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SCIENTIFIC ARTICLE

Volume of hip synovitis detected on contrast-enhanced magnetic resonance imaging is associated with disease severity after collapse in osteonecrosis of the femoral head

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Abstract

Objective To evaluate the relationship between the volume of hip synovitis detected on contrast-enhanced magnetic resonance imaging (MRI) and the disease stage of osteonecrosis of the femoral head (ONFH).

Materials and methods Sixty-three consecutive hips in 40 ONFH patients were reviewed using contrast-enhanced MRI. Ten unaffected hips in 10 patients with unilateral ONFH were used as controls. Based on the Japanese Investigation Committee system, these hips were classified according to stage and type. The volume and location of hip synovitis were semi-quantitatively measured on contrast-enhanced MRI. Clinicoradiological factors were statistically analyzed to determine the relationship with the volume of hip synovitis.

Results The mean synovial volume was significantly larger in ONFH hips (8,020 ± 6,900 mm^3) than in controls (910 ± 1,320 mm^3; $p = 0.001$). The area of synovitis in the anterior portion of the hip joint was double (mean: 2.17 ± 1.77) that in the posterior portion. The volume of synovitis was small in pre-collapse-stage hips (stage 1: 680 ± 690 mm^3, stage 2: 1,460 ± 1,200 mm^3), but significantly larger in post-collapse-stage hips (stage 3A: 7,820 ± 4,490 mm^3, stage 3B: 13,850 ± 7,110 mm^3; $p < 0.001$). Multiple regression analysis showed that disease stage was the only factor related to hip synovitis.

Conclusions Our study suggests that hip synovitis in ONFH might occur after femoral head collapse and worsen with collapse progression, mainly in the anterior portion.

Keywords Synovial volume · Contrast-enhanced magnetic resonance imaging · Osteonecrosis · Femoral head collapse

Introduction

In the natural course of osteonecrosis of the femoral head (ONFH), femoral head collapse results in a significant change in the radiological and clinical condition [1–3] and leads to joint disruption, which necessitates surgical treatments such as prosthetic replacement surgery. On the other hand, pre-collapse ONFH is also a target for therapeutic interventions intended to prevent the occurrence of collapse, such as core decompression combined with cell therapy [4–6]. Because treatments for the pre-collapse and post-collapse stage of ONFH are quite different [7], appropriate stage classification requires an understanding of the difference in characteristic image features between stages.

Perthes disease is an ischemic hip disorder in children that results in femoral head collapse [8, 9]. In patients with this disorder, synovitis is commonly observed at the time of diagnosis by MRI or ultrasound [10, 11], and persistent inflammation is seen in the advanced stages, including the fragmentation and reossification stages [11, 12]. Further, the severity of synovitis, which affects clinical outcome, correlates with the extent of epiphyseal necrosis [11, 13]. On the other hand, to the best of our knowledge, only one study has focused on synovitis in ONFH [14]; therefore, differences between stages in the characteristics of ONFH synovitis have not been identified.

A widely used imaging tool for evaluating synovitis in several joint diseases is contrast-enhanced magnetic

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resonance imaging (MRI) with gadolinium as a contrast agent, as this approach differentiates inflamed synovial membrane from surrounding tissues [15–17]. In ONFH, contrast-enhanced MRI is often performed to more clearly detect non-distinctive necrotic lesions [18, 19], but no attention has been paid to synovitis. In the current study, we utilized the clinical data from contrast-enhanced MRI to evaluate the relationship between the volume of hip synovitis and the disease stage of ONFH.

Materials and methods

Patients

Our institutional review board approved this study. At our institution, contrast-enhanced MRI examination of both hips is performed concurrently in cases in which it is difficult to identify the accurate boundary of necrotic lesion in the post-collapse ONFH hip on unenhanced MRI. Between July 2006 and February 2016, contrast-enhanced MRI was performed in 76 hips in 48 patients with nontraumatic ONFH. Both coronal and oblique axial planes were available in 63 hips in 40 patients, and these individuals were enrolled as the subjects of this study. Ten unaffected hips in 10 patients with unilateral ONFH were used as controls. ONFH was diagnosed based on the clinical presentation and imaging studies, including radiography and MRI findings [20]. Informed consent was obtained from all participants in the study.

Classification of ONFH stage and localization

Findings on two-dimensional radiographs (anteroposterior and lateral) and MRI were used for staging based on the Japanese Investigation Committee system [20, 21] as follows (Fig. 1a): stage 1, T1 low-intensity band on MRI without any specific findings on plain radiographs; stage 2, demarcating sclerosis without collapse on plain radiographs; stage 3A, less than 3-mm collapse; stage 3B, greater than or equal to 3-mm collapse; and stage 4, osteoarthritic changes. In borderline cases in which it was difficult to distinguish between pre-collapse and post-collapse stages, collapse was determined by the presence of bone marrow edema on MRI [22–24].

The localization of the necrotic area (type classification) was classified into four groups (Fig. 1b): type A, necrotic area occupies the medial one-third or less of the weight-bearing portion; type B, medial two-thirds or less; type C1, more than two-thirds but not extending to the acetabular rim; and type C2, more than two-thirds and extending to the acetabular rim.

Evaluation of hip synovitis on MRI

Magnetic resonance imaging examination was performed at our institution using a 1.5-T or 3.0-T MR system (Achieva; Philips Medical Systems, Best, The Netherlands) in 46 and 27 hips respectively. Coronal and oblique axial planes on unenhanced T1-weighted images (TR/TE: 400−600/10−18 ms respectively) and contrast-enhanced T1-weighted images with fat suppression (identical parameters to unenhanced T1-weighted images), were acquired in the supine position with 5-mm slice thickness, inter-slice gap of 0.5–2.5 mm (0.5 mm: 27 hips, 1.0 mm: 32 hips, and 2.5 mm: 4 hips), and field of view of 360 × 360 mm.

In this study, the method of measuring the area and volume of the inflamed synovium were based on reports by Neal et al. and Østergaard et al. [12, 25]. On contrast-enhanced T1-weighted images with fat suppression, we manually outlined the inflamed synovium around the

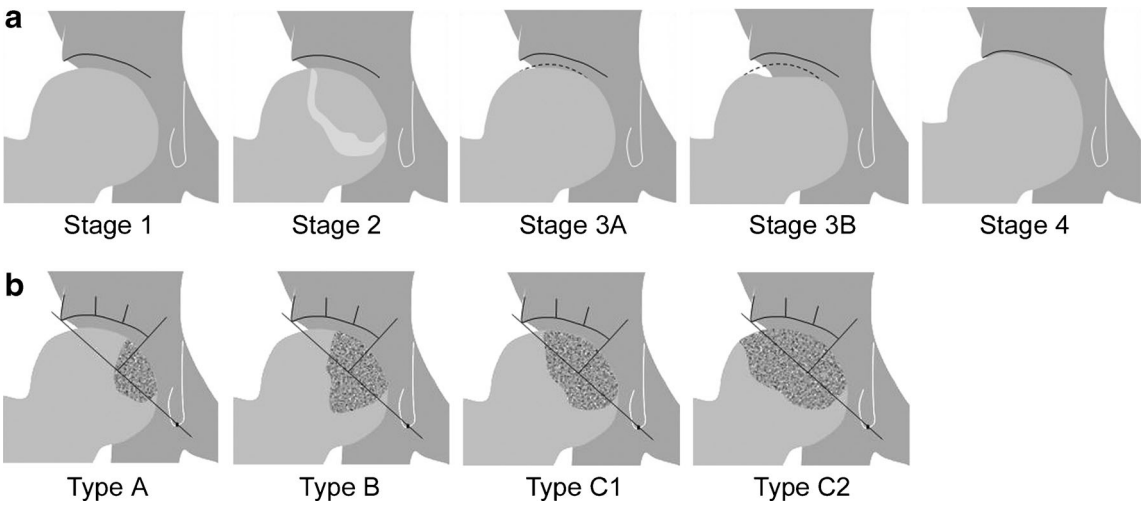

Fig. 1 Diagram of the Japanese Investigation Committee system. **a** Stage of osteonecrosis of the femoral head (ONFH). **b** Localization of the affected necrotic lesion. See text for a description of each stage and type

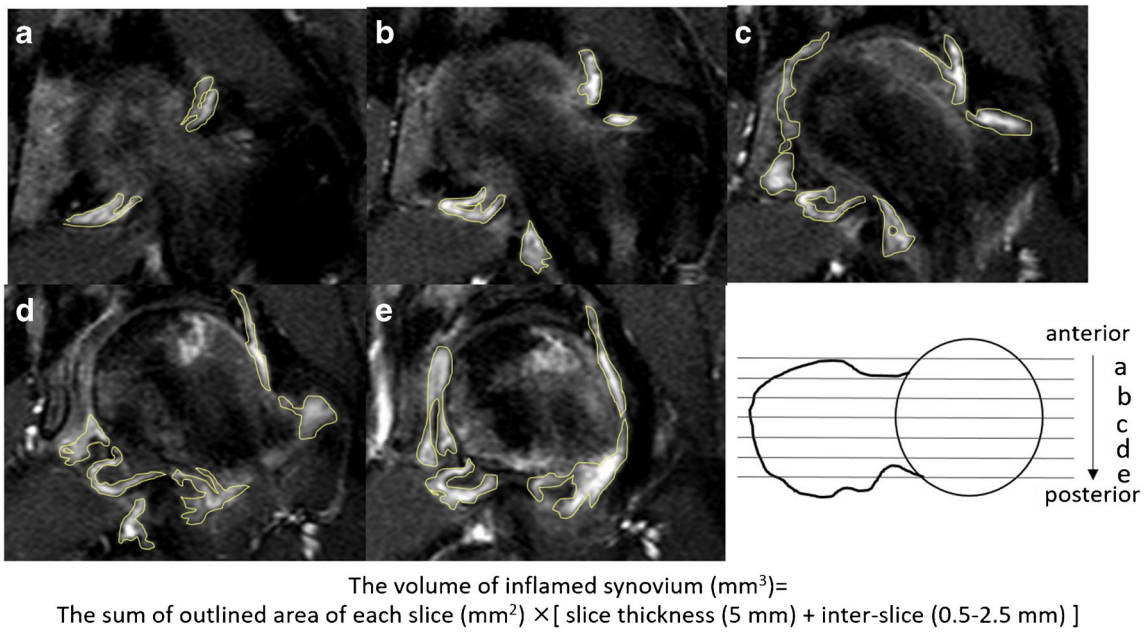

Fig. 2 Quantitative methods for evaluating the volume of the inflamed synovium on contrast-enhanced T1-weighted images with fat suppression (TR/TE: 400/18 ms). The volume (mm^3) of the contrast-enhanced inflamed synovium was calculated from the product of the sum of the *outlined areas* in each coronal slice and the sum of the slice thickness and gap thickness. The total volume of synovitis in this case was 11,353 mm^3. a-e are continuous coronal slices (a:anterior, e: posterior)

femoral head on each coronal slice. These outlined areas were automatically calculated as mm^2. The corresponding volume (mm^3) was obtained as the product of the sum of the outlined areas in each coronal slice and the sum of slice thickness and gap thickness (Fig. 2).

To localize the contrast-enhanced inflamed synovium, its areas in the anterior and posterior portions of the hip joint were measured on the mid-central oblique axial slice of each contrast-enhanced, T1-weighted image (Fig. 3). All measurements were performed using Onis 2.5 (DigitalCore, Tokyo, Japan) viewer software for Digital Imaging and Communications in Medicine files.

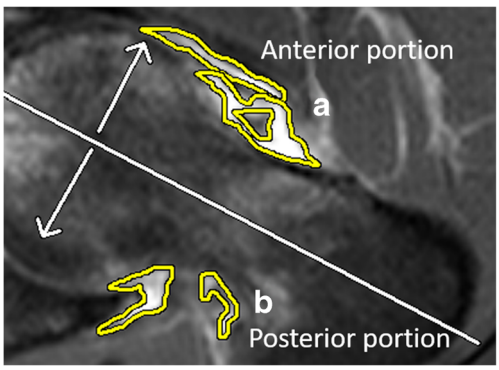

Fig. 3 Location of the contrast-enhanced inflamed synovium on contrast-enhanced T1-weighted images with fat suppression (TR/TE: 400/18 ms) was expressed as the ratio of the anterior/posterior areas, i.e., the sum of the outlined areas in the anterior portion (**a**) divided by the sum in the posterior portion (**b**) at the mid-central oblique axial slice. In this case, the areas of the anterior and posterior portions were 168 mm^2 and 113 mm^2 respectively

Statistical analysis

The volume of the inflamed synovium was expressed as a mean with standard deviation, and the location was expressed as the ratio of the anterior/posterior areas. The volume of the inflamed synovium was first compared in the ONFH and control groups. Univariate analyses using Student's *t* test, the Tukey–Kramer test, and the Pearson correlation coefficient were performed to assess the relationships between the volume of inflamed synovium and the following clinicoradiological factors: sex, age, BMI, coexistence of systemic inflammatory diseases (steroid-associated ONFH or nonsteroid-associated ONFH), present steroid administration, and staging and localization of ONFH. Additionally, stepwise multiple regression analysis was performed with regard to the factors influencing the volume of the inflamed synovium. The cut-off synovial volume for differentiating the pre-collapse and post-collapse stages of ONFH was calculated using receiver operating characteristic (ROC) curves. In the ROC curves, the area under the curve (AUC) was used to test the useful volume: an area of 1 represented a perfect test, and an area of 0.5 represented a worthless test. A value of $p < 0.05$ was considered to be significant. These statistical analyses were performed using JMP statistical analysis software (version 13; SAS Institute, Cary, NC, USA).

To test the reliability and reproducibility of evaluation of the volume of inflamed synovium, 15 randomly selected cases, more than 10% of the full sample size, were independently reviewed by two authors (HH, TU) who specialize in the diagnosis and treatment of ONFH and who were unaware

of the clinical data. In addition, one author reviewed the data a second time more than 1 month later. Intra- and inter-observer agreements were assessed using intraclass correlation coefficients (ICC 1,1 and ICC 2,1 respectively) [26]. We interpreted ICC values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 to be indicative of poor, moderate, good, and excellent reliability respectively [27]. Additionally, the correlation between the volume of the inflamed synovium and the sum of the areas of inflamed synovium in the anterior and posterior portions on the mid-central oblique axial slice was expressed by Pearson's correlation coefficient to assess the accuracy of the measurement results.

Results

Patients' clinical and radiological characteristics, including sex, age, body mass index, etiology, present steroid administration, stage classification, and type classification, are summarized in Table 1.

The mean synovial volume in hips with ONFH (8,020 ± 6,900 mm^3) was significantly larger than that in controls (910 ± 1,320 mm^3; $p = 0.001$). The area of synovitis in the anterior portion of the hip joint was double (mean: 2.17 ± 1.77) that in the posterior portion. Univariate analysis showed that the volume of hip synovitis was significantly associated with the following clinicoradiological factors: sex, stage, type, and BMI (Table 2). In the pre-collapse stage of ONFH, hip synovitis was small in volume (stage 1: 680 ± 690 mm^3, stage 2: 1,460 ± 1,200 mm^3), whereas in the post-collapse stage it was significantly larger (stage 3A: 7,820 ± 4,490 mm^3, stage 3B: 13,850 ± 7,110 mm^3; $p < 0.001$; Fig. 4). There was no significant difference in synovial volume between controls and pre-collapse stage hips (stage 1 and 2; Fig. 4). Regarding type classification, a significant difference in synovial volume was observed only between types B and C2. Stepwise multiple regression analysis showed that disease stage was the only factor affecting the volume of hip synovitis (Table 3). The cut-off synovial volume for differentiating the pre-collapse and post-collapse stages of ONFH was 2,240 mm^3 (sensitivity: 94%, specificity: 96%).

The ICCs for intra- and inter-observer assessment of the volume of inflamed synovium were 0.81 and 0.84. Pearson's correlation coefficient between the volume of the inflamed synovium and the sum of the areas (anterior and posterior portions) of the mid-central oblique axial slice was 0.68 ($p < 0.001$).

Table 1 Clinical and radiological characteristics in our patients

Characteristics	
Sex, number of hips	
Male	39
Female	24
Age (years), mean ± SD	36.6 ± 12.1
Body mass index (kg/m^2), mean ± SD	23.2 ± 3.47
Etiology for osteonecrosis, number of hips	
Steroid-associated	30
Nonsteroid-associated (alcohol-associated or idiopathic)	33
Present steroid administration, number of hips	
Presence	17
Absence	46
Stage classification, number of hips	
Stage 1	8
Stage 2	8
Stage 3A	27
Stage 3B	20
Stage 4	0
Type classification, number of hips	
Type A	2
Type B	8
Type C1	26
Type C2	27

Discussion

Several studies have already reported that synovitis occurs in rheumatoid arthritis, osteoarthritis (OA), and Perthes disease, and is related to these pathological conditions [12, 15, 25, 28, 29]. Because few reports have discussed synovitis in ONFH, however, the details are not well understood. In this study, we semi-quantitatively measured the volume of the inflamed synovium on contrast-enhanced MRI. The results revealed a difference in the volume of hip synovitis between stages of ONFH; in particular, the presence or absence of femoral head collapse was a significant determinant of the volume of synovitis.

Our results showed that the volume of synovitis was approximately equal in normal and pre-collapse hips. Using immunohistological methods, Rabquer et al. examined 20 synovial tissue samples collected during surgery on patients with ONFH [14]; however, all of their samples were limited to synovial tissues at the post-collapse stage, and therefore could not be used to explain differences between the stages. Inflamed synovium in the post-collapse stage of ONFH is often observed during total hip arthroplasty and could be evaluated by harvesting synovium. On the other hand, evaluation of synovitis in the pre-collapse stage of ONFH is difficult because this condition is primarily treated by core decompression and cell therapy without involving a hip joint [4–6]. Our method of MRI evaluation has the advantage that

Table 2 Univariate analysis of the association between volume of synovitis and clinicoradiological factors

Parameter	Volume of synovitis (mean ± SD, mm^3)	*p* value	Correlation coefficient
Sex (male/female)*	5,680 ± 4,490/9,460 ± 7,740	0.03****	–
Steroid-associated ONFH (±)*	6,980 ± 5,380/8,970 ± 8,010	0.26	–
Present steroid administration (±)*	7,150 ± 5,470/8,340 ± 7,390	0.55	–
Stage (1/2/3A/3B)**	680 ± 690/1,460 ± 1,200/7,820 ± 4,490/13,850 ± 7,110	1 vs 2: 0.99 1 vs 3A: 0.005**** 1 vs 3B: <0.001**** 2 vs 3A: 0.01**** 2 vs 3B: <0.001**** 3A vs 3B: <0.001****	–
Type (A/B/C1/C2)**	440 ± 620/1,230 ± 1,790/7,760 ± 5,270/10,840 ± 7,690	A vs B: 1.00 A vs C1: 0.38 A vs C2: 0.11 B vs C1: 0.05 B vs C2: 0.002**** C1 vs C2: 0.28	–
Age***	–	0.79	0.04
Body mass index (kg/m^2)***	–	0.04****	0.26

*Student's *t* test

**Tukey–Kramer test

***Pearson's correlation coefficient

****Indicates significance ($p < 0.05$)

synovitis can be evaluated not only in the post-collapse stage of ONFH, but also in the pre-collapse stage of ONFH by a less invasive examination.

We observed a difference in the volume of synovitis between stage 3A and 3B hips, suggesting that the volume of synovitis in ONFH might have been influenced by the degree

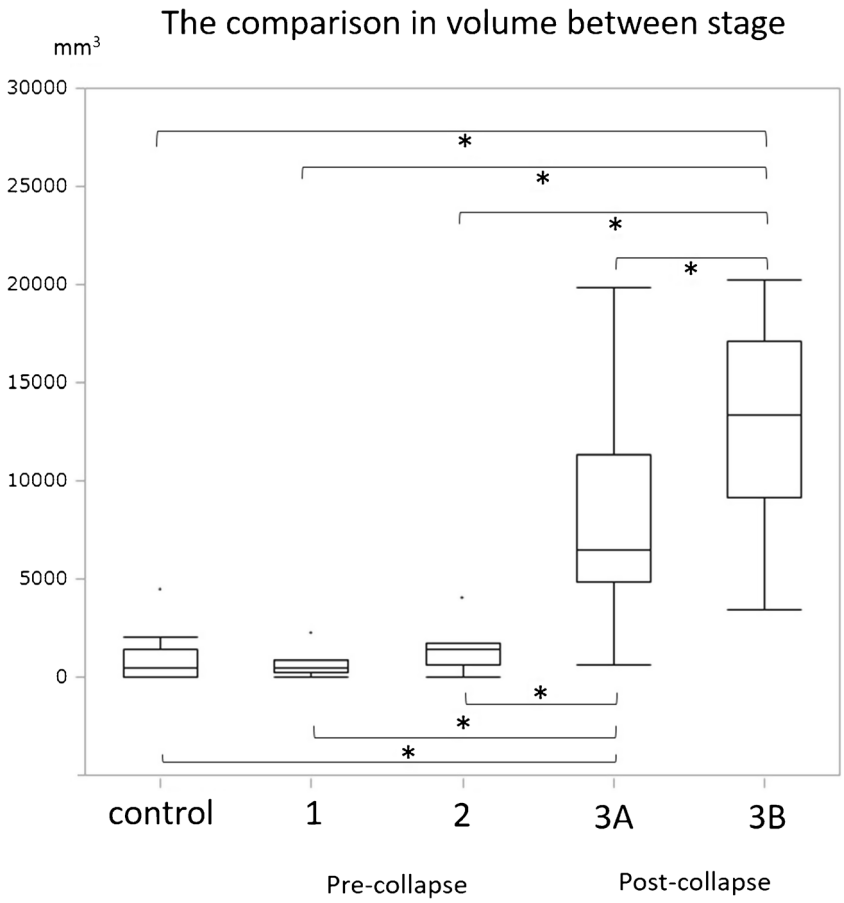

Fig. 4 Univariate analysis of the relationship between synovitis volume and stage. The volume in the post-collapse stage of ONFH (stage 3A and 3B) was significantly higher than that in the pre-collapse stage (stage 1 and 2). Also, there was a significant difference in volume between stages 3A and 3B. *Asterisk* indicates a significant difference; *p* value <0.05

Table 3 Stepwise multiple regression analysis of the volume of synovitis

Parameter	Estimate	Standard error	*t* ratio	*p* value	Lower 95%	Upper 95%
Intercept	−1.14	4.48	−0.25	0.80	−10.10	7.82
BMI	0.37	0.19	2.00	0.05	−0.00014	0.74
Stage{3B–3A&2&1}	2.91	0.75	3.89	<0.001*	1.41	4.42
Post-collapse vs pre-collapse	3.48	0.77	4.51	<0.001*	1.93	5.03

Model: stepwise (R = 0.74)

*Significant difference

of collapse. Sack et al. reported that the severity of synovitis correlates with inflammatory cytokine levels in the synovial fluid of rheumatoid arthritis [30]. Abe et al. found that levels of inflammatory cytokines such as IL-6 and TNF-α in stage 3B hips were significantly elevated compared with those in stage 3A hips [31]. If the severity of synovitis also correlates with inflammatory cytokine levels in the synovial fluid of ONFH, our result is consistent with Abe's result from the standpoint that stage 3B represents a more inflammatory state than stage 3A.

We consider that the occurrence of synovitis in ONFH is caused by a secondary phenomenon related to structural damages due to femoral head collapse; similarly, in the case of OA, synovitis is recognized as a secondary phenomenon related to cartilage and bone alternations [32]. One potential explanation for the uneven distribution of synovitis observed in our study is the influence of normal anatomical characteristics of the thickened anterior joint capsule [33]; moreover, another factor may be characteristics that cause the anterosuperior portion of the femoral head to easily collapse in ONFH [34].

Compared with unenhanced MRI, gadolinium-enhanced MRI has the advantage that it can distinguish synovial membrane thickening with hypervascularity from synovial joint effusion [15–17]. Several studies have quantitatively or semi-quantitatively evaluated synovitis using gadolinium-enhanced MRI [12, 25, 28, 35–37]. Østergaard et al. observed a high correlation between MRI-determined synovial membrane thickness and local clinical signs of inflammation in patients with rheumatoid arthritis. Loeuille et al. reported a good correlation between MRI-determined synovitis grade and both macroscopic and microscopic findings [28]. Therefore, semi-quantitative assessment of synovitis in ONFH may prove valuable as a marker of joint disease activity. Only the area of synovitis in the mid-central oblique axial slice correlated with the overall volume, suggesting that it might be sufficient to check the mid-central slice to confirm the presence of synovitis.

Our study had several major limitations. First, we evaluated the inflamed synovium using fat-suppressed contrast-enhanced T1-weighted images, whereas previous reports used a subtraction technique [12, 25]. The reason for this is that we do not routinely perform the subtraction technique in contrast-enhanced MRI examination of ONFH patients because of the additional time required for image reconstruction. A previous report [38] showed that fat-suppressed contrast-enhanced T1-weighted images depicted the proliferated synovium more clearly than standard MRI techniques, including unenhanced T1- and T2-weighted images and enhanced T1-weighted images without fat suppression. Therefore, we selected fat-suppressed contrast-enhanced T1-weighted imaging, which we use regularly in our clinical practice, for this study. Although our results clearly showed a significant difference between the pre-collapse and post-collapse stages of ONFH, in future work it will be necessary to determine whether the results obtained using our method are consistent with those described previously. Second, unaffected hips with unilateral ONFH were defined as controls in the current study. However, patients with unilateral ONFH may overuse their unaffected hips, leading to accelerated degeneration, which would disqualify the patient as a healthy control. Naturally, healthy individuals are ideal as controls, but because of ethical considerations, we were unable to carry out contrast-enhanced MRI on healthy individuals. Last, although our results showed that hip synovitis increased after femoral head collapse and that hip synovitis was greater in stage 3B than 3A, our study cannot identify the processes whereby worsening synovitis affects femoral head collapse and whether hip synovitis affects the cartilage. In a T1 rho MRI study, Sonoda et al. showed that although articular cartilage above the noncollapsed region remained intact, it began to degenerate in the necrotic region after collapse [39]. There have also been good long-term results after joint-preserving osteotomy [40–42]. Arnoldi et al. demonstrated the advantages of decreased intra-osseous and intra-articular pressure, subsequent increased vascularity and intra-osseous and intra-articular pressure, and subsequent increased vascularity in the case of OA [43]. In ONFH, acquisition of a postoperative intact ratio of the weight-bearing area is the most important consideration for obtaining informative results [40–42]. Considering these facts, it is quite unlikely that synovitis immediately affects articular cartilage. Further study is needed to elucidate the influence of synovitis on cartilage and progressive femoral head collapse.

In conclusion, our study suggests that hip synovitis in ONFH might occur after femoral head collapse and worsen with collapse progression, mainly in the anterior portion.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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