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Achilles tendon and enthesis assessment using ultrashort echo time magnetic resonance imaging (UTE-MRI) T1 and magnetization transfer (MT) modeling in psoriatic arthritis

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Abstract

The purpose of this study is to investigate the use of ultrashort echo time (UTE) magnetic resonance imaging (MRI) techniques (T1 and magnetization transfer [MT] modeling) for imaging of the Achilles tendons and entheses in patients with psoriatic arthritis (PsA) compared with asymptomatic volunteers. The heels of twenty-six PsA patients (age 59 ± 15 years, 41% female) and twenty-seven asymptomatic volunteers (age 33 ± 11 years, 47% female) were scanned in the sagittal plane with UTE-T1 and UTE-MT modeling sequences on a 3-T clinical scanner. UTE-T1 and macromolecular proton fraction (MMF; the main outcome of MT modeling) were calculated in the tensile portions of the Achilles tendon and at the enthesis (close to the calcaneus bone). Mann–Whitney-U tests were used to examine statistically significant differences between the two cohorts. UTE-T1 in the entheses was significantly higher for the PsA group compared with the asymptomatic group (967 ± 145 vs. 872 ± 133 ms, $p < 0.01$). UTE-T1 in the tendons was also significantly higher for the PsA group (950 ± 145 vs. 850 ± 138 ms, $p < 0.01$). MMF in the entheses was significantly lower in the PsA group compared with the asymptomatic group (15% ± 3% vs. 18% ± 3%, $p < 0.01$). MMF in the tendons was also significantly lower in the PsA group compared with the asymptomatic group (17% ± 4% vs. 20% ± 5%, $p < 0.01$). Percentage differences in MMF between the asymptomatic and PsA groups (−16.6% and −15.0% for the enthesis and tendon, respectively) were higher than the T1 differences (10.8% and 11.7% for the enthesis and tendon, respectively). The results suggest higher T1 and lower MMF in the Achilles tendons and entheses in PsA patients compared with the asymptomatic group. This study highlights the potential of UTE-T1 and UTE-MT modeling for quantitative evaluation of entheses and tendons in PsA patients.

KEYWORDS
Achilles tendon, enthesis, MRI, Psoriatic Arthritis, UTE-MRI

Abbreviations: 2D, two-dimensional; 3D-UTE, three-dimensional ultrashort echo time; AFI-VFA, actual flip angle-variable flip angle; FA, flip angle; FOV, field of view; FSE, fast-spin echo; MMF, macromolecular proton fraction; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; PD, proton-density; PsA, psoriasis arthritis; qMRI, quantitative magnetic resonance imaging; RF, radiofrequency; ROI, region of interest; SpA, spondyloarthropathies; TE, echo time; TR, repetition time; US, ultrasound.

1 | INTRODUCTION

Entheses are regions that connect tendons, ligaments, and joint capsules to bone.[1] Enthesitis is considered an important pathophysiological feature of spondyloarthropathies (SpA), particularly psoriatic arthritis (PsA).[2] Because enthesitis can represent a primary lesion in PsA, and in particular manifesting in the Achilles tendon, early detection can help in the timely diagnosis of PsA.[3–5] Clinical assessment of the entheses lacks sensitivity and specificity because of the deeper location, proximity to other pain generators such as the synovium, and a highly heterogeneous composition and structure.[5–8] Unfortunately, diagnosis failure can lead to treatment delays and long-term consequences.

With the advantages of modern imaging modalities such as ultrasound (US) and magnetic resonance imaging (MRI), the diagnosis of PsA has improved, and monitoring after the implementation of treatment strategies has been enhanced.[5] US can be used to visualize the enthesis, but it is operator dependent, and robust quantitative assessments are lacking.[5,6] Conventional MRI techniques such as T1-weighted and T2-weighted fat-suppressed fast-spin echo (FSE) sequences can demonstrate morphological changes of the Achilles tendon and enthesis when grossly abnormal. Quantitative MRI (qMRI) biomarkers such as T1, magnetization transfer ratio (MTR), and T2* can provide valuable information about the microstructural and compositional changes in PsA-affected tissues without requiring high spatial resolutions.[9–11] The presence of edema, inflammation, fibrosis, and tissue erosion are common features of PsA that involve microstructural and compositional changes.[11–13] However, intact tendons and entheses, as well as fibrotic tissues, have short T2s and show little or no signal, which limits their ability to be quantified by routine qMRI.[7,8]

Ultrashort echo time (UTE) MRI sequences use echo times (TEs) that are 100–1000 times shorter than those in clinical sequences, which allows direct imaging of traditionally MRI "invisible" tissues, such as tendons and entheses.[14,15] The high signal obtained with UTE-MRI can also be used to perform quantitative assessments. There has been increasing interest in recent years in the use of UTE-MRI for the evaluation of the Achilles tendon and its enthesis, both morphologically and quantitatively.[13,16–18]

Hodgson et al. used a two-dimensional (2D) UTE sequence before and after gadolinium administration to evaluate the signal intensity of the Achilles tendons in patients with SpA. They reported significantly higher signal enhancement in the entheses of SpA patients compared with healthy controls.[17] The same authors also employed a quantitative 2D UTE magnetization transfer (MT) technique to assess the Achilles tendon in one patient with PsA compared with eight asymptomatic volunteers. In the patient with PsA, they showed that the "bound proton fraction" which was generated from MT modeling and assumed to represent the macromolecular contents of tissues, was 16.4% lower than that of the asymptomatic volunteers.[18] Chen et al. used a three-dimensional (3D) Cones UTE sequence and demonstrated significantly higher T2* values and lower MTRs in the Achilles tendons and entheses of patients with PsA compared with the healthy control group.[13] Notably, T2* is sensitive to the magic angle effect[14] and may differ significantly only due to changes in the tissue direction relative to the B0 field. On the other hand, MTR values are difficult to interpret because of dependence on both the underlying physiology and the acquisition parameters (e.g., pulse power level, pulse duration, and frequency offsets).[18] Chen et al. also used UTE-MT modeling to evaluate normal cadaveric Achilles tendons and entheses and showed lower macromolecular proton fraction (MMF) values in the entheses compared with the tensile tendon regions.[16] UTE-MT modeling provides a magic angle insensitive evaluation of water and MMF in short T2 tissues.[14,19] Because T1 relaxation impacts the magnetization saturation in the macromolecular pool and the transferred saturation to the water proton pools, using a correct T1 value is necessary for accurate estimation of MMF in the UTE-MT modeling technique. The utilization of UTE-MT modeling in the evaluation of the Achilles tendons and entheses and distinguishing between PsA patients and asymptomatic volunteers remains to be investigated.

In the present study, we aim to evaluate the Achilles tendons and entheses in asymptomatic volunteers and PsA patients using 3D UTE-Cones sequences at 3 T. Quantitative measurements of T1 and MMF of the Achilles tendons and entheses were measured for each subject, and differences were analyzed between the two groups.

2 | MATERIALS AND METHODS

2.1 | Subjects

This cross-sectional study was approved by our institutional review board, and written informed consent was obtained from all subjects. From September 2021 to December 2022, adult participants aged 19–90 years without a history of trauma to the ankle, were recruited. The asymptomatic cohort consisted of volunteers from the University campus with no ankle symptoms of any sort. The PsA cohort consisted of consecutive patients referred from our rheumatology clinic with a diagnosis of PsA, as established by the standard, validated classification for Psoriatic Arthritis (CASPAR) criteria.[20,21] Participants with image artifacts that could not be corrected were excluded.

2.2 | Image acquisition

A 3-T clinical scanner (MR750, GE Healthcare Technologies, Milwaukee, WI, USA) employing a 7.6 cm. surface coil was used. The ankles of the participants were scanned in the sagittal plane using quantitative 3D UTE-T1 and 3D UTE-MT sequences with a Cones k-space trajectory, as well as with conventional clinical 2D proton-density (PD) and T2-weighted fat-suppressed FSE sequences. The quantitative 3D UTE-T1 sequence is based on the 3D-UTE actual flip angle-variable flip angle (AFI-VFA) method.[15] UTE-MT modeling requires T1 compensation as a short TR to reduce the total scan time.[15]

The detailed sequence parameters of the quantitative 3D-UTE imaging protocols and conventional clinical MRI were: (A) 3D UTE-AFI-VFA sequence: TE = 0.032 ms, TR = 18 ms, flip angles (FAs) = 5°, 12°, and 24°; (B) 3D-UTE-Cones-MT sequence: pulse power = 350°, 750°; frequency offset = 2, 5, 10, 20, and 50 kHz; FA = 7°; 11 spokes per MT preparation; slice spacing/thickness = 2.0 mm, field of view (FOV) = 12 × 12 cm^2, matrix size = 256 × 256; (C) 2D sagittal fat saturation T2-weighted FSE images were acquired with TE = 70 ms, TR = 4713 ms, slice spacing/thickness = 2.0 mm, FOV = 12 × 12 cm^2, matrix size = 352 × 256, receiver bandwidth = 162 kHz; and (D) 2D sagittal PD-weighted images were acquired with TE = 31.9 ms, TR = 2000 ms, slice spacing/thickness = 2.0 mm, FOV = 12 × 12 cm^2, and matrix size = 352 × 256. The total scan time was 23 min 5 s.

2.3 | Image/data analysis

For each patient, motion registration was performed using the Elastix software (https://elastix.lumc.nl/ based on the well-known Insight Segmentation and Registration Toolkit [ITK]). Specifically, a rigid, affine transformation was applied for coarse registration between images, followed by a nonrigid b-spline registration for more accurate registration.[22]

An experienced postdoctoral scholar, blinded to the patient group and clinical data, performed the data analysis using MATLAB (2022; MathWorks, MA, USA). Quantitative UTE analysis was performed on two sagittal slices 3 mm apart. On each slice, two different regions of interest (ROIs) were selected, including one in the tensile portion of the Achilles tendon and one in the enthesis (close to the calcaneus bone) (Figure 1D). For the selection of the ROIs, the tendon was approximated into deep and superficial halves by the readers. To avoid potential partial

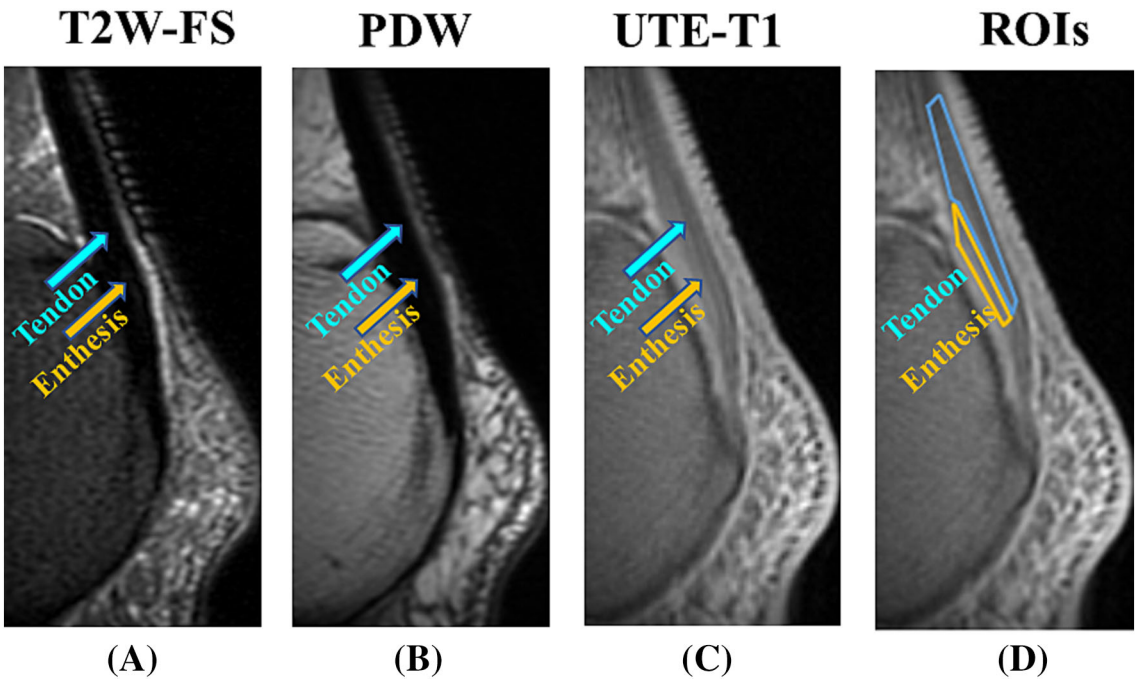

FIGURE 1 (A) T2-weighted fat-suppressed (T2W-FS), (B) Proton-density weighted (PDW), and (C) UTE-T1 images of the ankle for an asymptomatic 35-year-old male volunteer. Note that the Achilles tendon (blue arrow) and enthesis (yellow arrow) show no signal on conventional clinical MRI images (A and B). On the UTE-T1 image, the enthesis is evident as a region with a higher signal between the Achilles tendon and calcaneus (C). Using the UTE-T1 image, schematic ROIs were placed in the tensile tendon (blue polygon) and enthesis (yellow polygon) for measurement, as shown (D). For the selection of the ROIs, the tendon was approximated into deep and superficial halves by the readers. To avoid potential partial volume artifacts with structures of vastly different structure and composition, the selected ROIs for the entheses avoided the hypointense calcaneal cortex and immediately superficial, but variably hyperintense, fibrocartilage. ROI, region of interest; UTE, ultrashort echo time.

volume artifacts with structures of vastly different structures and compositions, the selected ROIs for the entheses avoided the hypointense calcaneal cortex and immediately superficial, but variably hyperintense, fibrocartilage. T1 measurements were performed using a single-component exponential fitting model based on a Levenberg–Marquardt algorithm using nonlinear optimization.[23] Two-pool MT modeling, which relies on the interaction between water and macromolecular protons, was performed to generate MMF values. In this technique, by selectively saturating the macromolecular proton pool using off-resonance radiofrequency pulses, magnetization is transferred to the water proton pool, resulting in a decrease in signal intensity that can be used to study these interactions.[14] T1 and MMF mean values, standard deviation, and fitting errors were recorded for each subregion. Spearman's correlation coefficient was calculated to evaluate the relationship between MFF and T1 values.

A second experienced postdoctoral scholar, also blinded to the patient group and clinical data and the results from the first postdoctoral scholar, performed data analysis similarly for all the participants to assess inter-rater reliability. One asymptomatic volunteer was scanned with the same protocol and scanner three times to assess repeatability.

2.4 | Statistical analysis

SPSS (IBM, Armonk, NY, USA) version 28.0 was used for all statistical analyses. The 3D UTE-T1 and MMF values in the Achilles tendons and entheses were compared between the asymptomatic volunteers and the PsA groups. The Kolmogorov–Smirnov test was used to examine whether the 3D UTE-Cones T1 and MMF values were normally distributed. The Mann–Whitney-U test (because they were not normally distributed) was used to examine the differences and their statistical significance between asymptomatic volunteers and PsA groups. To evaluate the inter-reader reliability and validity, intraclass correlation coefficients (ICCs) were calculated between the results of the two analyzers. To assess intra-reader reliability, ICCs were calculated between the results of the 10 randomly selected participants. To evaluate the test–retest reliability study, ICCs were calculated for the results of the one asymptomatic volunteer. p values less than 0.05 were considered statistically significant.

3 | RESULTS

Twenty-six asymptomatic volunteers and 27 patients diagnosed with PsA were recruited. However, because of severe motion artifacts that could not be resolved with retrospective motion correction, our final cohorts consisted of 20 patients with PsA (age 59 ± 15 years, 41% female) and 25 asymptomatic volunteers (age 33 ± 11 years, 47% female).

T1 and MMF pixel maps of two representative PsA patients and two asymptomatic volunteers in Figure 2A (a-f) and Figure 2B (c-h), respectively. The mean and standard deviation of UTE-T1 and MMF values in PsA and asymptomatic volunteer groups are presented in Table 1. The mean and standard deviation of T1 values in the entheses for PsA patients and the asymptomatic volunteer group were 967 ± 145 versus

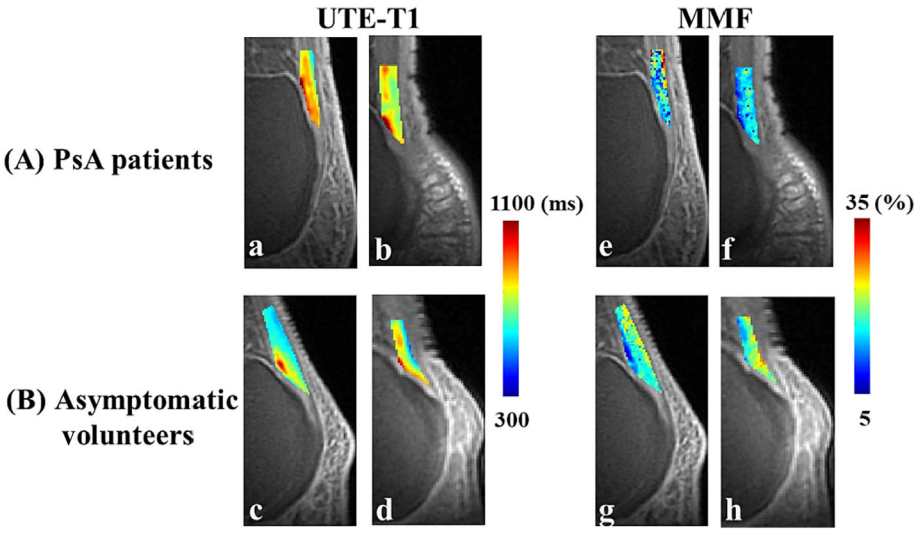

FIGURE 2 Representative UTE-T1 and MMF pixel maps overlaid onto the UTE images in (A) Two PsA patients, and (B) Two young asymptomatic volunteers. A higher mean value of T1 was observed for the PsA patients (a and b) compared with the volunteers (c and d) in both enthesis (967 ± 145 vs. 872 ± 133 ms) and Achilles tendon (950 ± 145 vs. 850 ± 138 ms). A lower mean value of MMF (%) was observed for the PsA patients (e and f) compared with the volunteers (g and h) in both enthesis (15% ± 3% vs.18% ± 3%) and Achilles tendon (17% ± 4% vs. 20% ± 5%). MMF, macromolecular proton fraction; PsA, psoriatic arthritis; UTE, ultrashort echo time.

TABLE 1 Mean and standard deviation of UTE-T1 (ms) and MMF (%) measures in patients with PsA and the asymptomatic group.

ROI	Groups	T1 (ms)	MMF (%)
Enthesis	PsA patients	967 ± 145	15 ± 3
	Asymptomatic	872 ± 133	18 ± 3
Tendon	PsA patients	950 ± 145	17 ± 4
	Asymptomatic	850 ± 138	20 ± 5

Abbreviations: MMF, macromolecular proton fraction; PsA, psoriatic arthritis; ROI, region of interest; UTE, ultrashort echo time.

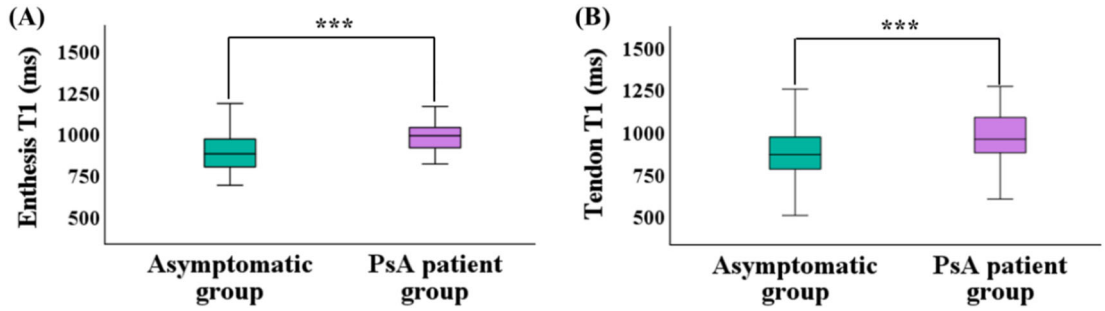

FIGURE 3 (A) Bar-plot of the enthesis T1 (ms) values comparing between asymptomatic and PsA groups (***$p < 0.01$). (B) Bar-plot of the Achilles tendon T1 (ms) comparing between asymptomatic and PsA groups (***$p < 0.01$). The central line in each plot indicates the median value, while the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Enthesis and the Achilles tendon in PsA patients showed significantly higher T1 values compared with the asymptomatic group (967 ± 145 vs. 872 ± 133 ms for enthesis, while 950 ± 145 vs. 850 ± 138 ms for the tensile tendon region). PsA, psoriatic arthritis.

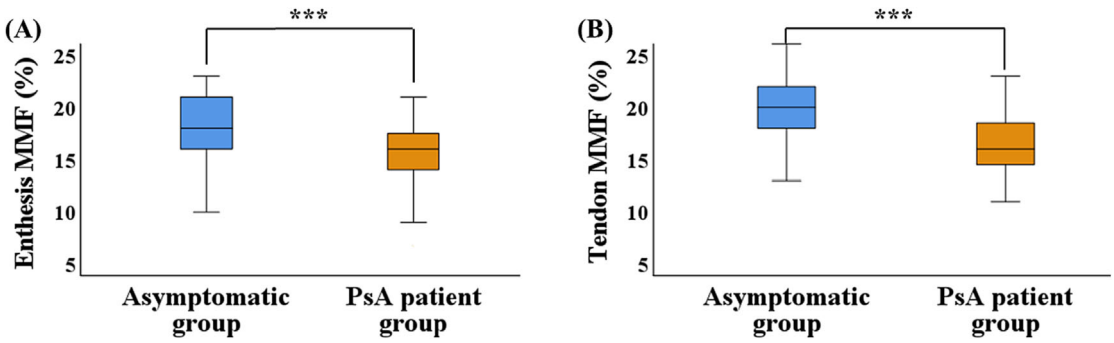

FIGURE 4 (A) Bar-plot of the enthesis MMF (%) values comparing between asymptomatic and PsA groups (***$p < 0.01$). (B) Bar-plot of the Achilles tendon MMF (%) comparing between asymptomatic and PsA groups (***$p < 0.01$). The central line in each plot indicates the median value, while the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. Enthesis and the Achilles tendon in PsA patients showed significantly lower MMF values compared with the asymptomatic group (15% ± 3% vs.18% ± 3% for enthesis, while 17% ± 4% vs. 20% ± 5% for the tensile tendon region). MMF, macromolecular proton fraction; PsA, psoriatic arthritis.

872 ± 133 ms, respectively ($p < 0.01$) (Figure 3A). The mean and standard deviation values of T1 values in the tensile tendon were 950 ± 145 versus 850 ± 138 ms for PsA patients and the asymptomatic volunteer group, respectively ($p < 0.01$) (Figure 3B). The mean and standard deviation of MMF values in the entheses for PsA patients and the asymptomatic volunteer group were 15% ± 3% versus 18% ± 3%, respectively ($p < 0.01$) (Figure 4A). The mean and standard deviation of MMF values in the tensile tendon for PsA patients and the asymptomatic volunteer group were 17% ± 4% versus 20% ± 5%, respectively ($p < 0.01$) (Figure 4B).

Percentage differences and the statistical significance of T1 values between PsA groups and asymptomatic volunteers in the entheses and the tensile tendon regions were 10.8% ($p < 0.01$) and 11.7% ($p < 0.01$), respectively. For MMF, there were significant percentage differences of −16.6% ($p < 0.01$) and −15.0% ($p < 0.01$) between the PsA groups and asymptomatic volunteers in the entheses and the tensile tendon regions,

TABLE 2 Percentage differences and their statistical significance (Mann–Whitney-U) in UTE-T1 (ms) and MMF (%) measures between patients with PsA and the asymptomatic group.

	Diff T1 (%)	Diff MMF (%)
Enthesis	10.8 ($p < 0.01$)	−16.6 ($p < 0.01$)
Tendon	11.7 ($p < 0.01$)	−15.0 ($p < 0.01$)

Abbreviations: MMF, macromolecular proton fraction; PsA, psoriatic arthritis; UTE, ultrashort echo time.

respectively (Table 2). Excellent inter-reader reliability was observed with ICC values of 0.97 or higher for 3D UTE-T1, and MMF performed on all datasets. Excellent intra-reader reliability was observed with ICC values of 0.96 or higher performed on 10 randomly selected datasets.

Excellent repeatability was demonstrated with ICC values of 0.80 or higher and 0.90 or higher for T1 and MMF values, respectively.

As an exploratory investigation, a significant correlation was observed between MFF and T1 values (Spearman's R = −0.32, $p = 0.004$). The T1 and MMF relationship is shown in Figure S1.

4 | DISCUSSION

This study evaluated the Achilles tendon and enthesis regions in patients with PsA and asymptomatic volunteers using 3D UTE-T1 and UTE-MT modeling techniques on a clinical 3-T scanner. We found significantly higher UTE-T1 values in the Achilles tendons and entheses of the PsA group compared with the asymptomatic volunteer group. Moreover, MMF from UTE-MT modeling showed significantly lower values in the Achilles tendon and the enthesis of the PsA patients' group. Lower MMF values in patients agreed with previous preliminary results by Hodgson et al. that compared one patient with eight asymptomatic volunteers.[18]

In recent years, US and MRI have been the main modalities used to evaluate enthesitis in patients with PsA.[5] Earlier US studies demonstrated the potential presence of enthesitis in asymptomatic patients with psoriasis.[24–26] However, Gandjbakhch et al. have reported that US shows low reliability (29%) and responsiveness (defined as the ability of the tool to demonstrate a change in response to intervention) (19%) for evaluating enthesitis because of the lack of a standardized protocol.[27] Nevertheless, US can detect abnormalities of the enthesis; it is operator dependent and is not routinely performed as a quantitative study.[5]

MRI plays a major role in the clinical diagnosis of enthesopathy. Conventional MRI sequences can show limited morphological changes in the Achilles tendon and surrounding tissues, such as the loss of the normal, flattened appearance, increased signal intensity, bone marrow edema, peri-entheseal inflammation, and distension of adjacent bursae.[2,7,28] Notably, semiquantitative grading systems have been developed for morphological and structural evaluations of the entheses, such as the Outcome Measures in Rheumatology (OMERACT) score, which uses pregadolinium and postgadolinium T1-weighted and fat-suppressed T2-weighted images.[9] However, such semiquantitative morphological gradings focused mainly on the surrounding tissues instead of the entheses, which possess short T2s and show little or no signal with clinical sequences.[29] Quantitative diffusion-weighted imaging (DWI) acquired with routine sequences has shown promising results evaluating sacroiliac joints[30–33]; however, its use in entheses and tendons is probably limited because of the lack of signal in these short T2 tissues. To the best of our knowledge, DWI has not been investigated for tendon or entheseal evaluation in the peripheral joints.

2D- and 3D-UTE sequences offer promising results in morphological and quantitative evaluation of tissues with short T2,[14,15] but few studies have used these techniques to evaluate the entheses.[13,16–18] 3D-UTE sequences have drawn more attention from the research community as there are several theoretical advantages, including greater anatomic coverage, thinner slices, increased signal-to-noise ratio (SNR), and potentially reduced scan time, all facilitating clinical applications.[14,19,34] Among the reported 3D-UTE techniques,[13,16] UTE-MT modeling provides a magic angle insensitive biomarker in short T2 tissues[14,19,35] and has been investigated previously for the tendon,[13,16,18,36–40] ligament,[41] cartilage,[42,43] and bone[42,44,45] evaluations.

Chen et al. investigated UTE-T1 and MMF values ex vivo on five normal ankle specimens and reported lower T1 and MMF values compared with our study (T1 = 780 ± 55 ms and MMF = 13.9% ± 1.9% for enthesis, T1 = 644 ± 22 ms and MMF = 18.0% ± 2.2% for tendon, respectively).[16] These are probably attributable to differences between the postmortem and in vivo conditions, including temperature (room temperature vs. body temperature).[46] Hodgson et al. investigated UTE-T1 and MMF (called the "bound proton fraction" in their study) values in Achilles tendons for eight volunteers compared with one PsA patient, but did not include the enthesis regions. They used a 2D UTE radial sequence on a 1.5-T scanner and observed lower MMF and higher T1 values in the PsA patient compared with the volunteers.[18] Compared with our study, they reported lower T1 but comparable MMF values (T1 = 501 ± 65 ms and MMF = 21.0% ± 1.2% in the eight volunteers vs. T1 = 606 ms and MMF = 16.4% in the PsA patient), which can be attributed to the differences in the field strength, pulse sequences, MR acquisition parameters,

and sample. In this study we used the 3D-UTE-Cones sequence, which provides higher SNR, allows for faster acquisition, and reduces eddy current artifacts compared with the radial 2D-UTE sequence.[13,35]

Tbini et al. also calculated UTE- T1 maps for asymptomatic volunteers and patients with confirmed tendinopathy in the ankle.[47] They reported higher T1 values for patients (575 ± 110 vs. 875 ± 425 ms for healthy volunteers and PsA patients, respectively), similar to our results. However, their reported low T1 values and large standard deviations can result from the heterogeneous and anatomically complex structure of the entheses. Chen et al. quantified T2* and MTR measurements of the Achilles tendon and its enthesis on seven healthy volunteers and nine PsA patients with 3D-UTE-Cones on a 3-T scanner. They reported a significantly higher T2*, while lower MTR, in both the tendon and enthesis of PsA patients.[13] As mentioned before, T2* is sensitive to the magic angle effect,[14] while MTR values are difficult to interpret because of the dependence on the acquisition parameters.[48–50] It is essential to note that MTR cannot produce direct quantitative information on macromolecular and water protons present in tissues.[19]

Nevertheless, the current study was the first to examine UTE-MT modeling for in vivo enthesis evaluation, and we have also demonstrated its potential for distinguishing between patients with PsA and asymptomatic volunteers.[14,19]

This study had several limitations. First, the number of participants was low in this pilot investigation. Future investigations should be performed with a higher number of participants. Second, the PsA patients were older than the asymptomatic volunteers, and some of the observed differences between the groups may be confounded by age. Future investigations should be performed comparing PsA patients with age- and body mass index-matched control groups. Third, patients who might be under treatment for PsA were not identified to be excluded from the study. Future investigations should be performed evaluating PsA patients at baseline and after administration of treatments (e.g., biologics) to assess the responsiveness of the effects. Fourth, only UTE-T1 and MT modeling were used in this study; however, other promising UTE-MRI techniques, such as UTE-T1ρ, are recommended for tendons.[51–53] Finally, there are many components of the Achilles enthesis organ, including the fibrocartilages, bursa, and fat pad.[54] In our study, we chose to exclude these components, but variations in these structures may be relevant to disease processes and should be investigated in the future.

5 | CONCLUSIONS

Significantly higher UTE-T1 and lower MMF values were found in the entheses and tendons of PsA patients compared with asymptomatic volunteers. This study highlights the potential of UTE-T1 and UTE-MT modeling for quantitative evaluation of entheses and tendons in PsA patients.

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