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ORIGINAL ARTICLE

Bone marrow lesion is associated with disability for activities of daily living in patients with early stage knee osteoarthritis

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Abstract

Osteoarthritis of the knee (knee OA) induces pain, loss of mobility and diminished activities of daily living (ADL). Although an understanding of the pathophysiology of early stage knee OA has been developed, the structural changes associated with disability for ADL in early stage knee OA are still unclear. The aim of the present study was to examine magnetic resonance imaging (MRI)-detected changes associated with disability for ADL in patients with early stage knee OA. One hundred and thirty-two patients with early stage medial knee OA (Kellgren–Lawrence grade ≤ 2) who first visited the outpatient clinic at our university hospital were included. They were also examined by 3.0-Tesla knee MRI. The OA-associated structural changes were scored using the Whole-Organ Magnetic Resonance Imaging Score (WORMS), and clinical manifestations were evaluated by the Japanese Knee Osteoarthritis Measure (JKOM). Median quartile regression was used for the analysis. Cartilage lesion, subchondral bone attrition and osteophytes were observed in all patients. Bone marrow lesions (BMLs) and synovitis were observed in 60% and 55% of the patients, respectively. Subchondral cysts and ligament changes were observed in 6% and 17% of the patients, respectively. Pain severity of the patients was associated with medial cartilage lesions (coefficient 2.50, 95% confidence interval 0.61–4.40, $p < 0.01$). Disability for ADL of the patients was associated with BMLs in the medial side of the knee joint (0.82, 0.21–1.02, $p = 0.04$). BMLs in the medial side of the knee joint were associated with disability for ADL of patients with early stage medial knee OA.

Keywords Knee osteoarthritis · MRI · Bone marrow lesion · Activity for daily living · Japanese Knee Osteoarthritis Measure (JKOM)

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Introduction

Osteoarthritis of the knee (knee OA) is an age-related progressive joint disease and is primarily characterized by cartilage degradation, which induces pain, and significant functional impairment, such as a loss of mobility and diminished activities of daily living (ADL) [1]. The prevalence of knee OA has increased due to the aging society. As a result, knee OA has become an important public health concern. Thus, the establishment of a better management system is required, not only for middle- and end-stage OA but also for early stage knee OA [2].

Currently, there are no interventions proven to restore cartilage or curtail the disease processes, and the current interventions are all symptom-modifying treatments [3]. As the symptoms of OA are often associated with a loss of mobility and disability for ADL, there has recently been more interest in understanding the symptoms in knee OA. In particular, understanding the pathophysiology of early stage knee OA that correlates with symptoms is necessary to develop a novel treatment strategy and methods for decreasing disease progression. Research for analyzing both the structural joint changes and metabolic changes due to OA using magnetic resonance imaging (MRI) and biomarkers, respectively, is currently underway to facilitate the understanding of the pathophysiology of early stage knee OA [4–10]. As a result, knowledge about the critical processes occurring within the OA joint has recently advanced greatly. Although cartilage is the primary and most important source of lesions that lead to knee OA, the importance of all parts of the joint, including the bone, especially subchondral bone, meniscus, ligaments, muscle, and synovium and the crucial role of inflammation in these parts that were previously considered to be irrelevant in this condition are now recognized to be important [2, 3, 11]. However, the structural changes associated with disability for ADL in patients with early stage knee OA are still unclear.

The aim of the present cross-sectional study was to examine the MRI-detected changes associated with disability for ADL in patients with early stage knee OA.

Materials and methods

Subjects and methods

This cross-sectional study was approved by the ethics committee of our university. Patients who first visited the outpatient clinic at our university hospital to seek therapy due to medial knee OA were asked to participate in the study. All patients who agreed to participate provided their written informed consent before enrolment in this study. All patients underwent the initial medical examination at our outpatient clinic between 2008 and 2011. The sample size of this study was determined by the number of patients who had the following conditions during the study period. The patients included in the analysis for this study were determined based on the following conditions.

The diagnosis of medial knee OA in the present study was conducted as follows—(1) subjects who were able to walk without walking aids and fulfilled the criteria for knee OA of the femoro-tibial joint; (2) subjects who were at least 40 years old, but ≤80 years old; (3) all subjects had radiographic knee OA of Kellgren–Lawrence (K/L) grade ≤2 as evaluated by weight-bearing antero-posterior X-rays of the femoro-tibial joint using the bilateral standing extended view and by postero-anterior X-rays of the femoro-tibial joint using the knee in 45 ° of flexed view [12, 13]; (4) medial joint space width (JSW) of all subjects was narrower than lateral JSW with radiographic knee joint [14] and higher medial compartment Whole-Organ Magnetic Resonance Imaging Score (WORMS) than the lateral compartment [15].

The exclusion criteria included (1) patients who had received either an oral, topical or intra-articular steroid during the four weeks before the study; (2) patients who had received intra-articular hyaluronic acid within four weeks before the study; (3) patients who had received either an oral, topical or suppository nonsteroidal anti-inflammatory drugs within two weeks before the study; (4) patients who had secondary knee OA; (5) patients with patello-femoral OA with a K/L grade of ≥3; (6) patients with rheumatoid arthritis; and (7) patients who had received joint replacement surgery in either knee or/and a hip.

Clinical evaluations

Although the patients with knee OA who were enrolled in the present study showed medial-type knee OA, they did not always complain of pain omitted to the medial compartment of the knee joint. Thus, the clinical manifestations, including pain, were evaluated using the Japanese Knee Osteoarthritis Measure (JKOM) [16]. The JKOM is a patient-based, self-answered evaluation score that includes five subcategories—category I, visual analog scale (VAS 0–100) for pain; category II, pain and stiffness (0–32); category III, ADL disability (0–40); category IV, social activities (0–20); and category V, general health conditions (0–8), with 100 points as the maximum score (category II–V). The JKOM score is higher in patients with more pain and physical disability. The measure was proven to have sufficient reliability and validity by means of statistical evaluation and comparison with other health-related scales such as the Western Ontario and McMaster Universities Arthritis Index (WOMAC) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [16]. The JKOM score was obtained for all subjects on the day that the radiographs were taken.

Radiographic evaluation

The standing, extended and antero-posterior and lateral view radiographs were taken during the first visit to the hospital according to the method reported previously [13, 17]. The JSW was determined at the center point of the medial femoro-tibial compartment on a radiograph. The alignment angle was measured by the method reported previously [18–20]. The femoral anatomic axis was found by drawing a line from the center of the tibial spines to a point 10 cm above the tibial spines, midway between the medial and lateral femoral surfaces. For the tibial anatomic axis, a line was drawn from the center of the tibial spines to a point 10 cm below the tibial spines, midway between the medial and lateral tibial surfaces. The internal angles between the femoral and tibial axis were measured using a computer and the angle was designated as the alignment angle (anatomical alignment angle, AAA). All radiographs were quantified independently by two experienced readers (RS and HS) who were blinded to the baseline characteristics of the patients. The intra-observer reproducibility (RS) of the radiographic grading of OA was measured at separate times for twenty patients (interclass correlation coefficient [ICC] 0.97; 95% CI 0.90–0.99). The inter-observer reproducibility was measured by two observers (RS and HS) who conducted 20 examinations (ICC 0.93; 95% CI 0.81–0.96).

MRI-based evaluation

All studies were performed with a MAGNETOM Verio MR whole-body scanner 3.0-T MRI system (Siemens Medical Solutions, Erlangen, Germany) as previously described [8, 10, 21]. A positioning device for the ankle and knee was used to ensure uniformity between the patients. Imaging sequences included proton-weighted spin-echo (coronal and sagittal; repetition time [TR]/echo time [TE]: 1800/20 ms; field of view [FOV]: 160 mm, slice thickness/inter-slice gap [SL/gap]: 3 mm/0.5 mm; matrix 384 × 307, TF:17, FA: 150 degrees), T2-weighted TSE (sagittal; TR/TE: 2200/80 ms, FOV: 160 mm; SL/gap: 3 mm/0.5 mm, matrix: 384 ×307; TF: 17, FA: 150 °) and sagittal fat-suppressed (FS) T2-weighted TSE (sagittal and coronal; TR/TE: 2500/90, FOV: 160 mm, SL/gap: 3 mm/0.5 mm, matrix 384 × 307, TF: 17, FA: 150 °) were also obtained.

Following a detailed reading protocol including atlas representations of each grade for each tissue lesion, the knee was scored using WORMS [15]. Specifically, three regions (anterior, central, and posterior) of the medial and lateral femoral condyles and tibial plateaus, and two regions (medial and lateral) of the patella were each scored separately for cartilage morphology, subarticular bone marrow lesions (BMLs), subchondral bone cysts (SBCs), subchondral bone attrition (SBA), and osteophytes. Each region of a compartment surface received its own score. The scores for a given tissue were then summed within each knee compartment to derive separate medial femoro-tibial, lateral femoro-tibial, and patello-femoral scores for that tissue [15]. The experienced intra-observer reproducibility (RS) of the WORMS evaluation by MRI measured twice for ten sections was high (inter-reader agreement [ICC] 0.98; 95% CI 0.96–0.99). Two experienced orthopedic specialists (RS and SH) conducted all ten examinations in order to assess the intra-observer reproducibility. In all cases, the inter-observer reproducibility was > 0.77, and most were > 0.90.

Statistical analysis

A correlation analysis between the pain severity or JKOM score and radiographic severities was conducted by Spearman's correlation coefficient. A median quartile regression analysis was used to examine the associations between either the pain severity or JKOM score and MRI lesion scores. p-values < 0.05 were considered to be statistically significant. All analyses were performed using the SAS system software program (version 9.1, SAS Institute, Cary, NC, USA) and were adjusted for age and body mass index (BMI).

Results

Patient characteristics

Among the 160 patients who were enrolled, 28 (17.5%) were excluded due to invalid clinical data or because of conflict with the exclusion criteria. The remaining 132 patients were included in the analysis. The characteristics of the patients in this study are shown in Table 1. The mean age of the patients was 64.4 years and most patients (90.1%) were female. Radiographic OA severity of K/L grade two was observed in 73% of the patients; the remaining 27% had K/L grade 1 OA.

Relationship between radiographic changes of the knee joint and clinical manifestations in early stage knee OA

No association was observed between the radiographic JSW of the knee joint and the pain VAS (r^2 = 0.0064) or total JKOM (r^2= 0.0004), while a weak association was observed between the radiographic JSW of the knee joint and disability for ADL (JKOM III, r^2 = 0.35). No association was observed between AAA and the pain VAS (r^2 = 0.0049),

Table 1 Characteristics of study patients

	Total	Min/Max
Number of patients (n)	132 (F: 119 M:13)	–
Age (years)	64.4 (8.5)	43/80
BMI (kg/cm^2)	23.2 (3.1)	17.8/36.5
Severity of OA	K/L 1; 36, K/L 2; 96	–
Medial JSW (mm)	4.1 (1.0)	1.7/7.2
AAA (°)	183.3 (3.5)	170/191
Pain VAS (0–100)	52.9 (26.7)	0/100
JKOM total (JKOM II–V, 0–100)	36.2 (18.5)	1/100
ADL disability (JKOM III, 0–40)	11.5 (9.2)	0/36

Data indicate the means (SD) *BMI* body mass index, *OA* osteoarthritis, *JSW* joint space width, *AAA* anatomical alignment angle, *VAS* visual analog scale, *JKOM* Japanese Knee Osteoarthritis Measure, *ADL* activity of daily living total JKOM ($r^2=0.014$) and disability for ADL (JKOM III, $r^2=0.010$).

MRI-detected structural changes associated with clinical manifestations in early stage knee OA

Among the OA-associated structural changes detected by MRI, cartilage lesion, osteophytes, SBA and meniscal pathology were observed in almost all patients (Table 2). BMLs and synovitis were observed in more than half of the patients, while ligament damage and SBCs were observed in 16.7% and 6.1% of the patients, respectively.

For pain VAS in patients with early stage knee OA, no total score of the MRI-detected OA changes was associated with pain VAS (Table 3). Similarly, no MRI-detected OA changes of the lateral compartment of the knee joint were associated with pain VAS. In the medial compartment of the knee joint of the patients, cartilage lesion was associated with pain VAS (coefficient 2.5; 95% CI: 0.61–4.40), although BMLs, SBCs, SBA, osteophytes and meniscal pathology of the medial compartment of the knee joint were not.

For disability for ADL in patients with early stage knee OA, no total score of the MRI-detected OA changes was associated with disability for ADL (Table 4). Similarly, no MRI-detected OA changes of the lateral compartment of the knee joint were associated with disability for ADL. In the medial compartment of the knee joint of the patients, BML was associated with disability for ADL (coefficient 0.82; 95% CI 0.21–1.62), although cartilage lesions, SBCs, SBA, osteophytes and meniscal pathology of the medial compartment of the knee joint were not.

Table 2 Prevalence of MRI-detected structural changes in the medial knee joint of the patients with early stage medial knee OA

MRI-detected OA changes	Frequency (%)		
	Total	Medial	Lateral
Cartilage lesion	100	100	93.2
BML	60.7	47.0	25.8
SBC	6.1	5.3	2.3
SBA	100	89.3	78.2
Osteophyte	100	97.0	95.4
Meniscus	94.0	94.0	8.9
Synovitis	54.5	–	–
Ligament	16.7	–	–

BML bone marrow lesion, *SBC* subchondral bone cyst, *SBA* subchondral bone attrition

Discussion

The present study examined the pathophysiology of knee OA associated with disability for ADL in patients with early stage medial knee OA. No association between symptoms, including pain and disability for ADL, and radiographic OA changes, such as JSW and AAA, was observed in patients with early stage knee OA. When the OA changes were evaluated using MRI, pain was associated with medial cartilage lesion in patients with early stage knee OA. In addition, to the best of our knowledge, it was demonstrated for the first time that disability of ADL was associated with BMLs in patients with early stage knee OA. Our data suggest a possible relationship between disability for ADL and BML in patients with early stage knee OA.

Knee OA is anticipated to be more influential in our society in the future. Establishment of a better management

Table 3 Tissue lesions associated with the pain severity in patients with early stage medial knee OA

Pain VAS	Coefficient (95% CI)					
	Total	p	Medial	p	Lateral	p
Cartilage lesion	−0.41 (−1.86, 1.04)	0.58	2.50 (0.61, 4.40)	<0.01*	−0.33 (−2.63, 1.97)	0.78
BML	−3.00 (−8.90, 2.90)	0.32	0.59 (−3.61, 4.80)	0.78	−5.55 (−13.55, 2.45)	0.17
SBC	−1.80 (−30.62, 27.03)	0.90	15.00 (−8.30, 2.68)	0.21	2.13 (−21.99, 26.25)	0.86
SBA	−1.09 (−5.28, 3.11)	0.61	−2.80 (−8.27, 2.68)	0.31	−2.10 (−7.44, 3.25)	0.44
Osteophyte	−0.51 (−1.78, 2.80)	0.44	0.69 (−1.40, 2.77)	0.51	2.01 (−1.50, 5.52)	0.26
Meniscus	0.67 (−7.15, 8.48)	0.87	−2.17 (−8.84, 4.49)	0.52	6.24 (−2.52, 15.00)	0.16

VAS visual analog scale, *CI* confidence interval, *BML* bone marrow lesion, *SBC* subchondral bone cyst, *SBA* subchondral bone attrition

*$p<0.05$. Adjusted for age and BMI

Table 4 Tissue lesions associated with disabilities for ADL in the patients with early stage medial knee OA

ADL disability (JKOM III)	Coefficient (95% CI)					
	Total	*P*	Medial	*p*	Lateral	*p*
Cartilage lesion	−0.01 (−0.19, 0.19)	0.98	−0.05 (−0.43, 0.33)	0.81	−0.04 (−0.53, 0.46)	0.88
BML	−0.49 (−0.28, 1.26)	0.21	0.82 (0.21, 1.62)	0.04*	−0.31 (−1.95, 1.33)	0.71
SBC	2.10 (−1.45, 5.63)	0.24	3.11 (−0.72, 6.95)	0.11	−2.59 (−7.61, 2.43)	0.31
SBA	−0.06 (−0.64, 0.53)	0.85	−0.21 (−1.37, 0.96)	0.73	−0.66 (−1.87, 0.55)	0.44
Osteophyte	−0.04 (−0.33, 0.26)	0.44	−0.06 (−0.47, 0.34)	0.76	0.16 (−0.56, 0.88)	0.65
Meniscus	−0.31 (−1.97, 0.15)	0.09	−1.16 (−2.42, 0.10)	0.07	−0.23 (−2.11, 1.66)	0.81

ADL activity of daily living, *JKOM* Japanese Knee Osteoarthritis Measure, *CI* confidence interval, *BML* bone marrow lesion, *SBC* subchondral bone cyst, *SBA* subchondral bone attrition

*$p < 0.05$. Adjusted for age and BMI

system of early, middle- and end-stage knee OA, which are diseases that induce walking disability, is required [2]. Although pain remains a prominent symptom in knee OA, individuals with pain due to knee OA reduce their physical activity to avoid pain [22]. These individuals do not have severe pain, but the impairment of their mobility remains, causing them to become physically inactive and inducing disability for ADL. Thus, we should pay more attention to disability for ADL of patients with knee OA.

Currently, patients who show radiographic end-stage knee OA, but do not have pain are not indicated to undergo surgical treatment, such as joint replacement surgery or osteotomy. Although all surgical treatments have a risk of side-effects during and after surgery, the symptoms, especially mobility impairment and disability for ADL, in addition to pain, should also be considered for setting the indications of surgery in knee OA [2]. Similar to end-stage knee OA, patients with early stage knee OA showed disability for ADL, as shown in the present study. Thus, we should take measures to manage early stage knee OA subjects and should pay more attention to the symptoms, especially mobility impairment and disability for ADL, in addition to pain, in early stage knee OA. This was the reason why we examined the pathophysiology associated with disability for ADL in patients with early stage knee OA.

It has been suggested that there is a relationship between cartilage lesions and symptoms in patients who develop from early to progressive-stage knee OA [23]. For example, elevated T2 cartilage values were associated with knee pain in subjects with knee pain without radiographic knee OA [24]. However, as articular cartilage is both aneural and avascular, it is incapable of directly generating pain [3]. It is important to note that this disease of the whole joint concurrently affects other tissues that do contain nociceptors. Therefore, the changes in articulation caused by the structural and associated changes in extracellular matrix turnover in the articular cartilage may result in the manifestation of pain in other joint tissues. This may be a consequence of alterations in joint mechanics resulting in structural changes elsewhere, and/or the generation of joint debris that may cause synovitis [7]. Synovitis and symptoms were well-correlated in patients with end-stage knee OA by Gd-enhanced MRI analysis, as well as histological analysis [25]. In other words, the narrowing area in a malaligned joint is subjected to increased load bearing that leads to increased cartilage damage, releasing debris into the joint space which then gets ingested by synovium, which becomes secondarily inflamed, and secretes excess fluid [26]. In the present study, synovitis detected by the WORMS was not associated with pain. This may be due to the fact that the WORMS scored joint changes using non-enhanced MRI, in which the border between the hypertrophic synovium and joint fluid is unclear.

During the initiation and progression of OA, subchondral bone is the site of numerous pathological processes [11, 27]. BMLs, subchondral bone marrow signal alterations, are characterized by ill-defined subchondral areas of MRI images. The presence of BMLs in subchondral bone marrow has been associated with increased bone turnover indices as well as structural deterioration in knee OA [28]. BMLs can be observed in most (~80%) and approximately half of the patients with advanced to end-stage painful knee OA and the patients with early stage painful knee OA, respectively [29–32]. Similarly, BMLs were also observed in about half of the patients with early stage knee OA in the present study. In addition to synovitis, the subchondral bone is considered to be another important source of nociceptive pain [21]. Subchondral bone changes, such as BMLs, were also speculated to be related to pain in population-based cohort studies

[33–35]. However, no association between pain severity and the size of BMLs was observed in the present study. This may be related to the fact that the size of BMLs fluctuated, and decreased especially in early stage knee OA [30, 35, 36]. As the present study was conducted as a cross-sectional study, the size changes of BMLs were hard to detect.

The current study revealed an association between disability of ADL and BMLs in patients with early stage knee OA. The symptoms of OA are generally initiated by inflammation, which may induce pain, followed by other symptoms, such as a loss of mobility and disability and diminished ADL [1]. As the present study was conducted at a university hospital, most of the patients who were enrolled in the study were introduced by outpatient clinics due to long-lasting symptoms, mainly pain. As pain in knee OA mainly occurs while movement, such as walking or stair climbing, patients with painful knee OA, especially those with severe pain, tend to avoid physical activity [22]. Knee OA patients with severe pain walk with painful claudication, which is induced by the limitation of weight bearing on the painful leg. As a result, the ADL of knee OA patient are impaired in combination with a reduction in muscle strength, especially the knee extensor muscle strength. Recently, knee OA has been shown to be associated with not only the affected joint but also other organs, especially the nervous system. The neurobiological mechanisms that contribute to knee OA pain have received increasing attention. It has been hypothesized that ongoing tissue injury and/or inflammation of the knee joint lead to increased responsiveness of the peripheral nociceptors (peripheral sensitization) and spinal dorsal horn transmission neurons (central sensitization) [37]. Alterations in the descending inhibitory pathways and facilitated central integration can also contribute to the experience of pain. A reduction in the pain threshold occurs to a certain extent in the affected knee of knee OA patients. In addition, as the reduction of the pain threshold occurs not only in the affected knee joint but also in places far from the affected knee joint, pain sensitization is suggested to occur in patients with knee OA [38]. The pain sensitization in knee OA patients has been confirmed by a large cohort study [37] and inflammation, especially synovitis, is associated with pain sensitization in knee OA [39]. We reported that synovitis in end-stage knee OA, which was associated with symptoms, was associated with MRI-detected subchondral pathologies, mainly BMLs [21]. Further studies are necessary to examine whether synovitis is associated with not only end-stage but also early stage knee OA and whether sensitization occurs in early stage knee OA patients in the present study. Based on these results, when patients with early stage knee OA show subchondral pathologies, especially BMLs, with consequent sensitization, the avoidance of physical activity and limited weight bearing on a painful leg (to avoid pain) may occur, resulting in disability of ADL. We therefore hypothesize that BMLs are associated with disability of ADL, but that there is no association between pain and BMLs, as explained above.

The current study is associated with some limitations. First, the current study focused on OA-induced structural changes associated with symptoms including pain in patients with early stage painful knee OA. However, the determinants of pain are believed to involve multiple interactive pathways, such as biological, psychological and social factors [40] [9]. The psychosocial factors that can predispose a patient to symptoms include self-efficacy and pain catastrophizing, and the social context of arthritis, such as social support and pain communication, are important considerations for understanding the experience of pain [9, 41]. Further studies that take these factors into consideration would be helpful for overcoming these limitations. Second, it has been recognized that radiography is unable to detect the early changes of knee OA, and MRI as well as chemical biomarkers are expected to overcome the limitation of radiography in the evaluation of early stage knee OA [2, 3, 5]. Although, the WORMS system has contributed to the precise and semi-quantitative detection of the structural changes of knee OA [15], it has also been revealed that WORMS has several limitations in relation to the detection of structural changes of knee OA [42]. Although the intra-observer and inter-observer reproducibility of the MRI evaluations were high, the evaluation of knee OA by MRI was associated with limitations and disadvantages in the present study. Third, in addition to cartilage lesions, which may be related to synovitis, and BMLs, numerous structural alterations detected by MRI, such as SBA, SBCs and meniscal pathology, have been reported to be related to knee pain in patients with early to advanced-stage knee OA [27, 43–45]. Although the current study focused on early stage knee OA, the relationships should be interpreted with caution, as it is currently unclear whether all of these associations were truly causal, or whether they were markers of the severity of known conditions, such as SBA, SBCs and meniscal pathology, and other unknown structural pathologies that are not included in the WORMS definitions [15]. Fourth, the loss of function of the medial meniscus has recently been revealed to be one of the most important factors for the symptoms and progression of early stage medial knee OA [46]. Although the present study was an observational study and not a longitudinal study, the morphology of the damaged meniscus, such as horizontal and/or transverse tear, and the malposition of meniscus, such as medial meniscus extrusion [10], were not evaluated in the present study, as WORMS, which cannot evaluate the meniscus damage precisely, was used for the evaluation of meniscal damage in the present study.

In conclusion, the present study revealed associations between MRI-detected OA-related structural changes and symptoms in early stage painful knee OA. While the pain severity was associated with the extent of articular cartilage damage, the presence of BMLs was associated with disability for ADL in early stage knee OA.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol, which complied with the principles outlined in the Declaration of Helsinki, was approved by the Ethical Committee Review Board at Juntendo University (approval number: 15-111). Since the studies with the patients with knee OA were categorized as a retrospective study, the Ethical Committee Review Board waived the requirement for patient informed consent for participation because of the anonymous nature of the data.

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