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ORIGINAL PAPER

Intra-articular pathology affects outcomes after joint preserving surgery for osteonecrosis of the femoral head

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Abstract

Purpose Currently, knowledge regarding the intra-articular pathology and its relationship to outcomes after joint-preserving surgery in patients with osteonecrosis of the femoral head (ONFH) is lacking. The purposes were to evaluate the intra-articular pathology and its relationship with outcomes of joint-preserving surgery in ONFH.

Methods We reviewed 41 hips with ONFH in 41 patients (27 women; mean age, 34.9 years old) who underwent intertrochanteric curved varus osteotomy. Radiographic evaluations were based on pre-operative imaging studies, including radiographs, computed tomography (CT), and magnetic resonance imaging (MRI). Intra-articular pathology was evaluated by arthroscopic inspection of the femoral head, labrum, and acetabular cartilage during surgery. In addition, we performed radiographic measurements of the hip, including the collapse of the femoral head and minimal joint space width at three years post-operatively and at final follow-up.

Results Arthroscopy revealed damage to the acetabular cartilage and labrum in 22 (54%) and 13 patients (32%), respectively. However, these lesions could be detected on imaging in only 13 (32%) and ten patients (24%), respectively. The change in joint space width after surgery was significantly higher in patients with cartilage degeneration and labral injury ($P = 0.02$, $P = 0.02$). Logistic regression analysis for subsequent progression of osteoarthritis showed an association with degenerative changes of articular cartilage and the labral tear as independent predictors ($P = 0.001$, $P = 0.03$).

Conclusions Our data demonstrate the presence of labral and acetabular cartilage lesions in ONFH patients, while images do not reveal the full extent of the tissue damage. These intra-articular pathologies can be associated with the outcomes after joint-preserving surgery.

Keywords Osteonecrosis of the femoral head · Intra-articular pathology · Arthroscopy · Hip preservation surgery · Articular cartilage · Labral tear

Introduction

Osteonecrosis of the femoral head (ONFH) typically affects relatively young and active patients in the third or fourth decade of life [1, 2]. If left untreated, mechanical instability may cause failure of the subchondral trabeculae and articular collapse of the femoral head that progresses to secondary osteoarthritis (OA) in 80% of patients [3]. The current understanding of the pathogenesis of ONFH describes it primarily as a disease of bone; nevertheless, several authors reported other disorders, including acetabular cartilage degeneration, labral tears, or loose bodies in patients with ONFH [4, 5]. These intra-articular pathologies are thought to be secondary to the periodic loss of the normal contour of the femoral head, where the necrotic cancellous bone is unable to withstand physiologic forces, causing mechanical disruption of the cartilage or labrum [4–6].

Magnetic resonance imaging (MRI) has become the gold standard for diagnosis and assessment of osteonecrosis and intra-articular pathology. Advances in higher-field magnets

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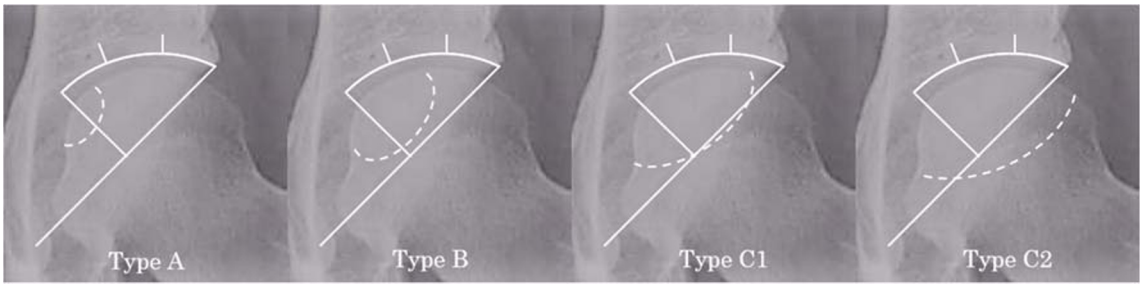

Fig. 1 The classification according to the Japanese Investigation Committee of Health and Welfare [22] Type A indicates that necrotic area occupies the medial one-third or less of the weight-bearing area. Type B indicates the medial two-thirds or less. Type C1 indicates more than two-thirds but not extending to the acetabular rim. Type C2 indicates more than two-thirds and extending to the acetabular rim

and improved designs and sequences have increased our diagnostic accuracy using high-resolution non-contrast and MR arthrographic (MRa) techniques [7, 8]. Despite these advances, MRI does not always identify accurate labral injury or chondral damage; arthroscopy remains the gold standard for detection and staging of chondral lesions [9–12]. A meta-analysis of studies of the diagnostic test accuracy of MRI, MRa, multidetector arrays in computer tomography (CT) arthrography and CT arthrography for the assessment of patients with chondral lesions of the hip in comparison to surgical findings (arthroscopy or open) as the reference confirmed that arthroscopy remains the most accurate method of assessing the cartilage in the hip joint [13]. Ruch et al. showed poor correlation between radiographic and arthroscopic assessment of femoral head cartilage in patients with early post-collapse osteonecrosis, as arthroscopic evaluation revealed lesions that had not been noted on radiograph or MRI [14].

The optimal surgical treatment for ONFH remains controversial. Consideration of joint preservation surgery for ONFH is important to avoid or delay joint replacement procedures; other surgical treatments were proposed for joint preservation such as osteotomy, vascularized bone grafting and core-decompression with/without cell therapy [15–17]. These procedures have been reported to be effective for the pre- or early post-collapse stage; however, these present some risks, the success rate varies, and sometimes they may even jeopardize the future success of hip replacements [18, 19]. Several studies demonstrated that extent of necrotic lesion, pre-operative collapse of femoral head and post-operative intact ratio were associated with post-operative clinical and radiographic results. It is likely that other factors such as degeneration of the cartilage or labral tear outweigh the success of available joint preserving procedures for the fact that the presence of reversible changes may cause a mechanical disruption of the hip joint. However, it is unknown whether intra-articular pathology has relationships with post-operative outcomes of joint preserving surgery. Furthermore, detailed intra-articular pathology in ONFH patients is also unknown.

The purpose of our study was 2-fold. The first was to evaluate intra-articular pathology in patients with ONFH by arthroscopic inspection and discuss the value of hip arthroscopy compared with traditional imaging techniques. The second was to evaluate whether intra-articular pathology has a

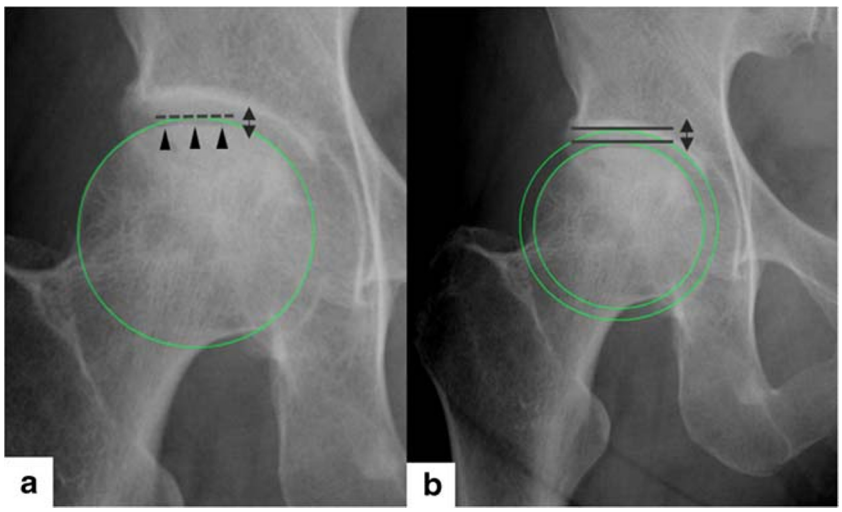

Fig. 2 Calculation of the height of collapse of the femoral head and the joint space width on plain radiograph. The approximate circles were set based on the morphology of the femoral head and acetabulum. **a** The length between the surface of the lesion and circle just above (dot lines) was calculated as the height of collapse of the femoral head (allow). **b** The length between the surface of both circles (black line) was calculated as the joint space width (allow)

Table 1 Demographic date of patients

Characteristic		Value
Gender	(*n*)	
Male		14
Female		27
Mean age	(y.o.)	34.9 ± 11
Association of osteonecrosis	(*n*)	
Steroid		29
Alcoholism		6
Idiopathic		6
Type	(hips, %)	
C1		34
C2		7
Stage	(hips, %)	
2		17
3		24
Duration to the op from ONFH development	(m)	14.4 ± 20
Follow-up duration after the operation	(months)	58.8 ± 21.6
Radiographic findings (plain radiograph)		
Collapse of the femoral head at pre-op	(*n*)	20
Height of collapse	(mm)	0.77 ± 0.78
Progression of the collapse at 3 years post-op	(*n*)	8
Height of collapse	(mm)	1.1 ± 1.0
Progression of the collapse at last follow-up	(*n*)	8
Height of collapse	(mm)	1.2 ± 1.1
Joint space width at pre-op	(mm)	3.8 ± 0.7
Progression of OA at 3 years post-op	(*n*)	12
Joint space width	(mm)	3.2 ± 1.1
Progression of OA at last follow-up	(*n*)	16
Joint space width	(mm)	2.9 ± 1.3

relationship with post-operative radiographic outcomes of joint preserving surgery in patients with ONFH in whom radiographs showed a well-preserved joint space. We hypothesized that there would be significant discrepancies between the findings of arthroscopic inspection and traditional imaging techniques and that these intra-articular pathologies has a relationship with post-operative outcomes of joint preserving surgery in patients with ONFH.

Methods

Study population

This was a retrospective study of patients diagnosed with ONFH who underwent intertrochanteric curved varus osteotomy (CVO) without acetabular osteotomy [20] between April 2011 and March 2014 at our university hospital. The subset of patients with the localization of the necrotic lesion of type C1 and C2 according to the Japanese Investigation Committee of Health and Welfare classification [21] (Fig. 1) and initial stages of ONFH of stage 2 (radiographically abnormal without collapse) and stage 3 (a crescent sign without osteoarthritic change) according to the Association Research Circulation Osseous (ARCO) staging system [22] were included. Furthermore, the patients who had the potential to obtain coverage of more than one-third of load-bearing area with intact surface of the femoral head on pre-operative AP hip radiographs in maximum abduction were considered suitable for this surgery.

Radiographic evaluation

All patients underwent biplanar radiographic imaging of the hip, including supine AP pelvic views in the neutral position and cross-table lateral views, CT, and MRI pre-operatively. MRI was performed pre-operatively using a 3.0 T GE (General Electric, Milwaukee, WI, USA) Excite Signa MR Scanner and phased array coil (USA Instruments, Inc., Cleveland, OH, USA). Image acquisition was carried out in the coronal, sagittal, and native axial planes. Pre- and post-operative radiographs were compared, and the patients with progression of collapse and narrowing of joint space more than 1 mm were considered "positive." On CT, collapse of the femoral head and cystic formation were evaluated pre-operatively. Collapse of the femoral head, damage to articular

Table 2 Radiographic and arthroscopic findings

	n (%)	X-p	CT	MRI	Arthroscopy
Femoral head					
Collapse		20 (49%)	24 (59%)	6 (15%)	10 (24%)
Cystic lesion			26 (63%)	24 (59%)	
Irregularity of the articular surface				13 (32%)	24 (59%)
Acetabulum					
Articular lesion				13 (32%)	22 (54%)
Labral tear				10 (24%)	13 (32%)

Results are expressed as number and percentage. X-p: X-ray photography

Table 3 Arthroscopic findings

	(*n*)
Femoral head	
Collapse	10
Folds formation	24
Acetabulum	
Articular lesion	22
All quadrant	13
Anterior quadrant	3
Superior quadrant	6
Posterior quadrant	0
Labral tear	13
All quadrant	1
Anterior quadrant	11
Superior quadrant	1
Posterior quadrant	0

cartilage, and labrum tear were also evaluated on MRI pre-operatively. For each acetabular sub-region, acetabular cartilage was evaluated using MRI-based modified Outerbridge grade and was assigned "positive" when the finding of the cartilage damage was over grade 1 [23]. They also underwent radiographic analysis of the hip at three years post-operatively and at final follow-up. Radiographic evaluations including the height of collapse of the femoral head and the minimal joint space width on X-ray were performed pre-operatively, at three years post-operatively and at final follow-up (Fig. 2) [24].

Intra-articular evaluation

Intra-articular pathology was evaluated by arthroscopic inspection of the femoral head, labrum, and acetabular cartilage for all the patients in the surgery. For the evaluation of the location of both the acetabular and labral lesions, the labrum and acetabulum were divided into three sections with clock-face markings, using an established mapping system based on anatomic landmarks [24]. The acetabular teardrop served as the landmark for the acetabular 6 o'clock position. The acetabulum was divided into three sections: the 10:00–2:00 o'clock position as the superior section; the 2:00–5:30 o'clock position as the anterior section; and the 6:30–10:00 o'clock position as the posterior section. Acetabular cartilage lesions were also graded using the Beck scale [25] and were assigned "positive" when the arthroscopic finding of the damage was over grade 2: grade 1, normal; grade 2, malacia; grade 3, debonding; grade 4, cleavage; and grade 5, full-thickness defect or complete loss of cartilage. The femoral head was visually classified according to its morphological appearance and localization of the lesion, including collapse, cartilage damage, or fold formation.

Surgical procedure

The CVO procedure was performed based on the technique developed by Nishio and Sugioka [20]. A longitudinal skin incision was made over the greater trochanter with the patient in the lateral position. After dissection of the deep fascia, the greater and lesser trochanters were exposed posteriorly by rotating the hip joint internally. The external rotators and quadratus muscle were retained with the preservation of the medial femoral circumflex artery. After the external rotator muscle was exposed, a small incision was made on the capsule at the distal side of the piriformis muscle so that arthroscope could be inserted into the intra-articular space. Arthroscopy was used to evaluate the intra-articular pathology, including labral tears or articular cartilage of the acetabulum and femoral head to verify that acetabular coverage of more than one-third of the intact articular surface could be obtained. An intertrochanteric curved osteotomy was then carried out from the lesser to greater trochanter using a bone chisel. The anterior periosteum was then dissected along the line of the

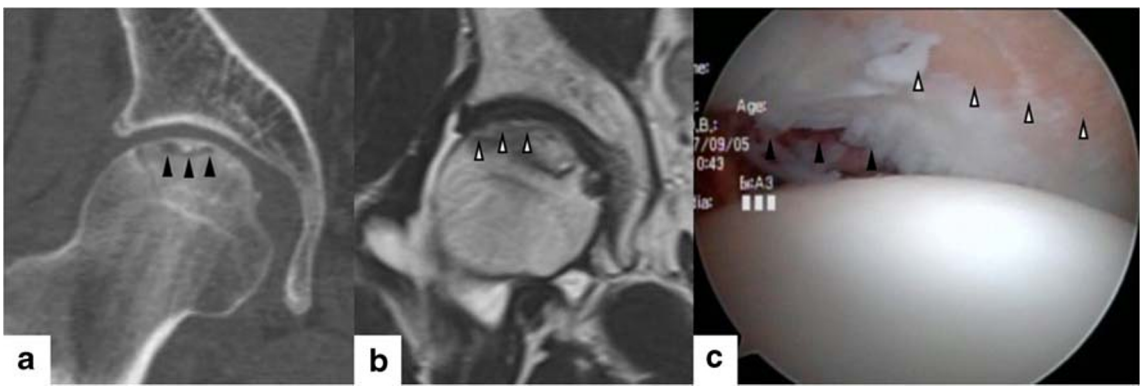

Fig. 3 **a** A pre-operative CT arthrography (coronal image); black arrow heads indicates the subchondral fractures in the femoral head. **b** A pre-operative MRI (coronal image of T2WI); white arrow heads indicates erosion around the femoral head. **c** Arthroscopic findings at osteotomy; black arrow heads indicates the labral lesions, and white arrow heads indicates chondral lesions in the acetabulum. However, there is no abnormal finding in the femoral head

Table 4 Demographic data of each finding

		Association of osteonecrosis			Type of ONFH		Stage of ONFH	
	Total	Steroid (29)	Alcoholism (6)	Idiopathic (6)	C1 (34)	C2 (7)	2 (17)	3 (24)
Femoral head								
Collapse (CT)	24	18 (62%)	3 (50%)	3 (50%)	20 (57%)	4 (67%)	0	24 (100%) *
Cystic lesion (CT)	26	19 (66%)	4 (66%)	3 (50%)	22 (63%)	4 (67%)	7 (41%)	19 (79%) *
Articular cartilage lesion (arthroscopy)	24	16 (55%)	5 (83%)	3 (50%)	18 (53%)	6 (86%)	6 (35%)	18 (75%) *
Acetabulum								
Articular lesion (arthroscopy)	22	15 (52%)	3 (50%)	4 (66%)	17 (50%)	5 (71%)	7 (41%)	15 (63%) *
Labral tear (arthroscopy)	13	10 (34%)	1 (17%)	2 (33%)	10 (29%)	3 (43%)	5 (29%)	8 (33%)

Results are expressed as number and percentage. ONFH, Osteonecrosis of the femoral head *; $P < 0.05$

osteotomy, and the femoral neck was shifted into a varus position by displacing the femoral neck in a cranial direction under the fluoroscopy. The fixation device was the Hip Osteotomy Plate system (HOP®, Nakashima Medical, Okayama, Japan).

Statistical analysis

All data were expressed as mean ± standard deviation (SD), and statistical analyses were performed using Stat-View-J version 5.0 software (Hulinks, Tokyo, Japan). The Mann-Whitney U test was used for the detection of differences between the groups. A multivariate analysis of risk factors for progressive collapse of the femoral head was performed using a logistic regression model for the variables with $P < 0.05$, including type of ONFH, association of osteonecrosis, cystic lesion in the femoral head, abnormal arthroscopic findings in the femoral head, and time between ONFH symptom onset and the CVO procedure. The required number of patients to detect the difference of the changes of joint space width as a primary endpoint with supposed delta under the power of 80% was performed using G*power 3.1.9.4 [26]. A multivariate analysis of risk factors for progressive joint degeneration was also performed using a logistic regression model for the variables with $P < 0.05$, including the time between ONFH symptom onset and the CVO procedure, degenerative changes of articular cartilage, and labral tear.

Results

During the study period, 41 patients (41 hips) who had severe pain of affected hip were included, with complete radiologic and arthroscopic datasets. Patient demographics are shown in Table 1. The mean follow-up duration after the surgery was 58.8 ± 21.6 months. The localization of the necrotic lesion was type C1 in 34 hips and type C2 in seven hips. Initial stages of ONFH were rated as stage 2 in 17 hips and stage 3 in 24 hips.

There were eight patients with progression of collapse at three years post-operatively and at final follow-up, and there were 12 and 16 patients with progression of OA at three years post-operatively and at final follow-up, respectively (Table 1). Radiographic and arthroscopic findings are shown in Table 2. The extent of femoral and acetabular damage and the location of lesions are shown in Table 3. The collapse of the femoral head was detected in 24 patients (59%) by CT, whereas collapse was detected only in ten patients by arthroscopy; the wave-like deformation or buckling of the articular surface was detected in 24 patients (59%) by arthroscopy.

On arthroscopy, damage to the acetabular cartilage and the labrum was seen in 22 (54%) and 13 patients (32%), respectively. However, on MRI, these lesions could be detected only in 13 (32%) and ten patients (24%), respectively. (Fig. 3) There was a similar pattern of damage to the acetabular cartilage and the labrum. Acetabular lesions were seen in the anterior and superior sections, and their appearance ranged from superficial roughening to defects extending to the subchondral

Table 5 Height of collapse in the femoral head

	Type of ONFH			Stage of ONFH			Cystic lesion in FH			Fold formation at FH		
	C1	C2	*P* value	Stage2	Stage3	*P* value	None	Present	*P* value	None	Present	*P* value
3 years post-op (mm)	0.27 ± 0.5	1.27 ± 1.3	0.001	0.55 ± 1.1	0.37 ± 0.5	0.48	0.64 ± 1.1	0.32 ± 0.5	0.22	0.29 ± 0.8	0.55 ± 0.7	0.3
Last follow-up (mm)	0.36 ± 0.7	1.3 ± 1.3	0.01	0.62 ± 1.2	0.44 ± 0.6	0.51	0.77 ± 1.2	0.37 ± 0.6	0.17	0.29 ± 0.8	0.68 ± 0.9	0.17

Results are expressed as mean ± SD or number. FH, femoral head; ONFH, osteonecrosis of the femoral head; op, operation

Table 6 Change of joint space width

		Type of ONFH			Stage of ONFH			Cartilage degeneration			Labral injury		
		C1	C2	*P* value	Stage2	Stage3	*P* value	None	Present	*P* value	None	Present	*P* value
3 years post-op	(mm)	− 0.45 ± 0.7	− 1.33 ± 1.3	0.01	− 0.84 ± 1.1	− 0.41 ± 0.7	0.11	− 0.28 ± 0.6	− 1.18 ± 1.2	0.004	− 0.33 ± 0.6	− 1.26 ± 1.1	0.01
Last follow-up	(mm)	− 0.63 ± 0.8	− 1.59 ± 1.5	0.02	− 0.85 ± 1.1	− 0.75 ± 1.0	0.77	− 0.45 ± 0.8	− 1.18 ± 1.2	0.02	−0.5 ± 0.7	−1.56 ± 1.4	0.02

Results are expressed as mean ± SD or number. ONFH, osteonecrosis of the femoral head; op, operation

bone. There were also tears of the labrum in the anterior and superior sections. The associations among radiographic and arthroscopic findings, including those between type and stage of ONFH in osteonecrosis, are shown in Table 4. The radiographic and arthroscopic findings varied according to the association of osteonecrosis. Collapse, cystic lesions, and articular cartilage lesions in the femoral head were significantly associated with ONFH stage. Furthermore, an acetabular lesion was associated with ONFH stage. The height of collapse and the change of joint space width at three years post-operatively and at final follow-up are shown in Tables 5 and 6. The height of collapse in type C2 was significantly higher than that of type C1 at three years post-operatively ($P = 0.001$) and at final follow-up ($P = 0.01$). The change of joint space width was significantly higher in patients with type C2 ($P = 0.02$), with the presence of cartilage degeneration ($P = 0.02$) and labral lesions ($P = 0.02$) at final follow-up. A logistic regression analysis of the subsequent collapse of the femoral head showed a significant association with type of ONFH ($P = 0.03$) and the time between ONFH symptom onset and the CVO procedure as independent predictors ($P = 0.04$) (Table 7). Furthermore, logistic regression analysis for the subsequent progression of OA at three years post-operatively and at final follow-up also showed a significant association with degenerative changes of articular cartilage ($P = 0.001$) and labral tears as independent predictors ($p = 0.03$) (Table 8 and 9).

Discussion

To the best of our knowledge, this study was the first in patients with ONFH to evaluate intra-articular pathology and its relationship with post-operative outcomes of joint-preserving surgery. Our findings suggest the chronic presence of labral and acetabular cartilage lesions in ONFH patients where the images, particularly CT and MRI, have not really shown the full extent of the tissue damage. Furthermore, these intra-articular pathologies can be associated with outcomes after joint-preserving surgery; hip arthroscopy has a role in accurate evaluation of intra-articular pathology and treatment of intra-articular lesions that are often associated with the disease.

In patients with ONFH, subcortical fracture and femoral head collapse are pathognomonic signs of advanced ONFH. Nevertheless, there is limited data regarding intra-articular pathology, including acetabular cartilage and labral lesions. The success of joint preservation surgery can be stratified by age, lesion size, lesion location, and disease stage. To our knowledge, there has no published investigation of the influence of these intra-articular pathologies on the success of joint preservation surgery. In the absence of specific information on the status of intra-articular pathology, the success of conservative treatment and head-sparing procedures may be based only on

Table 7 Multivariate analysis of the factors influencing progressive collapse of the femoral head

	Odds ratio	95%CI	*P* values
Presence of type C2 ONFH	10.8	0.17–4.59	0.03
Cystic lesion in the femoral head	0.08	− 5.29–0.25	0.075
Arthroscopic abnormal findings in the femoral head	6.1	− 0.76–4.39	0.17
Time between ONFH symptom onset and surgery	1.1	0.001–0.11	0.04
Association of osteonecrosis	0.3	− 2.74–0.46	0.16

CI, confidence interval; ONFH, osteonecrosis of the femoral head

the radiographic findings. However, the fate of the articular cartilage with conservative treatment or joint preservation surgery is of particular clinical importance, because it is presumed that the cartilage is to some degree functional and viable.

The imaging of cartilage lesions remains elusive in the hip joint, despite the fact that accuracy of MRI continues to improve [27, 28]. In ONFH patients, non-contrast MRI can hardly detect osteochondral damage in the cases with arthroscopically confirmed lesions. Ruch et al. showed poor correlation between imaging and arthroscopic assessment of the cartilage in patients with ONFH, and diagnostic hip arthroscopy was suggested to evaluate the present joint degeneration [29].

The gross and histologic changes in the cartilage without radiographic evidence of degeneration were reported by several authors [29–32]. Mukisi-Mukaza et al. mentioned that there is no correspondence between histopathology and radiological stage in ONFH patients [31]. Magnussen et al. reported osteonecrotic cartilage shows evidence of degeneration and corresponding changes in mechanical properties when compared with normal controls [32]. The labral tears in ONFH patients are also reported by several authors [33, 34]. However, the mechanism responsible for the cartilage and labral damage in patients with ONFH is controversial. Some authors have suggested that the damage to the acetabular cartilage and labrum originate from the "asphericity of the femoral head" caused by the subcortical fracture and femoral head collapse [35]. However, this seems unlikely, given the fact that the cartilage degeneration was observed before articular collapse according to the T2 mapping study in systemic lupus erythematosus patients with ONFH [36].

Our study indicates that an acetabular cartilage and labrum show evidence of degeneration in patients with pre-and early post-collapse stage, despite radiographic normal. It is also apparent that there is a wide variation in these properties among ONFH patients. For the progression of collapse, increasing the lesion size and the time between ONFH symptom onset and the CVO procedure were significantly associated, whereas arthroscopic abnormal findings in the femoral head were not associated. On the other hand, the degenerative changes of articular cartilage and labral tears in the acetabulum were significantly associated with the progression of OA after surgery. These findings may explain why some patients treated with joint-preserving surgery continue to experience pain although the joint space is maintained radiologically, and some patients suffer from OA progression, despite the absence of radiological evidence of collapse in the femoral head. Furthermore, these intra-articular pathologies cannot always be detected by MRI. These findings suggest that hip arthroscopy before or during surgery has a role if joint-preserving surgery is planned for ONFH patients with lesions of pre-collapse or mild post-collapse stage. This allows relatively accurate evaluation of the femoral head and acetabulum for treating any intra-articular lesions. Moreover, it may provide better information regarding histologic grade and mechanical properties; a report mentioned that the gross appearance of the femoral head was an accurate predictor of both histologic grade and mechanical properties [34].

Limitation

This study has several limitations. First, a relatively small study group of patients and a retrospective study pattern reflecting the rare nature of the disease is described. Furthermore, the evaluation protocol did not allow the problem of inter- and intra-

Table 8 Multivariate analysis of the factors influencing the progression of OA at 3 years post-op

	Odds ratio	95%CI	*P*-values
Degenerative changes of articular cartilage	6.4	1.34–30.1	0.01
Labral tear	5.35	1.12–25.5	0.03
Time between ONFH symptom onset and surgery	1.0	0.99–1.07	0.19

OA, osteoarthritis; ONFH, osteonecrosis of the femoral head

Table 9 Multivariate analysis of the factors influencing the progression of OA at final follow-up

	Odds ratio	95%CI	*P*-values
Degenerative changes of articular cartilage	13.6	2.72–68.1	0.001
Labral tear	5.14	1.17–22.7	0.03

OA, osteoarthritis; ONFH, osteonecrosis of the femoral head

observer reliability. Nevertheless, the presented cohort included hips that covered the entire spectrum of the disease (Japanese Investigation Committee of Health and Welfare stage 2–3 in which joint preserving surgery can be considered). Second, the imaging protocol did not allow MRA or radial MRI that were reported to be effective for the detection of articular cartilage and labral lesion. Comparing both techniques should be a subject for further studies.

Conclusion

Our data demonstrate the presence of labral tear and acetabular cartilage lesions in ONFH patients, while images, particularly CT and MRI, do not reveal the full extent of the tissue damage. These concomitant intra-articular pathologies can be associated with radiographic outcomes after joint-preserving surgery and may possibly influence the natural course of ONFH after surgery; hip arthroscopy has a potential role in accurate evaluation of intra-articular pathology that is often associated with the disease.

Compliance with ethical standards

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

Ethics approval Ethics approval was granted by the Institutional Review Board (# E-677, 7/Feb/2017), and informed consent was obtained from all individual participants included in the study.

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