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FULL PAPER

Ultrashort TE evaluation of the osteochondral junction *in vivo*: a feasibility study

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Objective: To determine whether differences in the osteochondral junction (OCJ) in two different age groups could be detected with ultrashort time-to-echo (UTE) MRI *in vivo*.

Methods: 10 healthy controls aged 20–30 years (Group 1) and 10 patients aged 40–50 years with knee pain but no evidence of osteoarthritis (OA) (Group 2) underwent 3-T MRI of the knee using a two-dimensional UTE sequence. Evaluation of the presence/absence of a high-signal-intensity (SI) line at the medial tibial/lateral tibial (MT/LT) OCJ was performed. Regions of interest (ROI) were created at the MT OCJ and LT OCJ. The peak OCJ SI ratio was calculated by measuring peak OCJ SI using averaged craniocaudal SI profiling, then dividing by the mean SI of a background ROI to standardize between studies. Groups were compared using χ^2 and Mann–Whitney *U* tests.

Results: A high SI line was present in significantly more Group 1 subjects at both MT ($p < 0.001$) and LT ($p = 0.002$). There was a significant difference ($p < 0.001$) in MT peak OCJ SI ratio between Group 1 (mean $\pm$ SD = 0.85 ± 0.10) and Group 2 (0.77 ± 0.12). There was no significant difference ($p = 0.19$) in LT peak OCJ SI ratio between Group 1 (0.81 ± 0.23) and Group 2 (0.80 ± 0.13).

Conclusion: Significant differences in the UTE MR characteristics of the OCJ were demonstrated between the two age groups.

Advances in knowledge: Alterations in the UTE appearances of the tibial plateau OCJ in the older group with knee pain compared with a younger, healthy control cohort may reflect the very early stages of OA.

INTRODUCTION

The term “osteochondral junction” (OCJ) is usually used to refer to the complex of the deep non-calcified layers of the articular cartilage, calcified articular cartilage and subchondral bone plate (Figure 1). This serves as a functional barrier between the synovial joint space and subchondral bone. It is believed to play an important role in the pathogenesis of osteoarthritis (OA).^{1,2} Electron micrographic studies have shown disruption of this barrier both with increasing age and in OA.^{3,4} This disruption may be a key initiating event in OA via several mechanisms, including exposure of the subchondral bone to neurogenic and angiogenic factors and upregulation of metalloproteinase activity within chondrocytes of the superficial cartilage layers, causing degradation of the extracellular matrix, loss of proteoglycan and reduction in cartilage load-bearing ability.^{5,6}

MRI plays a key role in OA research, allowing visualization of multiple joint structures, particularly the articular cartilage.⁷ However, MRI of the OCJ has proven to be difficult

owing to the inherent short transverse relaxation (T_2 or T_2^*) time of OCJ structures. Using sequences with conventional times to echo (TEs), signal from these structures decays to close to 0 before it can be encoded, and the OCJ appears as an area of low signal.

The advent of sequences able to provide TE of < 1 ms, known collectively as ultrashort time-to-echo (UTE) sequences, offers a way to overcome this limitation. Full details of these techniques have been described at length.^{8,9} In brief, two-dimensional (2D) UTE sequences use a half radiofrequency pulse with a slice-selection gradient and begin to acquire data as soon as excitation finishes. Filling of *k*-space is performed in a non-linear fashion, with radial and spiral trajectories described.¹⁰ The polarity of the slice selection is then reversed and the process is repeated, with the combination of the two data sets producing the image of the selected slice. Three-dimensional acquisition is also possible.¹¹ Various methods are available to suppress the signal from structures with longer T_2 to maximize short

Figure 1. Schematic line drawing of the surface of a synovial joint demonstrating different layers. The osteochondral junction is usually defined as the complex of the deepest layer of the non-calcified cartilage, calcified cartilage and subchondral bone plate.

T_2/T_2^* contrast, including preparatory inversion-recovery pulses and echo-subtraction techniques.^{12,13}

UTE sequences have provided a novel method of imaging multiple different musculoskeletal structures with short T_2/T_2^* , including the meniscus, cortical bone, tendon and OCJ.^{14,15} UTE demonstrates the normal OCJ as a thin, linear high-signal-intensity (SI) structure.¹⁶ Using cadaveric specimens, Bae et al¹⁷ demonstrated that the structures contributing to this high SI line were the deepest layer of uncalcified cartilage and the calcified cartilage layer. Some samples obtained from individuals with OA had thinning or absence of this high SI line. This was validated with histological correlation, and there is preliminary work suggesting that changes in quantitative UTE MR of the OCJ are associated with quantitative differences in the superficial articular cartilage layers.¹⁸

Studies of the OCJ using UTE to date have, in general, used cadaveric knees, with some descriptions provided of alterations in the OCJ appearances in advanced OA. No study has sought to determine changes occurring at the OCJ with normal ageing or very early degenerative changes *in vivo*.

This study featured two groups: one young (20–30 years) healthy control group and one older (40–50 years) group with knee pain. The older group had no established OA, but given the presence of non-traumatic knee pain, represent a group at high risk of developing OA.¹⁹

The primary aim of this study was to determine whether differences in the OCJ in two different age groups could be detected with UTE MRI. A secondary aim was to determine whether any differences in the OCJ were associated with differences in the overlying articular cartilage composition using T_2 mapping.

METHODS AND MATERIALS

Ethical approval for the study was obtained from the local research ethics committee. All subjects provided written, informed consent. This was a prospective, observational, feasibility study, carried out

at our institution (Norfolk and Norwich University Hospital) between September 2014 and January 2015.

Participants

Two groups of 10 participants were recruited. Group 1 contained 10 healthy control volunteers aged 20–30 years. Group 2 contained 10 participants aged 40–50 years, who had been referred for knee MRI at our institution for evaluation of non-traumatic knee pain.

Participants were excluded if there was a history of significant lower limb injury or lower limb surgery, OA, inflammatory arthritis, haematological malignancy, bone metastases, metabolic bone disease or if there was a contraindication to MRI.

Participants had their height and weight recorded at the time of their MR examination and completed an Oxford Knee Score questionnaire to assess the severity of symptoms.²⁰

MRI

Participants underwent MR of the knee on a GE 3.0 T wide-bore platform (GE Healthcare, Amersham, UK) using an eight-channel high-definition knee coil (GE WD 750). The UTE sequence selected to provide optimal visualization of the OCJ (Figure 2) following pilot testing was a coronal 2D high-spatial-resolution sequence [field of view (FOV) 12×12.3 cm, matrix 558×558 , flip angle 12° , TR 13.5 ms, TE 0.03 ms, number of excitations (NEX) 1, slice thickness 2.5 mm, interslice gap 2.5 mm and sequence duration $2 \text{ min } 30 \text{ s}^{-1}$]. The study MR protocol also featured a sagittal intermediate-weighted sequence with spectral fat saturation (fatsat) to evaluate for bone marrow lesions or focal cartilage defects (FOV 15×15.4 cm, matrix 352×288 , TR 3422 ms, TE 48.28 ms, NEX 1 and slice thickness 3 mm) and a multiecho coronal T_2 weighted sequence to allow cartilage T_2 mapping (FOV 12×12.3 cm, matrix 256×192 , TR 800 ms, TE 6.93/13.86/20.78/27.71/34.64/41.57/48.50/55.42 ms, NEX 1 and slice thickness 2.5 mm).

Clinical MR analysis

All MR studies were reviewed by a consultant musculoskeletal radiologist with 12 years' experience (AT). Any potential

Figure 2. Sample coronal ultrashort time to echo image of the knee of a 28-year-old male subject (representative of a Group 1 participant) demonstrating the osteochondral junction (OCJ) high-signal-intensity line at the tibial plateau (white arrow-heads). Regions of interest (ROI) placement at the medial tibial OCJ and lateral tibial OCJ is demonstrated (void boxes), including intermediate signal articular cartilage, high-signal OCJ and low-signal subchondral bone. Background ROI placement at the medial femoral condyle is also shown.

participants in Group 2 with MR evidence of established OA—full-thickness cartilage defects or bone marrow lesions—were excluded. The MR studies of Group 1 participants were also reviewed to ensure that there was no structural abnormality.

Sample size

There were no reliable pilot data available for this study; thus, a formal sample size calculation was not performed. However, the numbers included are at least equal to those in similar UTE feasibility studies *in vivo*.²¹ A sample size of 20 individuals gave 80% power to detect a difference of 0.12 in peak OCJ SI ratio between groups at the $p = 0.05$ level, assuming a standard deviation of 0.1.

Osteochondral junction qualitative analysis

Six coronal UTE images through the central weight-bearing tibial plateau were selected for each participant knee by reference to axial and sagittal localizers.

The presence or absence of a UTE high SI line at the medial tibial (MT) and lateral tibial (LT) OCJ on each selected image was recorded. Comparison of the proportion of OCJ high SI lines present at the MT and LT between groups was performed using χ^2 tests.

Evaluation was performed by two independent observers, both radiology residents with 3 years' (JM) and 1 year's (SL) experience. Interrater agreement was assessed using Cohen's Kappa.

Osteochondral junction quantitative analysis

Analysis was performed using ImageJ® (National Institutes of Health, Bethesda, Maryland). The same six coronal UTE images used for qualitative analysis were selected.

On each image, rectangular regions of interest (ROI) measuring approximately 15×5 mm were created across the MT and LT OCJ. The tibial articular surface was used in preference to the femoral articular surface, as the flatter morphology facilitated easier ROI placement. A square ROI measuring approximately 10×10 mm was then placed in the medial femoral condyle as a background ROI (Figure 2).

Craniocaudal SI profiles were then created for both the MT and LT ROIs, averaged across the width of the ROI (Figure 3). The peak in the intensity profile corresponding to the OCJ was identified, and the SI at this location was recorded. A similar method of analysing the OCJ using SI profiles has been described previously.²²

The MT and LT peak OCJ SI ratio was then calculated by dividing the OCJ peak SI by the mean SI in the background ROI, to standardize between studies using the background ROI as an internal reference. The measurement procedure was repeated on each coronal image.

We calculated peak OCJ SI ratios to assess for quantitative OCJ differences rather than perform direct measurement of thickness, as the depth of the OCJ (<1 mm) makes accurate measurement problematic.²³

Following assessment of the data for a normal distribution, non-parametric Mann–Whitney U tests were used to compare mean MT and LT peak OCJ SI ratios between groups. The Bonferroni method was used to account for multiplicity of testing, with a significant difference between the means defined by a p -value of <0.0167 (three comparisons per image).

ROI placement and interpretation of intensity profiles was performed by two independent observers (JM and SL). Interrater agreement for MT and LT peak OCJ SI ratio was assessed using the intraclass correlation coefficient (ICC)—single measures, consistency.

Cartilage analysis

Cartilage T_2 mapping was performed using a GE workstation with T_2 mapping capability (Functool, AW VolumeShare 5, GE Healthcare). This was to determine whether hypothesized differences in the OCJ were associated with quantitative differences in the overlying articular cartilage.

The MT and LT cartilage was segmented semi-automatically on the six coronal images corresponding to those used for OCJ analysis. The mean T_2 relaxation time for the medial and lateral cartilage on each image was recorded.

The mean medial and lateral cartilage T_2 values were compared between Groups 1 and 2 using a non-parametric Mann–Whitney U test (following assessment for a normal distribution), with significance levels set as above.

Statistical analyses were performed using SPSS® v. 20 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) and R v. 3.1.2 (www.r-project.org).

Figure 3. Ultrashort time to echo images of the medial tibial plateau of a sample Group 1 (a) and Group 2 (b) individual. Regions of interest (ROI) placement is demonstrated (void boxes), with corresponding signal intensity (SI) profiles, performed in a craniocaudal direction (white arrow) and averaged across ROI width. Black arrowhead represents osteochondral junction (OCJ) signal peak, black void arrowhead represents the low-signal subchondral bone plate and black arrow represents the subchondral bone marrow. The OCJ high SI line is less conspicuous in (b). Peak OCJ SI ratio in (a) = 0.88 and in (b) = 0.60. Thinning/absence of the OCJ high SI line in the Group 2 subject corresponds to a reduction in peak OCJ SI ratio.

RESULTS

Participants

Baseline characteristics of study subjects are summarized in Table 1.

Osteochondral junction qualitative analysis

Results are summarized in Table 2.

A high SI line was visible at the MT OCJ of 57/60 [95%, 95% confidence interval (CI) 89–100%] Group 1 images and 42/60 (70%, 58–82%) of Group 2 images. At the LT OCJ, a high SI line was visible in 40/60 (67%, 55–79%) of Group 1 images and 23/60 (38%, 26–51%) of Group 2 images.

This represented a statistically significant difference between groups at both the MT ($p < 0.001$) and LT ($p = 0.002$) OCJ.

There was moderate interrater agreement for qualitative analysis of the MT OCJ ($\kappa = 0.60$; 95% CI, 0.42–0.78) and fair interrater

agreement for qualitative LT OCJ analysis ($\kappa = 0.34$, 0.20–0.48), in keeping with standard interpretation of κ values.²⁴

Osteochondral junction quantitative analysis

Results are summarized in Table 2.

The mean MT peak OCJ SI ratio was statistically significantly ($p < 0.001$) higher in Group 1 (mean = 0.86, 95% CI 0.83–0.88) than in Group 2 (0.77, 0.74–0.80) (Figures 3 and 4).

The mean LT peak OCJ SI ratio was higher in Group 1 (0.81, 0.75–0.86) than in Group 2 (0.80, 0.77–0.84); however, this was not statistically significant ($p = 0.186$).

There was good interrater reliability for MT peak OCJ SI ratio, with ICC = 0.65 (95% CI 0.53–0.74). Similar results were obtained for the LT peak OCJ SI ratio, with ICC = 0.64 (0.52–0.73).

Table 1. Baseline characteristics of study subjects

Characteristic	Group 1	Group 2
Age ^a (years)	27.8 (26–29)	45.1 (41–48)
Body mass index (kg m ⁻²) ^a	23.5 (2.8)	26.2 (3.1)
Females/males	5/5	6/4
Right knee/left knee	7/3	3/7
Oxford knee score ^a	48 (0)	32.1 (7.8)

^aValues are mean (standard deviation) except age, which is mean (range).

Cartilage mapping

The mean MT cartilage T_2 value was statistically significantly ($p < 0.001$) higher in Group 2 (40.6 ms, 38.9–42.3) than in Group 1 (36.4 ms, 35.1–37.7).

The mean LT cartilage T_2 value was higher in Group 2 (35.3 ms, 34.2–36.3) than in Group 1 (34.6 ms, 33.3–35.9); however, this was not statistically significant ($p = 0.13$).

DISCUSSION

This study demonstrated significant qualitative and quantitative differences in the UTE MR characteristics of the OCJ in individuals aged 40–50 years with knee pain but no conventional features of OA compared with a healthy control cohort aged 20–30 years. There was a significant difference in the MT, but not the LT cartilage T_2 values between groups.

We propose two possible explanations for this difference. First, alterations demonstrated at the OCJ in the older group might be an aspect of normal ageing rather than a pathological disease state. Thinning of the calcified layer of the articular cartilage has been described with advancing age in *ex vivo* electron micrographic studies, and this would explain the fact that OCJ alterations were demonstrated in the absence of other conventional MR evidence of OA.⁴

Second, the differences demonstrated could reflect disruption of the OCJ as part of early OA. Medial compartment knee OA is significantly more common than lateral compartment OA, potentially explaining why significant quantitative OCJ alterations

were demonstrated at the MT, but not at the LT.²⁵ Non-traumatic knee pain, as experienced by Group 2 subjects, has been described as a portent of OA.¹⁹ There was also a significant difference in mean MT cartilage T_2 values between groups. Increased T_2 values of the articular cartilage correlate with histological degeneration, supporting the hypothesis that individuals in Group 2 did have early degenerative changes, despite the lack of conventional MR features.²⁶

The early OA hypothesis is further supported by previous studies demonstrating alterations at the OCJ in *ex vivo* specimens with OA. Bae et al¹⁷ demonstrated the absence of the UTE OCJ high SI line in cadaveric patellar samples with areas of cartilage loss due to OA. The same group demonstrated correspondence of thinning or absence of the OCJ high SI line to areas of thinning of the calcified cartilage layer and alterations of the subchondral bone plate, morphological alterations described in OA.²⁷

Two types of UTE OCJ signal abnormality are described in previous studies: thinning or absence of the high SI line and diffuse thickening of the high SI line. In this study, we demonstrated primarily the former in Group 2. Studies that have demonstrated diffuse thickening of the OCJ high SI line have used cadaveric samples from elderly individuals, some of whom had advanced OA. It may be the case that the thickened, diffuse morphology was not seen in our study because it relates to more advanced ageing or reflects a more advanced stage of OA.

This study has demonstrated the potential of UTE *in vivo* to resolve important questions surrounding the role of the OCJ in OA pathogenesis. While the conventional view is that initial changes in OA occur in the superficial cartilage layers with resultant abnormal mechanical loading and subchondral bone remodelling, there is an alternative hypothesis. This proposes that initial changes occur at the OCJ, damaging the functional barrier between the subchondral bone and the synovial joint space and predisposing the superficial layers of the articular cartilage to degradation.^{1,2} Longitudinal studies using UTE imaging of the OCJ could provide a method of differentiating changes in OCJ structure due to normal ageing from those seen in OA. How these changes relate to alterations in adjacent

Table 2. Between-group comparisons

Variable	Group 1	Group 2	<i>p</i> -value
Osteochondral junction			
MT high SI line present ^a	57/60 (95, 89–100)	42/60 (70, 58–82)	<0.001
LT high SI line present ^a	40/60 (67, 55–79)	23/60 (38, 26–51)	0.002
MT peak OCJ SI ratio ^b	0.86 (0.83–0.88)	0.77 (0.74–0.80)	<0.001
LT peak OCJ SI ratio ^b	0.81 (0.75–0.86)	0.80 (0.77–0.84)	0.186
Articular cartilage			
MT T_2 (ms) ^b	36.4 (35.1–37.7)	40.6 (38.9–42.3)	<0.001
LT T_2 (ms) ^b	34.6 (33.3–35.9)	35.3 (34.2–36.3)	0.13

LT, lateral tibia; MT, medial tibia; OCJ, osteochondral junction; SI, signal intensity.

^aData are proportion (%; 95% confidence interval).

^bData are mean (95% confidence interval).

Figure 4. Box plots comparing the medial tibial (MT) and lateral tibial (LT) peak osteochondral junction (OCJ) signal intensity (SI) ratio between groups. Notches indicate 95% confidence intervals for the median values. Median (interquartile range) MT peak OCJ SI in Group 1 = 0.83 (0.79–0.92) and in Group 2 = 0.75 (0.68–0.85). Median LT peak OCJ SI in Group 1 = 0.75 (0.65–0.84) and in Group 2 = 0.80 (0.73–0.88).

tissues—superficial articular cartilage layers and subchondral bone—could also be assessed.

Qualitative interrater agreement was moderate for evaluation of the MT but only fair for evaluation of the LT. Possible reasons for this include the more curved surface of the LT, making visual assessment more difficult. Evidence from animal studies suggests that regional variations in OCJ thickness develop in response to variable loading conditions.²⁸ As the MT tends to experience greater loading than the LT, the MT OCJ is likely to be thicker, making visual assessment easier and less susceptible to partial-volume artefacts. As familiarity with UTE sequences improves and technical optimization progresses (e.g. reduction in off-resonance artefacts which are a source of blurring of the UTE images), the reliability of qualitative assessment will likely improve.²⁹

Quantitative interrater agreement was good, indicating that our measurement technique may be suitable for further quantitative studies. Alternative quantitative approaches are available, including calculation of OCJ T_2^* values.²³ However, this method has only been described *ex vivo* using a 7.0-T system, and it is likely that the thinness of the OCJ would make this method less feasible on clinically available platforms at 3.0 T or less. In addition, our method has the advantage of shorter scan duration with only single TE than multiple TEs required for T_2^* mapping.

In future, the qualitative method is more likely to be of clinical utility, given that assessment is rapid and intuitive. The potential value of the quantitative method described would be to increase the level of confidence that a reader has in his/her qualitative assessment, as he/she becomes used to this sort of sequence.

As a feasibility study, this has several limitations. First, we do not provide histological verification that a reduction in peak OCJ SI ratio corresponds to OCJ thinning. However, previous studies

have demonstrated correlation between absence/thinning of the OCJ high SI line on UTE images with areas of OCJ absence/thinning on histology.¹⁷ Figure 3 demonstrates that the absence of the OCJ high SI line in the Group 2 image corresponds to a reduction in the peak OCJ SI ratio. Therefore, it is reasonable to assume that a reduced peak OCJ SI ratio does provide a good proxy indicator of OCJ thinning.

Second, our study was performed at a single point in time on a single MR platform. Test–retest reliability of our measurement technique remains unknown, as does its applicability across different platforms and types of UTE sequence. However, it is encouraging that other quantitative UTE assessments at the knee joint have demonstrated excellent test–retest reliability.³⁰

Third, we utilized a 2D UTE sequence to maximize signal-to-noise ratio. However, 2D sequences are more susceptible to partial-volume effects at the interface between low-signal OCJ and relatively high-signal articular cartilage. This may explain the absence of the high SI line in some healthy control subjects. Technical improvement in three-dimensional sequences may make these a more attractive option in future.

In summary, this study demonstrated significant qualitative and quantitative differences in the UTE MR characteristics of the OCJ in individuals aged 40–50 years with knee pain but no conventional features of OA compared with a younger, healthy control cohort.

CONFLICTS OF INTEREST

Dr Gavin C Houston is an employee of General Electric (General Electric had no role in the design or conduct of the study, data analysis or manuscript preparation).

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