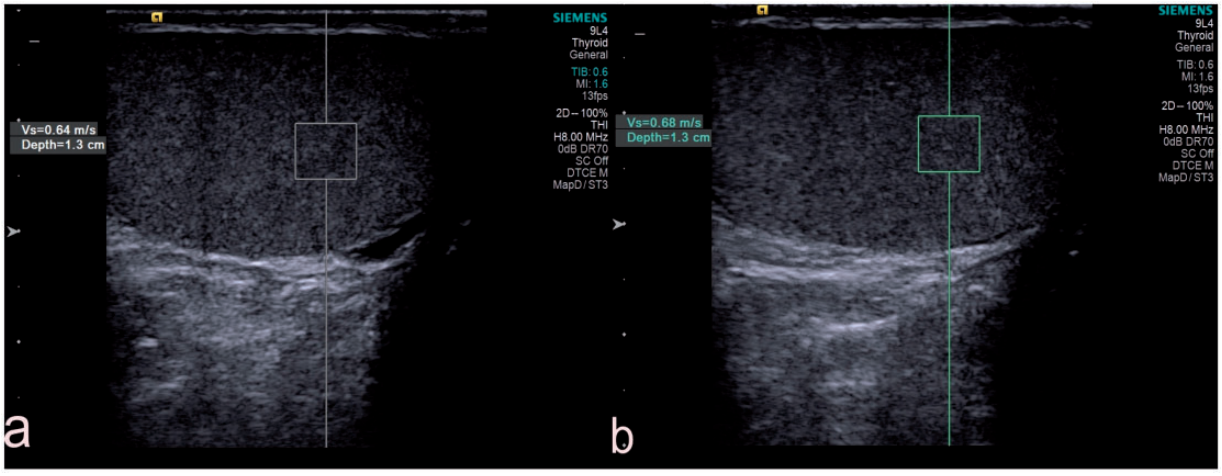

Fig. 6. ARFI elastography examination in case of the control group shows that measurement of the SWV of the testicles from the right (a) and left (b) in the axial section in a 17-year-old boy. ROI box was placed randomly on the testis by carefully avoiding vas deferens.

and the median (minimum–maximum). Shapiro–Wilk test was used for the normality of the data. Student's t-test and Mann–Whitney U test were used for comparison of the SWVs of the two groups. A P value <0.05 was considered statistically significant.

Results

Fifty normal testicles and 48 testicles with TML were examined. The average testis volume in the patient group and the average testicle volume in the control group are given in Table 2. There was no statistically significant difference between the testicular volume of the patient and control group ($P = 0.986$). The mean SWV of the testicles with TML and normal testicles are given in Table 3. The SWV of the testicles with

Table 2. The volume averages of testicles in both groups.

Volume (cm^3)	Mean	Range	P*
Patient group	1.14	0.77–1.68	0.986
Control group	1.21	0.64–1.06	

*Patient group vs. control group; $P < 0.05$ was statistically significant.

Table 3. Mean shear wave velocities (SWV) for testicles in patient and control group.

SWV (m/s)	Mean ± SD	Range	P*
Patient group	1.18 ± 0.22	0.77–1.68	<0.001
Control group	0.88 ± 0.11	0.64–1.06	

*Patient group vs. control group; $P < 0.05$ was statistically significant.

TML was higher than the control group and this was statistically significant ($P < 0.001$).

Discussion

Our study results demonstrated that the mean SWV of the testicles with TML was significantly higher than the mean SWV of the normal testicles at 1.18 ± 0.22 and 0.88 ± 0.11 cm/s, respectively. Trottmann et al. (15) found the mean SWV of the normal testicles to be 1.17 m/s in their adult age group. In a study carried out by D'Anastasia et al. (7), the SWV range of normal testicles was found to be 0.62–1.01 m/s in their adult group. Our study results were also similar to the study by D'Anastasia et al. (7). Pedersen et al. (14) found that the SWV range of microlithiasis areas of adults with TML to be 0.65–1.08 m/s and their study results demonstrated no significant difference between normal testes and testes with TML. In our study, the mean SWV range of testicles with TML was higher than the SWV range in the study by Pedersen et al. Furthermore, there was a statistically significant difference between the normal testicles and testicles with TML. This may be due to the fact that testicular tissue is more sensitive to developing TML in the pediatric age group and that TML development causes more microstructural changes than adults. However, there is a need for further investigation with larger groups to validate these findings.

Although ARFI elastography is less user-dependent than strain elastography, we still think that the results obtained vary depending on the user's experience. The wide range of mean SWV in the control or patient groups in our study and the differences observed with other studies may be related to this. Therefore, comparing absolute SWV values to assess the presence of fibrosis in the testis may not give accurate results.

In our study, the SWV values were higher in the patient group than in the control group, but there was no difference between the two groups when the testicle volumes were compared. High SWV values are indicative of increased fibrosis, with an expected corresponding decrease in testicular volume. This condition contradicted the fact that there was no difference in testicular volume between the two groups in our study. We think that this is due to the fact that the patient group of our study is composed of pediatric patients. Although our results suggest that testicular tissue in the pediatric age group is more sensitive to TML development and microstructural changes caused by TML, we believe that a certain time interval is required for fibrosis-associated testicular volume loss.

Some authors believe that TML is associated with testicular cancer, while others do not (16–18). Therefore, the relationship between TML and testicular cancer is still controversial. The study by Pedersen et al. (14) reported that no testicular cancer developed in patients with TML after the follow-up period of five years; as a result, TML alone may not be a risk factor for testicular cancer. There is still a need for further studies to validate these findings.

Recent studies have shown that elastography is effective in assessing the degree of liver fibrosis and it may be an alternative to liver biopsy (2). However, it is not known whether elastography has the same potential for testicular cancer. The European Society of Urogenital Radiology recommends an annual US follow-up in men who have testicular atrophy, TML, a family history of testicular cancer, or history of the undescended testes or orchiopexy (19). When US follow-up includes elastography, it is possible to evaluate the testicular stiffness yearly. In long-term follow-up ARFI elastography examinations, the change in SWV values can be used to assess the degree of testicular fibrosis and it may be effective when diagnosing testicular cancer in the pediatric population with TML.

The strengths of our study were that the ARFI measurements were without inter-individual variation. However, to introduce this method as a routine clinical toll, inter-observer data are needed. On the other hand, our study has some limitations. First, we studied a limited number of patients. Further studies with a larger population are needed. The second limitation is the lack of long-term follow-up of the patients. Studies in the literature have shown that none of the patients with TML developed testicular cancer after five-year follow-up in the adult group. However, there was no significant SWV difference between the patient group and the control group in a study (14). In our study, there was a statistically significant difference between the testicular SWV of the patient group and the control group. This demonstrates that the testes in the pediatric age group are more susceptible to microstructural changes and the importance of follow-up.

In conclusion, in our study, the mean testis SWV value in pediatric TML patients was significantly higher than the healthy pediatric group. To the best of our knowledge, our study is the first to investigate the SWE of pediatric patients with TML. There is still no clear consensus that TML is a predisposing factor for testicular cancer. We believe that adding US to the annual follow-ups for children with TML will give useful information on testicular stiffness and contribute significantly to predicting cancer development.

Declaration of Conflicting Interests

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