Predictors of cartilage degeneration in patients with subchondral insufficiency fracture of the femoral head: a retrospective study

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Abstract

Background

There is evidence that the cause of primary osteoarthritis (OA) is related to the changes in subchondral bone; however, it is not fully understood if subchondral insufficiency fracture (SIF) of the femoral head would affect degeneration of the hip joint and what the prognostic factors related to joint degeneration are. The objectives of this study were 1) to investigate the longitudinal joint space narrowing and 2) to investigate the associations between joint space narrowing and bone metabolic markers as well as magnetic resonance imaging (MRI) among the patients with SIF.

Methods

Between January 2010 and December 2019, 238 patients in whom band pattern of the femoral head were observed on MRI visited our hospital. Among these patients, 44 hips in 41 patients were diagnosed with SIF and eligible for this retrospective study. We evaluated the joint space width (JSW) of the hip on the radiograph obtained at the first and last visits, length of the band lesion on MRI, bone mineral density by dual-energy x-ray absorptiometry, and bone metabolism markers. We investigated the factors associated with the necessity of surgery and the progression of the narrowing of the joint space.

Results

Fifteen of the 44 hips required total hip arthroplasty (THA). The JSW showed a significant decrease from the first visit to the final follow-up. Changes in the JSW were associated with the length of band patterns, serum type 1 procollagen-N-propeptide (P1NP), and tartrate-resistant acid phosphatase 5b (TRACP-5b) at the date of diagnosis. Additionally, bone metabolic markers tended to be associated with the length of the band pattern.

Conclusions

SIF could cause joint space narrowing and hip OA. In addition to MRI findings as prognostic predictors of SIF, as previously described, bone metabolic markers were also associated with changes in JSW, suggesting that these parameters could be useful to predict the prognosis of SIF. Considering that bone metabolic markers trended to be associated with the length of band pattern, they might reflect the local severity.

Background
Subchondral insufficiency fracture (SIF) of the femoral head has recently been recognized as a cause of the femoral head collapse, resulting in degeneration of the hip joint, which is known to occur in association with osteonecrosis of the femoral head (ONFH) [1-3]. Although the precise prevalence of SIF is unknown, previous studies with histopathological re-evaluation showed that SIF was observed in 6.3% (460 out of 7,349) of patients with a preoperative diagnosis of osteoarthritis (OA), and in 11.1% (41 out of 369) of patients with ONFH [4]. Some cases of SIF have been reported to heal after conservative therapy, including rest, non-weight bearing, and traction [1, 5, 6], while other cases have been reported to undergo collapse necessitating surgery such as total hip arthroplasty (THA) and osteotomy [2, 3, 7, 8]. On the other hand, although there is evidence that the cause of primary OA is related to the changes in subchondral bone [9, 10], it is not fully understood if SIF would affect the degeneration of the hip joint and what the prognostic factors are related to joint degeneration among the patients with SIF.

SIF has been reported in adults of varying ages and activity levels [11-13]. Previous studies reported that the risk factors leading to THA were female sex [14], elderly onset [15], length [16], location [17] and luminance of band pattern [18]. On the other hand, although bone fragility due to osteoporosis could be considered the most important cause of SIF, similar to vertebral body fractures [19], another study reported that there were no differences in bone mass densitometry (BMD) between patients with SIF and those without (controls) [20]. Bone strength is determined by bone mass, geometry, and quality including bone turnover, microarchitecture, the degree and distribution of mineralization[21]. Among them, one review article reported that the levels of bone turnover markers varied throughout the course of fracture repair dependent on the size of the fracture and the time that it will take to heal[22]. Therefore, it would be of great interest whether and how bone turnover markers would affect the pathology of SIF.

Hence, the objectives of this study were 1) to investigate the longitudinal joint space narrowing and 2) to investigate the associations between joint space narrowing and bone metabolic markers as well as magnetic resonance imaging (MRI). The hypotheses of this study were that: 1) SIF could induce joint space narrowing and hip OA, and 2) bone metabolic abnormalities as well as MRI findings could
predict the prognosis and reflect the severity of SIF.

Patients And Methods

The institutional review board approved this retrospective study (# 015-0206). In total, 238 patients (401 hips) who showed a band pattern of the femoral heads on MRI visited our hospital from January 2010 to December 2019. Among these, SIF was diagnosed based on several published criteria [2, 23, 24] as follows: hip pain that began without any apparent history of trauma; radiographs that were normal or that showed the collapse of the femoral head, joint space narrowing and/or a linear patchy sclerotic area in the superior portion of the femoral head; a bone marrow edema pattern in the femoral head and/or neck on MRI; and a subchondral low signal-intensity band on T1 weighted MRI that was convex to the articular surface and parallel to the subchondral bone end-plate. We distinguished between SIF and ONFH via gadolinium enhanced MRI. Forty-seven hips in 44 patients (male: 10, female: 34) were diagnosed with SIF. In this study, 3 hips in 3 patients who showed rapid collapse and joint destruction, including that of the acetabular (AC), were excluded. Among those diagnosed with SIF, patients who could be diagnosed within 3 months after hip pain were supervised to avoid weight-bearing with crutches for 6 weeks[25] and were treated on an outpatient basis every 2 weeks. Patients with late diagnosis or poor compliance could not be treated with conservative therapy as an initial treatment.

Data on patient demographics including age, sex, and body mass index (BMI), the period from onset to the first visit, history of corticosteroid intake or alcohol abuse, and medical history of osteoporosis drug intake were collected from their medical records. Data regarding whether patients could be treated conservative therapy and whether they required THA within the follow-up period were also collected. The indication of THA was the failure to relieve the pain and disability of daily life regardless of nonsteroidal anti-inflammatory medications. Alcohol abuse was defined as the consumption of more than 400 ml of alcohol per week, which is known to be a significant risk factor for osteonecrosis of the femoral head [26].

Radiographs were taken using the same technique throughout the study period; a standardized position of the beam and radiographic penetration were adopted. The radiographs of all patients were
assessed using a picture archiving and communication system (PACS) on the anteroposterior (AP) radiographs. In the current study, the center-edge (CE) angle at the first visit and longitudinal joint space width (JSW) were investigated (Fig. 1A). For JSW analysis, concentric circles passing through three points set arbitrarily in the AC joint surface and the femoral head were drawn respectively (circle A and circle B in Fig. 1A). The distance between the intersection of each circle and the line, that runs through the center of the femoral head (O in Fig. 1A) and is perpendicular to the line between the bilateral teardrops (line A in Fig. 1A) was measured. The interobserver variability of the JSW between two observers (YK and TD) was 0.768.

The MRI examinations were performed by a 1.5-T system under 5-mm slice thickness. The T1- and T2-weighted spin-echo images and short tau inversion recovery (STIR) images on the coronal and axial (and/or oblique axial: paralleling the femoral neck axis) planes were available in all cases. The band lengths were measured at the slice in which the longest band was detected on T1-weighted MRI on the coronal plane as previously described [16](Fig. 1B). The interobserver variability of the band length between two observers (YK and TD) was 0.836.

Fasting blood samples were obtained to examine the biochemical markers of bone turnover related to osteoporosis, including the levels of intact type 1 procollagen-N-propeptide (P1NP) and tartrate-resistant acid phosphatase 5b (TRACP 5b). Areal BMD in the lumbar spine (LS, L2–L4) and femoral neck were assessed by dual-energy X-ray absorptiometry (DXA; Discovery A, Hologic Japan, Inc, Tokyo, Japan). Bone turnover markers and BMD were investigated at the definite diagnosis. Chi-squared or independent t-tests were used to compare the differences between the patients who required THA and those treated conservatively, and between patients who could comply with the weight-bearing limitation and those who could not. Cox regression analysis was performed to identify the risk factors for THA. Linear regression models adjusted for age, sex, anti-osteoporosis therapy, and the period from onset to diagnosis were built to determine the associations between changes in the JSW, band length, and bone metabolic markers. All statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY) with the significance level set at 0.05.

Results
The demographics and clinical data of the patients are summarized in Table 1. In total, 18 of 44 hips could complete the weight-bearing limitation for 6 weeks. Six hips that did not complete the weight-bearing limitation were the late diagnosis cases. Among 7 patients who had undergone anti-osteoporosis therapy, one patient was treated monthly with minodronic acid and the others were treated by active vitamin D3. Fifteen (14 patients) of 44 hips required THA. The mean period from the diagnosis of SIF to THA was 10.5 months (2–54 months). Ten hips (9 patients) had hip dysplasia (CE < 20 degrees).

| Table 1 Patient demographics |
|-------------------------------|
| 41 patients, 44 hips |
| Age, years | 61.6 (2.3) |
| Sex, male: female | 8: 33 |
| Body mass index, kg/m² | 25.5 (0.8) |
| Period from onset to first visit, months | 2.2 (0.4) |
| Follow-up period, months | 26.6 (2.3) |
| Glucocorticoid use, cases | 9 |
| Alcohol abuse, cases | 6 |
| Anti-osteoporosis therapy, cases | 7 |
| Weight-bearing limitation, hips | 18 |
| Total hip arthroplasty, hips | 15 |
| Data are represented as the mean (standard error of the mean). |

The JSW in the ipsilateral side showed a significant decrease from the first visit to the final follow-up (P < 0.001) (Fig. 2). There was no significant difference between the JSW from the first visit to the final follow-up on the contralateral side. The changes in the JSW on the ipsilateral side were associated with the length of the band pattern (β = 0.499, P < 0.001) (Fig. 3A), serum P1NP (Fig. 3B) (β = 0.564, P < 0.001) and TRACP 5b (Fig. 3C) (β = 0.452, P = 0.004). Additionally, the serum P1NP and TRACP 5b trended to be associated with the length of the band pattern (β = 0.376, P = 0.035 and β = 0.268, P = 0.140, respectively) (Fig. 4A and B).

The comparisons of clinical and radiological findings between patients who could complete the weight-bearing limitation therapy (WB limitation) and could not (Non-WB limitation) are summarized in Table 2. WB limitation group showed a younger age, shorter period from pain onset to visit, lower ratio of THA, and smaller changes in JSW than non-WB limitation group.
Table 2
Comparisons between patients who could complete weight-bearing limitation and those who could not

|                                | WB limitation (18 hips) | Non-WB limitation (26 hips) | P value |
|--------------------------------|-------------------------|----------------------------|---------|
| Male: Female                   | 5:13                    | 3:23                       | 0.170   |
| Age, years                     | 53.8 (4.3)              | 67.2 (2.0)                 | 0.003   |
| BMI, kg/m²                     | 26.4 (1.8)              | 25.1 (1.1)                 | 0.525   |
| Period from pain onset to visit, months | 1.1 (0.2) | 2.5 (0.4) | 0.008 |
| Osteoporosis therapy, case (%) | 1 (5.6%)                | 6 (22.2%)                  | 0.118   |
| Total hip arthroplasty, case (%) | 3 (16.7%)          | 12 (46.2%)                 | 0.042   |
| Radiography findings           |                         |                            |         |
| JSW at the first visit, mm     | 4.15 (0.19)             | 4.25 (0.21)                | 0.785   |
| Changes in JSW, mm             | 1.12 (0.36)             | 2.24 (0.36)                | 0.039   |
| Center-edge angle, degree      | 25.9 (1.6)              | 24.2 (1.4)                 | 0.428   |

WB: weight-bearing, BMI: body mass index, JSW: joint space width, AC: acetabulum, Data are represented as the mean (standard error of the mean).

The comparisons of the clinical findings, image evaluation, and bone metabolic markers between patients who received THA (THA group) and who did not receive THA (non-THA group) are summarized in Table 3. The non-THA group was younger (P = 0.028), had a shorter period from pain onset to visit (P = 0.002) and higher ratio of weight-bearing limitation (P = 0.042) than the THA group. No significant differences in JSW and CE angle at the first visit between the two groups were observed. The THA group exhibited a larger change of JSW from the first visit to the final follow-up than the non-THA group (P < 0.001). The THA group exhibited longer band length (P < 0.001), a higher ratio of the existence of band over the edge of AC (P = 0.006), and a larger intensity change of AC (P < 0.001) than the non-THA group. Although no significant differences were observed in BMD between both groups, the THA group exhibited higher P1NP (P = 0.002) and TRACP 5b (P = 0.001) levels than the non-THA group.
|                               | THA (15 hips) | Non-THA (29 hips) | P value |
|-------------------------------|---------------|-------------------|---------|
| Male: Female                  | 3:12          | 5:24              | 0.822   |
| Age, years                    | 69.6 (2.2)    | 57.8 (3.1)        | 0.014   |
| BMI, kg/m²                    | 24.9 (1.5)    | 26.0 (1.4)        | 0.593   |
| Osteoporosis therapy, case (%)| 2 (13.3%)     | 5 (17.2%)         | 0.737   |
| Period from pain onset to diagnosis, months | 3.8 (1.0) | 1.3 (0.2) | 0.002   |
| Weight-bearing limitation, case (%) | 3 (20.0%) | 15 (51.7%) | 0.042   |
| Radiography findings          |               |                   |         |
| JSW at the first visit, mm    | 4.26 (0.28)   | 4.18 (0.18)       | 0.793   |
| Changes in JSW, mm            | 3.79 (0.36)   | 0.75 (0.15)       | < 0.001 |
| Center-edge angle, degree     | 25.3 (1.6)    | 24.7 (1.4)        | 0.786   |
| MRI findings                  |               |                   |         |
| Band length, mm               | 23.3 (1.1)    | 14.2 (0.7)        | < 0.001 |
| Band over the edge of AC, case (%) | 10 (66.7%) | 7 (24.1%) | 0.006   |
| Intensity change of AC, case (%) | 14 (93.3%) | 6 (20.7%) | < 0.001 |
| YAM, %                        |               |                   |         |
| Lumbar                        | 93.9 (4.8)    | 92.6 (3.6)        | 0.824   |
| Femoral neck                  | 80.2 (2.7)    | 82.0 (2.3)        | 0.632   |
| Bone metabolic marker         |               |                   |         |
| P1NP, µg/ml                   | 73.0 (11.1)   | 39.7 (3.7)        | 0.002   |
| TRACP 5b, µU/dL               | 549.7 (40.6)  | 342.4 (38.1)      | 0.001   |

THA: total hip arthroplasty, BMI: body mass index, JSW: joint space width, AC: acetabulum, YAM: young adult mean, P1NP: intact type I procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b. Data are represented as the mean (standard error of the mean).

Univariate analyses identified age, the period from pain onset to visit, MRI findings, and bone metabolic markers as predictors for THA. Furthermore, MRI findings were identified as the potential predictors for THA in a Cox proportional hazard model adjusted for age, sex, anti-osteoporosis therapy and the period from pain onset to visit (Table 4) (Fig. 5).
Table 4
Univariate and multivariate Cox-regression analysis for the predictors of total hip arthroplasty in patients with subchondral insufficient fracture of the femoral head

| Variables                                 | Univariate analysis | Multivariate analysis |
|-------------------------------------------|---------------------|-----------------------|
|                                           | P value  | HR     | 95% CI     | P value | HR     | 95% CI     |
| Sex                                       | 0.493    | 1.56   | 0.438–5.557|          |        |          |
| Age                                       | 0.020    | 1.07   | 1.011–1.129|          |        |          |
| BMI                                       | 0.659    | 0.98   | 0.889–1.077|          |        |          |
| Osteoporosis therapy                      | 0.665    | 0.72   | 0.161–3.208|          |        |          |
| Period from onset to diagnosis            | 0.021    | 1.28   | 1.038–1.578|          |        |          |
| Weight-bearing limitation                 | 0.107    | 0.35   | 0.099–1.251| 0.581   | 0.66   | 0.151–2.888|
| MRI findings                              |          |        |            |          |        |          |
| Band length                               | < 0.001  | 1.30   | 1.152–1.455| 0.001   | 1.34   | 1.130–1.590|
| Band over the edge of AC                  | 0.014    | 3.87   | 1.317–11.375| 0.027  | 4.08   | 1.172–14.223|
| Intensity change of AC                    | 0.001    | 28.85  | 3.677–226.286| 0.004  | 23.85  | 2.684–211.877|
| Bone metabolic marker                     |          |        |            |          |        |          |
| P1NP, μg/ml                               | 0.018    | 1.013  | 1.002–1.024| 0.098   | 1.01   | 0.998–1.024|
| TRACP 5b, mU/dL                           | 0.007    | 1.005  | 1.001–1.008| 0.116   | 1.00   | 0.999–1.007|

Multivariate analyses were adjusted for age, sex, anti-osteoporosis therapy and period from pain onset. HR: hazard ratio, CI: confidence interval, BMI: body mass index, AC: acetabulum, P1NP: intact type 1 procollagen-N-propeptide, TRACP 5b: tartrate-resistant acid phosphatase 5b.

Discussion

This present study exhibited that JSW decreased significantly from the first visit to the final-follow up and approximately one-third of patients progressed to THA, suggesting that SIF could cause hip OA.

Since some cases of SIF resolved by weight-bearing limitation [2, 27, 28], nonoperative treatment would be the first choice in all patients. Although the multivariate Cox-regression analysis in this study showed that weight-bearing limitation could not prevent THA, it could reduce the progression of joint space narrowing. Additionally, considering that age and the period from pain onset to visit were significantly different between the WB and non-WB limitation groups, the association with THA, early detection and treatment are important for SIF. There might be some cases such as older patients with a lack of vision or low balance activity that have the necessity of treatment on not an outpatient basis, but an inpatient basis.

The findings of this study showed that bone metabolic markers and the length of band patterns were associated with the changes in JSW, suggesting that these parameters could be the predictors of poor progression in patients with SIF. The MRI findings of this study were consistent with those of previous reports regarding the association of clinical outcome and MRI [16, 25], suggesting that MRI findings,
including the length of band pattern and location of intensity change at the time of diagnosis, could be a prognostic predictor as well as a highly sensitive investigation for SIF. In addition, serum P1NP and TRACP-5b were associated with joint space narrowing, suggesting that the levels of bone metabolic markers might be predictors for OA among the patients with SIF. Considering that serum P1NP and TRACP-5b trended to be associated with the length of band pattern, bone metabolic markers might reflect the local severity.

While numerous groups reported the occurrence of SIF in patients with osteoporosis [1, 2, 6, 7], the current study showed that mean BMD did not fulfill the diagnostic criteria for osteoporosis. On the other hand, in some reports on young adults and adolescents, the activity levels did not correspond to a high occurrence of SIF [12, 29]. Therefore, the mechanisms of occurrence and joint space narrowing associated with osteoporosis in patients with SIF are still unclear. Contrary to findings in previous reports, the mean CE angle observed in this study did not fulfill the criteria for a dysplastic hip (CE < 20 degrees) [20]. In addition, the CE angle in the current study was not associated with the changes in JSW and clinical outcomes. A recent study reported that SIF with precollapse was associated with bony deformities and lateral labral tears [30]. Therefore, the instability of the hip joint induced by abnormal morphology such as dysplasia and femoroacetabular impingement might affect the occurrence and prognosis of SIF. Although the current study did not obtain radial MRI and investigate AC labral tears, future studies should address the association between labral tears and the prognosis of SIF.

There are some limitations to this study. First is the timing of the occurrence of SIF. Since SIF usually occurs without a history of trauma, it is hard to clarify the accurate timing of occurrence. The second is the method of JSW measurement. This study investigated the JSW following the technique shown in Fig. 1A and we believed that this method was highly reproducible. However, future studies should address the JSW measurement via computer-based radiographic quantification. The third is the short follow-up duration (mean 25.4 months) of JSW. Future studies are warranted to verify whether these prognostic predictors are related to the changes in JSW in longer follow-up periods.

Conclusion
In conclusion, SIF could cause joint space narrowing and hip OA. In addition to MRI findings as prognostic predictors of SIF, as previously described, bone metabolic markers were also associated with the changes in JSW, suggesting that these parameters could be useful to predict the prognosis of SIF. Considering that bone metabolic markers trended to be associated with the length of band pattern, they might reflect the local severity.

**Abbreviations**

AC: acetabular, AP: anteroposterior, BMD: bone mineral density, BMI: body mass index, CE: center-edge, JSW: joint space width, MRI: magnetic resonance imaging, OA: osteoarthritis, ONFH: osteonecrosis of the femoral head, PACS: picture archiving and communication system, P1NP: type 1 procollagen-N-propeptide, SIF: subchondral insufficiency fracture of the femoral head, THA: total hip arthroplasty, TRACP-5b: tartrate-resistant acid phosphatase 5b

**Declarations**

*Ethics approval and consent to participate*

The Institutional Review Board for Human Research approved this study design (# 015-0206).

*Consent for publication*

Not applicable.

*Availability of data and material*

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

*Competing interests*

The authors declare that they have no competing interests.

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*Authors' contributions*

TS and YS equally contributed to data collection, performed the analysis, interpreted the results and wrote the manuscript. YK, TA, HS and HI contributed to data collection, interpretation of the result,
and technical coordination. NI contributed to the design of the study and review the manuscript. TD contributed to the design of the study, interpretation of the result, and review the manuscript. Approval of the final version of the manuscript was obtained from all coauthors.

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Figures
Radiological evaluation. (A) The radiographic indices used for the evaluation of the hip are shown. O = center of the femoral head; Line A = line between the teardrops on both sides; Circle A = circle passing through three points set arbitrarily in the acetabular joint surface; Circle B = circle passing through three points set arbitrarily in the femoral head. (B) T1-weighted MRI image showing the method used to measure the length of the low-intensity band. CE: center-edge.
Figure 2

Comparisons of joint space width. Mean joint space width and change of joint space width from the first visit to the final follow-up in the ipsilateral and contralateral sides. Ipsi: ipsilateral, Contra: contralateral, and JSW: joint space width. Asterisks indicate $P < 0.05$. 
Figure 3

Association with the changes in joint space width. Scatter plot of changes in joint space width versus (A) length of band pattern, (B) type 1 procollagen-N-propeptide and (C) tartrate-resistant acid phosphatase 5b. P1NP: type 1 procollagen-N-propeptide, and TRACP 5b: tartrate-resistant acid phosphatase 5b.

Figure 4

Association between the length of band pattern and bone metabolic markers. Scatter plot of the length of band pattern versus (A) type 1 procollagen-N-propeptide and (B) tartrate-resistant acid phosphatase 5b. P1NP: type 1 procollagen-N-propeptide, and TRACP 5b: tartrate-resistant acid phosphatase 5b.
Figure 5

Kaplan–Meier curves for the requirement of total hip arthroplasty. Kaplan–Meier curves for the requirement of THA between (A) patients with and without intensity changes in the acetabulum, and (B) patients in whom the band pattern was over and under the edge of the acetabulum. AC: acetabulum; and HR: hazard ratio.