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Radiology

Sonoelastography of the Common Flexor Tendon of the Elbow with Histologic Agreement: A Cadaveric Study[1]

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Purpose: To determine the correlation of the results of conventional B-mode ultrasonography (US) and compression sonoelastography with histologic results in common flexor tendons of the elbow in human cadavers.

Materials and Methods: Twenty-five common flexor tendons were evaluated in 16 fresh, unembalmed cadavers of 11 women with a median age of 85 years (range, 71–101 years) and five men with a median age of 78 years (range, 70–88 years). Informed consent was provided according to the last will of the donors. B-mode US results were classified as grade 1, normal tendon with homogeneous fibrillar pattern; grade 2, tendon thickening or hypoechoic areas and/or calcifications in less than 30% of the tendon; or grade 3, hypoechoic areas and/or calcifications greater than 30% of the tendon. Sonoelastographic results were grade 1, blue (hardest) to green (hard); grade 2, yellow (soft); and grade 3, red (softest). The intraclass correlation coefficient was calculated to determine agreement with histologic findings for each B-mode US, sonoelastographic, and combined B-mode US and sonoelastographic examination. Histologic results were grade 1, normal, with parallel fibrillar pattern; grade 2, mild tendinopathy, with cellular infiltration, angiogenesis, or fatty vacuoles; or grade 3, severe tendinopathy, with loss of parallel collagen structure and necrosis.

Results: Histologic alterations were detected in 44% (11 of 25) of biopsy specimens. Intraclass correlation with histologic results was 0.57 for B-mode US, 0.68 for sonoelastography, and 0.84 for the combination of the two approaches.

Conclusion: The addition of sonoelastography to B-mode US provided statistically significant improvement in correlation with histologic results compared with the use of B-mode US alone ($P < .02$).

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B-mode ultrasonography (US) is an established tool for imaging the elbow for diagnosis of common flexor tendinopathy. (1). However, when compared with magnetic resonance (MR) imaging, US showed lower sensitivity, while specificity was similar (2). In the past few years, compression sonoelastography, an imaging technique that is capable of depicting elastic properties of anatomic structures and possible pathologic tissue alterations, has been used in musculoskeletal imaging (3). In patients with Achilles tendinopathy, sonoelastography was able to show more affected tendons than was B-mode US when compared with histologic results as the reference standard for diagnosis (4). For patients with clinically diagnosed lateral epicondylitis, sonoelastography has been shown to provide excellent sensitivity for detection of tendinopathy and excellent correlation with B-mode US findings (5). So far, data on sonoelastography as a diagnostic tool for medial epicondylitis are scarce. The correlation of B-mode US and sonoelastographic findings with histologic findings of the common flexor tendons of the elbow, to our knowledge, has not been well established in the literature. Our study was designed to correlate B-mode US and sonoelastographic findings with histologic results in the common flexor tendon of the elbow by using cadaveric samples.

Materials and Methods

Informed consent was provided according to the last will of the donors, who had dedicated their cadavers to human research studies and died between November 2013 and June 2014. All cadavers were in legal custody of the Anatomy Department of the Medical University of Innsbruck, Austria.

Advance in Knowledge

- B-mode US and sonoelastographic grades of medial epicondylitis in cadavers were correlated with histologic results.

Study Samples

We examined 25 common flexor tendons from 25 elbow joints in 16 cadavers. The study population included 11 female cadavers (median age, 85 years; range, 71–101 years) and five male cadavers (median age, 78 years; range, 70–88 years). All cadavers were examined within 30 hours after death (median, 16 hours; range, 6–27.5 hours) and were neither frozen nor embalmed. We did not have information regarding prior medical and surgical history or regarding prior elbow injuries for these cadavers.

US Image Acquisition

All examinations were performed by using a linear-array transducer (EUP-L75; Hitachi, Tokyo, Japan) with a frequency range of 18–5 MHz. Optimization of transducer coupling was achieved with copious amounts of contact US gel. For evaluation of the common flexor tendon, the cadaver was placed in a supine position with 90° abduction and full external rotation of the arm. The forearm and hand were placed in supine position. B-mode US images were obtained on longitudinal and axial planes for each portion of the common flexor tendon and were graded by one radiologist (A.S.K., with 15 years of experience in musculoskeletal US). We used a grading system in accordance with that described in Connell et al (6), where grade 1 indicated a normal-appearing tendon with a homogeneous parallel fibrillar pattern; grade 2 indicated tendon bulge and/or hypoechoic areas and/or calcifications in less than 30% of the tendon substance; and grade 3 indicated hypoechoic areas and/or calcifications greater than or equal to 30% of the tendon substance with or without tendon thickening. For calculation of sensitivity and specificity, grade 1 was considered normal,

Implication for Patient Care

- Sonoelastography may have the potential for use as an additional tool in the evaluation of medial epicondylitis.

and grades 2 and 3 were considered abnormal.

A second operator (M.M.H.A.E., a radiologist with 5 years of experience with sonoelastography) performed sonoelastographic examinations immediately after B-mode US. The second operator was blinded to the first observer's B-mode US results. The sonoelastographic examination was performed by using the technique of strain imaging, applying gentle repetitive compression with the hand-held transducer with approximately one compression per second. The elastogram was displayed in a rectangular region of interest on the screen, adjusted to include the entire common flexor tendon and surrounding tissues including the subcutaneous fat and part of the adjacent ulna. The elastogram was displayed as a translucent color-coded real-time image superimposed on the B-mode image. The color code corresponded to the relative tissue stiffness in the region of interest: blue to green indicated hard structures, yellow indicated soft structures, and red indicated the softest structures. The strength of compression was adjusted on the basis of a strain indicator on the screen according to the technique of De Zordo et al (5).

Elastograms were constructed with the same optimal settings throughout

our study as those suggested by Havre et al (7). The US transducer was held perpendicular to the tendon to minimize anisotropy. We carefully applied the same settings to all cadavers and held the transducer perpendicular to the common flexor tendon with appropriate pressure to avoid shifting. Each tendon was examined in two orthogonal planes (longitudinal and transverse). At least three successive compression-relaxation cycles were performed to ensure reproducibility of the results (8). As was done at B-mode US, sonoelastography was performed in each region of the common flexor tendon during longitudinal imaging. Images were saved as cine loops in the memory of the US device. Representative images were obtained from the middle of the compression-relaxation cycle for grading. On the basis of the grading system of De Zordo et al (5), blue and/or green color in the tendon indicated grade 1, yellow and/or red spots in less than 30% of the tendon indicated grade 2, and yellow and/or red spots in more than 30% of the tendon indicated grade 3. For calculation of sensitivity and specificity, grade 1 was considered normal, and grades 2 and 3 were considered abnormal. In addition to the independent assessments based on B-mode US and sonoelastography, we created a combination score, which was computed as the maximum of B-mode US and sonoelastographic scores. The B-mode US score, the sonoelastographic score, and the combination imaging score were each compared with histologic findings of tendon biopsy.

Biopsy and Histologic Analysis

Biopsy was performed from the common flexor tendon under US guidance. When an abnormality was detected with B-mode US or sonoelastography, biopsy was taken from the abnormality site. For any tendon in which no abnormality was detected at B-mode US or sonoelastography, a random biopsy was performed in the main bulk of the tendon. The biopsy was performed by using a 14-gauge 16-cm biopsy needle (Bard Max-core; Bard Peripheral Vascular, Tempe, Ariz), which was advanced

through a coaxial 13-gauge 7.8-cm needle (Bard Tru-Guide; Bard Peripheral Vascular). The coaxial needle was used to pierce the skin and position the biopsy needle as close to the tendon as possible. The biopsy needle tip was advanced to the tendon surface, where it was fired under US guidance.

One biopsy core was obtained from each of the examined common flexor tendons. We obtained 25 biopsy specimens from 25 tendons. The biopsy specimens were placed in 4% formalin solution, incubated for 24 hours, and embedded in paraffin. Each specimen was cut along the long axis of the tissue sample into sections 7–10 μm thick, which were stained with hematoxylin-eosin (the standard stain). A histology specialist (G.K., with 30 years of experience) who was blinded to B-mode US and sonoelastographic findings examined each specimen.

The following tendon alterations were considered as histopathologic signs of tendinopathy incorporated in a grading system used for histologic evaluation: grade 1 indicated that the samples showed no histologic alterations (parallel collagen fibrils, fatty infiltration, or capillary proliferation); grade 2 indicated that the samples showed mild alterations (accumulation of peripheral blood mononuclear cells, lymphocytes, monocytes, and granulocytes among the fibrils, termed inflammatory infiltrate; signs of neoangiogenesis, termed capillary proliferation; inclusion of fatty vacuoles, termed fatty degeneration); and grade 3 indicated moderate or severe tendinopathy (alteration of collagen fibers with loosening of the bonds and fluid aggregation within tendons, termed loss of parallel collagen structure; and necrotic areas, termed necrosis). For statistical analysis, grade 1 was considered normal, whereas grades 2 and 3 were considered abnormal.

Statistical Analysis

The sensitivity and specificity of each imaging mode were calculated with histologic results as the standard. The correlation of each imaging mode with histologic results was assessed according to calculation of an intraclass

correlation coefficient (ICC), which is the mathematical equivalent of κ analysis with quadratic weighting. The ICC was calculated with software (the "ICC" command in Stata 12.1; Stata, College Station, Tex) for the agreement of histologic results with each B-mode US and sonoelastographic examination and with the combined imaging approach. A bootstrap technique was used with the bootstrap command in Stata to estimate the standard error of each ICC, followed by a Wald test to determine whether the ICC was improved by using the combined imaging mode. A P value less than .05 was used to define a statistically significant difference (9).

Results

Histologic alterations were detected in 44% (11 of 25) of all biopsies. Inflammatory infiltrate was present in the majority of all pathologic biopsies (91%, 10 of 11), followed by capillary proliferation (45%, five of 11) and fatty degeneration (36%, four of 11). Necrosis was less common (27%, three of 11). The sensitivity of each B-mode and sonoelastographic examination relative to histologic abnormality was 55% (95% confidence interval [CI]: 28%, 79%), whereas specificity was 100% (95% CI: 79%, 100%). Use of the combination of modalities increased the sensitivity to 73% (95% CI: 43%, 90%). Although the combination of the modalities did yield increased sensitivity, this difference was not statistically significant (McNemar χ^2 P = .15). The ICC for B-mode US and histologic results was 0.57 (95% CI: 0.24, 0.78), the ICC for sonoelastographic and histologic results was 0.68 (95% CI: 0.40, 0.84), and the ICC for combined B-mode US and sonoelastographic results and histologic results was 0.84 (95% CI: 0.68, 0.93). The difference between the ICCs was not significant for the comparison of B-mode US with histologic results and sonoelastographic with histologic results. However, the ICC for the combined test was significantly better than that for B-mode US (P < .02) alone, which suggests that the combination of B-mode US with sonoelastography provided the
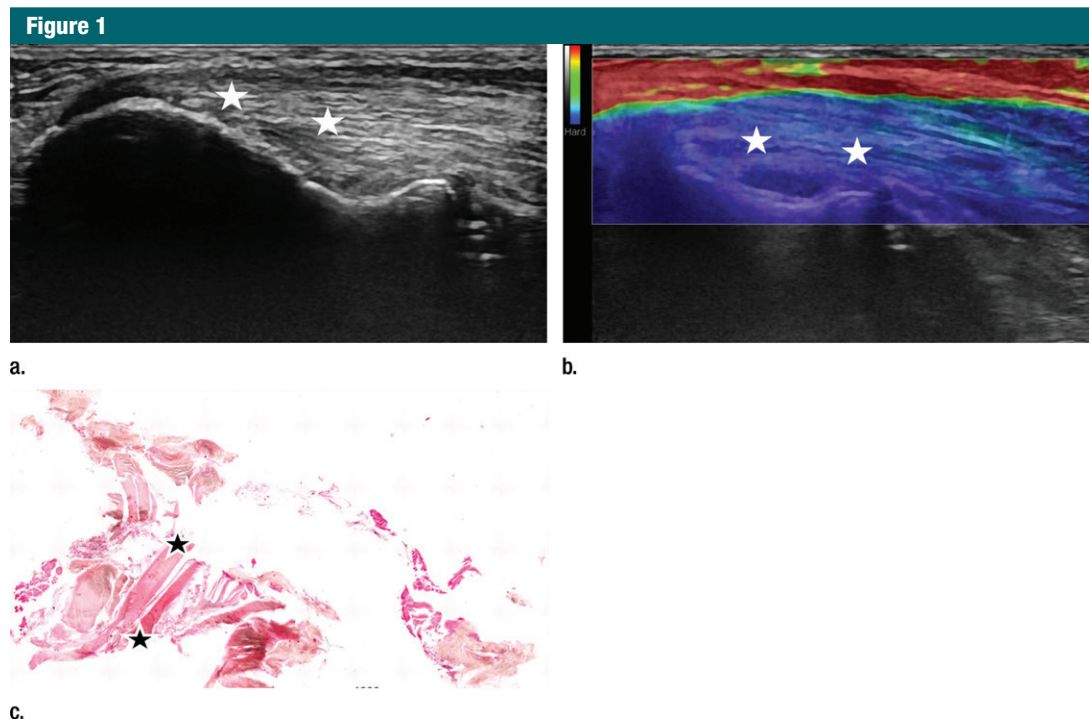
Figure 1: Image of normal common flexor tendon insertion at medial epicondyle. **(a)** B-mode US image of common flexor tendon insertion (right elbow) in longitudinal plane. ☆ = homogeneous fibrillar pattern (grade 1, normal). **(b)** Sonoelastographic image at same level as that in **a**. Blue area on elastogram (☆) indicates hard tissue (grade 1, normal), where biopsy was subsequently performed. **(c)** Histologic image (hematoxylin-eosin stain; magnification, ×500) shows parallel collagen fibrils (★), no fatty infiltration, and no capillary proliferation (grade 1, normal).

best agreement with histologic findings (Figs 1, 2, E1 [online]).

Discussion

Results of our study revealed 100% specificity for detection of medial epicondylitis of the elbow with combined B-mode US and sonoelastography in correlation with histologic result. However, just more than half (55%) of all pathologic tendons were correctly identified by using each individual method. Park et al (10) published higher values for sensitivity (95%) of B-mode US by using clinical examination as the diagnostic standard. It is likely that this difference is related to early and low-grade tendinopathy of the common flexor tendon that is apparent at histologic examination but may be difficult to detect with US. Nevertheless, our analysis of ICCs demonstrates that sonoelastography adds substantial information to B-mode US alone. The

proportion of positive findings in our study was greater than that which is typically found in clinical practice. Tendinopathy assessed at imaging or histologic examination could be frequent among asymptomatic subjects, and this might have implications in clinical practice. The high frequency (44%) of histologic alterations in our samples may be explained by the advanced age of the cadavers, a circumstance that has already been described in the literature (11).

Sonoelastography has been shown to reliably depict tendinopathy of the Achilles tendon with histologic evaluation and clinical examination as the diagnostic standard (4,12). The performance of sonoelastography in these studies was superior to the performance of sonoelastography in our study. The difference might be due to the smaller size of the anatomic structures in our study, as well as the more complex anatomy of the medial elbow

regarding osseous structures and conjoint tendons.

Several limitations of our study should be considered. We performed all examinations in a cadaver model. Post-mortem changes to the cadaver might influence elastic properties of tendons. Therefore, we decided to include in this study only cadavers that could be examined within 30 hours after death to reduce divergence from in vivo imaging results. In addition, we did not have information on the medical history of the body donors, and because of the advanced age of the donors, we found a much higher prevalence of alterations of the common flexor tendon than that described in the literature (13). A cadaver model also does not allow for color Doppler imaging, although the applicability of this method has already been shown (10).

Although we used a qualitative sonoelastographic grading system according to the color map in the region of
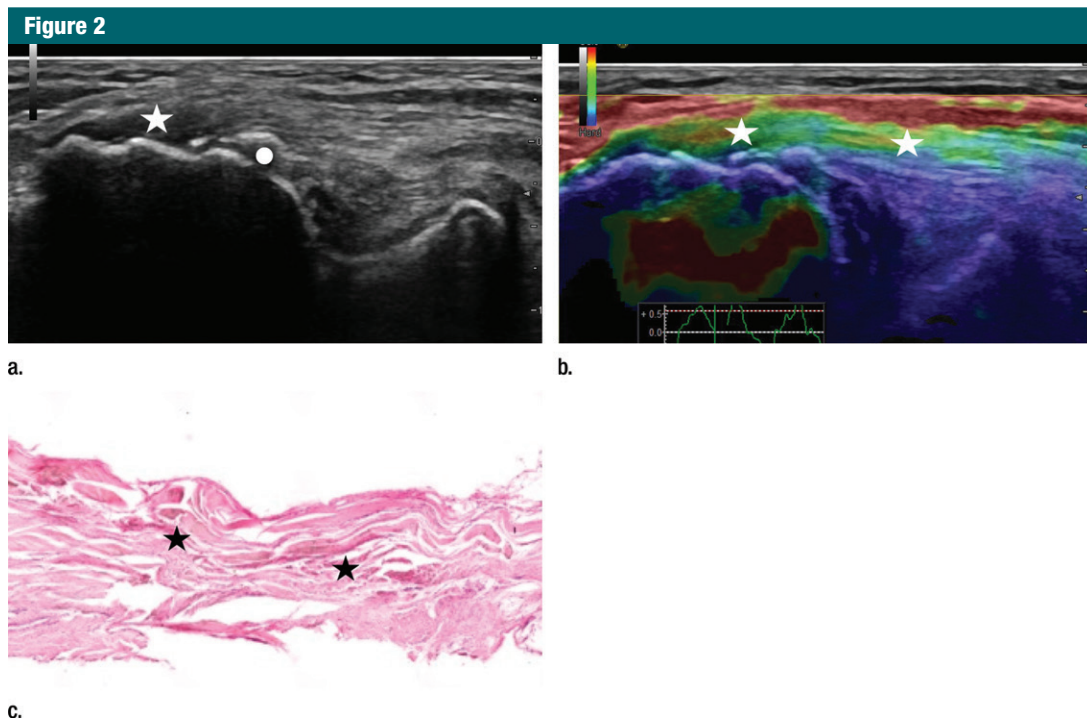
Figure 2: Example of a degenerative common flexor tendon insertion. **(a)** B-mode US image of common flexor tendon (left elbow) in longitudinal imaging plane. ☆ = Hypoechoic area with outward bowing of tendon. ○ = Irregularity of the ulnar bone surface and calcification within the tendon substance (grade 2). **(b)** Sonoelastographic image at the same level as that in **a**. ☆ = Green to yellow area (grade 2) on elastogram indicates abnormal softening, where biopsy was subsequently performed. **(c)** Histologic image (hematoxylin-eosin stain; magnification, ×500) shows inflammatory infiltrate, fatty degeneration, and capillary proliferation, with wavy appearance of collagen fibrils (grade 2). ★ = cellular and fatty infiltration within wavy collage fibrils.

interest, we did not perform quantitative measurement, which has been reported previously for lateral epicondylitis (14). Sonoelastographic grading was performed on the basis of cine loops of the compression-relaxation cycle to ensure reproducible results. We concentrated on the middle of each cycle, since the most reliable results are provided during this phase (15). In addition, the position of B-mode US and sonoelastography are not considered 100% comparable. Finally, we did not evaluate interobserver variability. Since the B-mode and sonoelastography were interpreted by different readers, the lack of correlation between these two tests could be related, in part, to differences between the readers. Finally, we note that our statistical analysis was limited by a relatively small study population. It is likely that a larger study sample would have allowed us to demonstrate a statistically significant improvement in sensitivity for

medial epicondylitis, as well as overall agreement with histologic results.

In our study, the addition of sonoelastography to B-mode US provided a statistically significant improvement in the agreement between imaging and histologic results compared with either B-mode US or sonoelastography alone ($P < .02$), although the improvement in sensitivity from 55% to 73% was not statistically significant ($P = .15$). Sonoelastography can be used as an adjunctive tool with B-mode US for evaluation of medial epicondylitis. Further studies to evaluate application of our technique in human subjects are required to validate our cadaveric study.

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