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T1ρ MRI of the talar articular cartilage is increased in those with chronic ankle instability

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SUMMARY

Objective: To determine if individuals with chronic ankle instability (CAI) demonstrate different talar cartilage T1ρ relaxation times compared to uninjured controls.
Design: Fifteen CAI (21.13 ± 1.81 years, 4.00 ± 2.07 previous ankle sprains) and fifteen controls (21.07 ± 2.55 years, no previous ankle sprains) participated. CAI inclusion criteria was in accordance with the International Ankle Consortium guidelines. Greater T1ρ relaxation times were interpreted as greater degenerative changes. Participants were non-weight bearing for 30-minutes prior to scanning to unload the cartilage. Voxel by voxel T1ρ relaxation times were calculated from a five image sequence. Segmentation of the talar cartilage was performed manually using ITK-SNAP software. T1ρ relaxation time means and variability across the entire talus and in the anteromeidal, anterolateral, posteromedial, and posterolateral regions of interest (ROIs) were compared between groups using mean differences and effect sizes (ES) with their corresponding 95% confidence intervals (95%CI).
Results: Individuals with CAI demonstrated higher T1ρ relaxation times (mean ± standard deviation) across the entire talus (CAI: 65.97 ± 10.45 ms, Control: 58.84 ± 7.68 ms; ES = 0.76, 95%CI = 0.02–1.50), in the anterolateral (ES = 1.00, 95%CI = 0.24–1.48), posteromedial (ES = 0.74, 95%CI = 0.01–1.49), and posterolateral region of interest (ES = 3.84, 95%CI = 2.63–5.04). The T1ρ relaxation time variability (mean ± standard deviation) also differed across the overall talus (CAI: 32.78 ± 4.06 ms, Control: 28.23 ± 4.45 ms; ES = 1.04, 95%CI = 0.28–1.80), in the anteriolateral, (ES = 1.07, 95%CI = 0.31, 1.84) and posteriolateral (ES = 1.00, 95%CI = 0.24–1.75) ROIs.
Conclusions: Individuals with CAI demonstrate greater T1ρ relaxation times and higher T1ρ variability compared to uninjured controls. This finding supports the existing literature illustrating early degenerative joint tissue changes consistent with early onset posttraumatic osteoarthritis in individuals with CAI.

Introduction

Lateral ankle sprain (LAS) is a common injury associated with physical activity and sport and at least 40% of individuals who sprain their ankle will go on to develop chronic ankle instability (CAI)[1]. Altered biomechanics and recurrent sprains[2] observed in those with CAI is associated with ankle post-traumatic osteoarthritis development[3]. Despite this link, the early pathogenesis of ankle post-traumatic osteoarthritis in those with CAI remains poorly understood. Intra-articular problems were visualized in 95% of CAI patients with a mean age of 28 years, at just over 48 months post index LAS[4]. Just 7 months after injury, 29% of those with CAI had osteochondral lesions while 50% of patients (average age: 29 years) had visually detectable degenerative changes[5]. Novel methods are needed to identify CAI patients at greatest risk of developing ankle post-traumatic ankle osteoarthritis as well as determining intervention effectiveness.

Early osteoarthritis pathogenesis begins with an initial loss of proteoglycan density followed by increases in water content and collagen fiber disorganization, changes that compositional MR techniques can assess[6,7]. Combined, the interaction of tissue fluid

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and structural macromolecules (i.e., collagen and proteoglycans) provides collagen with its mechanical properties (i.e., stiffness and resilience)[8]. Altered talar T2 mapping relaxation times have been demonstrated in individuals with CAI, indicating increased water content and/or diminished collagen fiber orientation[9–12]. However, no studies have determined if T1ρ MRI relaxation times or if T1ρ relaxation time variability differ between those with CAI and uninjured controls. T1ρ is an alternative marker of cartilage degeneration that is sensitive to macromolecular changes[6] but may also be influence by factors such as collagen fiber orientation[7]. T1ρ variability is thought to be associated with the diffuse distribution of degenerative changes previously visualized across the talar dome in those with a history of lateral ligament trauma[3,13]. Therefore the purpose of this investigation was to determine differences in T1ρ relaxation times and T1ρ relaxation time variability between those with CAI and uninjured controls. Based on the existing literature, we hypothesized that T1ρ relaxation times and variability will be higher, indicating greater and more diffuse degeneration of the talus in those with CAI.

Methods

Design & participants

A cross-sectional design was used. All participants were: 1) between 18 and 35 years of age and free from acute lower extremity and head injuries for at least 3-months prior to testing with the exception of a LAS. We excluded anyone with symptoms from musculoskeletal and head injuries sustained at any time, as well as those with equilibrium disorders. For this investigation, controls demonstrated an Identification of Functional Ankle Instability (IdFAI) of <11, a Foot & Ankle Ability Measure Activities of Daily Living subscale (FAAM-ADL) of ≥98%, and a Foot & Ankle Ability Measure Sport subscale (FAAM-S) of ≥98%. As recommended by the International Ankle Consortium[14], individuals with CAI demonstrated a history of at least one LAS and at least two episodes of giving way within the past 6 months; an IdFAI >11, a FAAM-ADL< 90%, and a FAAM-S < 80%[14]. If individuals presented with bilateral CAI ($n = 3$), the limb with more ankle sprains and worse self-reported function was used. Exclusion criteria for those with CAI also followed the recommendations of the International Ankle Consortium[14]. All participants provided written informed consent prior to participation and all study methods and recruitment procedures were approved by the biomedical institutional review board at the University of North Carolina at Chapel Hill. Sample size was based off of published T2 mapping relaxation times[9] that resulted in a bias corrected relative effect size of 0.54 (mean difference: 6.1, pooled standard deviation: 10.8). Coupled with an alpha level of 0.05 and 1-beta set at 0.80, a total sample size of 30 was needed. .

Image acquisition

Anatomical (Fast [Turbo] spin echo images) and T1ρ MR images were acquired using a Siemens Magnetom TIM Prisma 3T scanner using an 8-channel large flex coil (516 mm × 224 mm, Siemens, Munich, Germany). Participants were scanned supine and MR was performed with the foot/ankle complex in neutral (90° to the shank). A custom made Orthoplast® splint and an elastic bandage was used so lower leg muscles remained relaxed during the scan. All participants arrived 30-minutes prior to the scan and remained seated to unload the ankle cartilage[10,12]. Anatomical MR images were reviewed for chondral and subchondral bone defects in the talus by two authors (KMD, CP) and confirmed by a third (JNT). Discrepancies were discussed until consensus was reached.

A T1ρ prepared three-dimensional Fast Low Angle Shot (FLASH) with a bandwidth of 350 Hz/Px and spin lock power at 500 Hz was used[15]. Spin lock durations included 40, 30, 20, 10, and 0 ms. Voxel size was 0.8 mm × 0.4 mm × 3 mm (field of view = 288 mm, slice thickness = 3.0 mm, TR = 9.2 ms, echo time (TE) = 4.6 ms, 160 × 320 matrix, gap = 0 mm, flip angle = 10°, echo train duration time = 443 ms, phase encode direction of anterior/posterior). Total acquisition time was ~18 min with 1–2 min time between the anatomical and T1ρ scans.

Talar cartilage segmentation

A single investigator manually segmented the talar articular cartilage for all participants. Segmentations were performed with a T1ρ MR image acquired during the 0 ms spin lock duration using ITK-SNAP software[15]. During segmentation, four regions of interest (ROIs): anteromedial, anterolateral, posteromedial, and posterolateral were identified using anatomical images that registered with T1ρ MR images. First, medial and lateral regions were identified at the slice that represented the midpoint of the talar cartilage. The midpoint was based on the total number of frontal view images that showed clearly visible talar cartilage. In the sagittal view of the midpoint slice, anterior and posterior regions were identified using a drawing technique on ITK-SNAP. The length of the talar dome was first identified before a perpendicular line, at 50% of the length, was drawn vertically. The intersection of this line with the talar cartilage represented the division between anterior and posterior ROIs.

T1ρ relaxation time quantification

Voxel by voxel T1ρ relaxation times were calculated from a five image sequence created with a MatLab program (MatLab R2016b [9.1.0] MathWorks, Natick, MA, USA). T1ρ relaxations times were calculated using the following equation: $S(TSL) = S_0 \exp(-TSL / T1\rho)$[15]. The S corresponds to signal, TSL is the length of the spin-lock time, S_0 is the signal intensity when TSL equals zero, and T1ρ is the T1 relaxation time in the rotating frame. The segmented T1-weighted MR image was overlaid onto the calculated T1ρ image to determine T1ρ relaxation times. T1ρ mean and variability values were extracted for the overall talar surface and each ROI and used for the analyses. Greater T1ρ relaxation times were interpreted as greater degeneration[6,7]. Higher T1ρ variability was interpreted as a more diffuse distribution of degenerative changes in the talar cartilage. Volume was calculated to account for potential differences in ankle size and/or usable slices.

Statistical analysis

The mean T1ρ relaxation time for the overall talus was the primary outcome measure. Between group mean differences and bias corrected Hedge's g effect sizes with their corresponding 95% confidence intervals (95%CI) were calculated and used to determine group differences. SPSS Version 21.0 (SPSS Institute, Chicago, IL, USA) was used. The primary outcome measure was also submitted to a secondary between group analysis adjusting for weight and age with an alpha level of 0.05 used to determine statistical significance.

Results

The segmentation intra-rater reliability of the entire talus was 0.982, 95%CI: 0.927–0.996). Participant demographics are reported

in Table I. Group means, standard deviations, mean differences, effect sizes, and corresponding 95% confidence intervals (CI) are presented in Table II. Individuals with CAI demonstrated greater T1ρ relaxation times (i.e., 95%CI did not cross zero) over the entire talus and multiple ROIs relative to controls. T1ρ variability differed between the groups (i.e., 95%CI did not cross zero) over the entire talus and multiple ROIs. Volume over the entire talus and all ROI did not differ between the groups (i.e., 95%CI crossed zero). After adjusting for age and weight, T1ρ relaxation time over the entire talus remained different between the groups (Mean difference: 9.13, 95%CI: 2.27 to 15.99, $P = 0.036$).

Discussion

These results support our *a priori* hypothesis and are consistent with studies linking CAI to cartilage degeneration via T2 mapping[9–12] and arthroscopic visualization[3,13]. Greater T1ρ relaxation times suggest those with CAI already demonstrate deleterious changes in talar cartilage quality. Greater T1ρ variability is thought to be representative of a more distributed pattern of degenerative changes over the talus consistent with similar patterns observed in those with a history of a LAS during arthroscopic visualization[3,13]. However, it is difficult to contextualize the variability results as this variable has not been previously reported. Cumulatively, our results are consistent with the early stages of osteoarthritis development; compositional changes in articular cartilage (i.e., higher T1ρ values) without morphological degradation (i.e., no decline in cartilage volume)[8].

Increased T2 mapping relaxation times have been observed in a variety of CAI sub-groups[9,10,12] and lateral ankle sprains[9,11]. Compositional declines have been reported in individuals with CAI who are[10,12] and are not seeking medical attention[9]. While not reported, it is reasonable to hypothesize that patients seeking care would have significant functional impairments and persistent symptoms. However, those not seeking care also demonstrated self-reported functional limitations. Thus, future research should aim to better understand the relationships among self-reported function and compositional MR values in those with CAI.

The composition of the talar cartilage, as a whole, is consistently worse in those with CAI, but differences in specific ROIs vary among studies. Differences may be due to a variety of methodologies including how ROIs are defined, the number of slices used, the technique used (i.e., T1ρ or T2 Mapping), and/or the decision to separate the talar cartilage into superficial and deep layers. A six ROI model (i.e., anterior, middle, and posterior sections of the medial and lateral talus) has been used with sagittal plane sections being identified manually. We used a four ROI model to objectively generate sagittal plane ROIs based on talar anthropometrics.

Table I
Participant demographics, injury history characteristics, and self-reported function

	Control ($n = 15$)	CAI ($n = 15$)
Sex (Males, Females)	4, 11	4, 11
Age (years)	21.07 ± 2.55	21.13 ± 1.81
Height (cm)	167.18 ± 7.73	166.62 ± 8.08
Weight (kg)	69.21 ± 13.60	66.50 ± 8.27
Identification of Functional Ankle Instability	0.13 ± 0.52	22.67 ± 2.82
Foot & Ankle Ability Measure Activities of Daily Living subscale (%)	100.00 ± 0.00	86.19 ± 9.7
Foot & Ankle Ability Measure Sport subscale (%)	100.00 ± 0.00	68.33 ± 21.87
NASA PASS	5.13 ± 1.46	6.80 ± 1.37
Number of ankle sprains	–	4.00 ± 2.07
Number of giving way episodes within 6 months	–	6.87 ± 5.36
Morphological Findings and Location		
No visual defects and/or changes	$n = 10$	$n = 10$
T1 marrow edema	–	AM Talus($n = 1$), PM Talus ($n = 1$)
Subchondral cyst	AL Talus ($n = 3$)	AM Talus ($n = 1$), AL Talus ($n = 2$)
Osteochondral defect	PL Talus ($n = 1$)	–
Low signal intensity	AM & AL Talus ($n = 1$)	–

NASA PASS: National Aeronautics and Space Administration Physical Activity Status Scale captures a participant's self-reported level of physical activity over the past month. AM: Anteriomedial, AL: Anteriolateral, PM: Posteriomedial, PL: Posteriolateral.

Table II
Group means, standard deviations, effect sizes, and 95% confidence intervals (CI) for the dependent variables

	CAI ($n = 15$)	Control ($n = 15$)	Mean Difference (95% CI)	Effect Size (95% CI)
T1ρ Relaxation times (ms)				
Overall*	65.97 ± 10.45	56.84 ± 7.68	9.13 (2.27, 15.99)	0.76 (0.02, 1.50)
AnterioMedial	67.61 ± 13.31	60.91 ± 13.65	6.71 (−3.38, 16.79)	0.48 (−0.24, 1.21)
AnterioLateral*	66.93 ± 11.23	57.73 ± 5.90	9.20 (2.38, 16.01)	1.00 (0.24, 1.48)
PosterioMedial*	63.56 ± 12.43	54.71 ± 10.84	8.85 (0.13, 17.57)	0.74 (0.01, 1.49)
PosterioLateral*	65.94 ± 11.73	56.84 ± 7.67	11.74 (3.57, 19.91)	3.84 (2.63, 5.04)
T1ρ Variability (ms)				
Overall*	32.78 ± 4.06	28.23 ± 4.45	4.55 (1.36, 7.74)	1.04 (0.28, 1.80)
AnterioMedial	33.48 ± 5.40	29.17 ± 7.48	4.30 (−0.58, 9.20)	0.64 (−0.09, 1.38)
AnterioLateral*	31.03 ± 4.53	25.35 ± 5.71	5.68 (1.83, 9.54)	1.07 (0.31, 1.84)
PosterioMedial	30.18 ± 5.95	26.24 ± 5.69	3.94 (−0.42, 8.29)	0.66 (−0.08, 1.39)
PosterioLateral*	33.39 ± 4.64	28.44 ± 5.03	4.95 (1.33, 8.57)	1.00 (0.24, 1.75)
Cartilage Volume (mm^3)				
Overall	1581.92 ± 335.74	1480.58 ± 310.45	101.34 (−140.51, 343.20)	0.30 (−0.41, 1.02)
AnterioMedial	454.91 ± 113.04	420.89 ± 127.33	34.01 (−56.04, 124.07)	0.27 (−0.44, 0.99)
AnterioLateral	417.66 ± 118.16	377.88 ± 125.89	39.78 (−51.54, 131.09)	0.32 (−0.40, 1.04)
PosterioMedial	382.75 ± 86.44	380.74 ± 83.79	2.01 (−61.66, 65.69)	0.02 (−0.69, 0.74)
PosterioLateral	326.62 ± 81.43	301.06 ± 80.77	25.57 (−35.09, 86.23)	0.31 (−0.41, 1.03)

* Indicates the mean difference is significantly different at $P < 0.05$.

Frontal plane ROIs (i.e., medial, lateral) have used two slices in each ROI[9], three consecutive slices[12], and all available slices[10]. We segmented the entire talus to ensure the most comprehensive examination of T1ρ relaxation time means and variability possible. Contrary to the literature, we did not identify anteriomedial ROI differences. Higher T2 values in all medial ROIs are consistently noted in those with CAI[9,10,12] and these alterations are present in the superficial and deep talar cartilage layers[9,12]. While not different, our CAI T1ρ relaxation times and variability values were higher, relative to the control group, in the anteriomedial ROI and were associated with a moderate effect sizes. Higher T2 values were previously noted in lateral ROIs[9,10,12], consistent with the current investigation. Overall, the cumulative body of composition MR evidence supports the arthroscopic literature indicating that cartilage lesions are present over the entire talar dome of those with CAI[3,13].

The current study provides novel information regarding critical compositional differences between individuals with CAI and healthy controls; yet some limitations should be addressed to improve future research. First, a small sample size of recreational active individuals was used and thus these results may not generalize to more athletic populations and/or those actively seeking medical care. Our small sample size also limits our ability to understand how potential confounders such as age, sex, weight, and/or physical activity levels influence talar cartilage composition. Similarly, much larger data sets across a broader age range of individuals with CAI are needed to build upon the preliminary results of our secondary analysis. Future research is needed to determine how scan type and segmentation decisions influence resting state cartilage composition values.

Conclusions

Those with CAI have increased T1ρ relaxation times and greater T1ρ variability across the overall talar cartilage and in multiple ROIs relative to uninjured controls of a similar age. These findings support the existing literature illustrating early degenerative changes in CAI patients.

Author contributions

Erik Wikstrom, Kyeongtak Song, and Brian Pietrosimone contributed to the conception and design of the study. All authors contributed to the acquisition, analysis, and interpretation of data, as well as the drafting and critical revision of the article, and provided final approval of the version submitted. Erik Wikstrom, wikstrom@unc.edu, takes responsibility for the integrity of the work as whole.

Competing interests statement

No author has a competing interest, financial or otherwise.

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