Quantitative MRI measurements of the Achilles tendon in spondyloarthritis using ultrashort echo times

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Objectives: Tendon involvement is common in spondyloarthritis. The MRI signal from the Achilles tendon has been used to quantify mechanical tendinopathy; however, conventional MRI is limited by the short T_2 of normal tendon. Short and ultrashort echo time (UTE) MRI have the potential to better measure signal intensity reflecting changes in T_2 or gadolinium enhancement. Furthermore, UTE images could be used for normalisation to reduce variability. The aim of this work was to investigate such techniques in patients with spondyloarthritis (SpA).

Methods: The Achilles tendons of 14 healthy volunteers and 24 patients with symptomatic spondyloarthritis were studied. Combined UTE (TE=0.07 ms) and gradient echo (TE=4.9 ms) images were acquired before and after intravenous gadolinium together with pre-contrast gradient echo images (TE=2 ms). The signal intensity from a region of interest in the Achilles tendon above the calcaneus was measured. The relative enhancement at echo times of 0.07 ms (RE_{0.1}) and 4.9 ms (RE₅) were calculated. The ratios of the signal intensities from both 4.9 ms and 2 ms gradient echo images to the signal intensity from the UTE image were calculated (RTE₅ and RTE₂ respectively).

Results: Interobserver intraclass correlation coefficients were excellent (≥ 0.97). The contrast-to-noise ratio was higher for enhancement on UTE images than on gradient echo images. RE_{0.1}, RTE₅ and RTE₂ were significantly higher in SpA patients than controls.

Conclusion: Signal intensity ratios using UTE images allow quantitative measurements to be made which are sensitive to tendon T_2 or contrast enhancement and which are increased in spondyloarthritis. They therefore have the potential for use as measures of tendon disease in spondyloarthritis.

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A cardinal manifestation of seronegative spondyloarthritis (SpA) is inflammation at tendons or ligaments near their insertions, which is well described at many disease sites [1]; the Achilles tendon is the largest such structure in the body. SpA is associated with various MRI findings, including changes within and around the tendon near its insertion, and erosion and oedema of the adjacent bone [2].

Conventional MRI has been used to study the Achilles tendon in patients with mechanical tendinopathy and scoring systems have been devised that correlate with surgical outcome [3]. Techniques for quantifying Achilles tendinopathy in these patients based on signal intensity have been shown to correlate with pain and functional impairment [4]. However, measurements of signal intensity from conventional MRI are limited by the short T_2 of the normal Achilles tendon (1–2 ms) [5–7], which limits the detection of subtle increases in T_2 or contrast enhancement [8]. Short echo time (STE) gradient echo images can detect small increases in T_2 which may occur

in mild or early tendinopathy [9]. Ultrashort echo time (UTE) techniques reduce the time between excitation and acquisition still further, to under 100 μ s, directly visualising the tendon and enabling the demonstration of contrast enhancement despite the short T_2 relaxation times of the normal tendon.

Single measurements of signal intensity are prone to variation (e.g. due to radiofrequency coil inhomogeneities, coil loading and variation between patients). Unenhanced UTE images are insensitive to changes in T_2 due to their short effective echo times and can therefore be used to normalise contrast-enhanced or STE images to give a ratio that is strongly dependent on only contrast enhancement or T_2^* .

The aim of this work was to investigate such quantitative measurements from the Achilles tendon and to apply them in patients with symptomatic SpA.

Methods and materials

Patients

24 patients with a clinical diagnosis of SpA made by a consultant rheumatologist and symptoms relating to the

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Achilles tendon were recruited prospectively from a rheumatology outpatients clinic. The average age of the patients was 40 ± 11 years (mean $\pm$ standard deviation); 9 were female and 15 male. The mean disease duration was 6 ± 8 years (3 patients were diagnosed within 6 months of the scan) and C-reactive protein (CRP) levels were elevated in 14 patients. A control group of 14 healthy, asymptomatic volunteers comprising 9 males and 5 females aged 37 ± 9 years was also studied. Volunteers were excluded if they had a history of arthritis, Achilles disease, major trauma to the foot or ankle, or recent symptoms relating to the Achilles tendon or ankle.

The study was approved by the Local Research Ethics Committee and written consent was obtained from each participant.

MRI

Imaging was performed at 3 T using a Siemens Magnetom Verio MR scanner (Siemens Healthcare, Erlangen, Germany) with a 4 cm loop receive coil positioned at the distal Achilles tendon. The coil and ankle were comfortably immobilised using a purpose-designed fixation device. The technique for two-dimensional (2D) radial UTE imaging has been previously described [10]. Briefly, images were acquired using a half radiofrequency excitation with radial imaging of k -space from the centre out in one direction added to another half radiofrequency excitation with the slice selection gradient reversed, with centre-out radial mapping of k -space over 360° . Images were mapped to a square grid and reconstructed by 2D Fourier transformation on the scanner. UTE (with time between excitation and acquisition or effective TE=0.07 ms) and gradient echo (GE; TE=4.9 ms) signals were acquired from each excitation. Multislice images were acquired from 3 mm slices with a field of view of 16 cm and 320 radial steps. The repetition time was 100 ms and the flip-angle was 30° with an acquisition time of 1 min. UTE images were acquired before and approximately 10 min after 0.1 mmol kg^{-1} Gd-DOTA (Dotarem, Guerbet, France). An unenhanced STE three-dimensional (3D) spoiled gradient echo (SPGR) image was acquired with TE=2 ms, TR=7 ms, flip-angle= 15° and 0.55 mm isotropic resolution in 5 min; a 3D sequence was necessary to achieve an echo time as short as 2 ms with resolution comparable to that of the UTE images.

Image analysis

3D SPGR images were reconstructed into 3 mm axial slices corresponding to the UTE images. A region of interest (ROI) was defined consisting of the entire cross-section of the Achilles tendon outlined on a slice approximately 0.5–1 cm superior to the posterior, superior calcaneus (Figures 1c and 2c). The gradient echo images were used to define the ROI in preference to the UTE images because they showed greater contrast between tendon and surrounding tissue, helping to ensure that only tendon was included. ROIs were determined by a radiologist (RJH/NM) and in data sets from 12 subjects (8 patients, 4 asymptomatic volunteers), ROIs were drawn independently by both radiologists.

The signal intensity in the ROI was measured from each of the MR sequences and corrected for scaling factors introduced during the Fourier transform process. Ratios of signal intensities were calculated as follows:

$$RE_{0.1} = \frac{\text{enhanced UTE (TE = 0.07 ms)} - \text{unenhanced UTE (TE = 0.07 ms)}}{\text{unenhanced UTE (TE = 0.07 ms)}} \quad (1)$$

$$RE_5 = \frac{\text{enhanced GE (TE = 4.9 ms)} - \text{unenhanced GE (TE = 4.9 ms)}}{\text{unenhanced GE (TE = 4.9 ms)}} \quad (2)$$

$$RTE_2 = \frac{\text{unenhanced SPGR (TE = 2 ms)}}{\text{unenhanced UTE (TE = 0.07 ms)}} \quad (3)$$

$$RTE_5 = \frac{\text{unenhanced GE (TE = 4.9 ms)}}{\text{unenhanced UTE (TE = 0.07 ms)}} \quad (4)$$

Contrast-to-noise ratios (CNRs) were calculated from signal intensities from the 0.07 ms and 4.9 ms echo time images as follows:

$$CNR_{0.1} = \frac{\text{enhanced UTE (TE = 0.07 ms)} - \text{unenhanced UTE (TE = 0.07 ms)}}{\text{noise}} \quad (5)$$

$$CNR_5 = \frac{\text{enhanced GE (TE = 4.9 ms)} - \text{unenhanced GE (TE = 4.9 ms)}}{\text{noise}} \quad (6)$$

Statistical analysis

CNRs were compared from UTE and gradient echo (TE=5 ms) images using the Wilcoxon matched pairs signed-rank test. Interobserver intraclass correlation coefficients (ICC_{3,1}) and reproducibility errors were calculated for each of $RE_{0.1}$, RE_5 , RTE_2 and RTE_5 from the 12 repeated ROIs, where

$$\text{Reproducibility error} = \frac{\left[\sum (x_{\text{obs1}} - x_{\text{obs2}})^2 / n \right]^{1/2}}{\sum x_{\text{obs1}} / n} \quad (7)$$

where x_{obs1} is the measurement of the MR ratio made by one radiologist, x_{obs2} is the measurement of the same ratio made by the other radiologist and Σ is the sum over the subjects with repeated measurements. The two-tailed Mann-Whitney U -test was used to look for differences in $RE_{0.1}$, RE_5 , RTE_2 and RTE_5 between arthritis patients and controls; these were the primary outcome measures of the study. The Mann-Whitney U -test was chosen prior to data analysis in view of the relatively small size of the study and the absence of previous data to show the measurements are normally distributed. Correlations were sought between age, disease duration and CRP *vs* the MRI ratios for the patient group using the Spearman correlation coefficient. Receiver operator curves were constructed using the clinical diagnosis of SpA with

the presence of symptoms as the gold standard. Statistical analysis was performed using SPSS v. 19 software (IBM, Armonk, NY).

Results

The mean CNR between enhanced and unenhanced tendon was higher on UTE images with a 0.07 ms effective echo time ($CNR_{0.1}$) than on the gradient echo images with $TE=4.9$ ms (CNR_5), with median (interquartile range) values of 2.7 (1.0–8.4) vs 0.8 (0.2–3.8) ($p<0.001$).

Examples of images from a healthy volunteer and a patient with psoriatic arthritis are shown in Figures 1 and 2.

Table 1 shows the $ICC_{3,1}$ and reproducibility errors. $ICC_{3,1}$ were 0.97 or greater for all measurements. Reproducibility errors were between 4% and 15%. Reproducibility errors were better for T_2 weighted measurements than for relative enhancement, with shorter echo times performing better.

Table 2 shows the comparison between healthy volunteers and SpA patients for each of the MRI measurements. $RE_{0.1}$, RTE_2 and RTE_5 were significantly higher in the patients with arthritis than controls. Table 3 shows the results divided according to the clinical diagnosis of the type of SpA.

Table 4 shows the correlation between the MR measurements and patient age, disease duration and CRP. There was a negative correlation with age, greatest for relative enhancement ($\rho=-0.4$).

Receiver operating characteristic (ROC) curves for each of the measurements are shown in Figure 3, assuming the gold standard of the clinical diagnosis, with the areas under the curve reported in Table 5. These reflect the differences between the patients and healthy volunteers, and were greatest for RTE_2 , followed by $RE_{0.1}$ and RTE_5 .

Discussion

This study has demonstrated quantitative measurements from UTE MRI of the Achilles tendon that are robust, straightforward and increased in spondyloarthritis.

The measurements used in this study are simple ratios of signal intensity on two scans. $RE_{0.1}$ and RE_5 are measures of enhancement, and will depend on tendon vascularity, capillary permeability and extracellular oedema [11]. In tendinopathy due to SpA these parameters may therefore depend on inflammatory activity in the tendon [12], in contrast to chronic degenerative tendinopathy, where there is little evidence of inflammation [13]. RTE_2 and RTE_5 are measures of relative signal intensity at

Figure 1. Example images of a healthy volunteer. (a) Ultrashort echo time (UTE) unenhanced. (b) Three-dimensional spoiled gradient echo $TE=2$ ms unenhanced. (c) Gradient echo $TE=4.9$ ms unenhanced (acquired with UTE images). (d) UTE enhanced. (e) Gradient echo $TE=4.9$ ms enhanced. The region of interest of the Achilles tendon is outlined on the unenhanced gradient echo images (c).

Figure 2. Example images of a patient with psoriatic arthritis. (a) ultrashort echo time (UTE) unenhanced. (b) Three-dimensional spoiled gradient echo TE=2 ms unenhanced, showing high signal intensity within the tendon (arrow). (c) Gradient echo TE=4.9 ms unenhanced (acquired with UTE images). (d) UTE enhanced, showing abnormal enhancement in the tendon (arrow). (e) Gradient echo TE=4.9 ms enhanced, showing abnormal enhancement in the tendon (arrow) and enhancement of the retrocalcaneal bursa (arrowhead). The region of interest of the Achilles tendon is outlined on the unenhanced gradient echo images (c).

different echo times and are therefore likely to depend strongly on the T_2 relaxation time of the Achilles tendon.

The results show a significant difference between patients with symptomatic spondyloarthritis compared with healthy controls (Table 2). This is also reflected in the ROC curves (Figure 3). Relative enhancement following intravenous contrast agent was significantly greater in patients compared with the control group using UTE images with an effective echo time of 0.07 ms, but not using gradient echo images with an echo time of 4.9 ms. This is probably due to the short T_2 of the healthy Achilles tendon (1–2 ms) [6, 7], which impairs visualisation of contrast enhancement on conventional MRI unless the T_2 of the tendon is substantially increased by disease. UTE imaging, with its short effective TE, is relatively independent of the tendon T_2 and is therefore better able to show contrast enhancement.

Table 1. Interobserver agreement

Parameter	RE _{0.1}	RE ₅	RTE ₂	RTE ₅
ICC _{3,1}	0.99	0.99	0.99	0.97
Reproducibility error	9%	15%	4%	7%

ICC, intraclass correlation coefficient.

The T_2 dependent measurements were also significantly increased in patients with SpA. The fractional increase and p -values are greater for the RTE₂ measurement, suggesting it may be better than RTE₅ for differentiating patients from healthy volunteers. This is also reflected in the ROC curves, although the area under the ROC curves from different sequences were not statistically significantly different. Previous work has looked at measurements using echo times as short as 10 ms and has found them to be more sensitive [4], but has raised questions about the specificity of shorter echo time sequences [14]. Although no significant difference was shown between measurements, the ROC curves presented here suggest that, if anything, echo times as short as 2 ms may be better for differentiating patients from controls. They also suggest that intravenous contrast may not be necessary and that the T_2 -based measurements without gadolinium may be as good or even better.

Unlike previous measurements of signal intensity and enhancement in the Achilles tendon [4, 15–17], this study has normalised signal intensity in the Achilles tendon to that from a pre-contrast UTE image. The time between excitation and acquisition in UTE sequences is very short, making them insensitive to changes in T_2 . Normalisation removes confounding effects of patient

Table 2. Achilles tendon MR measurements in healthy volunteers and patients with spondyloarthritis (SpA): median and interquartile range (IQR)

RE and RTE	Controls, median (IQR)	SpA patients, median (IQR)	<i>p</i> -value ^a
RE _{0.1}	0.04 (0.02–0.08)	0.10 (0.04–0.40)	0.023
RE ₅	0.06 (0.03–0.11)	0.15 (0.03–0.69)	0.071
RTE ₂	6.1 (5.0–8.1)	11.5 (8.9–13.7)	<0.001
RTE ₅	0.20 (0.15–0.21)	0.22 (0.19–0.26)	0.018

^aTwo-tailed Mann–Whitney *U*-test.**Table 3.** Median Achilles tendon MR measurements in patients split by clinical diagnosis

Diagnosis	Number of patients	RE _{0.1}	RE ₅	RTE ₂	RTE ₅
Psoriatic arthritis	14	0.17	0.28	10.4	0.20
Ankylosing spondylitis	5	0.06	0.11	11	0.23
Crohn's	2	0.21	0.36	16.5	0.27
Undifferentiated spondyloarthritis	3	0.07	0.00	12.6	0.23

Table 4. Correlation between Achilles tendon MR measurements and age, disease duration and C-reactive protein (CRP) for patients with spondyloarthritis. Spearman's ρ (*p*-value)

Patient characteristics	RE _{0.1}	RE ₅	RTE ₂	RTE ₅
Age	−0.40 (<i>p</i> =0.05)	−0.44 (<i>p</i> =0.03)	−0.03 (<i>p</i> =0.91)	−0.20 (<i>p</i> =0.36)
Disease duration (years)	−0.23 (<i>p</i> =0.29)	−0.22 (<i>p</i> =0.31)	0.04 (<i>p</i> =0.87)	0.32 (<i>p</i> =0.13)
CRP	0.14 (<i>p</i> =0.51)	0.14 (<i>p</i> =0.51)	0.04 (<i>p</i> =0.86)	0.23 (<i>p</i> =0.27)

variation, coil sensitivity, coil loading, tendon depth, coil positioning and radiofrequency penetration, providing a more robust measurement than a single measure of signal intensity or normalising to other tissues (*e.g.* fat) or noise. It represents a pragmatic compromise between intensity measurements from a single image and fitting data to models such as T_2^* calculation [5–7] or dynamic contrast-enhanced MRI [13], which may be more time-consuming and less robust.

All the measurements showed good interobserver reproducibility. Interobserver ICCs were excellent at ≥ 0.97 for all measurements. These compare favourably with ICCs for measuring inflammation in synovium and bone in arthritis using the well-validated RAMRIS (rheumatoid arthritis MRI score) scoring system [18–21], and are also superior to those reported for semi-quantitative measures of tendinopathy using ultrasound [22]. This may be because in this study observer input was restricted to outlining the Achilles tendon and the measurements (which depend on the entire tendon area) are relatively insensitive to small differences in the perimeter. However, ICCs are also strongly dependent on the underlying patient population, and high values may also reflect the large measurement range in our study (Table 2). Interobserver errors for the UTE measurements (4–9%) are similar to reproducibility of computer-assisted measurement of tendon volume and signal intensity [16], and are much less than the intersubject variability (Table 2). Although tendon segmentation was performed by a radiologist in this study, the technique does not require specialist training or skills and is fast, typically taking under 1 min to outline the tendon on a gradient echo image. Segmentation of the tendon by computerised methods has been previously validated [16], and such

techniques would allow measurements to be made in three dimensions.

The imaging sequences used in this study are clinically feasible; the data for RTE₂ take approximately 6 min to acquire while RE measurements required a total of 13 min, including the administration of intravenous contrast. Either could therefore reasonably be included

Figure 3. Receiver operating characteristic curves for MRI measurements taking clinical diagnosis of arthritis as gold standard.

Table 5. Area under receiver operating characteristic curves with 95% confidence intervals (CIs)

	RE _{0.1}	RE ₅	RTE ₂	RTE ₅
Area (95% CI)	0.72 (0.56–0.88)	0.68 (0.51–0.85)	0.85 (0.73–0.97)	0.73 (0.57–0.89)

in routine imaging assessments of the Achilles tendon. Further work will be required to determine whether the time between the administration of intravenous contrast agent and image acquisition could be reduced; however, in practice it may be more appropriate to acquire sequences targeting other tissues (e.g. bone) in this time. Using computerised segmentation it would be feasible in the future to semi-automate or even fully automate the process for clinical practice.

No correlations were demonstrated between the MRI measurements and disease duration or CRP levels in patients with SpA. This is consistent with previous semi-quantitative studies using ultrasound [23, 24]. There was a negative correlation between enhancement and patient age, which may reflect a reduction in the immune-mediated neovascularisation with age; further work will be required to confirm this and determine its significance.

The study has a number of limitations. The numbers of subjects are relatively small (24 patients and 14 controls), which limits the ability to differentiate between the accuracy of the different measurements; the data presented here could be used to power a formal study comparing the measurements. The presence of mechanical or degenerative tendinopathy could be a confounding factor. RTE₂ and RTE₅ are influenced by differences in the definition of the echo time between UTE and gradient echo images [25], and the susceptibility of UTE imaging to time-dependent eddy currents [6], as well as the T₂ relaxation time of the tendon. Furthermore, the differences between the 2D UTE multislice sequence and the 3D SPGR image mean that the RTE₂ measurement depends on T₁ as well as T₂, although this is likely to be relatively small. 2D SPGR sequences directly comparable with the UTE sequence were not feasible with similar in-plane resolution at echo times as short as 2 ms on the clinical scanner. The ROI was positioned relative to the posterior, superior angle of the calcaneus, the shape of which may vary from patient to patient. Finally, only a single slice was included in the measurement, although extension to a larger volume of interest would be straightforward (albeit time-consuming, without automation).

Given the potential of the measurements used in this study to quantify disease in the Achilles tendon in SpA, future studies to look at early disease in asymptomatic tendons, disease progression and response to treatment would be useful. These would help to determine the value of these measurements as biomarkers of tendon disease for use in clinical trials of novel treatments and for helping to obtain tighter disease control in the management of individual patients with spondyloarthritis. Since both relative enhancement and T₂-based measurements were greater in disease, it may be useful to combine these into a single measurement; for example, by calculating the ratio of an enhanced 2 ms echo time image to an unenhanced UTE image, which may be even better for detecting disease. The techniques presented here could also be extended to tendons elsewhere in the body.

Conclusion

This study has presented straightforward, practical, quantitative measurements from the Achilles tendon using UTE MRI, which show good interobserver reproducibility and are raised in symptomatic SpA. They may therefore be good measures of tendon disease.

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