CLINICAL ARTICLE

Posterior Pelvic Tilt in the Standing Position Might Be Associated with Collapse Progression in Post-Collapse Stage Osteonecrosis of the Femoral Head

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Objective: Excessive pelvic tilt has been reported to impair the biomechanical loading of the hip joint. However, the influence of pelvic tilt in osteonecrosis of the femoral head (ONFH) remains unclear. This study aims to assess whether sagittal pelvic posture in the standing position correlates with progression of femoral head collapse in post-collapse stage ONFH.

Methods: This is a single-center retrospective study. We investigated 107 patients (107 hips; 73 males and 34 females; mean age, 48 years) diagnosed with Association of Research Circulation Osseous (ARCO) stage III ONFH at the first visit and who subsequently underwent surgical treatment in our institution from July 2016 to December 2020. The sagittal pelvic posture in the standing position before surgery was quantified as the angle formed by the anterior pelvic plane and the vertical z-axis in the sagittal view (APP angle). An APP angle <0° indicated posterior pelvic tilt. Progression of femoral head collapse was calculated as collapse speed. The following factors potentially associated with collapse speed were evaluated by exploratory data analysis followed with multiple linear regression analysis: sex, age, BMI, etiology, pelvic incidence, contralateral hip condition, time interval between the first visit and surgery, size of necrotic lesion, location of necrotic lesion, and APP angle.

Results: As ONFH progressed from ARCO stage IIIA to stage IV, APP angle decreased significantly and continuously (stage IIIA, −0.2° ± 5.5°; stage IIIB, −3.7° ± 5.8°; stage IV, −7.1° ± 6.4°). The factors significantly associated with collapse speed were size of necrotic lesion ($p = 0.0079$), location of necrotic lesion ($p = 0.0190$), and APP angle ($p < 0.0001$). APP angle showed a negative correlation with collapse speed ($r = -0.40$, $p < 0.0001$). After stratifying by size of necrotic lesion (<50% and ≥50% involvement) and location of necrotic lesion (JIC type C1 and C2), a significant negative correlation was observed between APP angle and collapse speed in each group (JIC type C1 with <50% involvement, $r = -0.69$, $p < 0.0001$; JIC type C1 with ≥50% involvement, $r = -0.58$, $p = 0.0475$; JIC type C2 with <50% involvement, $r = -0.51$, $p = 0.0124$; JIC type C2 with ≥50% involvement, $r = -0.39$, $p = 0.0286$).

Conclusions: Our results suggest that posterior pelvic tilt in the standing position occurred as ONFH progressed from ARCO stage IIIA to stage IV, which might be associated with progression of femoral head collapse in ONFH.

Key words: Collapse; Osteonecrosis of the femoral head; Sagittal pelvic posture; Standing position

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Introduction

In osteonecrosis of the femoral head (ONFH), the patient generally remains asymptomatic in the early stage, and most cases are diagnosed after the onset of hip pain with a collapsed femoral head[1]. *Femoral head collapse often occurs when the necrotic lesion is located in the weightbearing area under the acetabulum*[2–5]*. As the collapse progresses, hip osteoarthritis (OA) change is often inevitable, and total hip arthroplasty is the final treatment option, even for young people*[6]. Since femoral head collapse progression significantly influences the process of hip degeneration in patients with ONFH, identifying a previous unknown factor associated with collapse progression is of great importance. *Recently, the mechanism of femoral head collapse has become a hot research topic. However, most of the published studies have focused on the effects of the necrotic lesion inside the femoral head without considering the functional pelvic posture in the standing position.*

Excessive pelvic tilt has been reported to impair the biomechanical loading of the hip joint[7]. Several studies have reported that, in both dysplastic and nondysplastic hips, posterior pelvic tilt in the standing position decreases the anterior femoral head coverage and alters the loading environment of the hip joints, which might accelerate the process of hip degeneration[8–13]. In addition, posterior pelvic tilt in the standing position has been observed in patients with primary OA and rapidly destructive coxopathy[12]. Although the abovementioned information indicated that pelvic tilt could influence the load on the femoral head, it has not been greatly researched in patients with ONFH. We hypothesis that posterior pelvic tilt in the standing position might influence the femoral head collapse progression in patients with ONFH. The purpose of this study was to (i) evaluate the sagittal pelvic posture in the standing position before surgery in patients with ONFH; and (ii) assess whether the sagittal pelvic posture in the standing position before surgery correlates with progression of femoral head collapse in ONFH.

Methods

Inclusion and Exclusion Criteria

The inclusion criteria were: (i) onset age ≥ 18 years; (ii) diagnosis of atraumatic ONFH of Association Research Circulation Osseous (ARCO) stage III at the first visit to our hospital. The exclusion criteria included: (i) unavailability of a standing plain radiograph of the hip just before surgery; (ii) unrecognizable femoral head morphology on the plain radiographs at first visit and just before surgery; (iii) history of surgery at spine, hip, or lower extremities; and (iv) hip dysplasia.

Patients

The ethics committee of our hospital, Kyushu University Hospital, approved the study protocol (IRB No.2019-584). From July 2016 to December 2020, 234 patients diagnosed with ONFH who underwent surgical treatment at our institution were evaluated for potential inclusion in this retrospective analysis. Plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) of the hip joint were obtained as part of routine practice at our institution. The diagnosis of ONFH was based on MRI and plain radiographs[14]. Since the dysplastic hip joint is characterized by reduced femoral head coverage and joint instability,[9] patients with hip dysplasia were excluded from this study. Hip dysplasia was defined as a lateral center-edge angle <20° on plain radiographs[15]. In patients with bilateral ONFH, the more severely collapsed side was included. Finally, 107 patients (107 hips) were included in this study (Figure 1). An orthopedic surgeon (MX) determined the ARCO stage at the first visit and just before surgery[5], as well as the size and location of necrotic lesion. The location of necrotic lesion was classified according to the Japanese Investigation Committee (JIC) classification system[16].

Of the 107 patients, 73 (68%) were male and 34 (32%) were female. The mean age was 48 years (SD, 13 years; range, 19–77 years). The mean body mass index (BMI) was 23 kg/m^2 (SD, 4 kg/m^2; range, 16–36 kg/m^2). Regarding the etiology of ONFH, 46 (43%) patients reported a history of

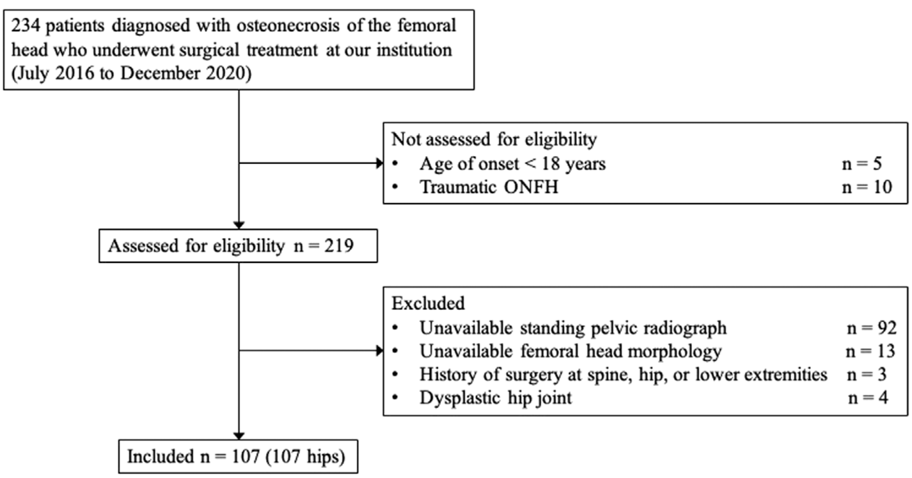

Fig. 1 Flowchart of patient inclusion

steroid intake, 17 (16%) had a diagnosis of alcohol abuse, and 44 (41%) were diagnosed with idiopathic ONFH. As for the contralateral hip condition, 45 (42%) patients were diagnosed with a healthy contralateral hip joint, 24 (22%) were diagnosed with a necrotic contralateral hip joint with a collapsed femoral head at the first visit, 25 (23%) were diagnosed with a necrotic contralateral hip joint that remained intact from the first visit to surgery, and 13 (12%) were diagnosed with a necrotic contralateral hip joint that progressed to collapse between the first visit and surgery. In addition, eight (7%) patients were classified as JIC type B, 44 (41%) as JIC type C1, and 55 (51%) as JIC type C2. At the first visit, 65 (61%) patients were classified as ARCO Stage IIIA, and 42 (39%) as ARCO Stage IIIB. Before surgery, 26 (24%) patients were classified as ARCO Stage IIIA, 43 (40%) as ARCO Stage IIIB, and 38 (36%) as ARCO stage IV. *From the first visit to surgery, 27 (42%) patients progressed from ARCO Stage IIIA to IIIB, 12 (18%) patients progressed from ARCO Stage IIIA to IV, and 26 (62%) patients progressed from ARCO Stage IIIB to IV.* The median time interval between the first visit and surgery was 2.9 months (range, 0.4–107.0 months; lower quartile, 1.8 months; upper quartile, 5.8 months).

Radiological Data

CT images of the pelvis performed with patients in the supine position were obtained from the superior acetabular rim to the distal femur (scanner: Aquilion; Toshiba, Tochigi, Japan) using a tube voltage of 120 kVp with 1 mm intervals. Standing pelvic radiographs were obtained before surgical treatment with patients standing in a relax position which will not influence the natural pelvic tilt. MRI of the hip joint were obtained within 1 week after the first visit using one of the two units: a 1.5T MR unit (Vantage Titan; TOSHIBA, Japan) or a 1.5T MR unit (Achieva; Philips Healthcare, Netherlands). T1-weighted images were obtained in the coronal, sagittal and axial planes, with repetition times (TR) of 400 to 540 ms and echo times (TE) of 10 to 18 ms (TR/ TE = 400 to 540/10 to 18). In all planes, the section thickness was 4 or 5 mm, with an interslice gap of 1 mm and a field of view of 360 × 360 mm.

Measurement Details

Sagittal Pelvic Posture in the Standing Position

The sagittal pelvic posture in the standing position just before surgery was measured by a 2D–3D matching method as previously described[9]. Using CT data in DICOM format, we digitally reconstructed the pelvic radiographs with image-processing software (LEXI, Tokyo, Japan) to perform the following measurements. First, pelvic position was standardized with reference to the anterior pelvic plane, defined by the bilateral anterosuperior iliac spines and the midpoint between the pelvic tubercles. The x- and y-axes corresponded to the transverse and sagittal axes on the axial CT slice, respectively. The z-axis was perpendicular to the x–y plane. Second, by rotating the CT-reconstructed pelvis along the x-axis in the sagittal view, the vertical-to-horizontal ratio of the pelvic foramen of digitally reconstructed radiograph was matched with the standing anteroposterior-view radiograph obtained before surgery (Figure 2(A, B)). Then, in the sagittal view of the digitally reconstructed radiograph, the sagittal pelvic posture in the standing position was quantified as the angle formed by the anterior pelvic plane and the z-axis (APP angle) (Figure 2(C)). A positive APP angle was defined as anterior pelvic tilt, a negative angle as posterior pelvic tilt, and an angle of 0° as neutral position.

Pelvic Incidence

As an important factor for determining the orientation and position of the pelvis in the standing position[17,18], pelvic incidence was measured as the angle between the line perpendicular to the sacral plateau at its midpoint and the line connecting this point to the femoral head axis (Figure 2(C)).

Size of Necrotic Lesion

The size of necrotic lesion was measured on axial T-1 weighted MRI using method 4 reported in a previous study[8], which has been described to have a reasonable intra- and inter-observer reliabilities[8]. The largest anteroposterior diameter of the head (r), the longest anteroposterior length of the necrotic lesion (a) and the longest mediolateral length of the necrotic lesion (b) were measured on axial images. The size of necrotic lesion was calculated with the following formula:

$$\%\ \text{size of necrotic lesion} = \frac{(a \times b)}{r^2} \times 100$$

Then, the size of necrotic lesion was furtherly stratified as <50% involvement and ≥50% involvement.

Collapse Speed

Femoral head collapse progression in post-collapse stage ONFH was quantified as collapse speed. Collapse speed was calculated with the following formula:

$$\text{collaspe speed} = \frac{(\text{collapse extent before surgery} - \text{collaspe extent at first visit})}{(\text{time from first visit to surgery})}.$$

The collapse extent of the femoral head was measured as the distance between the circle overlying the intact femoral head and the maximal collapse of the femoral head using Mimics software (Materialize NV, Leuven, Belgium); measurements were based on anteroposterior (Figure 3(A)) and lateral (Figure 3(B)) plain radiographs of the hip obtained at the first visit and just before surgery, with patients in the supine position. To eliminate magnification errors, we measured the diameter of the femoral head at the first visit and before surgery (Figure 3(A, B)).

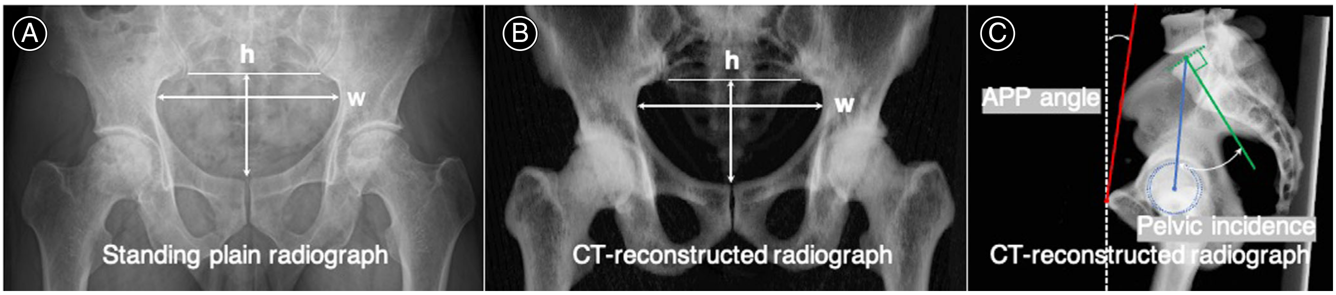

Fig. 2 Method of measuring sagittal pelvic posture in the standing position. (A) On the standing plain radiograph, the foramen ratio was calculated as the vertical diameter of the pelvic foramen between the bilateral sacroiliac joint and pubic symphysis (*h*), divided by the maximum horizontal diameter of the pelvic foramen (*w*). (B) On the CT-reconstructed radiograph, the pelvis was rotated in the sagittal view until the ratio (h/w) was consistent with that on the standing plain radiograph. (C) In the sagittal view of the matched radiograph, the sagittal pelvic posture in the standing position was quantified as the angle formed by the anterior pelvic plane (solid red line) and the vertical *z*-axis (dotted white line) (APP angle). In addition, pelvic incidence was measured as the angle between a line (solid green line) perpendicular to the midpoint of the sacral plateau and a line (solid blue line) from this point to the femoral head axis

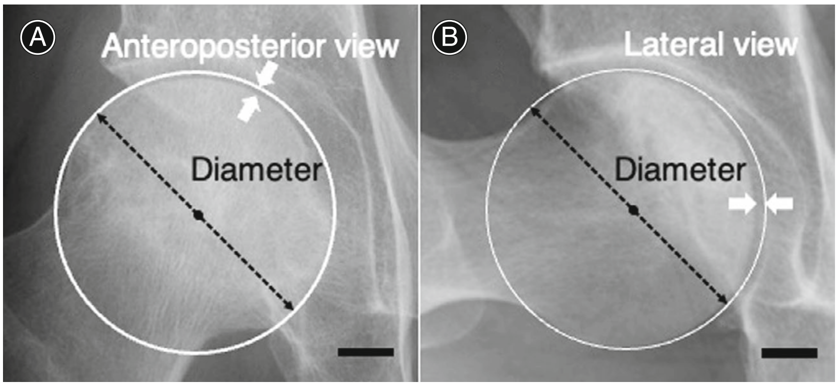

Fig. 3 Method of measuring the extent of femoral head collapse. (A) The anteroposterior radiograph of the hip joint; (B) The lateral radiograph of the hip joint. On both the anteroposterior and lateral radiographs, the extent of femoral head collapse was measured as the distance between the circle overlying the intact femoral head and the maximal collapse of the femoral head (white arrows). To eliminate magnification errors, we measured the diameter of the femoral head at the first visit and before surgery (black dotted line). (Black bar = 10 mm)

Statistical Analysis

All the statistical analyses were performed using JMP version 13.0 (SAS Institute, Cary, NC). The intraclass correlation coefficients was used to assess intra- and inter-observer reliabilities. The intraclass correlation was defined as substantial when the value was 0.61–0.80, and as almost perfect when the value was >0.80. Student–Newman–Keuls test was used to compare measurement data of patients across different ARCO stages before surgery depending on the normality (Shapiro–Wilk test). Exploratory data analysis, including Mann–Whitney *U* test and Kruskal–Wallis test by ranks, was performed to evaluate the relationship between categorical data and collapse speed depending on the normality (Shapiro–Wilk test). Exploratory data analysis using Pearson correlation coefficient was performed to evaluate the relationship between measurement data and collapse speed. Multiple linear regression analysis was performed to identify associated variables for collapse speed. Dummy coefficients were used for conversion of classified variables. To deal with the multicollinearity, we tested the variance inflation factors (VIFs) for each of the variables. VIFs between 1 and 5 suggest

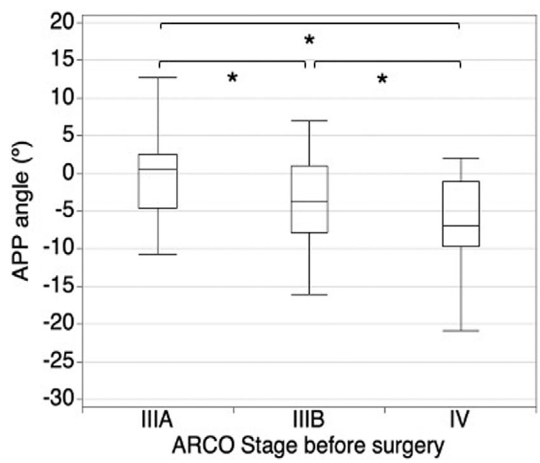

Fig. 4 Comparison of APP angle in patients with ONFH of different ARCO stages. Student–Newman–Keuls test revealed that the mean APP angle continuously and significantly decreased as ONFH progressed from ARCO stage IIIA to stage IV. (*: *p* value is significant)

TABLE 1 Results of exploratory data analysis and multivariate regression analysis of factors potentially associated with collapse speed

Factor	Exploratory analysis *p* value	Multivariate analysis *F* ratio	*p* value
Sex	0.26	0.54	0.47
Age	0.06	0.68	0.41
BMI	0.69	0.45	0.50
Etiology	0.15	0.38	0.68
Pelvic incidence	0.14	0.71	0.40
Contralateral hip condition	0.23	0.25	0.86
Time interval between the first visit and surgery	0.04	1.39	0.24
Necrotic lesion size	0.0001	7.39	0.0079
JIC type	<0.0001	4.14	0.0190
APP angle	<0.0001	17.40	<0.0001

Note: JIC, Japanese Investigation Committee; APP angle, the angle formed by the anterior pelvic plane and the *z*-axis in the sagittal view of the hip joint. (*p* value <0.05 indicates significance).

TABLE 2 Results of Pearson correlation coefficient for evaluating the relationship between APP angle and collapse speed after stratifying by size of the necrotic lesion and JIC type C1 and C2

		JIC type C1	JIC type C2
Size of necrotic lesion	<50%	$r = -0.69$, $p < 0.0001$	$r = -0.51$, $p = 0.0124$
	≥50%	$r = -0.58$, $p = 0.0475$	$r = -0.39$, $p = 0.0286$

Note: APP angle, the angle formed by the anterior pelvic plane and the *z*-axis in the sagittal view of the hip joint; JIC, Japanese Investigation Committee. (*p* value <0.05 indicates significance).

that the correlation does not severely influence the measurements, and VIFs less than 10 are acceptable. Dunn's test with Bonferroni correction was used to compare measurement data across patients with different JIC types. Differences were considered significant when the *p* value was <0.05.

Results

Intra- and Inter-Observer Reliabilities of Measurements

The APP angle, pelvic incidence and collapse speed evaluations were performed by two orthopedic surgeons (KK and MX) who were blind to each other's measurements. Intra-observer reliabilities for the measurements of APP angle, pelvic incidence, and collapse speed were good (0.96, 0.95, and 0.95, respectively), as were inter-observer reliabilities (0.87, 0.88, and 0.91, respectively).

General Results of Measurements

The mean APP angle just before surgery was −4° (SD, 6°; range, −27° to 13°), the mean pelvic incidence was 46° (SD, 10°; range, 30° to 77°), the mean size of necrotic lesion was 48% (SD, 15%; range, 15% to 90%), and the median collapse speed was 0.42 (range, 0.01 to 3.0) mm/month.

Comparison of APP Angle in Patients with ONFH of Different ARCO Stages

As ONFH progressed from ARCO stage IIIA to stage IV, APP angle decreased significantly and continuously (stage IIIA, $-0.2° \pm 5.5°$; stage IIIB, $-3.7° \pm 5.8°$; stage IV, $-7.1° \pm 6.4°$) (Figure 4).

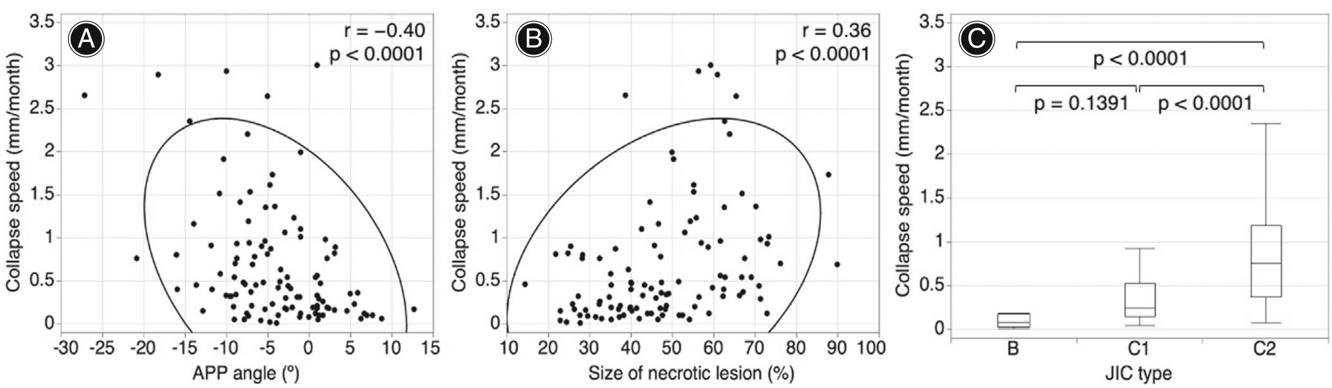

Fig. 5 The relationship between different factors and collapse speed. (A) Pearson correlation coefficient shows that APP angle is negatively correlated with collapse speed; (B) and the size of necrotic lesion is positively correlated with collapse speed. (C) Dunn's test with Bonferroni correction shows that the median collapse speed in patients with JIC type C2 ONFH is significantly faster than in patients with type C1 or type B. (*p* value <0.05 indicates significance)

Exploratory Data Analysis Followed with Multivariate Regression Analysis of Variables Potentially Associated with Collapse Speed

After accounting for all the analyzed factors, specifically sex, age, BMI, etiology, pelvic incidence, contralateral hip condition, time interval between the first visit and surgery, size of necrotic lesion, JIC type, and APP angle, both the exploratory data analysis and multiple linear regression analysis demonstrated that size of necrotic lesion, JIC type, and APP angle were significantly associated with collapse speed in patients with post-collapse stage ONFH (Table 1). In multiple linear regression analysis, all the VIFs were smaller than 5. In addition, the APP angle showed a negative correlation with collapse speed ($r = -0.40$, $p < 0.0001$) (Figure 5(A)), and size of necrotic lesion showed a positive correlation with collapse speed ($r = 0.36$, $p < 0.0001$) (Figure 5(B)). Collapse speed was significantly higher in patients with JIC type C2 ONFH than those with JIC type C1 ($p < 0.0001$) or JIC type B ($p < 0.0001$) (Figure 5(C)).

Furthermore, after stratifying by size of necrotic lesion (<50% involvement and ≥50% involvement) and location of necrotic lesion (JIC type C1 and C2), a significant negative correlation was observed between APP angle and collapse speed in each group (JIC type C1 with <50% involvement, $r = -0.69$, $p < 0.0001$; JIC type C1 with ≥50% involvement, $r = -0.58$, $p = 0.0475$; JIC type C2 with <50% involvement, $r = -0.51$, $p = 0.0124$; JIC type C2 with ≥50% involvement, $r = -0.39$, $p = 0.0286$) (Table 2).

Discussion

The Importance of Sagittal Pelvic Posture in the Standing Position

It is important to understand the mechanism of femoral head collapse progression in ONFH because it generally leads to a hip OA change, which significantly worsens patient prognosis[6,19]. Recently, high pelvic incidence was reported to be associated with femoral head collapse occurrence during pre-collapse stage ONFH, potentially mediated by posterior pelvic tilt[20]. Moreover, posterior pelvic tilt in the standing position has been reported to cause decreased femoral head coverage and impair the hip loading environment in both dysplastic and nondysplastic hips[7–13]. Although the above information suggests that posterior pelvic tilt in the standing position might influence the femoral head collapse progression in ONFH, no research has investigated this issue. In this study, ONFH progression from ARCO stage IIIA to stage IV was associated with a significant and continuous increase in posterior pelvic tilt in the standing position before surgery. In addition to the size and location of the necrotic lesion, our results demonstrated that sagittal pelvic posture in the standing position before surgery was associated with collapse speed in patients with post-collapse stage ONFH.

Sagittal Pelvic Posture in the Standing Position in Patients with ONFH of Different ARCO Stages

Our results demonstrated that, in post-collapse stage ONFH, posterior pelvic tilt before surgery increased significantly and continuously as the disease progressed from ARCO stage IIIA to stage IV. Watelain *et al.* reported that as hip OA worsened, limited hip range of motion (ROM) could be partly compensated for by increased pelvic motion, including in the sagittal plane[21]. Shimizu *et al.* also reported that the extent of hip contraction increased as a function of posterior pelvic tilt in the standing position[22]. Moreover, after femoral head collapse in patients with ONFH, disease progressed from the asymptomatic to symptomatic stage, and limited hip ROM was generally observed[2,4,19,23]. Therefore, we think that limited hip ROM might partially explain the occurrence of posterior pelvic tilt in post-collapse stage ONFH.

Potential Effects of Posterior Pelvic Tilt in the Standing Position on Collapse Speed

According to our results, posterior pelvic tilt in the standing position before surgery is associated with faster femoral head collapse speed in patients with post-collapse stage ONFH. Several studies have reported that, in both dysplastic and nondysplastic hips, posterior pelvic tilt in the standing position reduces the femoral head coverage and changes the loading environment of the hip joint, which might be responsible for hip degeneration[8–13,24]. Furthermore, this study demonstrated that posterior pelvic tilt in the standing position before surgery significantly increased as ONFH progressed from ARCO stage IIIA to stage IV. Therefore, posterior pelvic tilt in the standing position might worsen the loading environment of the necrotic femoral head and consequently accelerate the femoral head collapse speed in post-collapse stage ONFH. Further research is necessary to assess whether posterior pelvic tilt could cause impaired stress distribution in the necrotic femoral head and consequently induce faster collapse progression.

The size and location of the necrotic lesion have been recognized as the two major factors influencing femoral head collapse in ONFH[2,6,14]. Consistent with these findings, our results showed that larger necrotic lesions and those located laterally under the acetabulum (JIC type C2) were associated with faster collapse speed in post-collapse stage ONFH. However, ONFH progression is a complex, multifactorial process. In this study, we found that sagittal pelvic posture in the standing position before surgery was significantly associated with collapse speed in patients with post-collapse stage ONFH, and its effects were comparable to that of necrotic lesion size ($r = -0.4$ vs. $r = 0.36$, respectively). These results suggest that attention should be paid to the sagittal pelvic posture in the standing position in patients with ONFH.

Pelvic incidence is an important factor for determining the posture of the pelvis in the standing position[17,18]. As noted above, Kwon *et al.* reported that in pre-collapse stage ONFH, high pelvic incidence was associated with femoral head collapse[20]. They proposed that high pelvic incidence may cause posterior pelvic tilt, leading to decreased femoral head coverage[20]. This study demonstrated that pelvic incidence was not associated with collapse speed in post-collapse stage ONFH, perhaps due to the decompensation of the adjustment of pelvic posture induced by limited hip ROM.

Limitations of the Study

To the best of our knowledge, this is the first study assessing the effects of sagittal pelvic posture in the standing position on patients with ONFH. This study demonstrated that posterior pelvic tilt in the standing position before surgery might be associated with femoral head collapse progression in post-collapse stage ONFH. However, this study also has several limitations. First, we could not assess the APP angle at the first visit since pelvic radiographs in the standing position were only performed before surgical treatment for preoperative surgical planning. Although the present study could show the possible association between the APP angle in the standing position before surgery and collapse progression, we could not demonstrate the effects of sagittal pelvic posture in the standing position on collapse progression. Second, it included no JIC type A hips and only eight JIC type B hips. That was because patients of JIC type A were reported to have a collapse rate of 0% and patients of JIC type B were reported to have a low collapse rate[19]. Therefore, we think our findings are meaningful for management of patients with ONFH. Third, since the standing pelvic radiograph has not been considered as a routine for patients with OFNH, a high proportion of 92 patients were excluded due to unavailable standing pelvic radiographs. However, our study firstly gave insight into the potential influence of sagittal pelvic posture on patients with ONFH. Forth, the distribution of time interval between the first visit and surgery is abnormal and too wide. However, since Pearson's correlation does not assume normality and we furtherly performed multiple linear regression analysis to describe the association, we believe our results are reliable. Fifth, it might be difficult for clinicians to evaluate sagittal pelvic posture in the standing position using CT data. A standard lateral pelvic plain radiograph in the standing position is an alternative method.

Conclusion

This study demonstrated that posterior pelvic tilt in the standing position occurred as ONFH progressed from ARCO stage IIIA to stage IV, which might be associated with femoral head collapse progression in patients with post-collapse stage ONFH. In addition to the size and location of the necrotic lesion, sagittal pelvic posture in the standing position should be evaluated in patients with ONFH.

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Author contributions

Mingjian Xu and Goro Motomura contributed to the design of this study. Mingjian Xu, Goro Motomura, Koichiro Kawano, Satoshi Ikemura, and Yasuharu Nakashima contributed to the acquisition of data. Mingjian Xu, Koichiro Kawano, Noriko Yamamoto, Hidenao Tanaka, and Yusuke Ayabe contributed to the study execution. Mingjian Xu contributed to the writing of the original draft. Goro Motomura, Satoshi Ikemura, and Ryosuke Yamaguchi contributed the review and editing of the draft.

Ethics Statement

All the authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and that all authors are in agreement with the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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