Bone marrow abnormality associated with painful osteoarthritis of the knee:
A cross-sectional study of magnetic resonance imaging findings with the radiographic stage and clinical findings

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Background: Bone marrow abnormalities (BMAs) are frequently found in osteoarthritis (OA) of the knee with magnetic resonance imaging (MRI). Some reports have suggested BMA was correlated with the X-ray stage of OA and also with knee pain, but the reports depended on two-dimensional images without considering the spatial expansion of BMAs.

Objectives: To determine whether three-dimensional expansion of a BMA with MRI in patient with medial-type OA of the knee is correlated with the radiographic stage of OA and clinical findings using a semi-quantitative method.

Design: Cross-sectional study

Materials and Methods: This study enrolled 238 patients with medial-type OA. Radiography and MRI of the knee were taken in all participants. X-rays were graded using the Kellgren-Lawrence (K/L) grade (1-4). T2-weighted fat-suppressed MRI images were used to score the size of the BMA according to the whole-organ MRI score (WORMS). A new scoring system defined as the spatial BMA score (s-score), which specifically addressed the spatial expansion of BMAs, was examined to assess the size of the BMA. BMA frequency was examined in subdivisions of the articular surfaces of the knee according to the X-ray stages of the K/L grade and the correlation of the s-score to the clinical findings.

Results: BMA frequency in the medial femorotibial joint (MFTJ: 74%) was significantly higher than in the lateral femorotibial joint (LFTJ: 14%) and patellofemoral joint (PFJ: 14%; P < 0.01). The s-score of the MFTJ was strongly correlated with the X-ray stage assessed by the K/L grade. The s-score of the MFTJ was also correlated with the clinical findings.

Conclusion: The frequency and spatial expansion of BMAs in the MFTJ are strongly correlated with the X-ray stage of medial-type OA as well as the clinical findings.

Key words: osteoarthritis (OA), knee, MRI, bone marrow abnormality (BMA), spatial BMA score

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Introduction

Osteoarthritis (OA) of the knee, the most common form of arthritis, is the leading cause of morbidity-related disability in the elderly\(^1\). As the population ages, the prevalence of osteoarthritis is increasing in Japan. OA is a slowly progressive disease, therefore ideally, slowing or reducing its progression is required; however, the factors affecting the course of OA are unknown. Bone marrow abnormalities (BMAs) were first reported as transient bone marrow edema (BME) by Wilson et al. in 1988\(^2\). According to Kijowski et al., a BMA is defined as an ill-defined area of increased signal intensity on T2-weighted images in subchondral cancellous bone, extending away from the articular surface over a variable distance\(^3\). BMAs are frequently seen in patients with OA on magnetic resonance imaging (MRI) \(^4\)^\(^5\). While several methods have been used to assess BMAs, few reports have described a semi-quantitative method for assessing BMAs in OA\(^6\)^\(^7\). Whole-organ magnetic resonance imaging scoring (WORMS) introduced by Peterfy et al. is a semi-quantitative method for evaluating BMAs in OA of the knee, but they assessed BMAs with two-dimensional expansion\(^8\). A BMA is a lesion with three-dimensional expansion, and efforts were made to assess BMAs using three-dimensional expansion.

The objectives of this study were to investigate the relationship of BMAs to structural changes of the knee joint and to the clinical findings with a semi-quantitative three-dimensional method using WORMS.

Materials and methods

Study design and Subjects (Table-1)

A total of 238 patients from five hospitals (Juntendo University Hospital, Juntendo University Urayasu Hospital, Juntendo University Nerima Hospital, Koto Hospital and Tokyo Rinkai Hospital) who presented with knee pain due to OA of the knee from January 2006 to May 2008 were recruited for this study. All patients had complained of pain in the study knee for at least the preceding month and they fulfilled the criteria of OA of the medial femorotibial joint defined by the American College of Rheumatology (ACR) criteria\(^9\). The subjects were excluded if they were positive for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or reactive arthritis, if they experienced problems with the kidneys that resulted in the need for hemodialysis or peritoneal dialysis, if they had undergone bilateral knee arthroplasty, or if they were unable to walk without the help of another person or a walker. This study was cross-sectional, with the intent to clarify the relationship between BMAs and the X-ray stage and clinical findings of OA. The study protocol was approved by the institutional review boards of each hospital and we obtained written consent from each patient for this study.

Radiograph and MRI assessment

Standing, extended and antero-posterior views, lateral and skyline view radiographs and MRI (T1-, T2-weighted and fat-suppressed T2-weighted images) were taken at the first visit. Antero-posterior view radiographs were taken according to Ravaud et al.\(^10\). The staging of OA on the radiographs was

![Figure-1 Bone marrow abnormalities (BMAs) on magnetic resonance imaging](image)

Lesions were designated as an ill-defined area of increased signal intensity on fat-suppressed T2-weighted images in subchondral cancellous bone, extending away from the articular surface over a variable distance (A: coronal view, B: lateral view).

Subchondral bone cyst (C) and lesions far from articular surface (D) were excluded.
assessed using the Kellgren-Lawrence (K/L) grade (1-4)\(^{11}\). All radiographs were taken by experienced technicians. All radiographs were quantified by a single reader (H.K.) who was blinded to the treatment assignment of the patient.

All studies were performed with a MAGNETOM Symphony syngo MR 1.5-Tesla MRI system, a MAGNETOM Avanto MR 1.5-Tesla MRI system (Siemens AG Medical Solutions, Erlangen, Germany) and an Excelart vantage MR 1.5-Tesla MRI system (Toshiba Medical System, Tokyo, Japan).

A positioning device for the ankle and knee was used to ensure uniformity among patients. Coronal and sagittal images were obtained for each patient. Sagittal fat-suppressed T2-weighted images were obtained (repetition time : 2500 ms ; echo time : 80 ms ; slice thickness : 3/3.5 mm ; interslice gap : 0.5 mm).

Sagittal T2-weighted fat-suppressed images were used to evaluate bone marrow abnormalities (BMAs), which were assessed as an ill-defined area of increased signal intensity on fat-suppressed T2-weighted images in the subchondral cancellous bone, extending away from the articular surface over a variable distance\(^{3,12}\) (Fig. 1 A, B). Well-defined areas, a subchondral bone cyst, or circular/oval form and lesions far from the articular surface were excluded from the study\(^{3,12}\) (Fig. 1 C, D). BMAs were independently analyzed using the whole-organ MRI scoring method (WORMS) reported by Peterfy et al.\(^{8}\). BMAs were evaluated in fifteen different regions subdivided by anatomical landmarks of the knee (Fig. 2 a, b, c). According to WORMS, BMAs were classified into each of the fourteen articular surface regions from 0 to 3 based on the extent of regional involvement: 0 : none ; 1 : <25% of the region ; 2 : 25% to 50% of the region ; 3 : >50% of the region (Fig. 2 d). With regard to the three-dimensional expansion of BMAs in the medial femorotibial joint (MFTJ) where BMAs are most frequently found, a new BMA score was devised by multiplying the maximum grade (0 to 3) and the number of slices in which the BMA was found on the sagittal views of the MFTJ. Each knee had nineteen sagittal slices in all cases. The score was named the spatial BMA score (s-score). All MRI findings were

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(n = 238)</th>
</tr>
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<tbody>
<tr>
<td>Age, y (range, 54-85)</td>
<td>70.4 ± 7.4</td>
</tr>
<tr>
<td>Female : Male</td>
<td>221 : 17</td>
</tr>
<tr>
<td>BMI, kg/m(^2) (range, 17.8-36.8)</td>
<td>25.0 ± 3.7</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>VAS (range, 0-100)</td>
<td>58.8 ± 24.0</td>
</tr>
<tr>
<td>JKOM (range, 0-100)</td>
<td>42.0 ± 20.1</td>
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</table>

Values presented with plus/minus sign are the means ± standard deviation. BMI = body mass index : VAS = visual analog scale : JKOM = Japanese Knee Osteoarthritis Measure.
Clinical assessment

To assess the correlation of BMAs and stiffness of the knee, range of motion (ROM) was calculated by the difference between active and maximum flexion and extension degrees. ROM was measured at the angle between the femoral axis and tibial axis using a long-shaft (length = 30 cm) goniometer on the lateral side of the lower limb. In addition, body weight and height were measured in order to calculate the body mass index (BMI). Subjects also completed a visual analog scale (VAS) for pain and the Japanese Knee Osteoarthritis Measure (JKOM) 13).

VAS is calculated from a point on a 100 mm scale: 0 mm = no pain at all, 100 mm = the most severe pain the patients have ever had. JKOM is a self-ad-

quantified by a single reader (H. I.) who was blinded to the treatment assignment of the patient.

**Figure-3** The BMA (bone marrow abnormality) frequency

The BMA frequency of the medial femorotibial joint (MFTJ), the lateral femorotibial joint (LFTJ), patellofemoral joint (PFJ) and the portion of the tibia beneath the tibial spines (region S) was 72.8%, 14.9%, 16.3% and 39.9%, respectively. The BMA frequency in the MFTJ was highest among all compartments of the knee.

BMA frequency of the MFTJ, MFc, MTa and MTc (72.8%, 66%, 51% and 57%, respectively) were significantly higher than the other subdivisions of the knee (*P < 0.01 ; by Chi-square test).

MP : medial facet of the patella, LP : lateral facet of patella, MFa : anterior part of the medial femoral condyle, LFa : anterior part of the lateral femoral condyle, PFJ : patellofemoral joint (= MP + LP + MFa + LFa) : MFc : center part of the medial femoral condyle, MFP : posterior part of the medial femoral condyle, MTa : anterior part of the medial tibial condyle, MTc : center part of the medial tibial condyle, MTp : posterior part of the medial tibial condyle, MFTJ : medial femorotibial joint (= MFc + MFp + MTa + MTc + MTp) ; LFc : center part of the lateral femoral condyle, LFp : posterior part of the lateral femoral condyle, LTa : anterior part of the lateral tibial condyle, LFc : center part of the lateral tibial condyle, LFTJ : lateral femorotibial joint (LFc + LFp + LTa + LFc + LTp) ; S : non-articulating portion of the tibial plateau beneath the tibial spine.

**Figure-4** The BMA (bone marrow abnormality) frequency at the X-ray stage of Kellgren-Lawrence (K/L) grade

The BMA frequency of the MFTJ in Kellgren-Lawrence (K/L) grade 1, 2, 3 and 4 was 22%, 43%, 85% and 96%, respectively. The BMA frequency of the MFTJ (medial femorotibial joint) in the K/L grade 3 and 4 is significantly higher than in the K/L grade 1 and 2. The correlation was adjusted for age, sex and BMI.

**P < 0.001 ; by a multivariate analysis of variance (MANOVA), multiple comparisons were made using the Tamhane test.**

**Figure-5** The spacial BMA score (s-score) and the X-ray stage of Kellgren-Lawrence (K/L) grade

Average s-score of the MFTJ in K/L grade 1, 2, 3 and 4 was 3.1, 4.6, 14.8 and 23.4, respectively. The s-score in K/L grade 3 and 4 was significantly higher than in grade 1 and 2. Furthermore, the s-score in grade 4 is significantly higher than in grade 3 (*P < 0.01, **P < 0.001 ; by a multivariate analysis of variance (MANOVA), multiple comparison using the Tamhane test).

The s-score was correlated with the X-ray stage of K/L grade in the linear regression (relative coefficient = 0.607, P < 0.01).

The correlation was adjusted for age, sex and BMI.
ministered, disease-specific measure and is divided into four subcategories: pain and stiffness (0–32), activities of daily living (0–40), general activities (0–20) and general health conditions (0–8). JKOM is higher in patients with more pain and physical disabilities.

**Statistical analysis**

To test the frequency of BMAs in the subdivided regions by WORMS, the chi-square test was used. Multivariate analysis of variance (MANOVA) was used to compare the BMA frequency and the s-score with K/L grade corrected for age, sex and BMI. Furthermore, MANOVA was used to compare VAS and JKOM with the s-score corrected for age, sex and BMI. Furthermore, multiple comparisons between subjects were performed using the Bonferroni test. Statistical significance (two tailed) was calculated using SPSS 16.0 for Windows version 16.0. P values ≤ 0.05 were considered significant.

**Results**

The 238 subjects included 221 women and 17 men (Tab.1). There was MRI evidence of a BMA in 183 patients (77%). The BMA frequency of the medial femorotibial joint (MFTJ), the lateral femorotibial joint (LFTJ), patellofemoral joint (PFJ) and the portion of the tibia beneath the tibial spines (region S) was 72.8%, 14.9%, 16.3% and 39.9%, respectively (Fig. 3). The BMA frequency of MFTJ was higher than that of LFTJ, PFJ and S (P < 0.01). BMA frequency in the central part of the medial femoral condyle (MFc), anterior part of the medial tibial condyle (MTa) and center part of the medial tibial condyle (MTc) was significantly higher than in other subdivisions of the knee (66%, 51% and 57%, respectively, P < 0.01).

BMA frequency of the MFTJ in Kellgren–Lawrence (K/L) grade 1, 2, 3 and 4 was 22%, 43%, 22% and 33%, respectively.
85% and 96%, respectively (Fig. 4). The BMA frequency of the MFTJ in Kellgren-Lawrence (K/L) grade 3 and 4 was significantly higher than in grade 1 and 2 (P < 0.001). Furthermore, the BMA frequency of region S in Kellgren-Lawrence (K/L) grade 1, 2, 3 and 4 was 13%, 23%, 29% and 60%, respectively. The BMA frequency of region S in K/L grade 4 was significantly higher than in grade 1, 2 and 3 (P < 0.001); however, the BMA frequencies of LFTJ and PFJ showed almost no change as the K/L grade progressed.

In addition, there was a significant correlation between the s-score of the MFTJ and the K/L grade (Fig. 5). The average spatial BMA score (s-score) of the MFTJ in K/L grade 1, 2, 3 and 4 was 3.1, 4.6, 14.8 and 23.4, respectively. The s-score of the MFTJ was higher as the stage of osteoarthritis increased. The s-score in K/L grade 3 and 4 was significantly higher than in grade 1 and 2 (P < 0.001). Furthermore, the s-score in K/L grade 4 was significantly higher than in grade 3 (P < 0.01).

The s-score was correlated with the X-ray stage of the K/L grade in linear regression (relative coefficient = 0.607, P < 0.01).

When all the s-scores (0-72 points) were separated into 4 groups, the s-score of quantiles 1, 2, 3 and 4 was 0, 0.1-10.5, 10.6-25.0 and 25.1-72.0, respectively (Tab. 2). VAS (visual analog score) of quantile 1, 2, 3 and 4 was 47.2, 59.4, 61.9 and 66.1, respectively. VAS of quantile 1 was significantly lower than that of quantile 2, 3 and 4 (quantile 1 vs 2 : P < 0.05, quantile 1 vs 3 : P < 0.05 quantile 1 vs 4 : P < 0.01). JKOM (Japanese knee osteoarthritis measure) of quantile 1, 2, 3 and 4 was 34.8, 40.4, 46.3 and 48.5, respectively. JKOM of quantile 1 was significantly lower than that of quantile 2, 3 and 4 (quantile 1 vs 2 : P < 0.05, quantile 1 vs 3 : P < 0.05 quantile 1 vs 4 : P < 0.01). ROM (range of motion) of quantile 1, 2, 3 and 4 was 133.1, 124.6, 122.1 and 113.4, respectively. ROM of quantile 1 was significantly higher than that of quantile 3 and 4 group (quantile 1 vs 3: P < 0.01, quantile 1 vs 4 : P < 0.001). The s-score was associated with VAS, JKOM and ROM.

The correlation was assessed between the clinical data (VAS, JKOM and ROM) and the s-score of the MFTJ in knees with X-ray stage K/L grade 2 corrected for age, sex and BMI (Tab. 3). There were 44 cases in K/L grade 2. About half of the knee joints had no BMAs of the MFTJ in K/L grade 2 and they were divided into three groups by the s-score for the appropriate statistical assessment. In K/L grade 2 knees, the higher s-score groups had higher VAS scores and JKOM and lower ROM than lower s-score groups; however, the association of the VAS score, JKOM and ROM in the s-score groups was not statistically significant.

Discussion

Many studies have addressed the correlation between OA of the knee and BMAs since Bergman et al.14). They found ill-defined bone marrow hyper-intensities on T2-weighted MRI in patients with debilitating knee and hip pain. The corresponding standard radiographs were normal or demonstrated nonspecific osteopenia. The authors termed these findings bone marrow edema because of the lack of a better term and to emphasize the generic character of the condition. Histopathologic examination showed that the BME zone mainly consisted of normal tissue (53% of the area was fatty marrow, 16% was intact trabeculae, and 2% was blood vessels) and a smaller proportion of several abnormalities (11% of the area was bone marrow necrosis, 8% was abnormal [necrotic or remodeled] trabeculae, 4% was bone marrow fibrosis, 4% was bone marrow edema (BME), and 2% was bone marrow bleeding)15). Therefore, these findings should not be attributed routinely to edema. Recently, this pattern was called a bone marrow abnormality (BMA)8)16) or bone marrow lesion (BML)17)18)19). Using the Kellgren-Lawrence scale to grade the severity of the articular cartilage degeneration, Link et al. identified BMAs in 30% of patients with grade 1 OA, 36% of patients with grade 2 OA, 77% of patients with grade 3 OA, and 81% of patients with grade 4 OA of the knee12). Felson et al. also noted that BMAs were more commonly observed in patients with higher K/L grades of knee OA17). They reported that a BMA was found in 77.5% of individuals with knee pain in comparison to 30% of those without knee pain; however, among those with knee pain, BMAs were not associated with pain severity. Some reports have suggested that the size of the BMA was correlated with the X-ray stage, but it was not correlated with pain or the WOMAC (Western Ontario and McMas-
Several studies have addressed the correlation between BMA frequency and the X-ray stage and clinical findings. Some studies have analyzed BMAs by a semi-quantitative method in two dimensions; however, a BMA is actually a lesion not only in one plane but also with spatial expansion.

The current study demonstrated that the BMA frequency of the medial femorotibial joint (MFTJ) in medial OA increased as the X-ray stage increased. These findings were consistent with those published in other reports. In addition, the spatial size of the BMA 's-score' was significantly correlated with the clinical scores (VAS and JKOM) and the X-ray stages of medial OA were strongly and linearly correlated with the spatial expansion of the BMA in the MFTJ. These results were different from other reports. A correlation could be obtained because the BMAs assessed three-dimensional expansion in this study.

As the frequency of BMAs increases as the knee tends toward the varus of the MFTJ, the mechanism of the occurrence and enlargement of the BMA may be thought to be medial overloading with the progression of OA, but a BMA was also frequently seen in region S where there is minimal compressive loading; therefore, there may be another factor in BMA formation other than mechanical overloading.

There are some limitations of this study. First, there were no control subjects with knee OA without pain (radiological OA). Secondly, there were fewer OA knees in the early stage (K/L grade 1 and 2 = 76) than in the advanced stage (grade 3 and 4 = 162). Finally, the study is a transverse investigation and the significance and fate of BMAs in the course of OA was not clarified.

Conclusion: The frequency and spatial expansion of BMAs in the MFTJ are strongly correlated with the X-ray stage of medial-type OA as well as the clinical findings.

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Conflicts of interest

The authors did not receive and will not receive any benefits or funding from any commercial party related directly to the subject of this article.

References


Bone marrow abnormality associated with painful osteoarthritis of the knee:
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And English translation

Mitsuaki Kubota, Hisashi Kurosawa, Hiroshi Ikeda, Yuji Takazawa, Takayuki Kawasaki, Muneaki Ishijima, Sung-Gon Kim, Hiroaki Seto

目的: 变形性膝関節症 (膝OA) においてbone marrow abnormality (BMA) といわれる骨髄病変
がMRI上しばしば認められる。BMAは膝OAのX線分類や疼痛に関係すると報告されているが,
BMAのサイズ評価法はいずれも2次元的な評価である。われわれは内側型膝OAに対しBMAの3
次元的なサイズを半定量的に評価し、さらにX線分類、臨床所見と比較検討した。

方法: 対象は内側型膝OA 238例で、全例X線、MRIを撮像した。X線分類はKellgren-Lawrence
(K/L) 分類 (1-4) を使用した。MRI T2強調脂肪抑制画像でBMAの大きさをWORMSにしたが
い2次元的に評価し、さらに3次元的なサイズを評価するため新しいスコア (spacial BMA score =
s-score) を使用した。臨床症状は関節可動域 (ROM)、臨床スコアとしてVAS (visual analog scale)
とJKOM (Japanese Knee Osteoarthritis Measure) を使用した。s-scoreとX線分類、臨床所見と比較
検討した。

結果: BMAの頻度は内側大腿筋骨関節において74％であり、外側大腿筋骨関節 (14％) および膝
蓋大腿関節 (14％) に比べ有意に高値であった (P<0.01)。内側大腿筋骨関節におけるs-scoreの増
加はK/L分類の進行と有意に相関した。さらにs-scoreの増加はROMの縮小、VASおよびJKOM
の増大と有意に相関した。

考察: 内側大腿筋骨関節における2次元的なBMAの拡がりは内側型膝OAのX線分類および臨
床所見と有意に相関した。