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Original article

Quantitative evaluation of bone-resorptive lesion volume in osteonecrosis of the femoral head using micro-computed tomography

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ABSTRACT

Objectives To quantify the volume of bone-resorptive lesions in post-collapse osteonecrosis of the femoral head (ONFH) using micro-computed tomography (micro-CT) and assess their characteristics in post-collapse ONFH.

Methods We investigated 35 femoral heads resected from 35 patients with ONFH (20 men and 15 women; mean age, 47.2 years). On each of seven coronal high-resolution micro-CT slices of the femoral head, the bone-resorptive areas were extracted using bone microstructure measurement software. Next, the total bone-resorptive volume ratio, defined as the ratio of all bone-resorptive cross-sectional areas to all femoral head cross-sectional areas in all seven slices, was calculated. Associations between total bone-resorptive volume ratio and sex, age, ONFH-associated factors, patient workload levels, ONFH stage, ONFH type, necrotic volume on magnetic resonance imaging, and duration from the onset of pain to surgery were analyzed. Lesion location and the association between bone-resorptive lesion and collapse were also evaluated.

Results The mean total bone-resorptive volume ratio was 7.0 ± 6.0%, which varied significantly by ONFH stage (ARCO collapse quantitation 3A, 3.5 ± 2.1%; 3B, 6.8 ± 3.0%; and 3 C, 13.6 ± 8.8%). ONFH stage was independently associated with total bone-resorptive volume ratio ($P < 0.05$). Furthermore, high bone-resorptive volume ratios were found in the anterior femoral head and were associated with collapse.

Conclusions This study demonstrated that bone-resorptive volume in post-collapse ONFH was significantly associated with the disease stage, which was more widespread in the anterior portion of the femoral head than in the posterior portion.

1. Introduction

Nontraumatic osteonecrosis of the femoral head (ONFH) is characterized by femoral head collapse several months to years after the occurrence of osteonecrosis [1]. Previous studies have demonstrated that a collapsed femoral head with ONFH inevitably involves a subchondral fracture [2], which might be the mechanism of collapse initiation. After collapse (or a subchondral fracture), some femoral heads might preserve a relatively spherical shape, while others might become severely deformed. The shape of the femoral head after collapse is essential to consider when selecting a therapeutic strategy; however, the pathomechanisms of collapse progression remain unclear.

In post-collapse ONFH, bone-resorptive lesions can be seen within the femoral head [3,4]. Bone resorption in ONFH is considered to be caused by osteoclasts during the initial phase of the repair process [5], while both the extent and location of bone resorption seem to be different among patients in ONFH. Plenk et al. reported that there are several types of repair processes in ONFH, in which femoral heads with predominant bone resorption undergo more destruction with time [4], suggesting the possible association between bone resorption and collapse progression.

On the other hand, to the best of our knowledge, there have been no studies that have quantitatively characterized bone resorption in ONFH. With conventional clinical computed tomography (CT), detailed analysis of bone-resorptive lesions including their distribution and dimensions has been difficult. However, using micro-CT allows us to evaluate the three-dimensional bone structure of the entire femoral head in detail and quantitatively at the micro-level [6–8]. Therefore, the purposes of this study were

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to quantify bone-resorptive lesions using micro-CT and assess the characteristics of bone-resorptive lesions in post-collapse ONFH.

2. Methods

2.1. Patients

This study was approved by the institutional review board. Informed consent was obtained from all individual participants included in the study. Between April 2012 and August 2017, 77 hips in 67 patients with ONFH underwent primary joint replacement surgery (total hip arthroplasty or bipolar hemiarthroplasty) at our institution. Of these 77 hips, 27 were excluded from this study for the following reasons: 21 hips had severe osteoarthritic changes, four hips had severe femoral head deformity due to collapse, and two hips had eccentrically-located necrotic lesions. In addition, five hips in five patients treated with a bisphosphonate intake for osteoporosis were excluded. In 10 patients who underwent bilateral joint replacement surgery, one hip in each patient was randomly selected for analysis to fulfill the statistical assumption of independent observation. Thus, we investigated 35 entire femoral heads resected from 35 patients with ONFH (20 men and 15 women) with a mean age of 47.3 years (median 46 years, range 18–81 years). Factors associated with ONFH included corticosteroid use (> 2 g of prednisolone or its equivalent within a 3-month period) in 20 hips and alcohol abuse (> 320 g/week) in 15 hips, which were classified based on the Association Research Circulation Osseous (ARCO) etiologic classification criteria [9,10]. In addition, we classified patient workload levels into three groups: low activity (unemployed) for 12 hips, moderate activity (work in an office environment or the hospitality industry, etc.) for 17 hips, and high activity (nursing, working for a delivery service or in construction, etc.) for six hips. Based on the ARCO international classification of osteonecrosis, all 35 femoral heads were classified into stage 3 [11]. In the current study, 15 femoral heads with ≤ 2 mm of collapse were defined as stage 3A, 12 femoral heads with 2–4 mm of collapse as stage 3B, and eight femoral heads with ≥ 4 mm as stage 3 C, by reference to the ARCO quantitation of a dome depression [11]. Even in patients with no obvious severe deformity of the femoral head, we considered joint replacement surgery to be indicated when there was an extensive necrotic lesion with a subchondral fracture confirmed on CT or bone marrow edema suggestive of a subchondral fracture on magnetic resonance imaging (MRI) [12]. In addition, the location of necrotic lesion was classified using the Japanese Investigation Committee classification system [13]: type C1 (more than the medial two-thirds of the weight-bearing portion but not extending laterally to the acetabular edge) in 14 hips, and type C2 (extending laterally to the acetabular edge) in 21 hips. The mean duration from the onset of pain to surgery was 11.7 ± 9.3 months (median 7 months, range 1–36 months). Furthermore, the volume of the necrotic lesion on MRI was defined as a combined necrotic angle using the modified Kerboul method [14]. Briefly, the angles of the femoral surface with necrosis on a mid-slice in T1-weighted coronal and axial views were measured and summed. The mean combined necrotic angle was 277.4 ± 63.4 (median 262, range 170–465).

2.2. Quantification of bone-resorptive lesions

All 35 samples were scanned with high-resolution micro-CT (R_mCT T1, Rigaku, Tokyo, Japan) immediately after surgery. Micro-CT was performed at a voltage of 60 kV, current of 60 μA, voxel size of $133 \times 133 \times 133\ \mu m^3$, and slice thickness of 0.4 mm. In the current study, a bone-resorptive area was defined as a space ≥ 1 mm in diameter and coronal images of micro-CT were investigated. On each coronal micro-CT slice, bone-resorptive areas were extracted using bone microstructure measurement software (TRI/3D-BON, Ratoc System Engineering, Tokyo, Japan) following a previously reported method (Fig. 1A–F) [8]. Briefly, bone regions including the bone trabeculae and the cortical shell were depicted by binarizing CT images using a bone threshold (Fig. 1B). Next, the entire region was depicted (Fig. 1C). Empty regions not involving bone were depicted by subtracting the bone regions from the entire region (Fig. 1D). In order to identify empty regions of ≥ 1 mm in diameter, empty regions < 1 mm in diameter were cleared to erode the all empty regions three-dimensionally by 0.5 mm decrements from their surface (Fig. 1E). To restore the original shape of the

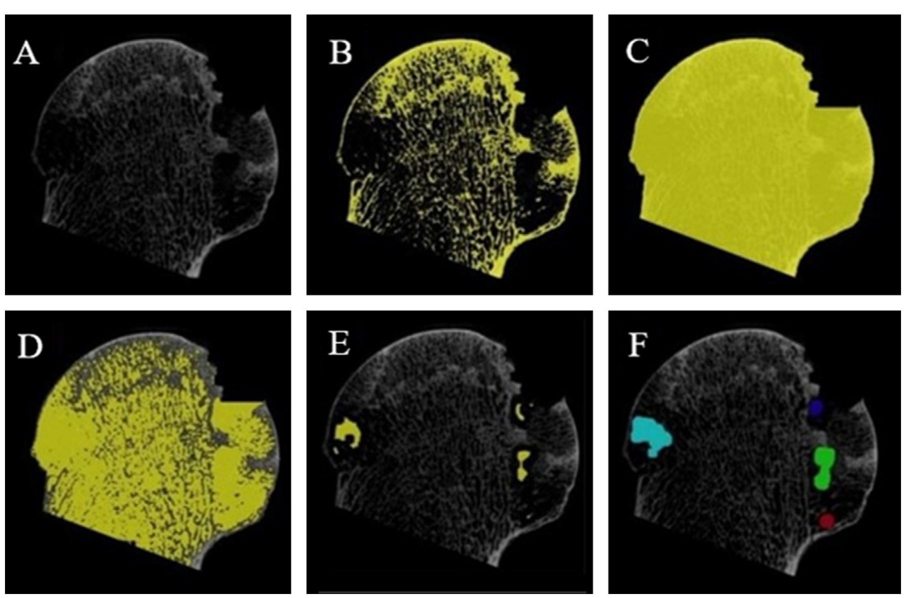

Fig. 1. Quantification of bone-resorptive areas defined as spaces ≥ 1 mm in diameter using bone microstructure measurement software (TRI/3D-BON, Ratoc System Engineering, Tokyo, Japan). A. A coronal micro-CT image; B. Bone regions, including the bone trabeculae and the cortical shell, are depicted after binarizing CT images using a bone threshold; C. The entire region of a femoral head is depicted; D. Empty regions not involving bone are depicted by subtracting the bone regions from the entire region; E. In order to identify empty regions of > 1 mm in diameter, empty regions less than 1 mm in diameter are cleared to erode from the surface three-dimensionally in 0.5 mm decrements; F. To restore the original shape of the remaining empty regions in the above process, their surfaces are dilated by 0.5 mm increments from their surface. Of the remaining empty regions, a bone-resorptive area is defined as a region connected to a necrotic lesion.

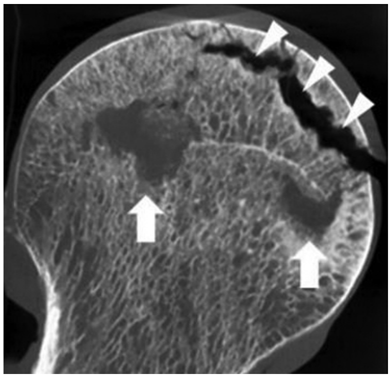

Fig. 2. Distinguishing between bone-resorptive areas and bone defect areas.
Bone-resorptive areas (white arrows) are distinguished from bone defect areas (white arrowheads) caused by a subchondral fracture or collapse based on CT values.

remaining empty regions in the above process, their surfaces were dilated by 0.5 mm increments (Fig. 1F). Of the remaining empty regions, a bone-resorptive area was defined as a region connected to a necrotic lesion and distinct from areas of bone defect caused by a subchondral fracture or collapse based on CT values (Fig. 2). The definition of each bone-resorptive area was based on consensus among three observers (S.B., T.U., and H.H.); they also confirmed the area of necrosis with MRI. After micro-CT, all samples were made a confirmed diagnosis of ONFH by a histopathological evaluation based on previously reported histopathological criteria of ONFH [15,16].

2.3. Assessment of bone-resorptive lesion characteristics

In order to quantitatively assess the bone-resorptive volume in the entire femoral head, at first, the coronal slices of femoral head were divided equally into seven slices (Fig. 3). In each slice, the cross-sectional area of the femoral head was defined as the area of a concentric circle centered on the center of the femoral head. Both bone-resorptive and femoral head cross-sectional areas were calculated using the Image J software program (National Institutes of Health, Bethesda, MD, USA). The mean ratio of bone-resorptive areas to femoral head cross-sectional areas was calculated for each slice. In addition, the total bone-resorptive volume ratio in each femoral head was defined as the ratio of all bone-resorptive areas to all femoral head cross-sectional areas in seven slices. Univariate associations between the degree of total bone-resorptive volume ratio and sex, age, associated factors of ONFH (steroid or alcohol), stage and type of ONFH, patient workload levels, combined necrotic angle, and duration from the onset of pain to surgery were analyzed first. Subsequently, after confirming the area of necrosis with MRI, the ratio of the bone-resorptive area to femoral head area in both intra-necrotic and extra-necrotic lesions were investigated for each slice. Furthermore, the presence or absence of collapse in the seven slices was recorded for all 35 femoral heads, and the relationship between bone-resorptive areas and femoral head collapse was investigated by comparing bone-resorptive areas between slices with and without collapse. In the current study, collapse was defined as a breakage of the femoral head contour, including a subchondral fracture. Finally, the correlation between collapse progression rate and bone-resorptive volume ratio was investigated using 31 of 35 femoral heads that underwent clinical CT for preoperative planning at an average of 72.7 days (median 13 days, range 1–837 days) before surgery. Briefly, the progression of collapse per day was defined as the difference between the collapse depth on corresponding mid-coronal CT slices before and after surgery divided by the number of days between the two scans. Collapse depth after surgery was measured using the micro-CT images of surgically resected femoral heads scanned immediately after surgery. On each of CT and micro-CT images, collapse depth was measured as the distance between the concentric circle that fits the femoral head and the maximum incursion into the femoral head on the line passing through the center of the femoral head.

2.4. Statistical analysis

Data are expressed as means ± SD. All variables were tested for normality with the Shapiro-Wilk test and for homoscedasticity with Levene's test. Associations between sex, associated factors, type of ONFH, and bone-resorptive volume ratio, respectively, were compared using Wilcoxon rank sum test. The association between bone-resorptive volume in slices with versus without collapse was also investigated using Wilcoxon rank sum test. The bone-resorptive volume ratio for each stage or patient workload level were compared using Steel-Dwass multiple-comparison test. The correlations between age, duration from the onset of pain to surgery, combined necrotic angle, and bone-resorptive volume ratio, respectively, were analyzed using Spearman's correlation coefficient. The correlation between the progression of collapse per day and bone-resorptive volume ratio was also analyzed

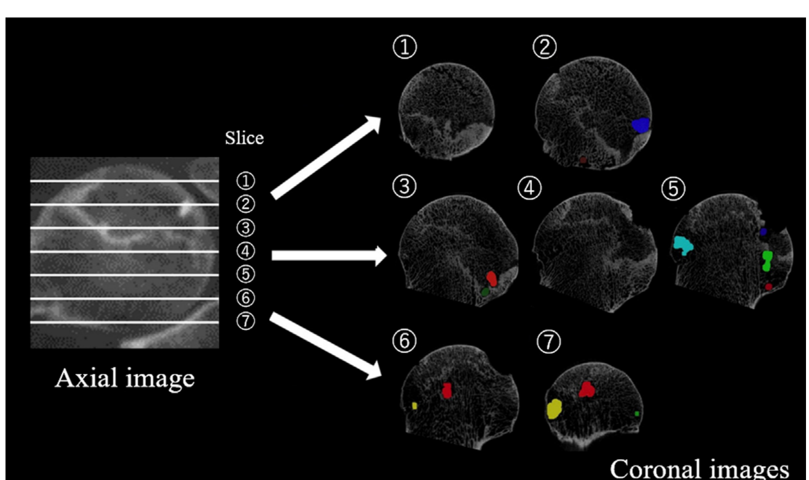

Fig. 3. Methods used to quantify the bone-resorptive volume of the entire femoral head.
In order to quantitatively assess the bone-resorptive volume in the entire femoral head, the coronal slices of a femoral head are divided equally into seven slices. The total bone-resorptive volume ratio in each femoral head is defined as the ratio of all bone-resorptive areas to all femoral head cross-sectional areas in seven slices.

using Spearman's correlation coefficient. Significant factors associated with bone-resorptive volume ratio were identified using multivariate analysis with stepwise regression that included all parameters. All statistical analyses were performed using the JMP software program (version 13.0, SAS Institute Inc., Cary, NC, USA). *P*-values less than 0.05 were considered to be statistically significant.

3. Results

The mean total bone-resorptive volume ratio was 7.0 ± 6.0%, which was significantly dependent on ONFH stage (3A, 3.5 ± 2.1%; 3B, 6.8 ± 3.0%; and 3C, 13.6 ± 8.8%; $P < 0.05$), while duration from the onset of pain to surgery and patient workload levels were not associated with bone-resorptive volume ratio (Table 1). Based on multivariate analysis, ONFH stage was identified to be independently associated with total bone-resorptive volume ratio ($P < 0.01$).

With respect to the location of bone-resorptive areas, a high percentage of bone-resorptive cross-sectional areas tended to be seen in the anterior femoral head (Fig. 4). There was more bone-resorptive area in slice 1 than in slices 4–7 ($P < 0.01$, respectively) and in slice 2 compared with slice 6 ($P < 0.05$). Furthermore, most bone-resorptive areas in each slice and 81.9% of all bone-resorptive areas were found within necrotic lesions. Mean bone-resorptive area in intra-necrotic lesions (5.9 ± 7.1%) was significantly larger than in extra-necrotic lesions (1.3 ± 3.2%; $P < 0.001$). In addition, slices with femoral head collapse were also more likely to be found in the anterior portion. Regarding the correlation between bone-resorptive lesions and femoral head collapse, slices with collapse had a significantly higher mean ratio of bone-resorptive areas (9.4 ± 10.6%) than slices without collapse (2.9 ± 3.3%; $P < 0.001$; Fig. 5A). The mean progression of collapse per day was 87.1 ± 115.9 μm (median 26.8 μm, range 0–400 μm). There was a significant positive correlation between the progression of collapse per day and bone-resorptive volume ratio, ($\rho = 0.59$, $P < 0.001$; Fig. 5B).

4. Discussion

The current quantitative study demonstrated that bone-resorptive volume within the femoral head is significantly associated with the post-collapse stage of ONFH. In addition, the collapse progression rate and bone-resorptive volume ratio were positively correlated. These findings suggest that the degree of bone resorption might increase as collapse progresses. On the other hand, we found no other factors influencing bone-resorptive volume, including the duration from the onset of pain or patient workload levels. Although it remains unclear whether bone resorption is an antecedent phenomenon to collapse or a subchondral fracture, the current results suggested a cause-and-effect relationship between bone resorption and collapse progression in post-collapse ONFH.

Several studies support the relationship between bone resorption and collapse progression. Plenk et al. reported that there are several types of repair processes in ONFH, in which femoral heads with predominant bone resorption undergo more destruction with time [4]. Karasuyama et al. histopathologically demonstrated that significantly more osteoclasts are present at the boundary of the necrotic lesion with collapse versus without collapse [17]. In an animal study, increased bone resorption was shown to be associated with the loss of structural integrity, leading to femoral head deformity [18]. Considering these reports and our findings, we hypothesize that the failure of mechanical stabilization due to excessive bone resorption may lead to the progression of collapse.

Bisphosphonates, which are osteoclast inhibitors, were used on a trial basis to prevent the occurrence of femoral head collapse based on the concept that osteoclastic bone resorption initiates collapse [5]. Previous reports have indicated that bisphosphonates may have the potential to postpone the progression of femoral head collapse [19–21], which suggests that bone resorption may be a cause of collapse progression. However, to the best of our knowledge, there have been no studies that have quantitatively characterized bone-resorptive lesions in ONFH. Although we cannot conclude whether bone-resorptive lesions are a cause or a consequence of femoral head collapse due to the design of this study, this is the first study that quantitatively characterized

Table 1
Univariate analysis of the relationship between bone-resorptive volume ratio and patient characteristics.

	Bone-resorptive volume ratio (%)			*P*-value	Correlation coefficient
	Mean ± SD	Median (IQR)	Range		
Sex[a]					
Male	5.9 ± 6.7	4.2 (1.9–7.0)	0.5–31.2	< 0.05	
Female	8.4 ± 4.7	6.7 (4.7–12.3)	2.0–18.5		
Associated factor[a]					
Steroid	7.4 ± 4.8	6.7 (3.3–11.2)	0.5–18.5	0.22	
Alcohol	6.4 ± 7.5	4.7 (2.0–7.2)	1.3–31.2		
JIC type[a]					
C1	6.8 ± 4.3	5.8 (3.2–10.9)	1.9–15.2	0.56	
C2	7.0 ± 7.0	6.0 (2.0–7.9)	0.5–31.2		
ONFH stage[b]					
3A	3.5 ± 2.1	3.1 (1.9–5.4)	0.5–7.2	3A vs 3B: < 0.01	
3B	6.8 ± 3.0	6.8 (4.2–9.0)	1.6–11.9	3A vs 3C: < 0.01	
3C	13.6 ± 8.8	12.6 (7.2–17.7)	2.0–31.2	3B vs 3C: < 0.05	
Workload levels[b]					
Low	9.1 ± 4.7	7.8 (6.1–12.2)	1.9–18.5	Low vs Mod.: 0.15	
Moderate	6.4 ± 7.3	3.4 (2.0–7.9)	0.5–31.2	Low vs High: 0.09	
High	4.1 ± 2.2	4.1 (1.9–5.9)	1.6–7.2	Mod. vs High: 0.92	
Age[c]				0.27	0.19
Duration from the onset of pain to surgery[c]				0.99	< 0.01
Combined necrotic angle[c]				0.46	0.13

SD: standard deviation; IQR: interquartile range; JIC: Japanese Investigation Committee; ONFH: osteonecrosis of the femoral head.
[a] Wilcoxon rank sum test.
[b] Steel-Dwass multiple-comparison test.
[c] Spearman's correlation coefficient.

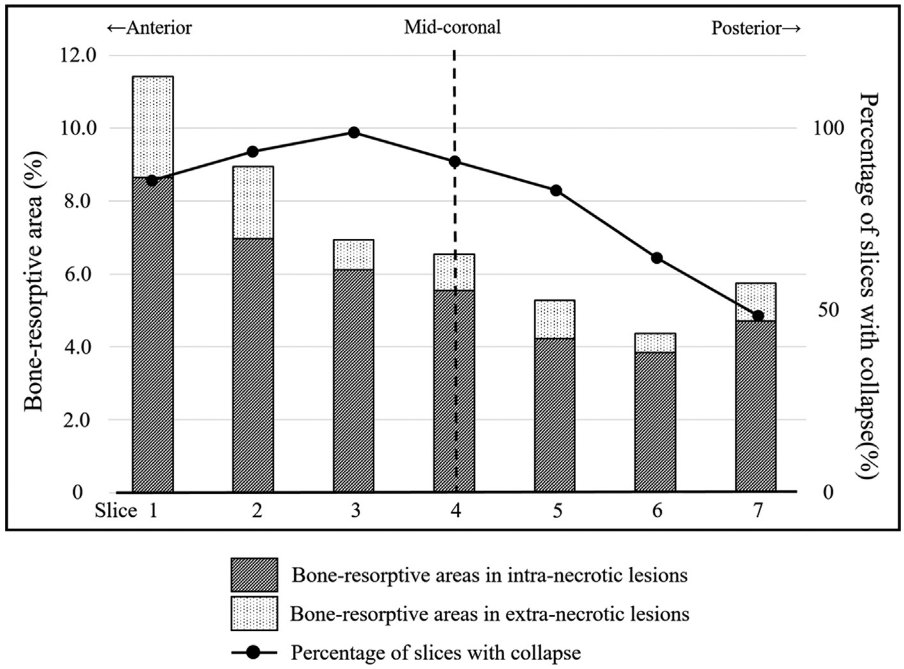

Fig. 4. Mean ratio of bone-resorptive cross-sectional area to femoral head cross-sectional area and percentage of bone-resorptive area in intra-necrotic versus extra-necrotic lesions by slice. The mean ratio of bone-resorptive areas (bar graph) and percentage of slices with collapse (line graph) tend to be higher in the anterior portion of the femoral head. There is more bone-resorptive area in slice 1 than in slices 4–7 ($P < 0.01$, respectively), as well as in slice 2 versus slice 6 ($P < 0.05$). In addition, within each slice, most bone-resorptive areas are found in intra-necrotic lesions. The total bone-resorptive area in intra-necrotic lesions (5.9 ± 7.1%) is significantly larger than the total bone-resorptive area in extra-necrotic lesions (1.3 ± 3.2%; $P < 0.001$).

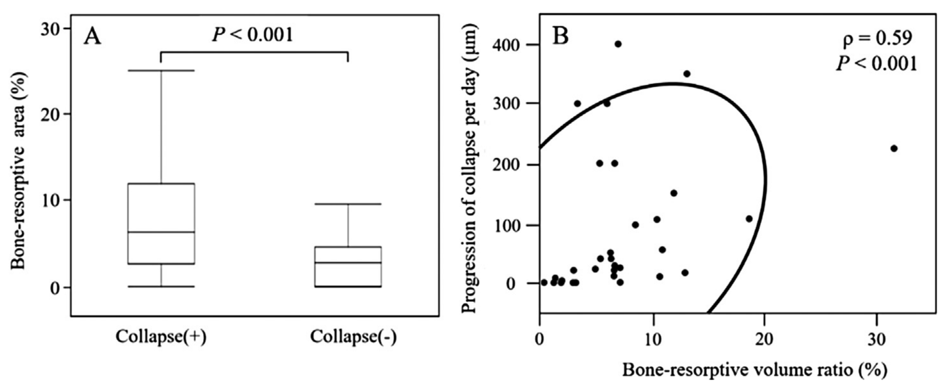

Fig. 5. A. The association between bone-resorptive lesion and femoral head collapse.
The mean ratio of bone-resorptive areas in slices with collapse (9.4 ± 10.6%) is significantly higher than that in slices without collapse (2.9 ± 3.3%, $P < 0.001$); B. The correlation between the progression of collapse per day and the bone-resorptive volume ratio. There is a significant positive correlation between the bone-resorptive volume ratio and progression of collapse per day ($\rho = 0.59$, $P < 0.001$). The curved line indicates a 95% confidence ellipse that contains 95% of the data.

bone-resorptive lesions in post-collapse ONFH and demonstrated a possible association between bone-resorptive volume and degree of femoral head collapse as well as the collapse progression rate. Therefore, we believe that this study provides valuable information for a better understanding of bone-resorptive lesions in collapsed femoral head and serves as a basis for future investigations to prevent femoral head collapse in patients with ONFH.

In the current study, bone-resorptive lesions were more common in the anterior portion of the femoral head, and lesion location was significantly associated with the presence of collapse. Since the anterior portion of the femoral head is susceptible to mechanical stress due to the nature of acetabular coverage [22], it seems reasonable that collapse was more commonly seen in the anterior portion of the femoral head. On the other hand, to the best of our knowledge, no studies have demonstrated bone resorption before collapse in ONFH. Although the current study showed simply bone-resorptive volume after collapse, we speculated that bone resorption being predominantly in the anterior portion may be due to the influence of collapse.

The main limitation of this study was the inability to assess time-dependent changes in bone-resorptive volume prospectively. Since we limited the subjects of the current study to whole femoral heads resected from patients with ONFH in order to assess the detailed characteristics of bone-resorptive lesions using micro-CT, the findings of the current study reflect only the state of bone-resorptive lesions at the time of surgery. However, the current study demonstrated no significant correlation between duration from the onset of pain to surgery and bone-resorptive volume. Therefore, we believe that this study provides useful information about bone resorption in post-collapse ONFH, even though evaluation occurred at one-time point. Second, regarding the relationship between bone-resorptive volume and collapse progression rate per day, bone-resorptive lesion volume should be ideally assessed at baseline to evaluate its causal relationship with collapse progression. However, it is not possible to perform micro-CT before surgery. Alternatively, we utilized clinical CT images taken for preoperative planning. Since the image quality of clinical CT scans was too poor to quantify the volume of bone-resorptive lesions, we assessed the correlation between collapse progression rate and bone-resorptive volume of the resected femoral head. Although not ideal, we believe the current results provide valuable data to support a relationship between bone resorption and collapse progression in post-collapse ONFH. Finally, the patient age distribution was wide and we did not evaluate patient activities of daily living, which may be associated with the progression of femoral head collapse. Although this study demonstrated that patient age and workload levels were not significantly correlated with bone-resorptive volume, in a future prospective study, evaluation of patient activity and detailed examination by age group should be performed to elucidate the pathomechanism of bone resorption in ONFH using high-resolution radiological equipment in vivo.

5. Conclusions

This study demonstrated that bone-resorptive volume in post-collapse ONFH was significantly associated with the disease stage and collapse progression rate, which was more widespread in the anterior portion of the femoral head than in the posterior portion. We believe that this study provides a better understanding of bone resorption in collapsed femoral heads and potential clinical therapeutic targets for ONFH.

Authors' contributions

Study design: S.B. and G.M. Acquisition of data: S.B, G.M, S.I., and Y.N. Study execution: S.B., Y.K., T.U., H.H., and K.K. Drafting of the manuscript: S.B. Revision of the manuscript: GM, SI, and YK. Approval of the final version of the manuscript: S.B., G.M., S.I., Y.K., T.U., H.H., K.K., and Y.N. All authors take responsibility for the integrity of the data analysis.

Disclosure of interest

The authors declare that they have no competing interest.

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