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The relationship between bone marrow edema size and knee pain

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Abstract The purpose of our study was to determine the changes in the size of the edema observed on MRI scans and its relation to the activity pain of the patient and the rest pain in bone marrow edema (BME). A total of 51 patients were followed up at 3-month intervals for a period of 1 year. During the follow-ups, MRI scans of the patients' knees were obtained; the scores obtained on the Stanmore functional rating scale and visual analog scale were determined. The changes in these parameters and the correlation between them were examined. The following are the observations recorded during the bone marrow edema follow-ups: the size of the edema as observed on MRI scans decreased, and the activity pain and the rest pain decreased. While there is a correlation between the decrease in the edema size observed on MRI scans and decrease in the activity pain, there is no correlation between the decrease in the edema size observed on MRI scans and the decrease in rest pain. No changes were observed after a particular period of time with regard to decrease in the edema size observed on MRI scans, decrease in activity pain, and decrease in rest pain in follow-ups of BME patients.

Keywords Bone marrow edema · Knee · Activity pain · Rest pain · Size of edema

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Introduction

Bone marrow edema (BME) syndrome occurs due to diffuse subacute ischemia and generally heals completely due to an adequate repair mechanism [10]. No radiological findings can be observed in the first 4–6 weeks of bone marrow edema syndrome cases; however, a mild demineralization may be observed in later stages. The characteristics of bone marrow edema syndrome that distinguish it from other diseases causing the same condition are as follows: diffuse extension of bone marrow edema syndrome, lack of morphological alterations, absence of a history of trauma, and reversibility [9, 10]. Spontaneous recovery is observed in 3–12 months (average, 6 months). Bone marrow edema syndrome is, however, a poorly defined term that is rarely used in present-day literature. Increased signal intensity over the bone marrow, as visualized by performing MRI on fat-suppressed or STIR sequences [1, 9, 18], was previously considered to be reflective of bone marrow edema syndrome; however, such findings on MRI are now known to be more commonly associated with trauma, osteoarthritis and osteonecrosis [3, 5, 12, 14, 16].

Bone marrow edema is an MRI finding accompanying pain. Patients suffering from BME of the knee complain of knee pain. No objective examinations exist presently for the follow-up of these patients. Pain and the functional condition of the patients are the most important parameters examined in the follow-up. During follow-ups, clinical alterations are observed in addition to alterations in the size of the edema observed on MRI scans. However, the clinical condition of the patient, and whether a correlation exists between the clinical condition and the lesion size observed in the MRI scans, is not clear. The clarification of this situation may provide significant

information to establish the follow-up criteria for BME patients.

We aimed to determine the course and direction of the alterations in the size of edema observed in the MRI scans, in rest pain and in activity pain of BME patients. We also aimed to determine the correlations between these three factors during the follow-ups of these patients. So, we hypothesized that there is no correlation between the edema size observed on MRI scan and the knee pain.

Materials and methods

Between 2003 and 2005, 277 patients were diagnosed with bone marrow edema on the basis of MRI scans obtained following complaints of knee pain. Among these patients, the following patients were excluded from this study: (1) patients with osteoarthritis, which narrows the joint gap, Kellgren and Lawrence grade ≥ 2, determined with bilateral non-weight-bearing and weight-bearing roentgenograms; (2) patients with grade 3 or grade 4 chondral defect (Outerbridge classification) in any of the knee compartments diagnosed on the basis of MRI findings. Grade 3 is defined as: deep ulceration, fissure or flap that involves more than 50% of the depth of the articular cartilage without exposure of the subchondral bone; grade 4: full-thickness chondral defect with exposure of the subchondral bone; (3) patients with meniscal rupture that opens to the articular surface, on MRI before or during follow-ups; (4) patients with spontaneous osteonecrosis on MRI before or during follow-ups. The findings on MRI are large cystic cavity in the subchondral bone and surroundings, with bone marrow edema, buckling of hyaline cartilage and location of irregular cartilage on the center of the weight-bearing surface; (5) patients with osteonecrosis (avascular necrosis) on MRI; (6) patients with complex regional pain syndrome in the knee region. Clinical signs are changes in temperature, discoloration of the skin, swelling and sudomotor activities, patchy subchondral osteopenia on plain roentgenograms and bone marrow edema on MRI; (7) patients with osteochondritis dissecans; (8) patients with microfracture, stress fracture or bone bruise in the initial diagnosis or follow-ups. Bone bruises could be distinguished from BME in the case of patients who had a history of major knee injury and for whom micro-fractures were observed on MR images; (9) patients with tumor tissue in the region with bone marrow edema; (10) patients in whom follow-ups were not possible as specified below and whose consents could not be obtained. The number of the patients who were excluded from the study and their exclusion criteria are summarized in Table 1. In some patients, more than one exclusion criteria were noted. Only BME patients with no significant history of knee trauma history were included in this study.

Table 1 The causes of exclusion and number of patients

Causes of exclusion	Number of patients
Osteoarthritis or/and grade 3 or 4 chondral deficiency	94
Grade 3 meniscal tear before or during the follow-up	73
Spontaneous osteonecrosis of knee before or during the follow-up	23
Osteonecrosis (avascular necrosis)	8
Complex regional pain syndrome	3
Osteochondritis dissecans	14
Microfracture, stress fracture, bone bruise	28
Previous knee surgery	11
Tumor	1
Patients who have not followed systematically or have not given consent for the study	37

The clinical and radiological control examinations of the patients for this study were performed at 0, 3, 6, 9 and 12 months. In each control examination, the activity pain was assessed on a Stanmore functional rating scale (SFRS) and rest pain was assessed on a Visual Analog Scale (VAS) of 0–10. SFRS was designed for simultaneously assessing the intensity of pain and the level of functional activity. It is a simple questionnaire framed in the multiple-choice format, as seen in Table 2 [15]. The VAS questioning was performed using a ten-part VAS scale, which is constituted from a scale with numbers increasing from 0 to 10. The patients were asked to show his/her level of pain on this scale. Radiological follow-up included MRI of the knee. A follow-up performed 15 days before or after the specified follow-up time was accepted as a timely follow-up for both clinical as well as MRI examinations. The patients in whom the follow-ups were performed beyond this time period were excluded from the study. In the subsequent follow-ups in cases where MRI revealed complete disappearance of lesions, further follow-ups included only clinical examination and MRI was not performed. Fifty-one patients who completed the follow-up were included in

Table 2 The demographic parameters, affected knee ($n = 51$) and the time of start of pain

Number of females	32
Number of males	19
Mean age	52 (27–65)
Affected knee	
Right knee	35
Left knee	16
Time point at which pain was experienced prior to the first clinical presentation	2.5 (0.5–6) months

the study. The demographic parameters, the affected knee and the time point at which pain was experienced prior to the first clinical presentation were all recorded (Table 2).

The patients underwent standard conservative treatment after they were diagnosed with BME during the first examination. For the first 3 weeks of this treatment, the patients were instructed to walk with crutches without weight-bearing, and in the following 3 weeks, to walk with partial weight-bearing. Further, diclofenac sodium 1×75 mg day^{-1} was administered in the first 3 weeks, and paracetamol 3×500 mg day^{-1} in the following 3 weeks.

MRI follow-ups and assessment

All MRI examinations were performed at the same center and by using the same MRI device. The MRI device and technique used were as follows: 1.5 T superconductor magnet (Magnetom Expert, Siemens, Erlangen, Germany); sagittal conventional spin-echo T1 TR/TE:640/14, T2 TR/TE:1590/22; coronal conventional fast spin-echo fat-sat T2 TR/TE:1590/22; axial conventional fast spin-echo fat-sat T2 TR/TE:1590/22; slice thickness: 4 mm, FA: 90; matrix: 256 × 156; NEX: 2; FOV: 220 × 165. The bone marrow edemas of the patients were measured by performing MRI of their knees during the abovementioned months. We used coronal T2-weighted fat-saturated images to evaluate bone marrow lesions. In the coronal plane, measurements were made using all cross sections from the beginning till the end of the edema. In all cross sections, the measurement was carried out by using a transparent measurement template consisting of 1 mm multiple squares (mm^2) (Fig. 1). All measurements were carried out by the same physician. All 1 mm squares with bone marrow edema were counted, and the total area of all these squares were calculated and recorded as the bone marrow edema of the patient during that follow-up period.

When the size of the lesion measured in the MRI scan was zero for a patient, MRI was not performed in the subsequent follow-ups of that patient. Five MRI scans were taken in the course of five follow-ups for 23 patients; four MRI/five follow-ups for 15 patients; three MRI/five follow-ups for 8 patients; and two MRI/five follow-ups for 5 patients. The MRI was performed on 51 patients on their first visit, 51 patients in the third month, 46 patients in the sixth month, 38 patients in the ninth month and 23 patients in the twelfth month.

The locations of bone marrow edema were classified anatomically as femur medial condyle, femur lateral condyle, tibia medial plateau, tibia lateral plateau, femur medial condyle together with tibia medial plateau, and femur lateral condyle together with tibia lateral plateau. The starting region of the lesion and the region where the lesion was concentrated were together identified as comprising the anatomical region of the edema. The data regarding the anatomic localization of bone marrow edema in the patients has been provided in Table 3.

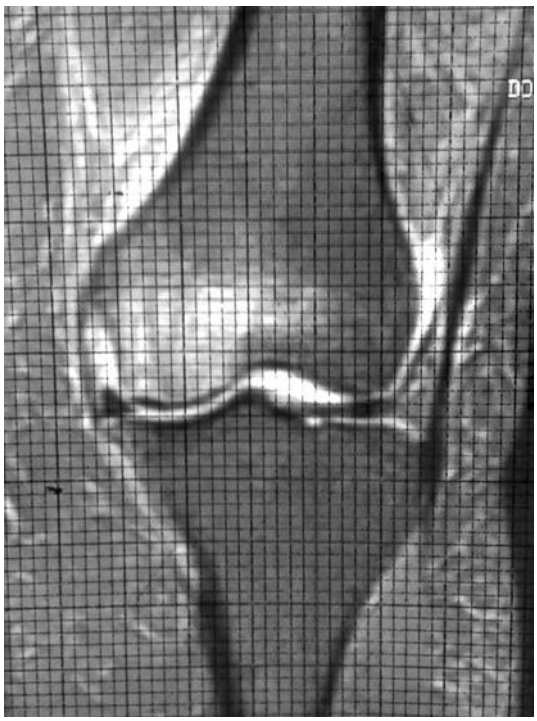

Fig. 1 Edema measurement by MRI with 1 mm transparent measurement template

In addition, the patients were divided into two groups: those who exhibited BME at or after 9 months (≥9-month group) and those who did not exhibit BME at or after 9 months (<9-month group). These two groups were compared in terms of age, edema size of the initial MRI, and BME localization.

Table 3 The anatomical localizations of the edema

The anatomical localizations of the edema	Number of patients ($n = 51$)
Medial femoral condyle	21
Lateral femoral condyle	9
Medial tibial plateau	7
Lateral tibial plateau	3
Medial and lateral femoral condyle	3
Medial and lateral tibial plateau	2
Medial femoral condyle and medial tibial plateau	4
Lateral femoral condyle and lateral tibial plateau	2

Statistics

In this study, the statistical analyses were performed by using the GraphPad Prisma V.3 program (GraphPad Software, Inc.11452 El Camino Real, #215 San Diego, CA, USA). Friedman test was used for the comparison of repetitive measurements of SFRS, VAS and edema size observed in the MRI, along with definitive statistical measures (mean, standard deviation) for the assessment of the data. To determine the trends among these comparisons and the course of alterations occurring between follow-ups, post hoc Dunn's multiple comparison test was used. To determine the correlations between VAS and SFRS, SFRS and BME, and VAS and BME size, the Pearson correlation test was used. To determine the differences in the average age and the size of the edema noted during the initial MRI between the ≥9-month and <9-month groups, we performed unpaired t tests. Further, the Chi-square test was used to determine the differences in BME localization between the ≥9-month and <9-month groups. A p value of <0.05 was considered to be statistically significant.

Results

A statistically significant decrease was observed in the average area of the edema observed on MRI scans in the first visit and the third, sixth, ninth and twelfth months [$p = 0.0001$] (Table 4). No statistically significant differences were observed between the values of the first visit and third month, and ninth and twelfth months obtained during the control examinations [$p > 0.05$; $p > 0.05$, respectively], but the differences observed in the other intervals of the months were statistically significant (Table 5).

A statistically significant decrease was observed in the SFRS averages obtained in the first visit and in the third, sixth, ninth and twelfth months [$p = 0.0001$] (Table 4). No statistically significant differences were observed between the first visit and third month, and sixth and ninth month values obtained during the control examinations [$p > 0.05$], but the differences observed in the intervals of the other months were statistically significant (Table 5).

A statistically significant decrease was observed in the VAS score averages in the first visit and the third month, sixth, ninth and twelfth months ($p = 0.0001$) (Table 4). No statistically significant differences were observed between the first visit and third month, third and sixth, and sixth and ninth month values obtained during the control examinations [$p > 0.05$; $p > 0.05$; $p > 0.05$, respectively], but the differences observed in the intervals of the other months were statistically significant (Table 5).

In MRI measurement, the average percentage of alteration ± standard deviation is 79.30 ± 62.73; in SFRS, the average percent alteration ± standard deviation is 63.23 ± 42.13 and in VAS score average percentage of alteration ± standard deviation is 73.43 ± 30.42.

Statistically significant positive correlations were observed between the decrease in edema area observed on MRI scans and the recoveries in the SFRS scores ($r = 0.313$; [$p = 0.025$]); and between the recovery in the SFRS scores and the recovery in the VAS scores ($r = 0.943$; [$p = 0.0001$]). No statistically significant positive correlation were observed between the decrease in edema area observed on MRI scans and the recoveries in the VAS score ($r = 0.203$; [$p = 0.153$]).

No statistically significant differences were observed between the ≥9-month and <9-month groups with regard to age, size of the edema noted during the initial MRI and BME localization ($t = -1.19$ [$p = 0.238$]; $t = -0.87$ [$p = 0.389$]; $\chi^2 = 4.47$ [$p = 0.727$], respectively) (Table 6).

We observed that the patients did not strictly comply with the instructions of using crutches without weight-bearing. Decrease in pain within 2–3 weeks had led to irregular use of the crutches by the patients.

Table 4 The follow-ups and Friedman test results of MRI, SFRS and VAS

	MRI (mm^2)	Stanmore	VAS
First visit	442 ± 287	3 ± 1	8 ± 2
3 month	293 ± 233	3 ± 1	7 ± 3
6 month	175 ± 180	2 ± 1	5 ± 3
9 month	94 ± 159	2 ± 1	3 ± 3
12 month	53 ± 106	1 ± 1	2 ± 2
Fr[a]	**145.8**	**90.11**	**109.7**
p	**0.0001**	**0.0001**	**0.0001**

[a] Friedman statistic value

Discussion

The principal finding of the present study was the presence of a correlation between the decrease in bone marrow edema size on MRI and decrease in activity pain with the absence of a similar correlation between the decrease in edema size and decrease in rest pain.

It is important to define the relationship between the edema size in bone marrow edema and the pain of the patient, because no defined follow-up criteria have been established for bone marrow edema. It is necessary to take into account the clinical and radiological progress of the disease while defining the follow-up criteria. In our study, the activity or rest pain of the bone marrow edema patients and the progress of pain were determined. In addition, the

Table 5 The follow-ups and post hoc Dunn's multiple comparison test results of MRI, SFRS and VAS

Dunn's multiple comparison test	MRI		Stanmore	VAS	
	Average of changes (mm^2)	*P* value	*P* value	Average of changes	*P* value
First visit/3 month	149	>0.05	>0.05	1.06	>0.05
First visit/6 month	267	**<0.001**	**<0.05**	3.04	**<0.001**
First visit/9 month	347	**<0.001**	**<0.001**	4.45	**<0.001**
First visit/12 month	389	**<0.001**	**<0.001**	6.92	**<0.001**
3 month/6 month	118	**<0.05**	**<0.05**	1.98	>0.05
3 month/9 month	198	**<0.001**	**<0.001**	3.39	**<0.001**
3 month/12 month	240	**<0.001**	**<0.001**	4.88	**<0.001**
6 month/9 month	81	**<0.05**	>0.05	1.41	>0.05
6 month/12 month	122	**<0.001**	**<0.001**	2.9	**<0.001**
9 month/12 month	41	>0.05	**<0.05**	1.49	**<0.01**

p value of <0.05 was considered to be statistically significant

relation between these clinical conditions and the results of MRI examinations were also defined.

Our study has certain limitations. First, we did not examine the interobserver and intraobserver differences in the MRI measurements that were used. However, the measurements were made by a single physician. In literature, alternative measurements and classifications have been mentioned for bone marrow edema [7, 13]. In these studies, bone marrow edema is classified into three types according to the size of the lesion. However, our measurement techniques are more valuable for statistical studies. It was difficult to handle a very focal bone marrow edema; therefore, minimal errors in the bone marrow edema measurements could be ignored. As much as 37 patients who could not be systematically followed up or did not provide their consent for participation in the study were excluded. The 51 patients included in the study is not a small number. We have used large exclusion criteria. Though this seems to limit our study group, the use of pain questioning helped in diminishing other known causes of knee pain than bone marrow edema, as far as possible. The follow-up interval in our study was 3 months. Even shorter intervals would increase the value of such studies; however, it is ethically inappropriate to request the patient to visit the clinic to undergo MRI. The compliance of the patients with the instructions to be followed during the prescribed conservative treatment was not uniform. This makes the group heterogeneous with respect to the prescribed treatment. However, there are no significant evidences indicating that the conservative treatments prescribed for bone marrow edema alter the clinical condition of patients [9]. Non-steroidal anti-inflammatory treatment does not alleviate the pain [9]. It is known that using crutches has a limited effect, and the patients experience relief from pain only during the night [9]. We followed up the patients for 1 year; therefore, our data and conclusions are relevant only for this time period. However, differences in the date of visit to the clinic and the date of onset of pain, and the failure to precisely determine the date of onset of bone marrow edema from the MRI scan, will

Table 6 The ≥9-month and <9-month groups with regard to age, size of the edema noted during the initial MRI and BME localizations

	≥9-month		<9-month		*t*	*p*
N	29		22			
Size of the initial edema (mm^2)	411 ± 294		482 ± 279		−0.87	0.389
Age	50 ± 11		5 ± 10		−1.19	0.238
Lateral femoral condyle	5	17%	4	18%		
Lateral femoral condyle and lateral tibial plateau	2	7%		0%		
Medial and lateral femoral condyle	2	7%	1	5%		
Medial femoral condyle	12	41%	9	41%		
Medial femoral condyle and medial tibial plateau	2	7%	2	9%		
Lateral tibial plateau	2	7%	1	5%		
Medial and lateral tibial plateau	0	0%	2	9%	χ^2:4.47	
Medial tibial plateau	4	14%	3	14%	$p = 0.727$	

inevitably result in a heterogeneous group in such studies. Although the slice thickness used (4 mm) was the same as that conventionally used for MRI of the knee, it may have hindered the determination of the size of the edema.

In follow-ups of bone marrow edema cases, decreases in the size of the lesions are observed over a period of time [9]. In our study, the sizes of the edema observed on MRI scans were significantly lower than the initial measurements obtained in the first visit. This trend of decreases continued in the third and sixth months. However, in the ninth and twelfth months, no significant changes were observed. This indicates that the decrease in the lesion size continued until the ninth month, after which no significant changes occurred in the size of the lesion. This may be due to two reasons. First, the patients whose bone marrow edema lesion is maintained until the ninth month may have another etiological factor. In our study, we excluded patients who were initially followed-up as bone marrow edema patients and who subsequently displayed findings of spontaneous osteonecrosis. However, in some of the patients, whose lesions have not decreased till date, spontaneous osteonecrosis and/or osteoarthritis is expected to develop after the first year [4, 5, 11]. Second, there might be no changes in the size of edema between the ninth and twelfth months during the natural progression of the disease. Some of the patients, in whom edema had disappeared before the second measurement, may have already been in recovery period.

Loss of hyaline articular cartilage is a central pathologic event in the clinical course of osteoarthritis; however, its pathogenesis is poorly understood. Increased uptake noted on bone scans is associated with a parallel finding on MR images, i.e., bone marrow edema. In patients with knee osteoarthritis, bone marrow edema lesions in the cartilage beneath the bone markedly increase the risk for structural progression of the condition in the knee, especially in the compartment affected by the bone marrow lesions. Further, these lesions are strongly related to malalignment along the frontal plane. An extraordinarily high prevalence of medial bone marrow lesions is noted in varus limbs [4, 5, 11]. In our study, bone marrow edema was commonly localized to the medial femoral condyle. We did not measure malalignment because this parameter was irrelevant to the objective of the study. Both primary and secondary osteonecrosis of the knee seem to follow a natural clinical course involving several sequential stages. Osteonecrosis is believed to be characterized by a unique appearance on MR images, with extensive edema-like signals in the bone marrow. MRI of patients with early stage avascular necrosis occasionally reveals focal changes that are consistent with a diagnosis of avascular necrosis, accompanied by a surrounding pattern that is typical of bone marrow edema [6, 17].

There are no defined clinical forms of or scores for bone marrow edema. Objective data specific to the disease are important to establish clinical forms. For follow-up of the patients, we used Stanmore functional rating scale, which is a form of functional scoring of activity pain [15]. During our study, a significant recovery was observed between the values in the first visit and those in the follow-ups. However, there was no decrease in activity pain between the sixth and ninth months. This finding indicates that if the functional recovery is not completed by the sixth month, this process will continue for some more time without alteration.

In bone marrow edema, pain is the most important symptom, which helps to establish the identity of the condition [2, 8]. With the help of VAS, pain, which is subjective, may be scored. In our study, the rest pain of the patients had significantly decreased as compared to the rest pain reported during the first visit. However, in some cases, there is no decrease in rest pain between the third and sixth months, and the sixth and ninth months. In this case, it is possible to say that the complaints of a patient, whose rest pain does not decrease after the third month, will continue into the ninth month.

In patients with bone marrow edema, the method of follow-up of patients is important. Patients complain of pain and request for a remedy. The functional restriction of the patients depends on the severity of pain [8]. There are no defined symptomatic mechanical problems. In our study, significant correlations were found between the edema size observed on MRI scans and Stanmore functional rating scale recovery and also between Stanmore functional rating scale and VAS recoveries. In other words, the activity pain of the patient and the decrease in the edema size are parallel. In this case, since the functional progress of the disease corresponds with the decreasing edema size observed on MRI scans, MRI can be used as functional follow-up and may support clinical findings. However, there are no correlations between edema sizes observed in MRI and VAS recoveries. In this case, the definition of the rest pain symptoms by the patients is not consistent with the edema sizes observed on MRI scans. Considering that pain is the sole symptom of bone marrow edema, we believe that the edema size observed on MRI scans is not a valuable finding in the follow-up of bone marrow edema.

Bone marrow edema may persist until the ninth month. Bone marrow edema that persists beyond this duration may be related to osteoarthritis [3, 5]. We divided the patients into two groups: the $\geq$9-month group and the $<$9-month group. Age, size of the edema noted during initial MRI and the bone marrow edema localization did not differ significantly between the groups. The etiology of continued bone marrow edema must be clarified.

In our study, the edema size observed on MRI scans, activity pain and rest pain progress have been defined. In bone marrow edema follow-ups, decrease in edema size, decrease in activity pain, and decrease in rest pain were observed. There is no decrease in edema size between the ninth and twelfth months, no decrease in activity pain between the sixth and ninth months, and no decrease in rest pain between the third and sixth months and the sixth and ninth months. While there is a correlation between the decrease in edema size and decrease in activity pain, there is no correlation between the decrease in edema sizes and decrease in rest pain.

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