Medial meniscus extrusion is directly correlated with medial tibial osteophyte in patients received reconstruction surgery for anterior cruciate ligament injury: A longitudinal study

Shinnosuke Hada a, Haruka Kaneko a, Lizu Liu a,b, Takako Aoki b, Tomohiro Takamura c,e, Mayuko Kinoshita a, Hitoshi Arita a, Jun Shiozawa a, Yoshifumi Negishi a, Masahiro Momoeda a, Mitsuaki Kubota a, Shigeki Aoki c, Yasunori Okada d, Muneaki Ishijima a,b,*

a Department of Medicine for Orthopaedics and Motor Organ, Juntendo University Graduate School of Medicine, Tokyo, Japan
b Sportology Center, Juntendo University Graduate School of Medicine, Tokyo, Japan
c Department of Radiology, Juntendo University Graduate School of Medicine, Tokyo, Japan
d Department of Pathophysiology for Locomotive Diseases, Juntendo University Graduate School of Medicine, Tokyo, Japan
e Department of Radiology, Shizuoka General Hospital, Shizuoka, Japan

ARTICLE INFO

Keywords:
Medial meniscus extrusion (MME)
Osteophyte
Anterior cruciate ligament injury
Knee osteoarthritis

ABSTRACT

Objective: Anterior cruciate ligament (ACL) injury is one of the causes for post-traumatic knee osteoarthritis (OA), and ACL reconstruction surgery is reportedly unable to prevent OA development. In early-stage knee OA, medial meniscus extrusion (MME) is closely correlated with tibial medial osteophyte width, which consists of bone and cartilage parts. However, the relationship between MME and osteophyte in ACL-injured patients remains elusive. We examined MME and osteophyte and their relationship in ACL-injured patients before and after surgery.

Design: Thirty ACL-injured patients who underwent surgery (30.7 years old, on average) were enrolled. Correlations between magnetic resonance imaging (MRI)-detected OA changes and MME before and after surgery (7.6 months interval) were analyzed.

Results: MME (>3 mm) was present in 16.7% and 26.7% of the patients before and after surgery, respectively, and MME was significantly increased after surgery (2.4 ± 1.3 mm) than before surgery (1.9 ± 1.2 mm) (p < 0.0001). Full-length tibial osteophyte width measured by T2 mapping MRI was significantly increased after surgery (1.9 ± 0.7 mm) than before surgery (1.4 ± 0.6 mm) (p < 0.0001). Among OA structural changes, only medial tibial osteophyte width directly correlated with MME before surgery (β = 0.962) (p < 0.001) and after surgery (β = 0.928) (p = 0.001). All the patients with MME had medial tibial osteophyte before and after surgery. A direct correlation was observed between changes of MME and those of medial tibial osteophyte width before and after surgery (r = 0.63) (p < 0.0001).

Conclusion: MME and medial tibial osteophyte were simultaneously increased after surgery. In addition to close correlation between MME and medial tibial osteophyte width, changes of MME and medial tibial osteophyte width before and after surgery were directly correlated.

1. Introduction

Anterior cruciate ligament (ACL) injury is a common and serious knee joint problem, which is one of the major causes for post-traumatic knee osteoarthritis (OA) [1]. ACL-injured knees are commonly treated by reconstructing the ligament with tissue grafts. The purpose of this surgery is mainly to improve stability of a mechanically unstable knee joint and thus to reduce the risk of subsequent meniscal and/or chondral
damage, both of which ultimately lead to OA. However, long-term studies have indicated that ACL reconstruction does not prevent the development of post-traumatic OA [1], suggesting the possibility that some risk factor(s) other than knee joint instability are implicated for a cause of OA changes in knee joint [2]. However, the risk factors involved in OA development in patients with ACL injury and reconstruction surgery remain elusive.

Menisci, an essential component of the knee joint, functions as a shock absorber against the local mechanical stress to articular cartilage and maintains the joint stability [3]. Meniscal injury is known to be a potential risk factor for post-traumatic OA [4], and indeed malposition and tears of meniscus contribute to the development of knee OA [5]. Medial meniscal extrusion (MME) [6–8] is another risk factor for cartilage damage and progression of knee OA, since MME is involved in joint space narrowing of the medial side of the knee joint and increases mechanical stress to the cartilage of the femur and tibia [9]. Despite many studies on ACL injury and its reconstruction surgery, reports are limited on the occurrence and progression of MME in patients with ACL injury and reconstruction surgery.

Osteophyte, which is one of the characteristics of knee OA, develops at the peripheries of the articular cartilage [10,11]. Histological studies on murine OA models have demonstrated that osteophytes are formed at the junction of the synovium and periosteum through the processes of endochondral ossification and they are composed of the cartilage and bone parts [10]. Although osteophyte formation was originally thought to be a repair process of damaged articular cartilage as a late event in knee OA [12], recent studies using magnetic resonance imaging (MRI) have revealed that osteophyte is frequently detected prior to the cartilage damage in patients with early-stage knee OA and those without radiographic knee OA [13,14]. However, since proton density-weighted MRI as well as radiography detect only the bone part, but not the cartilage part, of osteophyte, rate and size of osteophytes were underestimated by these diagnostic methods. To overcome this problem, we have introduced T2 mapping MRI technique to evaluate the whole osteophyte composed of bone and cartilage parts in patients with early-stage knee OA, and revealed that width of osteophyte determined by T2 mapping MRI is directly correlated with MME [15]. According to the data obtained, we have proposed the hypothesis that MME may be resulted from the junction of the synovium and periosteum and be the cause of MME [5]. In the present study, therefore, we longitudinally examined the degree of MME and osteophyte and their relationship in ACL-injured patients before and after ACL reconstruction surgery by proton density-weighted and T2 mapping MRI. The hypothesis of this study was that MME would be increased and directly correlated with medial tibial osteophyte width even after the reconstruction surgery.

2. Methods

2.1. Subjects

The study protocol is complied with the principles outlined in the Declaration of Helsinki and was approved by the Ethical Review Board Committee of our University (approval number: 15–111). As the present study was categorized as a retrospective study, the Ethical Review Board Committee waived the requirement for patients’ informed consent because of the anonymous nature of the data. The sample size of this study was determined by number of the patients who had the following conditions during the study period (05/2012 to 09/2015). Thirty patients (20 men and 10 women) who underwent arthroscopic ACL reconstruction surgery were enrolled. Eligibility for the participation of the present study was evaluated based on arthroscopic evaluation and standard questionnaires. The inclusion criteria were as follows: (1) The patients were from 20 to 50 years of age, and (2) had body mass index (BMI) of 20–30 kg/m² and (3) no radiographic knee OA [Kellgren-Lawrence (K/L) grade 0 or 1] [16]. (4) They received isolated ACL reconstruction using hamstring tendon autografts [17], and (5) took MRI before and after ACL reconstruction surgery. The exclusion criteria were (1) presence of cartilage lesion evaluated by either arthroscopy [International Cartilage Regeneration & Joint Preservation Society (ICRS) grade ≥2] or MRI [Whole Organ Magnetic Resonance Imaging Score (WORMS) grade ≥2] before operation [19], (2) presence of a root tear of medial meniscus on MRI, (3) presence of a concomitant collateral ligament injuries (≥grade 2) [20], and (4) past history of concomitant meniscectomy or meniscal sutures in the affected knee joint.

2.2. Radiographic evaluation

The radiographic OA severity using K/L grade was evaluated by the weight-bearing antero-posterior radiographs of the femoro-tibial joint for both knees using the bilateral standing extended view and by the weight-bearing postero-anterior radiographs of the femoro-tibial joint using the knee in flexed view [21]. The medial joint space width of the knee joint was determined at the center point of the medial femoro-tibial compartment on a radiograph [22]. The femoro-tibial angle was measured on standing, extended and antero-posterior view radiograph [23]. A femoral and tibial tunnel position after ACL reconstruction surgery was evaluated by the quadrant method (Supplementary Fig. S2) [24–26].

2.3. MRI-based evaluation

MRI scan was taken twice in the patients at just after ACL injury (1st MRI) and after ACL reconstruction (2nd MRI).

2.4. Proton density-weighted MRI

The affected knee joints of the patients were examined by 3.0-T MRI system (Siemens Medical Solutions, Erlangen, Germany) as we previously described [14,15,27,28]. Imaging sequences included coronal and sagittal proton density-weighted images, T2-weighted images, and fat-suppressed T2-weighted images. The MRI data were evaluated in the medial tibio-femoral joint. The OA morphological changes including cartilage lesion, bone marrow lesions, subchondral bone attrition, subchondral bone cyst, osteophyte, and meniscal tears were scored according to the WORMS system. Each region of a compartment surface received its own score according to the methods reported previously [29]. The cartilage morphology was scored 0–6. Bone marrow lesions, subchondral bone attrition, and subchondral bone cyst were scored 0–3. Osteophytes were scored 0–7. Medial meniscus tears were scored 0–6. These scores were added together [14,29]. MME distance was measured as the distance from the outermost edge of medial meniscus to a line connecting the femoral and tibial cortices (Fig. 1) [5]. Occurrence frequency of MME was evaluated by proton density-weighted MRI in which presence of MME was defined as ≥3 mm, as previously reported [30].

2.5. T2 mapping MRI

The regions of interest (ROIs) on T2 mapping MRI were manually drawn using a three-dimensional image analysis software program (Virtual Place; AZE, Tokyo, Japan). T2 values of the medial meniscus and cartilage were calculated, as described previously [14,15]. Cartilage and bone parts of osteophyte were identified by T2 mapping MRI (Fig. 1). Osteophyte width was calculated by sum of the width of cartilage and bone parts, which were separately measured on T2 mapping images in
the medial femoral and tibial osteophyte (Fig. 1) [15]. Osteophytes in the medial side of the knee joint were evaluated by radiography, proton density-weighted MRI and T2 mapping MRI, and the occurrence rate was obtained by defining positive osteophyte that showed radiographic K/L grade ≥2 and WORMS grade ≥2, as previously reported [13,15].

2.6. Reproducibility measurements

Two observers (SH and TT) conducted the examination in order to assess the inter-observer reproducibility. They were blinded to any patient information during the evaluation process. The intra-observer reproducibility of T2 value measurement, WORMS evaluation, MME distance and osteophyte width by MRI were as follows: Interclass correlation (ICC) for inter-reader agreement 0.91 (95% CI 0.64 to 0.98) for T2 value; 0.94 (95% CI 0.91 to 0.96) for WORMS; 0.95 (95% CI 0.78 to 0.99) for MME; and 0.94 (95% CI 0.85 to 0.98) for osteophyte width. The inter-observer reproducibility was also high: ICC 0.91 (95% CI 0.63 to 0.97) for T2 value measurement; 0.90 (95% CI 0.86 to 0.93) for WORMS; 0.93 (95% CI 0.76 to 0.98) for MME; and 0.94 (95% CI 0.84 to 0.97) for osteophyte width. The weighted kappa coefficients of inter- and intra-observer reliability for the readings of WORMS were 0.66 and 0.65, respectively.

2.7. ACL reconstruction surgery

An arthroscopically assisted anatomic single-bundle ACL reconstruction surgery was performed using hamstring tendon autograft [17]. Before ACL reconstruction, we evaluated whether there was any meniscal injury and/or articular cartilage lesion by arthroscopy. The five strands of hamstring tendon were utilized as the graft for augmentation, and the graft composite was fixed to the lateral femoral cortex by flipping the Telos Button (Ai-Medic, Tokyo, Japan) and pulling the graft distally. A double stapling technique was used for graft fixation to the tibial side at 30° of knee flexion. All procedures were performed at one hospital and the same technique was used throughout in this study. A knee joint laxity after ACL reconstruction surgery was evaluated by Pivot shift test.

2.8. Statistical analysis

All analyses were performed using the SPSS 21.0 software program (SPSS Institute; Chicago, IL, USA). Associations between MME and OA-related alterations were determined by a logistic regression and multiple logistic regression analyses. The OA structural alterations detected by MRI taken before ACL reconstruction surgery (1st MRI) of the patients with ACL injury were compared with those detected by MRI obtained after surgery (2nd MRI) using a paired t-test. Correlations between the changes of MME and those of OA structural alterations were examined using a Spearman’s correlation coefficients. The p values < 0.05 were considered to be significant.

3. Results

3.1. Characteristics of the patients with ACL injury

We analyzed 30 patients with ACL injury (20 males and 10 females) (Table 1). The average age of the patients was 30.7 years of age. Eighty percent of the patients showed K/L grade 0 for knee OA on radiograph, while remaining 20% had K/L grade 1. The femorotibial angle and
When the size of osteophyte composed of bone and cartilage parts was density-weighted MRI showed only a few cartilage lesions (3.3%) and no radiographic OA severity K/L: 24 (80%); K/L: 6 (20%) Femoro-tibial angle (°) 175.9 (2.3) Medial joint space width (mm) 4.1 (0.5) Tunnel positions Femoral tunnel position: Depth (X) 24.7% (4.0) Femoral tunnel position: Height (Y) 30.9% (3.6) Tibial tunnel position: A-P direction (AP) 40.1% (4.7) Tibial tunnel position: M-L direction (ML) 44.0% (2.5) Pivot Shift test (after operation) Grade 0 24; Grade 1 6 Medial joint space width (mm) 4.1 ± 0.5 (mean ± standard deviation) Femoral osteophyte width (mm) 23.3% ± 0.7% (mean ± standard deviation) Tibial osteophyte width (mm) 1.8 ± 1.0 mm (mean ± standard deviation) Root tear of medial meniscus (Table 2). While the medial meniscus lesion was minimal (1.1 ± 1.3 of WORMS), MME was significantly increased after ACL reconstruction surgery (2.4 ± 1.3 mm) compared to before surgery (1.9 ± 1.2 mm) (p < 0.0001) (Table 2). One of the representative cases before and after the surgery is shown in Fig. 1. The full-length sizes of femoral and tibial osteophyte width measured by T2 mapping MRI after the surgery were 1.8 ± 0.6 mm and 1.9 ± 1.0 mm, respectively (Table 2).

Among the structural alterations detected by the proton density-weighted MRI, cartilage lesion, bone marrow lesion, subchondral bone attrition, subchondral bone cyst and medial meniscus lesion in the patients after ACL reconstruction surgery were not significantly changed as compared to those before surgery (Table 2). However, osteophyte score (3.7 ± 2.8) and MME (2.4 ± 1.3) after ACL reconstruction surgery were significantly increased compared to those before surgery (1.8 ± 2.3 and 1.9 ± 1.2, respectively) (p < 0.0001) (Table 2). On T2 mapping MRI, the full length medial osteophyte width (1.8 ± 0.6 mm) and tibial osteophyte width (1.9 ± 1.0 mm) after the ACL surgery were significantly increased compared to those before surgery (1.2 ± 0.7 and 1.4 ± 0.8 mm, respectively) (p < 0.0001), and this was due to increased width of the bone part, but not the cartilage part (Table 2). The T2 values of medial meniscus were significantly increased after surgery compared to before surgery (24.4 ± 3.3 vs 23.1 ± 3.0) (p = 0.041), although there was no change in the T2 values of femoral and tibial cartilage before and after the surgery (Table 2).

When the cut-off level for the presence of MME was defined as more than 3 mm on MRI [30], the prevalence of MME before and after surgery was 16.7% (5 of 30 cases) and 26.7% (8 of 30 cases), respectively (Table 2). Osteophyte in the medial tibio-femoral joint was not detected on radiography (data not shown). However, the proton density-weighted MRI showed medial tibial osteophyte in 20.0% of the patients before surgery, and T2 mapping MRI demonstrated osteophyte on the medial side of the femur and tibia before surgery in 23.3% (7 of 30 cases) and 33.3% (10 of 30 cases) of the patients, respectively (Table 2). All the patients with MME (5 of 5 cases) had the medial tibial osteophyte, and there were no cases with MME who had no osteophyte (p = 0.002, data not shown). After the reconstruction surgery, radiography and proton density-weighted MRI showed osteophyte in the medial tibio-femoral joint in 10.0% and 43.3% of the patients (Table 2 and data not shown for radiography), but T2 mapping MRI demonstrated osteophyte on the medial side of the femur and tibia after surgery in 40.0% (12 of 30 cases) and 50.0% (15 of 30 cases) of the patients, respectively (Table 2). The second MRI analysis was conducted with a 7.6-month interval on average from the first MRI. Like the findings before surgery, the proton density-weighted MRI showed only a few cartilage lesions (3.3%) and no root tear of medial meniscus (Table 2).
patients with MME of $>3$ mm (8 of 8 cases) had the medial tibial osteophyte after the surgery and there were no cases with MME who had no osteophyte ($p = 0.001$, data not shown).

3.3. Correlations of MME with knee joint structural alterations in patients with ACL reconstruction surgery

We analyzed correlations between MME and MRI-detected structural alterations of the medial tibio-femoral joint. Although MME was significantly correlated with cartilage lesion and medial tibial osteophyte width before the surgery, MME after the surgery showed significant correlations with several parameters including cartilage lesion, osteophyte, meniscus lesion, femoral osteophyte width, tibial osteophyte width, and T2 value of meniscus (Table 3). However, multiple logistic regression analyses indicated that among these structural changes that showed positive associations with MME, only tibial osteophyte width significantly correlated with MME in the patients before surgery ($\beta = 0.962, p < 0.001$) and after surgery ($\beta = 0.928, p = 0.001$) (Table 3).

We then investigated whether knee joint laxity after ACL reconstruction surgery is correlated with MME and osteophyte development. Although mild residual knee joint laxity was observed in 6 cases after ACL reconstruction surgery, the remaining 24 cases showed no joint laxity (Supplemental Table 1). There were no differences between MME and femoral and tibial osteophyte width in the patients with or without residual knee joint laxity (Supplemental Table 1).

We also examined whether femoral and tibial tunnel positions are correlated with MME and osteophyte development. The average femoral tunnel position of the ACL graft of the subjects was 40.1 $\pm$ 2.5% for medio-lateral directions and 34.9 $\pm$ 3.6% for height (Table 1) (Supplementary Fig. S2A), which were similar to the data shown by the previous study (26.1 $\pm$ 5.5% for depth and 34.9 $\pm$ 10.0% for height) [26]. The average tibial tunnel position of the ACL graft of the subject was 40.1 $\pm$ 4.7% for antero-posterior directions and 44.0 $\pm$ 2.5% for medio-lateral directions (Table 1) (Supplementary Fig. S2B). No positive correlations were observed between MME or femoral and tibial osteophyte development and tunnel positions (Supplemental Table 2).

3.4. Direct correlation of changes of MME with those of medial tibial osteophyte width in patients with ACL reconstruction surgery

We further examined correlations between changes of MME and those of MRI-detected structural alterations, which were determined by calculation of the data obtained by proton density-weighted MRI and T2 mapping MRI before and after the surgery. MME did not correlate with changes of MRI-detected structural alterations including cartilage lesion, osteophyte score, bone marrow lesion, subchondral attrition, and meniscus lesion evaluated by WORMS (Table 4). However, there was a direct correlation between changes of MME and those of medial tibial osteophyte width evaluated by T2 mapping MRI ($r = 0.63, p < 0.0001$) (Table 4 and Fig. 2), although no correlations were observed between changes of MME and those of T2 mapping MRI-detected femoral osteophyte width, T2 value of femoral cartilage, tibial cartilage, or medial meniscus (Table 4).

| Table 4 | Association between the changes of MME and those of MRI-detected structural changes of the medial tibio-femoral joint of the knee in patients with ACL injury. |
| Factor | r | p value |
|--------|---------|----------|
| Proton density-weighted MRI | | |
| Cartilage | 0.23 | 0.24 |
| Osteophyte | 0.33 | 0.08 |
| Bone marrow lesion | −0.139 | 0.48 |
| Subchondral bone attrition | 0.31 | 0.11 |
| Subchondral bone cyst | − | − |
| Medial meniscus lesion | −0.074 | 0.71 |
| T2 mapping MRI | | |
| Femoral osteophyte width | 0.04 | 0.84 |
| Tibial osteophyte width | 0.63 | $<0.0001^*$ |
| T2 value | | |
| Femoral cartilage | −0.11 | 0.59 |
| Tibial cartilage | −0.16 | 0.43 |
| Medial meniscus | 0.045 | 0.82 |

Spearmann’s correlation coefficient. MME, medial meniscus extrusion; MRI, magnetic resonance imaging; ACL, anterior crucial ligament.

**Fig. 2.** Correlation between changes of medial meniscal extrusion (MME) and those of medial tibial osteophyte width in patients with anterior cruciate ligament (ACL) injury. Changes of MME and medial tibial osteophyte width were calculated by subtracting MME distance and medial tibial osteophyte width obtained before surgery (1st MRI) from those after surgery (2nd MRI) in each case, and then the data were analyzed by Spearman’s rank correlation test.
4. Discussion

The present longitudinal observational study of the patients with ACL injury and reconstruction surgery has demonstrated that among the proton density-weighted and T2 mapping MRI-detected OA changes, osteophyte formation and degree of MME are significantly increased after the surgery, and a logistic regression and multiple logistic regression analyses have indicated that MME is directly correlated only with medial tibial osteophyte width. These data suggest that medial tibial osteophyte formation may be implicated in development of MME in patients with ACL injury and reconstruction surgery.

Previous studies showed that osteophyte is commonly observed in knee OA joints and formed as a repair process of damaged articular cartilage [31]. However, studies on murine experimental OA models have demonstrated that osteophyte formation begins within a few days after the induction of OA, i.e., a very-early stage prior to the appearance of overt OA cartilage changes, suggesting that osteophyte formation is not a secondary effect from damaged articular cartilage [10]. In accordance with these experimental data, studies using MRI confirmed that osteophyte is frequently observed prior to the cartilage damage in patients with early-stage knee OA [14] and middle-aged healthy populations [13]. We have also demonstrated that T2 mapping MRI enabled us to efficiently detect cartilage part as well as bone part of osteophyte, and revealed that medial tibial osteophyte composed of cartilage and bone parts is present in almost all patients with early-stage knee OA [15]. In the present study, to the best of our knowledge, we have demonstrated for the first time that the full-length sizes of tibial and femoral osteophytes detected by T2 mapping MRI are significantly increased in all the ACL patients without showing OA cartilage changes at 7.6 months (on average) after ACL reconstruction surgery. Altogether, these data suggest that osteophyte formation is a very early and common event in knee joint prior to cartilage damage.

MME has recently been attracted attention as an important abnormality related to the progression of knee OA [9,32–36]. Since meniscus is essential to protection of the articular cartilage from concentrations of mechanical stress and contributes to load distribution [3], MME is considered to cause increased mechanical stress to the medial sites of the tibial and femoral cartilage because of an increase in area of the tibia uncovered by meniscus. According to these processes, MME plays a key role in development and progression of knee OA by accelerating degradation of the articular cartilage [5,37]. In this study, we found that degree of MME is significantly increased in patients with ACL injury after surgery. Since impairments of the meniscus such as meniscal and/or root tears were not present in the patients, MME may be one of the most important risk factors for the knee OA progression after the surgical joint stabilization in ACL-injured patients without meniscal damage.

There are several mechanisms by which MME is generated. Since the medial meniscus is anchored to the tibia by the posterior and anterior root attachments [38], MME can be readily induced not only when the medial meniscus suffers from the rupture but also when one of the root attachments is torn [39,39]. In early-stage knee OA, however, most patients are free from the medial meniscus rupture or root tears, but MME is commonly found [40]. Thus, mechanism of the development of MME in early-stage knee OA patients with neither rupture of the medial meniscus nor root tears was unknown. Our previous study has confirmed that MME is frequently observed by MRI analysis in the early-stage knee OA patients, who had no disorders of the medial meniscus, and further disclosed that the degree of MME is directly correlated with the medial tibial osteophyte width determined by T2 mapping MRI [15]. Since all the part of the medial meniscus other than the sites of root attachments tightly attaches to the medial tibial plateau via the coronary ligament [38], we have hypothesized that MME formation is initiated by stretching and displacement of the coronal ligament by medial tibial osteophyte in these patients without the medial meniscus problem, leading to degradation of the meniscus and articular cartilage (Supplementary Fig. S1). Although our previous study was a cross-sectional study without longitudinal data [15], the present study has provided the first evidence that osteophyte formation and MME occur prior to articular cartilage destruction, and

Fig. 3. Schematic diagram showing the hypothesis on the development of knee joint OA in patients with anterior cruciate ligament (ACL) injury and its reconstruction surgery. A, Knee joint just after ACL injury. ACL injury such as rupture occurs in normal knee joint, in which medial meniscus is tightly fixed to the medial tibial plateau by the coronary ligament. B, Knee joint at a couple of months after the ACL reconstruction surgery. The injured ACL is reconstructed according to the anatomic single-bundle ACL reconstruction using hamstring tendon autograft. Osteophyte formation begins at the peripheral areas of articular cartilage and medial meniscus extrusion (MME) may be induced by displacement of the coronary ligament by the tibial osteophyte. C, Early-stage OA knee joint in patients with ACL injury and its reconstruction surgery. Osteophyte-mediated MME promotes degradation and destruction of articular cartilage and medial meniscus due to increased mechanical stress to these joint structures, leading to development of post-traumatic knee OA. MM, medial meniscus.
changes of MME are directly correlations with those of medial tibial osteophyte width in ACL-injured patients received reconstruction surgery. According to these data in the current study, we now propose the similar hypothesis on the development of post-traumatic knee joint OA in patients with ACL injury and its reconstruction surgery, in whom osteophyte-mediated MME promotes degradation and destruction of articular cartilage and medial meniscus, inducing OA changes in the knee joint (Fig. 3).

Although it is difficult to conclude the causal relationship between osteophyte formation and MME, our data of the simultaneous association of osteophyte and MME in the patients suggest the possibility that medial tibial osteophyte may be involved in the MME development. Previous experimental studies using animal models showed that osteophytes are generated by repeated mechanical stresses [41,42] or intra-articular injections of growth factors such as transforming growth factor-β and bone morphogenetic protein-2 [10]. Thus, mechanical stresses and/or these factors are thought to play a critical role in development of osteophyte [10], but only limited information is available for the suppressors for osteophyte formation [7,11,43]. Studies on inhibitors of osteophyte formation and development of experimental model systems in which osteophyte formation is selectively blocked will be needed to examine the causal relationship between osteophyte and MME in knee OA.

The present study has potential limitations. First, although we have provided the first evidence about simultaneous progression of medial tibial osteophyte formation and MME, this was based on the MRI data of the subjects in a supine, non-weight-bearing position, which may lead to underestimation of the findings obtained in axially loaded knees. Thus, more definite correlations between MME and medial tibial osteophyte width could be obtained with the knee bearing a full load by the recently developed upright positional MRI. Second, our study contained the small number of patients (n = 30) and we cannot deny the possibility that the present study may have introduced certain bias into the results. Third, it is unclear whether the patients in the present study would result in knee OA. A longer observational study must conduct to elucidate this question. Further longitudinal studies with more patients and longer period are necessary. Fourth, the measurement method used in this study may have bias due to dependent error. Although we obtained high inter- and intra-observer reliability for the measurements by analyzing the images independently by the two investigators, the same observers measured both MME and osteophyte width on the same image. Thus, the data should be obtained preferably by an automated method. Fifth, although no correlation was found between femoral and/or tibial tunnel positions and/or instability of the knee joint and progression of MME in the present study, we cannot deny the possibility that it may become detectable in a longer observational period. We believe that the formation of osteophyte in the short period of time observed in this study may be due to cytokines and/or growth factors released intraarticularly at the ACL injury and/or at the drilling for creating the tunnels during surgery, although further study with a longer observational period is needed.

5. Conclusion

The degree of MME and medial tibial osteophyte width measured by proton density-weighted MRI and T2 mapping MRI were simultaneously increased after surgery, and a close correlation was obtained between MME and medial tibial osteophyte width. In addition, changes of MME and those of medial tibial osteophyte width before and after surgery were directly correlated.

Authors’ contribution

SH conceived and designed the study, had the major role in analysis and interpretation of the data, and contributed to drafting the report. HAK also conceived and designed the study, collected and registered patients, and had the role in analysis and interpretation of the data. LL had the role in analysis and interpretation of the data, and contributed to drafting the report. TA had the role in analysis and contributed to drafting the report. TT had the role in analysis and contributed to drafting the report. HA also had the role in analysis and interpretation of the data, and contributed to drafting the report. JS had the role in interpretation of the data and contributed to drafting the report. YN had the role in interpretation of the data and contributed to drafting the report. MM had the role in analysis and contributed to drafting the report. MIK had the role in interpretation of the data and contributed to drafting the report. SA had the role in analysis. YO conceived and designed the study, had the role in interpretation of the data, and contributed to drafting the report. MI conceived and designed the study, had the major role in analysis and interpretation of the data, and contributed to drafting the report.

Role of the funding source

This study was supported in part by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) to MI (15K10494 and 18K09082), HK (15K20019 and 18K09083), SH (16K20069), TA (19K17290) and YO (16H05454 and 19H03788). This study was also funded in part by a High Technology Research Center Grant and the Program for the Strategic Research Foundation at Private Universities (2014–2019) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) and by a JOA (Japanese Orthopaedic Association)-Subsidized Science Project Research 2022-2024.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgments

We express our deep appreciation to Mr. Tatsuya Miyazaki and his colleagues at the Medical Scanning Hospital (Tokyo, Japan) for their help with the MRI analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocarto.2022.100320.

References

[1] F.W. Roemer, R. Frobell, L.S. Lohmander, J. Niu, A. Guermazi, Anterior Cruciate Ligament Osteoarthritis Score (ACLOS): longitudinal MRI-based whole joint assessment of anterior cruciate ligament injury, Osteoarthritis Cartilage 22 (2014) 668–682. https://www.ncbi.nlm.nih.gov/pubmed/24657830.
[2] L.S. Lohmander, P.M. Englund, L.L. Dahl, E.M. Roos, The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis, Am. J. Sports Med. 35 (2007) 1756–1769. https://www.ncbi.nlm.nih.gov/pubmed/17761605.
[3] H. Kurosawa, T. Fukubayashi, H. Nakajima, Load-bearing mode of the knee joint: physical behavior of the knee joint with or without menisci, Clin. Orthop. Relat. Res. 149 (1980) 283–290. https://www.ncbi.nlm.nih.gov/pubmed/7408315.
[4] B.T. Hanypsiak, K.P. Spindler, C.R. Rothrock, G.J. Calabrese, B. Richmond, T.M. Herrenbruck, et al., Twelve-year follow-up on anterior cruciate ligament reconstruction: long-term outcomes of prospectively studied osteous and articular injuries, Am. J. Sports Med. 36 (2008) 671–677. https://www.ncbi.nlm.nih.gov/pubmed/18326830.
[5] D.J. Hunter, Y.Q. Zhang, J.B. Niu, X. Tu, S. Amin, M. Clancy, et al., The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis, Arthritis Rheum. 54 (2006) 795–801. https://www.ncbi.nlm.nih.gov/pubmed/16508930.
[6] J.G. Adams, T. McAlindon, M. Dimasi, J. Carey, S. Eustace, Contribution of meniscal extrusion and cartilage loss to joint space narrowing in osteoarthritis, Clin. Radiol. 54 (1999) 502–506. https://www.ncbi.nlm.nih.gov/pubmed/10484216.
[7] B.A.M. Snoeker, M. Ishijima, J. Kumm, F. Zhang, A.T. Turkiewicz, M. Englund, Are structural abnormalities on knee MRI associated with osteophyte development? Data from the Osteoarthritis Initiative, Osteoarthritis Cartilage 29 (2021) 1701–1708. https://www.ncbi.nlm.nih.gov/pubmed/34284113.
