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ORIGINAL STUDY

Joint Space Width, but not Osteophyte Thickness, is a Reliable Indicator of Degeneration of Lateral Knee Joint Cartilage

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In this histologically controlled in vitro study, we evaluated the validity of plain radiography for the assessment of lateral knee joint cartilage degeneration (25 specimens). We examined the correlation between histological grade and radiography findings along with patient demographics. Our study indicated that the Mankin score had a significant inverse correlation with middle joint space width (JSW ; r=-0.19,P=0.02), but not with inner and outer JSW (inner : r=-0.11,P=0.10, outer : r=-0.14,P=0.06) under a non-weight bearing condition. The Mankin score had a significant inverse correlation with middle and outer JSW (middle : r=-0.17,P=0.04, outer : r=-0.14,P=0.04), but not with inner JSW (inner : r=-0.15,P=0.06) under valgus stress. There was no significant correlation between the Mankin score and osteophyte thickness (r=0.004,P=0.76). We also examined the correlation with patient demographics. We found that only the preoperative femorotibial angle had a significant inverse correlation with the Mankin score. These results indicate that JSW, but not osteophyte thickness, is reliable for evaluating lateral femoral cartilage degeneration.

Keywords : osteoarthritis, osteophyte, joint space width, cartilage degeneration, Mankin score

INTRODUCTION

Osteoarthritis (OA) is the most common age-related disorder of synovial joints and primarily involves the articular cartilage, synovium, and subchondral bones. In the past decade, there have been tremendous advances in understanding and implementing joint preservation methods. Unicompartmental knee arthroplasty (UKA) and high tibial osteotomy (HTO) were developed to treat medial compartment arthritis of the knee. Even though they are very different procedures with different concepts, they share the same indications, including unicompartmental medial OA or femoral condyle avascular necrosis with intact lateral compartments.

Many authors have reported the survival rates following UKA *(2,4,5,8,12,22)* or HTO, *(1,7,15,35)* ranging from 79% to 100% at 5-15 years of follow-up, with some patients undergoing revision surgery because of progression of OA. Sierra et al. *(32)* reported on 175 revisions of medial UKA, of which 59 knees (34%) were revised owing to progressive arthritis. Howells et al. *(15)* showed

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that the Kaplan-Meier survival estimate was 79% at 10 years. However, Epinette et al. *(10)* identified disease progression as the second leading reason for failure of UKAs in a multicentre study. Both HTO and UKA are effective for managing medial compartment knee OA, but properly selecting patients with the appropriate indications, including those with intact lateral compartments, is essential for obtaining durable and predictable results with both techniques.

Pathologically, OA is characterized by a focal loss of articular cartilage in weight-bearing areas and new bone formation as osteophytes in joint margins. Magnetic resonance imaging (MRI), such as T1ρ and T2 mappings, and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) are reported to be useful diagnostic tools for the assessment of articular cartilage *(3,21,33,35)*. However, these methods are not so easily available that they can be used for all osteoarthritic patients. On the other hand, plain radiography is a simple and cost-effective procedure. With the progression of the disease, medial osteoarthritic changes become apparent on plain radiographs *(19)*. The extent of cartilage loss can be estimated by measuring the joint space width (JSW). Newly formed bone tissue is observed as osteophytes at the joint margins. However, little is known regarding how to identify the degree of lateral joint cartilage degeneration with the progression of medial compartment OA.

In this study, we evaluated the validity of plain radiography for the assessment of lateral knee joint cartilage degeneration. We conducted a histologically controlled in vitro study by using femoral lateral condyle specimens with various grades of cartilage degeneration, and we examined the correlation between histological grade and radiographic findings, including JSW, osteophyte thickness, and patient demographics.

MATERIALS & METHODS

This prospective cohort study was approved by the Ethics committee, and all patients provided informed consent. All samples were obtained in accordance with the institutional protocol, with review board approval. Human articular cartilage samples were obtained from primary end-stage OA patients, that is, from 25 knees of 21 patients who underwent primary total knee arthroplasty (TKA) from April 2011 to November 2012. No patients had undergone chemotherapy or had any traumatic episodes related to the knee. Patients with rheumatoid arthritis or other inflammatory diseases were also excluded. We also extracted age, sex, and body mass index (BMI) for patient's demographic data.

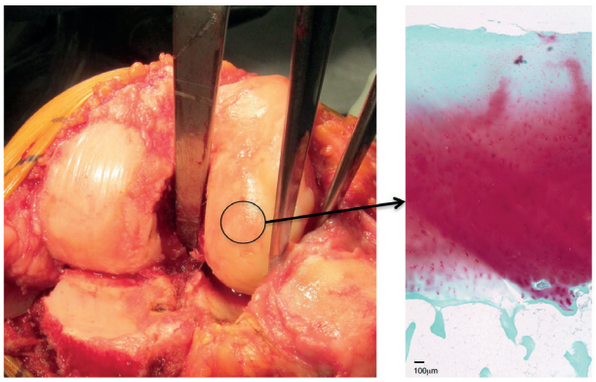

Figure 1. — Full-thickness cartilage samples were harvested from the weight-bearing area of the lateral femoral condyle. The samples were stained with Safranin and Fast Green. The degree of cartilage degeneration was analysed based on the Mankin system.

Cartilage samples

A full-thickness cartilage sample (plug-shaped samples ; diameter, 8 mm) was harvested from the weight-bearing area of the lateral femoral condyle of 25 knees with end-stage OA (Figure 1), and they were removed as a cylindrical shape that included a section from the surface of the articular cartilage to the subchondral bone by using a biopsy tool.

Microscopic assessment

The harvested cartilage sample was fixed in 10% buffered formalin (pH 7.4) for 24 h and then decalcified with 10% EDTA solution for 2 weeks. The samples were then embedded in a paraffin block, cut into 5-μm histological sections, and stained with Safranin O (Wako Pure Chemical Industries) and Fast Green (Sigma-Aldrich) (Figure 1). The degree

of cartilage degeneration based on the Mankin system, which is widely used for histological evaluation of cartilage degeneration, was analysed as previously described *(16, 29)*. The Mankin score assesses structure (0-6 points), cellularity (0-3 points), matrix staining (0-4 points), and tidemark integrity (0-1 points), with a maximum score of 14 points.

Radiographic assessment

Standard non-weight bearing and valgus stress knee radiographs were obtained by using a semi-flexed protocol. A maximal valgus stress was applied to obtain the valgus stress knee radiograph. To assess the femorotibial angle (FTA) as an indicator of knee joint deformity for OA patients, coronal radiography was performed in accordance with the standing semi-flexed protocol prior to surgery *(17)*. The knee was flexed until the tibial plateau was horizontal and perpendicular to the film. To control for rotation, the foot was rotated until the tibial spines were centrally aligned within the femoral notch. The FTA is the lateral angle created by the intersection between a bisector of the femoral shaft and a bisector of the tibial shaft, which serves as a good marker for the extent of deformity of the knee. Two orthopaedic surgeons evaluated the FTA using the radiographs of the OA patients. JSW was defined as the tibiofemoral inter-bone distance, measured in millimetres on non-weight bearing and valgus stress radiographs of the tibiofemoral joint as previously reported. *(40)* Pre-operatively, the same three sites (inner, middle, and outer part of the tibiofemoral joint, based on subdividing the lateral compartment into four quarters), were chosen to measure JSW. The osteophyte thickness was defined as the height from lateral tibia joint surface to the top of the osteophyte (Figure 2).

Statistical analysis

A power analysis (two-tailed α error of 5% and β error of 20%) was performed before the study. The calculation of the required sample size was based on the histological assessment of cartilage degeneration in a previous study following TKA with MRI imaging study. *(6)* Nineteen patients were required in order to reveal a statistically significant difference. Correlations among age, FTA, JSW, and Mankin score were analysed via linear regression analysis followed by Spearman's rank correlation coefficient. These analyses were performed with GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA). A P-value < 0.05 was considered significant.

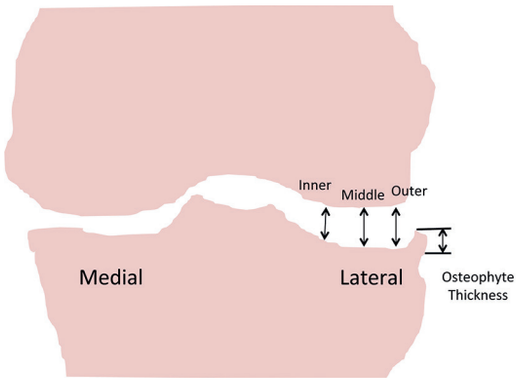

Figure 2. — Diagrammatic representation of measurements for osteophyte thickness and joint space width sites (inner, middle, and outer) of the lateral compartment.

RESULTS

Demographic and clinical data

Twenty-five knees (21 patients) were included in this study, and patient characteristics are shown in Table I. The overall study population in this study had a mean age of 72.4 years (range, 51-86 years). The mean BMI was 26.4 kg/m2 (range, 17.0-37.0 kg/m^2). All patients underwent TKA owing to the primary OA. Seventeen patients (21 knees) had

Table I. — Patient Characteristics Figure legends

Parameters	
Age, mean (range)	72.4 (51-86)
Sex, n	
Male	2
Female	23
Body mass index, mean (range)	26.4 (17.0-37.0)
Diagnosis, n	
Osteoarthritis	25
Femorotibial angle (degrees) mean (range)	182.5 (156-205)

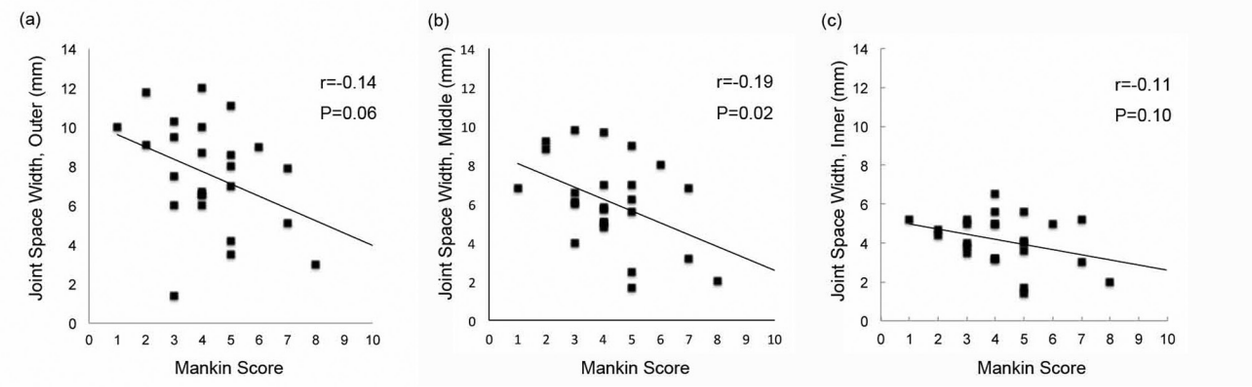

Figure 3. — Correlation between the Mankin score and joint space width under a non-weight bearing condition. (a) Outer, (b) Middle, (c) Inner.

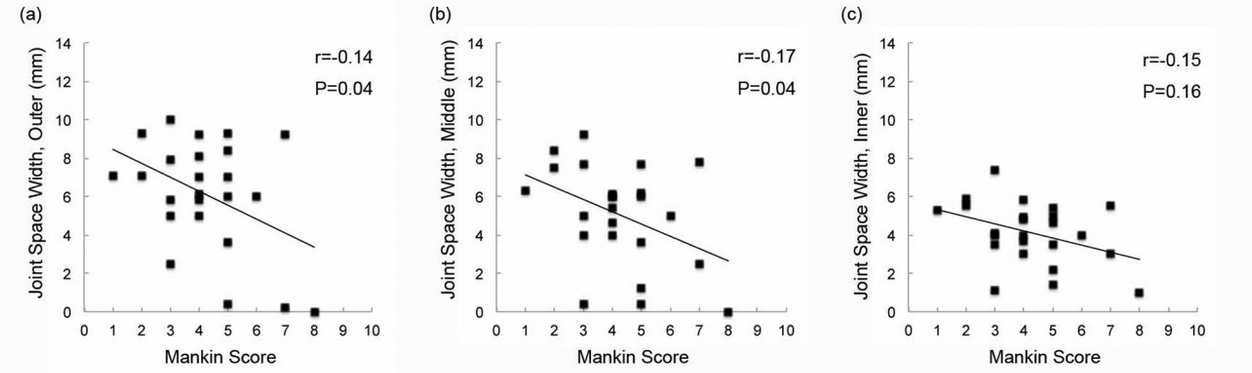

Figure 4. — Correlation between the Mankin score and joint space width using valgus stress radiographs. (a) Outer, (b) Middle, (c) Inner.

varus knee deformities, and four patients (four knees) had valgus knee deformities. The mean FTA was 182.5° (range, 156-205°). The distribution of the Mankin score is shown as follows : Grade 1, one patient ; Grade 2, two patients ; Grade 3, five patients ; Grade 4, seven patients ; Grade 5, six patients ; Grades 6, 7, and 8, one patient each.

Correlation between Mankin score and JSW

We examined the correlation between the Mankin score and JSW of the lateral tibiofemoral joint under the non-weight bearing condition. The Mankin score had a significant inverse correlation with middle JSW (r = -0.19, P = 0.02), but not inner and outer JSW (inner : r = -0.11, P = 0.10 ; outer : r = -0.14, P = 0.06) under the non-weight bearing condition (Figure 3a-c). Next, we examined the correlation between the Mankin score and JSW of the lateral tibiofemoral joint using valgus stress radiographs. The Mankin score had a significant inverse correlation with middle and outer JSW (middle : r = -0.17, P = 0.04 ; outer : r = -0.14, P = 0.04), but not inner JSW (inner : r = -0.15, P = 0.06 ; Figure 4a-c). Therefore, these findings suggest that middle JSW is reliable to evaluate the degree of lateral joint cartilage degeneration.

Correlation between the Mankin score and osteophyte thickness or other factors

We analysed whether osteophyte measurements could predict the degree of articular cartilage degeneration, and we examined the correlation between the Mankin score and osteophyte thickness. Interestingly, there was no significant correlation (r = 0.004, P = 0.76 ; Figure 5a), which suggests that osteophyte thickness is not an indicator of lateral

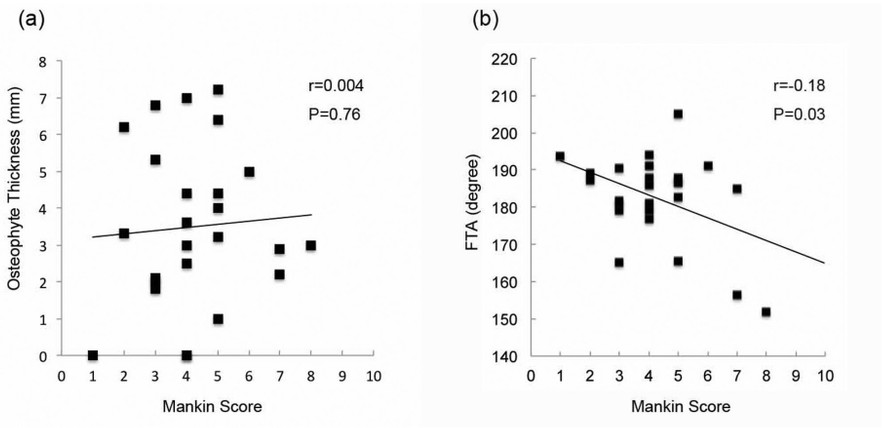

Figure 5. — Correlation between the Mankin score and osteophyte thickness (a), femorotibial angle (b). FTA, femorotibial angle.

femoral cartilage degeneration. We also examined the correlation between the Mankin score and age, body mass index, or preoperative FTA, and we found that only preoperative FTA had a significant inverse correlation with the Mankin score (r = 0.18, P = 0.03 ; Figure 5b).

DISCUSSION

OA is characterized by focal loss of articular cartilage in weight-bearing areas and by new bone formation as osteophytes at joint margins. Osteophytes are an important indicator for evaluating the grade of medial compartment OA *(19)*. In this study, we evaluated the validity of plain radiography for the assessment of lateral knee joint cartilage degeneration, including JSW and osteophyte thickness. Interestingly, we found that osteophyte thickness was not associated with lateral cartilage degeneration, but that JSW, especially middle JSW, on plain radiographs was a reliable indicator of lateral cartilage degeneration.

Recently, UKA and HTO were developed for treatment of medial compartment arthritis of the knee. Selecting patients based on the appropriate indications is essential to obtaining durable and predictable results with both techniques. One of the important factors for successful UKA and HTO is intact lateral compartments. Therefore, in this study, we evaluated the validity of plain radiography as well as histological samples for the assessment of lateral knee joint cartilage degeneration.

In this study, we found that JSW, especially at the middle portion, is the most reliable indicator for degeneration of lateral joint cartilage. JSW on plain radiographs reflects the thickness of joint cartilage and the meniscus. Initial osteoarthritic changes include proteoglycan and hyaluronan (HA) loss and deterioration of the collagen network within the cartilage. Macroscopically, cartilage degeneration has been described as fibrillation of the articular surface, the presence of cracks or fissures, and the partial or complete loss of the tissue *(31)*. HA is a large, linear polymer of repeating disaccharide units composed of N-acetyl-D-glucosamine and D-glucuronic acid and has a pronounced hydrophilic capacity *(24,25,27)*. The proteoglycan and HA provides cartilage with a unique gel-like property and resistance to deformation through water absorption *(24,26)*. Collagen networks provide tensile strength to the cartilage *(11)*. Alterations of these molecules affects the biomechanical properties of articular cartilage. The Outerbridge Classification *(28)* of cartilage defects is the most commonly used scale for macroscopic cartilage degeneration in the literature. However, even though the lateral joint cartilage is slightly altered macroscopically, which is demonstrated Outerbridge Classification Grade I (cartilage with softening and swelling), the defect could start with proteoglycan loss and alter the biomechanical properties. In the present study,

middle and outer JSW on valgus stress radiographs correlated with degeneration of articular cartilage. Valgus stress radiographs may be more accurate as they reflect not only JSW, but also the biomechanical properties of articular cartilage.

Radiography is simple and is the most popular method for identifying OA. Radiographic hallmarks of knee OA include joint space narrowing and osteophyte formation. Although osteophytes are viewed as a remodelling and reparative feature of OA, factors determining osteophyte formation and growth are still unknown. Animal studies indicate that joint instability is a biomechanical trigger to osteophyte formation, with osteophyte and bone remodelling being viewed as an attempt to stabilize and broaden the compromised joint to better withstand loading forces *(23,39)*. Growth factors also influence osteophyte formation in experimental joint damage models *(36,37),* and cartilage damage initiates osteophyte growth in both human *(18,20,30)* and animal studies *(38)*. Furthermore, osteophytes may develop as an isolated feature associated with age *(14)* ; moreover, in animal studies, osteophyte formation precedes, rather than follows, cartilage loss *(13)*. These studies suggest that multiple factors influence osteophyte formation and contribute to the marked heterogeneity of OA. Therefore, our results that osteophyte thickness was not correlated with the Mankin score, suggest that osteophyte thickness cannot be used for evaluating lateral knee cartilage degeneration.

Previously, Buckland-Wright et al. *(9)* reported that JSW reliably measured cartilage thickness in the medial but not the lateral compartment of knees with medial compartment OA. They took knee radiographs at a 130° angle in the weight-bearing or modified tunnel view, which involved the patient sitting on the edge of a stool. In the case of medial compartment OA, the weight-bearing condition promotes varus deformities, and the lateral joint space could be increased. Thus, we may have overestimated the lateral JSW compared with actual cartilage thickness under a weight-bearing condition. In the current study, we used non-weight bearing and valgus stress knee radiographs. These differences may explain the discrepancies between these studies.

There are several limitations of this study. First, the sample size was small. Second, although macroscopically normal or early OA cartilage was obtained from patients who underwent knee surgery, complete intact cartilage could not be collected. Therefore, data regarding plain radiographs and osteophyte thickness in intact cartilage are lacking. Third, we did not perform preoperative MRI, such as T1ρ and T2 mappings or dGEMRIC *(3,21,33,35)*. Plain radiography is a simple and cost-effective procedure. Therefore, a future study on radiography combined with MRI, such as T1ρ and T2 mappings and dGEMRIC, may be required to determine their utility for evaluating lateral articular cartilage degeneration.

In summary, we evaluated the validity of plain radiography for the assessment of lateral knee joint cartilage degeneration, combined with a histologically controlled in vitro study including femoral lateral condyle specimens with various grades of cartilage degeneration. We found that osteophyte thickness does not reflect degeneration of lateral femoral joint cartilage and that JSW is a good indicator of lateral knee joint cartilage degeneration. Therefore, when indications for UKA or HTO for medial compartment OA are considered, lateral JSW, rather than osteophyte thickness, should be referenced. Further studies are needed to determine the threshold of lateral joint cartilage degeneration for successful UKA or HTO.

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Author contributions

K. Matsumoto : Design of the study, writing the paper, revision of the manuscript, performed surgeries.

D. Ishimaru : Data collection, data analysis, review of analysis of the data.

H. Ogawa : Data collection, data analysis, review of analysis of the data, helped to write the paper.

H. Akiyama : Helped to design the study, review of analysis of the data.