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Femoral cartilage defects initiate from medial meniscus extrusion or tibial cartilage lesions and expand in knee osteoarthritis as revealed by 3D MRI analysis

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Knee osteoarthritis is characterized by articular cartilage wear, with its morphological progression not fully understood. This study aimed to elucidate factors contributing to femoral cartilage defects and their expansion in medial knee osteoarthritis, using a novel approach analyzing cross-sectional MRI data arranged by disease severity. From a cohort of 277 women in the Kanagawa Knee Study, we selected 17 knees that showed a cartilage area ratio < 0.99 in the posteromedial femoral cartilage region as the subjects for this study. The morphological relationships between femoral cartilage defects and menisci, as well as between femoral cartilage defects and tibial cartilage lesions, were investigated. Among subjects aged 30 to 79 years, the proportion was significantly higher in the 70–79 age group. In 11 cases, the outer edge of the cartilage defect was observed to coincide with the inner edge of the medial meniscus. Tibial cartilage lesions corresponded to femoral cartilage defects in 15 cases. Our 3D MRI analysis demonstrated that femoral cartilage defects were initially caused by either medial meniscus extrusion or kissing tibial cartilage lesions, with subsequent expansion of these defects resulting from the combined effects of ongoing medial meniscus extrusion and progressive tibial cartilage degeneration.

Trial registration: UMIN, UMIN000032826; September 1, 2018.

Keywords Knee, Osteoarthritis, 3D MRI, Femoral cartilage, Medial meniscus extrusion

Abbreviations

MRI	Magnetic resonance imaging
3D MRI	Three-dimensional MRI
2D MRI	Two-dimensional MRI
OA	Osteoarthritis
SPGR	Spoiled gradient
PDW	Proton-density weighted
DICOM	Digital imaging and communications in medicine

Knee osteoarthritis (OA) is a disease characterized primarily by the wear of articular cartilage due to aging [1]. Elucidating the process underlying its morphological progression is crucial for developing prevention and treatment methods. While there have been reports based on cadaveric knee observations [2], surgical resection specimens [3], and 2D MRI studies [4], the process has not been fully clarified. Large-scale longitudinal studies, such as the NIH-funded Osteoarthritis Initiative (OAI) database and the Multicenter Osteoarthritis Study (MOST)

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database, have provided valuable insights into OA progression [5,6]. However, further research is still needed on the detailed morphological progression of medial knee OA, which is a representative form of knee OA.

Recent advances in artificial intelligence (AI) have made it possible to fully automatically extract bones, cartilage, and menisci from 2D knee MRI information and non-invasively elucidate the morphological relationships between cartilage and menisci, as well as between femoral and tibial cartilage lesions, using 3D images [7]. However, to clarify the progression of knee OA using this image extraction method, it is necessary to periodically observe MRI images of specific subjects from pre-OA to late-stage OA. This requires data collection over a considerable period and is difficult to achieve.

To address this issue, we developed an approach that collects cross-sectional MRI data from a relatively homogeneous population, arranges them in order of OA severity using highly sensitive quantitative evaluation, and analyzes them morphologically assuming that OA progresses in the same order. In our previous research on the tibial joint surface, we observed and analyzed 3D MRI images of medial tibial cartilage defects arranged from smallest to largest. We reported that cartilage defects begin with medial meniscus extrusion and expand along the inner edge of the medial meniscus as the extrusion progresses [8]. While this approach has proven effective for understanding tibial cartilage changes, the progression of femoral cartilage defects remains less clear. The purpose of this current study was to use this approach to elucidate the factors contributing to femoral cartilage defects in medial knee OA and the process of their expansion.

Methods

The Kanagawa knee study

This study was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University, and written informed consent was obtained from all subjects. All methods were performed in accordance with the relevant guidelines and regulations. The protocols were enrolled in a database of the National University Hospital Council of Japan (UMIN000032826) on 01/06/2018 and disclosed. The first subject (registration number: KS-001) was included in the study 28/09/2018. The last subject (registration number: KS-573) was included on 05/09/2019.

The purpose of the Kanagawa Knee Study is to clarify the epidemiology and natural history of knee OA. The main inclusion criteria are (1) employees of the Kanagawa Prefectural Office, retired employees of the Kanagawa Prefectural Office, or those who work in Kanagawa Prefecture or live in the Tokyo metropolitan area, and (2) those who work at a desk for at least 4 h per day or perform similar work during their employment. The main exclusion criteria are those who have (1) a history of surgery on either the left or right knee and (2) a past history of consecutive visits to the hospital for more than 3 months for knee injuries on either the left or right side, from birth to the start of data collection[9–11].

MRI scanning

The MRI system (Achieva 3.0TX, Philips, Amsterdam, Netherlands) was used at 3.0 T with 16-channel coils. During the MRI scan, the knee was positioned at approximately 15 degrees of flexion. The sagittal plane of the knee joint was acquired to obtain both a fat-suppressed spoiled gradient echo sequence (SPGR) image and a proton-density weighted (PDW) image. For the SPGR sequence, the repetition time (TR) was 20 ms, and the echo times (TEs) were 7 ms and 13.8 ms for the first and second echoes, respectively. The flip angle was 35°. For the PDW sequence, the TR was 1000 ms, the TE was 35 ms, and the flip angle was 90°. Both sequences used an echo train length of 32 for the PDW image (not applicable for the SPGR image). For both images, the acquisition voxel size was $0.6 \times 0.6 \times 0.6$ mm, reconstructed to $0.3 \times 0.3 \times 0.3$ mm. The slice thickness was 0.3 mm, with no gap between slices, and 320 slices were acquired. The field of view was 150×150 mm. Total scan durations were 7 min 30 s for the SPGR image and 7 min 10 s for the PDW image[9–11].

MRI 3D images

The MRI analysis was conducted using SYNAPSE 3D (version 6.8, Fujifilm Corporation, Tokyo, Japan), a 3D image analysis system. This software automatically registers the SPGR and PDW images together. Cartilage regions were automatically extracted from the SPGR images, while bone and meniscus regions were obtained from the PDW images (Fig. 1A-i, ii). The software allows for the projection of reconstructed 3D images in any direction [9–11] (Fig. 1A-iii). Our previous validation of this software reported high segmentation accuracy, as measured by Dice similarity coefficients (DSC). Specifically, the mean DSC values were 0.985 for femoral bone, 0.980 for tibial bone, 0.911 for femoral cartilage, 0.892 for tibial cartilage, 0.916 for medial meniscus, 0.891 for lateral meniscus, 0.905 for the region of interest (ROI) of the femoral subchondral bone, and 0.888 for the ROI of the medial/lateral tibia plateau [7]. These high DSC values indicate excellent agreement between manual and automated segmentations. In the current study, all images were successfully segmented without failures due to image quality issues.

Vertically and radially projected cartilage

In the vertically projected cartilage area, the femoral and tibial cartilage was projected vertically onto a plane using the long axis of the bones (Fig. 1B-E). The software provides cartilage thickness mapping by displaying cartilage thickness as a color scale; thick areas of cartilage are indicated in white and thin areas in red.

In the radially projected cartilage area, the centers of the medial and lateral condyles were determined by approximating the condyles to ellipses in a lateral view (Fig. 1F), and the femoral cartilage was projected radially around the intercondylar axis (Fig. 1G) [12].

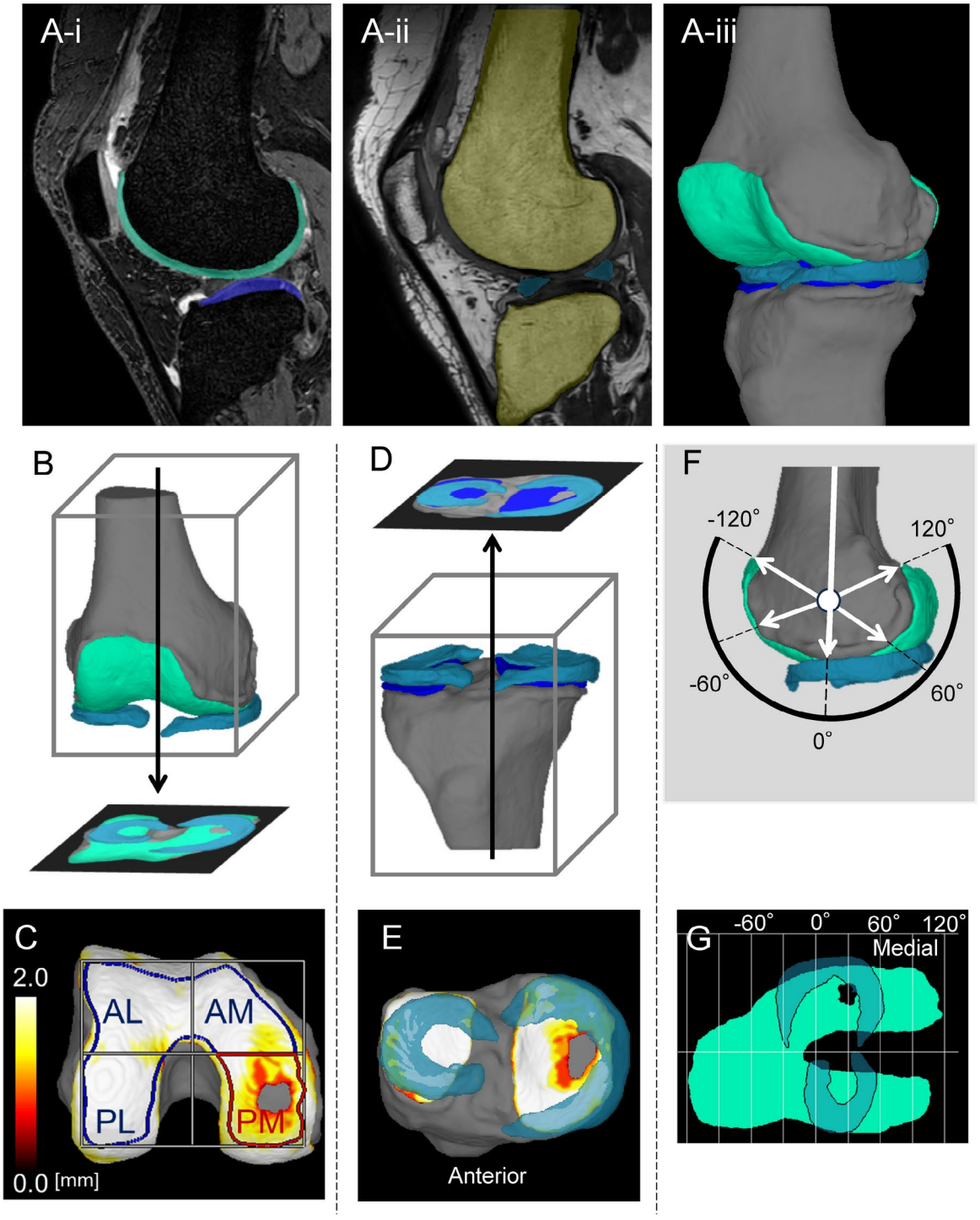

Fig. 1. 3D MRI analysis of the right knee with medial OA. (**A**) Sagittal and 3D images. (i) Sagittal SPGR image. Fully automatically extracted femoral cartilage is shown in green and tibial cartilage in dark blue. (ii) Sagittal PDW image. Fully automatically extracted bone is shown in yellow and meniscus in blue. (iii) 3D image. Bone is shown in gray, cartilage in green and dark blue, and menisci in blue. (**B**) Scheme showing the vertically projected cartilage area from 3D femoral cartilage and menisci. (**C**) Cartilage thickness mapping and 4 regions of the femoral cartilage. PM, posteromedial femoral; AM, anteromedial; PL, posterolateral; and AL anterolateral. (**D**) Scheme showing the vertically projected cartilage area from 3D tibial cartilage and menisci. (**E**) Cartilage thickness mapping of the tibial cartilage and menisci. (**F**) Scheme showing the vertically projected cartilage area from 3D femoral cartilage and menisci. The centers of the medial and lateral epicondyles are determined in the lateral view. A plane perpendicular to the line connecting these centers is established. The cartilage and meniscus are then radially expanded. A line parallel to the femoral long axis passing through the center is set as 0 degrees. (**G**) Radially projected cartilage area from 3D femoral cartilage and menisci.

Segmentation of cartilage area and the cartilage ratio

In the vertically projected femoral cartilage area, the software automatically drew a closed curve line for the ROI based on the bone contour. The rotation was determined in a way that generated a horizontal tangent line between the ROI at the posteromedial cartilage and the ROI at the posterolateral cartilage. The software drew lines that split the ROI equally in the longitudinal and transverse directions, resulting in 4 regions. In this study, the ROI was set 5 mm inward from the bone contour. The cartilage ratio was defined as the proportion of the area where cartilage is present relative to the total area of the ROI (Fig. 1C) [12].

Medial meniscus extrusion width

Coronal cross-sectional images were reconstructed from MRI data of SPGR sagittal cross-sectional images. The slice in which the tibia was at its maximum transverse diameter was selected. A curve along the original medial edge of the tibia was drawn subjectively. A vertical straight line was drawn from the medial edge of the tibia, excluding osteophytes. A straight line was then drawn from the outer edge of the medial meniscus. The distance between these two lines was defined as the medial meniscus extrusion width (based on the tibia). Similarly, a curve along the original medial edge of the femur was drawn subjectively. A vertical straight line was drawn from the medial edge of the femur, excluding osteophytes. The distance between this line and the medial meniscus outer edge line was defined as the medial meniscus extrusion width based on the femur (Fig. 2). Based on previous studies, we defined medial meniscus extrusion width as an extrusion width of 3 mm or more from the tibial edge [9–11].

Enrollment of subjects

The Kanagawa Knee Study consisted of 573 subjects (Fig. 3). Eleven subjects were excluded due to withdrawal and one for ineligible data. Then, 284 males were excluded. The remaining 277 females consisted of 56 in their 30 s, 61 in their 40 s, 53 in their 50 s, 55 in their 60 s, and 52 in their 70 s. From these 277 females, 17 subjects with a cartilage area ratio at the posteromedial region < 0.99 were selected for analysis. From the remaining 260 subjects, one was randomly selected as a normal control.

Statistical analysis

To examine whether there was a bias in the proportion of women with a cartilage area ratio less than 0.99 in the posteromedial region of the femoral cartilage across age groups, a chi-square test was performed using the BellCurve software for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). If a bias was observed, pairwise comparisons using Fisher's exact test were conducted to determine which age groups differed. The significance level was set at 0.05.

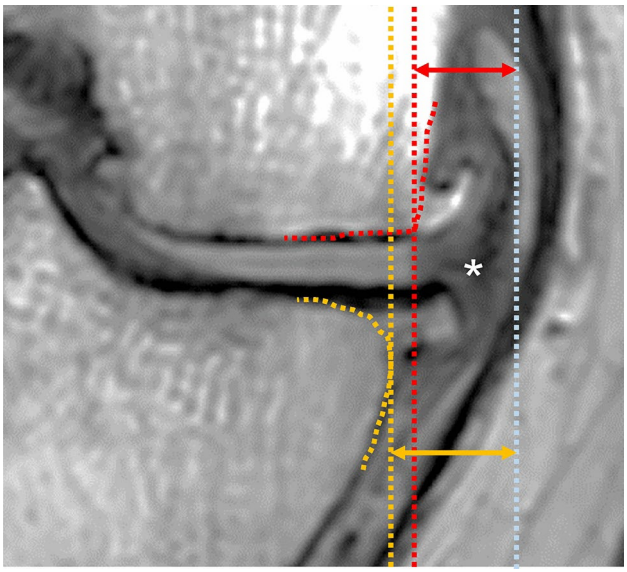

Fig. 2. Measurement of the medial meniscus extrusion width. The SPGR coronal image is shown at the level of the maximum tibial width. An orange curve was drawn subjectively along the original medial edge of the tibia. A straight vertical orange line was drawn from the medial edge of the tibia, excluding osteophytes. A straight blue line was then drawn from the outer edge of the medial meniscus (star). The distance between the orange and blue lines (orange double-headed arrow) was defined as the medial meniscus extrusion width (based on the tibia). Similarly, a red curve was drawn subjectively along the original medial edge of the femur. A straight vertical red line was drawn from the medial edge of the femur, excluding osteophytes. The distance between the red and blue lines (red double-headed arrow) was defined as the medial meniscus extrusion width based on the femur.

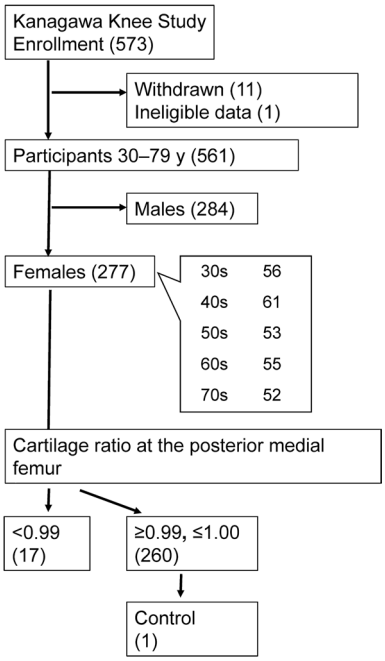

Fig. 3. Enrollment of subjects. The Kanagawa Knee Study consisted of 573 subjects. Eleven subjects were excluded due to withdrawal and one for ineligible data. Then, 284 males were excluded. The remaining 277 females consisted of 56 in their 30 s, 61 in their 40 s, 53 in their 50 s, 55 in their 60 s, and 52 in their 70 s. From these 277 females, 17 subjects with a cartilage area ratio at the posteromedial region < 0.990 were selected for analysis. From the remaining 260 subjects, one was randomly selected as a normal control.

Results

Characteristics of subjects

There were 17 females with a cartilage area ratio less than 0.99 at the posteromedial region of the femoral cartilage. The proportion of females with this condition was 0% (0/56 cases) in their 30 s, 0% (0/56 cases) in their 40 s, 4% (2/53 cases) in their 50 s, 4% (2/55 cases) in their 60 s, and 25% (13/52 cases) in their 70 s. Chi-square test revealed a statistically significant difference in cartilage area ratio across age groups ($p = 4.6 \times 10^{-8}$). Pairwise comparisons using Fisher's exact test showed that the 70 s age group had a significantly higher proportion compared to all other age groups. Femoral cartilage thickness mappings were arranged in descending order of the cartilage ratio at the posteromedial region in Fig. 4.

Femoral cartilage defects and medial meniscus extrusion

Among the 17 cases studied, the outline of the cartilage defect touched the inner edge of the medial meniscus in 11 cases (Fig. 5A,B). Of these, in one case (No. 10), the cartilage defect outline appeared to touch the inner edge of the medial meniscus in a more extended position, while in another case (No. 16), this occurred in a more flexed position. Medial meniscus extrusion was observed in 15 cases (No. 3 to 17) out of the 17 cases (Fig. 5C).

Femoral cartilage defects and tibial cartilage lesions

Tibial cartilage defects corresponded to femoral cartilage defects in 10 out of 17 cases when examining the relationship between these two types of defects (Fig. 6). In 5 other cases, areas of worn tibial cartilage that had not yet progressed to full defects (considered as lesions) corresponded to medial femoral cartilage defects (Fig. 7). In total, 15 cases showed correspondence between tibial cartilage abnormalities (including both defects and lesions) and femoral cartilage defects.

Discussion

We performed a 3D analysis of knee MRIs from 277 female subjects in the Kanagawa Knee Study to clarify the etiology and progression process of femoral cartilage defects in medial knee OA. Seventeen knees (17/277, 6%) showed a cartilage area ratio of less than 0.99 in the posteromedial femoral cartilage region. Among subjects aged 30 to 79 years, the proportion of knees with this ratio was significantly higher in the 70–79 age group. In 11 cases (11/17, 65%), the outer edge of the cartilage defect was observed to coincide with the inner edge of the medial meniscus. Tibial cartilage lesions corresponded to femoral cartilage defects in 15 cases (15/17, 88%).

Medial meniscus extrusion is a significant factor in medial OA [13]. In our previous study on tibial cartilage using 3D MRI analysis, we demonstrated that medial meniscus extrusion leads to cartilage defects at the inner edge of the medial meniscus in the tibial cartilage [8]. In the current investigation, we identified 11 knees where the inner edge of the medial meniscus coincided with the outline of the femoral cartilage defect, suggesting that medial meniscus extrusion is the cause of femoral cartilage defects in these cases. Among these, two cases

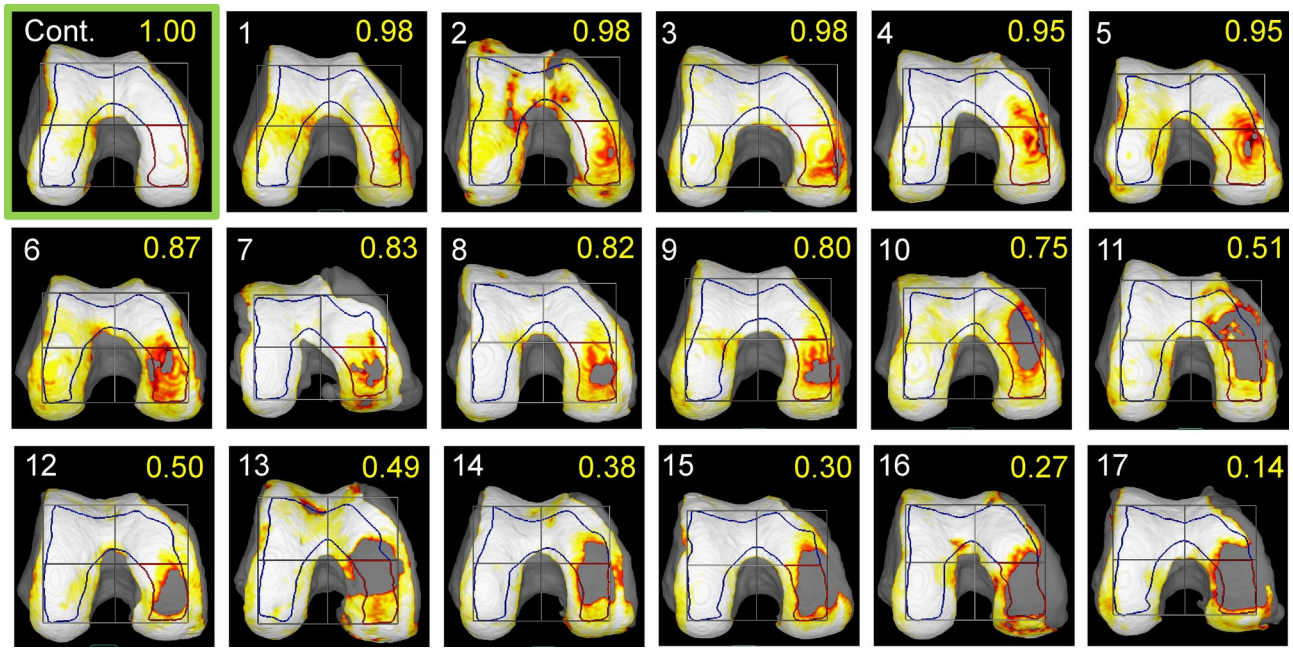

Fig. 4. Vertically projected cartilage thickness mapping for the femoral cartilage arranged in order from mild to severe OA. The cartilage ratio in the PM regions is shown in the upper right corner. The images are arranged in descending order of the cartilage ratio, with the ranking number shown in the upper right corner.

(Cases 1 and 2) showed that the femoral cartilage defect touched the inner edge of the medial meniscus, despite no apparent medial meniscus extrusion on 2D MRI. Since MRI is performed in a supine position and medial meniscus extrusion becomes more pronounced in a standing position [14], it is likely that these two cases may exhibit medial meniscus extrusion when standing.

Lesions in the tibial cartilage are likely to cause damage to the corresponding femoral cartilage. This occurs because damage to the tibial cartilage reduces its shock-absorbing capacity in that area, resulting in excessive pressure and friction on the corresponding femoral cartilage, a phenomenon known as "kissing lesions" [15]. In this study, kissing lesions were observed in 15 out of 17 knees. Tibial cartilage defects are mainly caused by medial meniscus extrusion, and these tibial cartilage lesions can lead to femoral cartilage lesions. Furthermore, femoral cartilage lesions can in turn cause tibial cartilage lesions, potentially leading to an expansion of cartilage defects throughout the entire medial compartment.

Regarding the etiology and progression process of femoral cartilage defects in medial knee OA, we summarize the following based on our current research findings and previous reports. Femoral cartilage defects were initiated either due to medial meniscus extrusion or due to kissing tibial cartilage lesions. Subsequently, these defects expanded due to both medial meniscus extrusion and kissing tibial cartilage lesions (Fig. 8).

This figure arranges the cartilage area ratios in ascending order, combining the posteromedial and anteromedial regions of the femoral cartilage, to visually demonstrate the progression of medial knee OA in an easy-to-understand manner. Our study screened for knees with a cartilage area ratio of less than 0.99 in the posteromedial femoral cartilage region. We did not include the anteromedial femoral cartilage in this screening to exclude cases of patellofemoral OA [16].

There are several reports that demonstrate how femoral cartilage changes in knee OA progress morphologically. Gulati et al. studied patterns in medial and lateral unicompartmental OA, finding significant differences: medial OA lesions centered at 11° flexion, expanding posteriorly, while lateral OA lesions centered at 40° flexion, expanding both anteriorly and posteriorly [3]. This suggests distinct progression patterns due to different mechanical factors in each compartment. Arno et al. conducted a retrospective analysis of 97 total knee arthroplasty cases with medial OA [17]. They found that on the medial femoral condyle, the predominant lesion was a band central to the condyle, curving inwards anteriorly toward the trochlea and extending 10 to 15 mm anterior to the intercondylar notch. Using MRI studies, Arno et al. also observed MRI and found that initial cartilage loss occurred in areas of direct femoral-tibial contact, particularly in regions not covered by the meniscus [18]. As OA progressed, cartilage wear spread medially, anteriorly, and posteriorly, with diminishing meniscal protection, possibly due to meniscal subluxation or substance loss. These studies collectively suggest that femoral cartilage changes in knee OA follow specific patterns influenced by mechanical factors and anatomical structures such as the meniscus. Compared to these studies, our current report offers a novel perspective by demonstrating the initial femoral cartilage changes in relation to the meniscus and tibial cartilage using high-resolution, fully automated MRI 3D image extraction. This approach provides new insights into the early stages of cartilage degeneration.

Full-thickness cartilage defects were the primary focus of our study, as our aim was to elucidate the morphological changes in OA by analyzing cartilage area ratios in descending order from highest to lowest

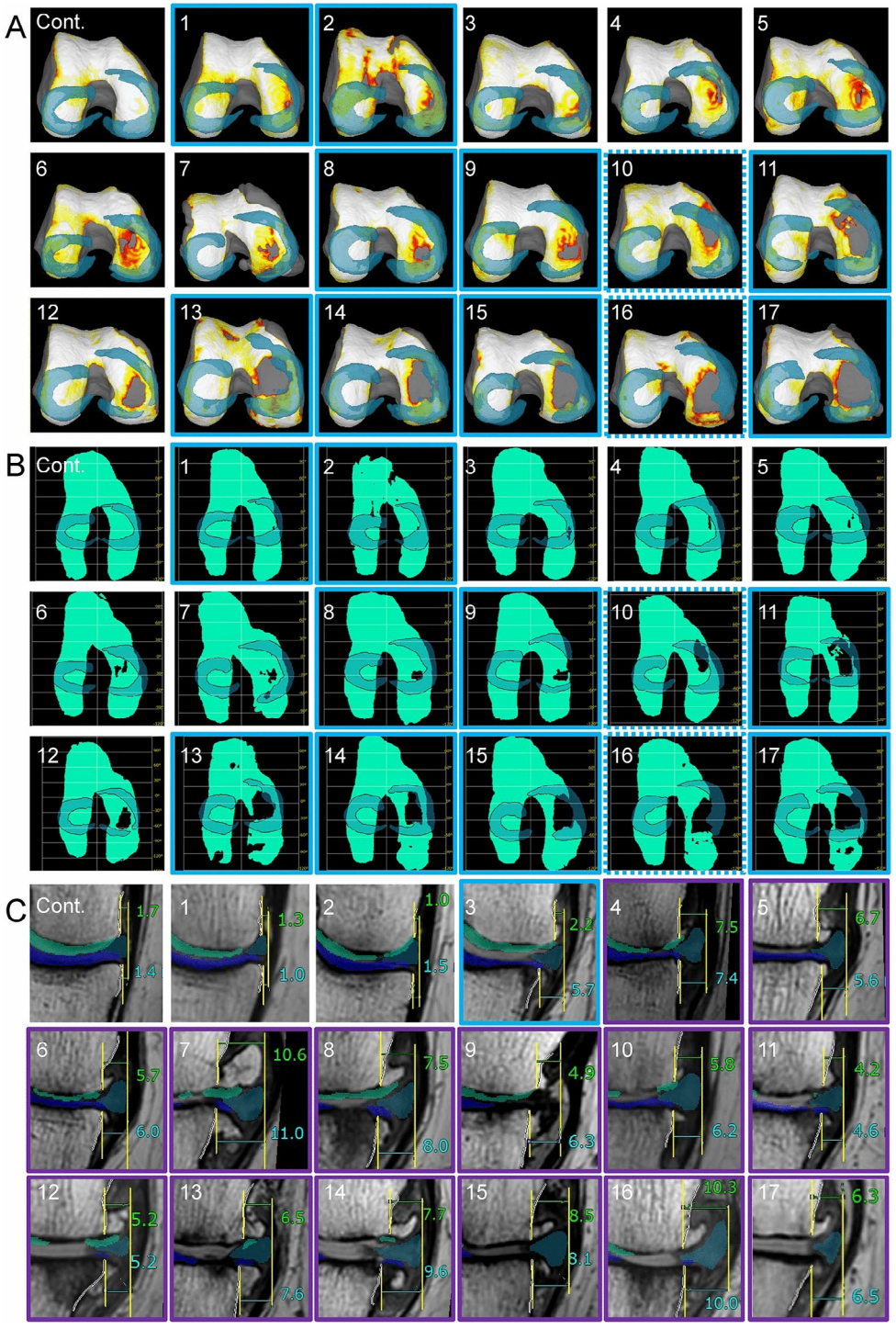

Fig. 5. Association between femoral cartilage defects and the medial meniscus. (**A**) Overlay of vertically projected cartilage thickness mapping of the femoral cartilage and menisci. Blue frames indicate cases where the outline of the cartilage defect touches the inner edge of the medial meniscus. No. 10 shows the cartilage defect outline touching the inner edge of the medial meniscus in a more extended position, while No. 16 shows this in a more flexed position. (**B**) Overlay of radially projected cartilage area of the femoral cartilage and menisci. (**C**) Medial meniscus extrusion on 2D MRI. The SPGR coronal image is shown at the level of the maximum tibial width. Femoral cartilage is shown in green, tibial cartilage in dark blue, and the medial meniscus in blue. The width from the inner edge of the femur (excluding osteophytes) to the outer edge of the medial meniscus is indicated by a green number (mm), and the width from the inner edge of the tibia (excluding osteophytes) to the outer edge of the medial meniscus is indicated by a light blue number (mm). The purple frame indicates a meniscus extrusion of 3.0 mm or more for both femur and tibia, and the light blue frame indicates a meniscus extrusion of 3.0 mm or more for the tibia only.

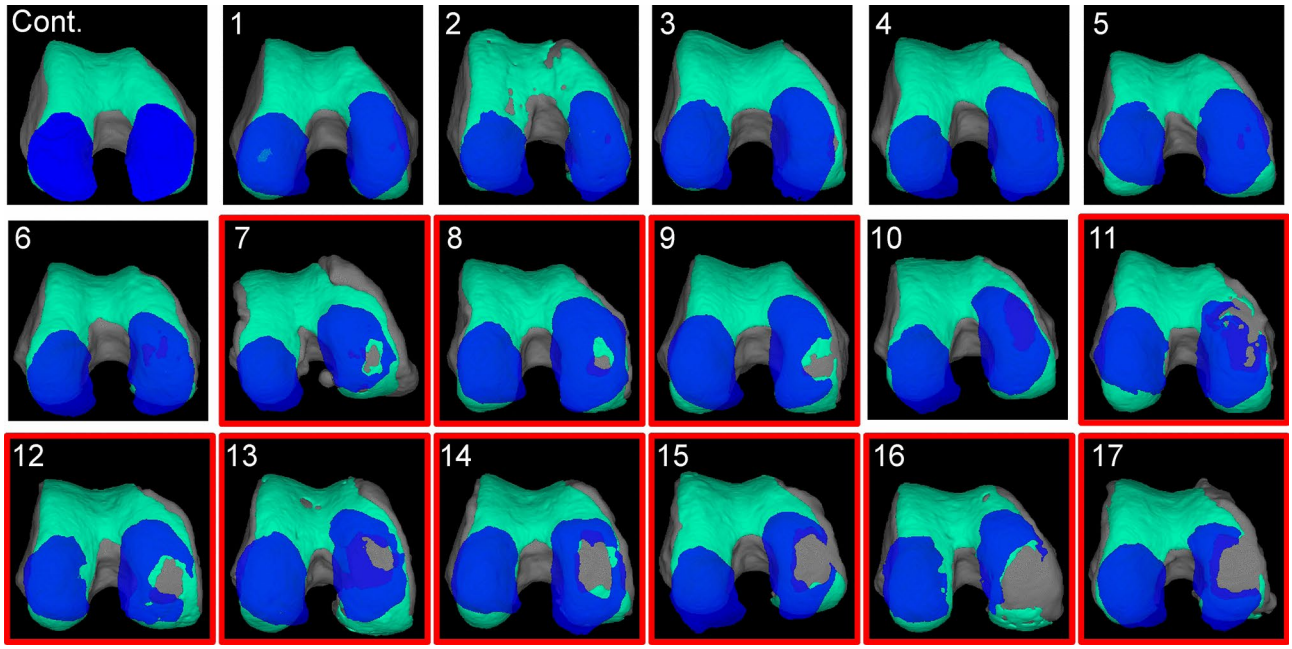

Fig. 6. Association between femoral cartilage defects and tibial cartilage defects. Tibial cartilage area (blue) is overlaid on the vertically projected femoral cartilage area (green). Red frames indicate cases where femoral cartilage defects correspond to tibial cartilage defects.

values. The software we employed can quantify cartilage area ratios by adjusting the thickness threshold, thereby enabling the assessment of OA at various stages. This flexibility opens up possibilities for future research to evaluate cartilage changes across different severity levels. We have previously reported a correlation between 3D MRI analysis of cartilage thickness and ICRS classification by arthroscopy in patients with OA and medial meniscus injuries [19], strengthening the validity of our MRI-based approach.

Female participants were exclusively chosen for this study for two primary reasons. First, maintaining a homogeneous study population was essential to reduce confounding factors and to improve the reliability of our findings. The prevalence of cartilage defects in knee osteoarthritis is generally higher in women than in men [20]. Additionally, significant anatomical differences are evident between male and female knees, with men typically having larger skeletal structures and thicker cartilage [21]. Our research methodology required a detailed, case-by-case analysis of knees with cartilage defects, and this was more feasible with a focused female cohort, given the space constraints of this paper.

Our cross-sectional study design limits our ability to establish causal relationships definitively. While we observed a spatial association between the inner edge of the medial meniscus and femoral cartilage defects in 11 knees, this alone does not prove causation. The relationship between meniscal extrusion and cartilage defects is likely complex and possibly bidirectional. Two of our cases showed femoral cartilage defects touching the meniscal edge without apparent extrusion on 2D MRI, highlighting the dynamic nature of knee joint biomechanics and the limitations of static imaging.

We propose additional limitations to our study. Our sample size of 17 knees with cartilage area ratios < 0.99 is relatively small, which may affect the generalizability of our findings. However, the detailed 3D MRI analysis of each case provided valuable insights, and the consistent patterns observed suggest the relevance of our results. We performed MRI scans with the knees only in a slightly flexed position, without evaluating different flexion angles. Despite this limitation, we were able to observe significant relationships between the femoral cartilage defects, the inner edge of the medial meniscus, and the tibial cartilage lesions at the imaging angle used. Our evaluation of these positional relationships was subjective; thus, a quantitative approach could enhance the reliability of our findings. We also did not assess in detail the condition of the meniscus, which is crucial for understanding how meniscal pathology affects extrusion and contributes to cartilage lesions in OA progression.

Conclusion

Our 3D MRI analysis provided insights into the initiation and progression of femoral cartilage defects in knee OA. The initial defects were found to originate from either medial meniscus extrusion or kissing tibial cartilage lesions. Subsequently, these defects expanded due to the combined effects of continued medial meniscus extrusion and progressive tibial cartilage degeneration, highlighting the complex interplay between different joint structures in the progression of OA.

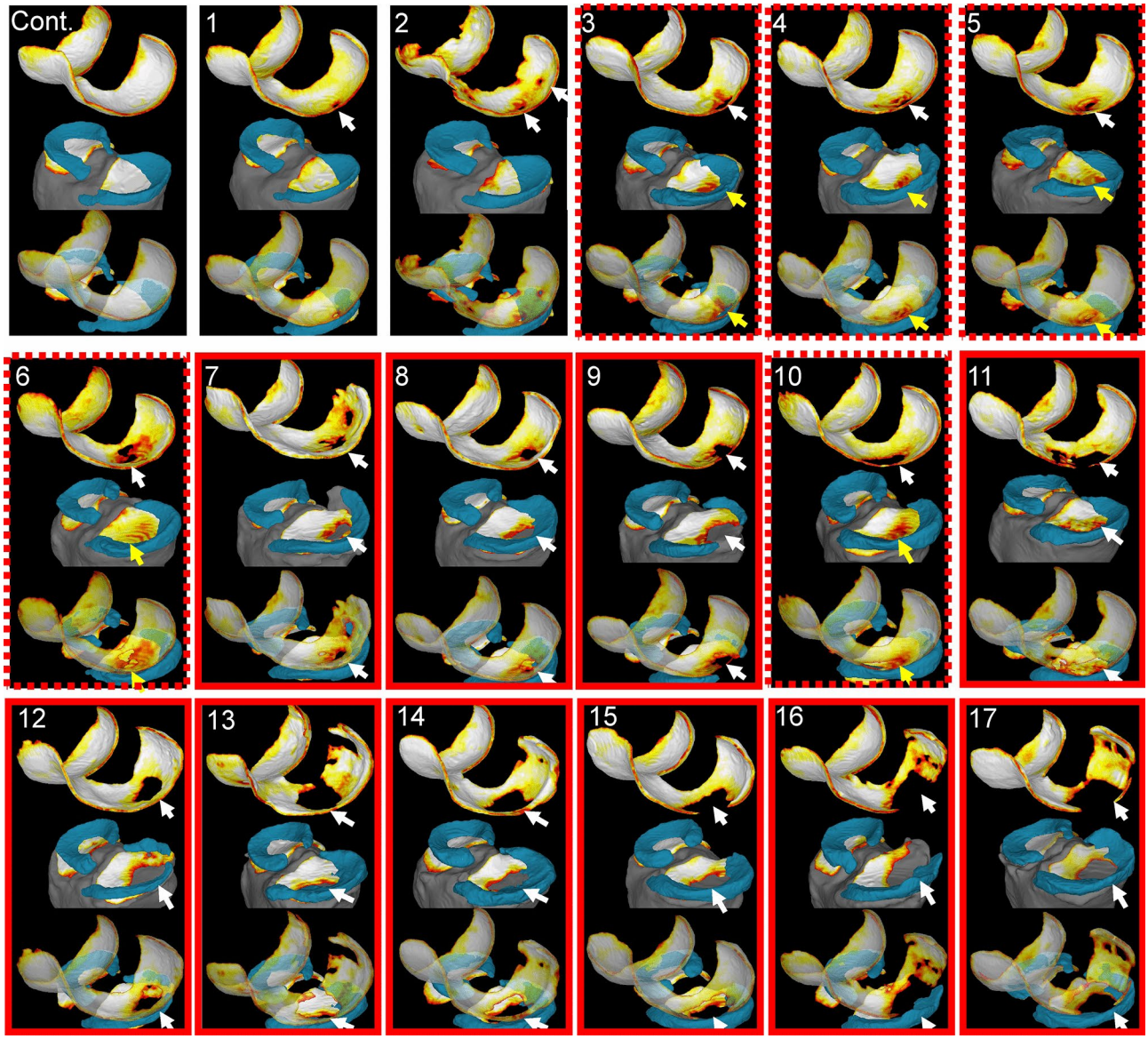

Fig. 7. Association between femoral cartilage defects and tibial cartilage lesions. The figure shows vertically projected femoral cartilage thickness mapping (top row), tibial cartilage thickness mapping with menisci (middle row), and a transparent overlay of these two (bottom row). Solid red frames indicate cases where femoral cartilage defects correspond to tibial cartilage defects, while dashed red frames indicate cases where femoral cartilage defects correspond to worn tibial cartilage that has not yet reached the point of defect. White arrows indicate cartilage defects and yellow arrows indicate tibial cartilage wear.

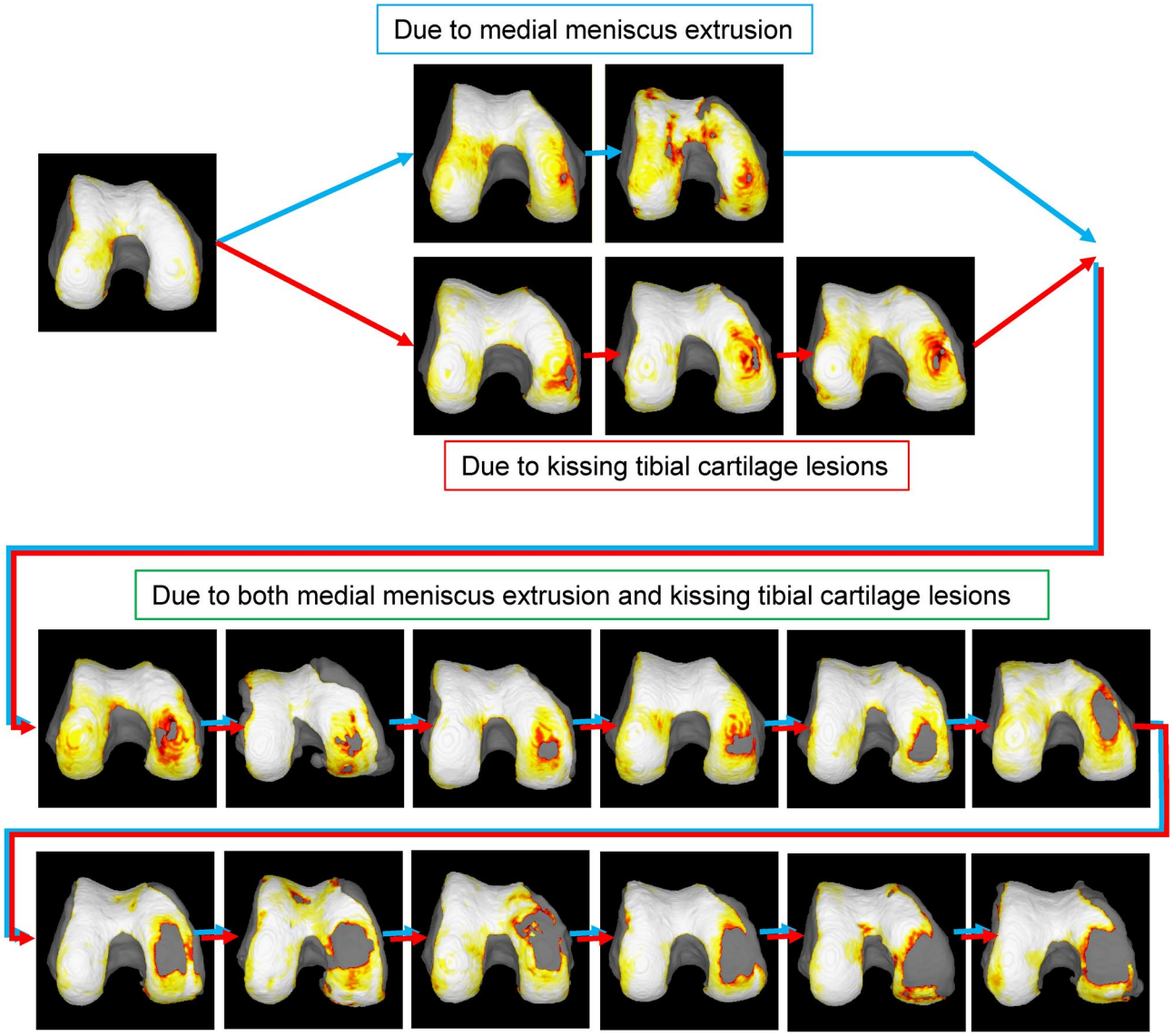

Fig. 8. Proposed model for the etiology and progression of femoral cartilage defects in medial knee OA. Our analysis suggests that femoral cartilage defects may be initiated by either medial meniscus extrusion or kissing tibial cartilage lesions. We hypothesize that these defects subsequently expand due to the combined effects of ongoing medial meniscus extrusion and progressive tibial cartilage degeneration. In this figure, the knees are arranged according to decreasing cartilage area ratio in both the posteromedial (PM) and anterolateral (AL) regions, which we propose may represent different stages of disease progression.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Author contributions

H.Ka. and I.S. wrote the main manuscript text and prepared all figures. N.O., M.M., K.E. and H.Ko. brushed up the manuscript. J.M. developed the software. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Medical Research Ethics Committee of.
Tokyo Medical and Dental University, and written informed consent was obtained from all subjects. The protocol was enrolled in a database of the National University Hospital Council of Japan (UMIN000032826) and disclosed.

Additional information

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