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ORIGINAL ARTICLE

# Osteonecrosis of the femoral head in SARS patients: seven years later

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**Abstract** This study is aimed to explore the progression of osteonecrosis of the femoral head (OFNH) in severe acute respiratory syndrome patients 7 years after steroid administration and to analyze factors affecting the prognosis. One-hundred and ninety hips in 117 patients with more than 7 years of follow-up were studied. The prevalence of progression to symptoms and collapse was determined. The total dose of steroid, gender, age, stage, lesion location, volume of necrosis, viable lateral column and bone marrow edema were analyzed and correlated with progression. During the 7 years of follow-up, 66 hips progressed to symptoms, 50 hips collapsed and 10 hips showed complete regression. Fifty-seven hips (86.36 %) caused pain and 32 (64.00 %) collapsed within 3 years of steroid administration. The lesion was relatively larger, and there was relatively less viable lateral column in hips that exhibited symptoms or collapsed. Mechanical failure of the necrotic segment of bone principally occurred within 3 years after the administration of steroids. Larger lesions and less viable lateral column were the main risk factors for progression. Small ONFH lesions seldom collapsed.

**Keywords** Osteonecrosis · Hip · Pain · Steroid · SARS · Prognosis

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## Background

Severe acute respiratory syndrome (SARS) first emerged in southern China during the last quarter of 2002. In the early spring of 2003, the epidemic reached Beijing and many patients were given high doses of steroids [1, 2]. From June 2003 to January 2004, osteonecrosis of the femoral head (ONFH) was diagnosed in 211 hips in 127 medical staff who contracted with SARS while rescuing patients. All of these medical staff were healthy person before they contracted SARS. Follow-up was approved by ethics committee and organized by the Beijing Municipal Government. The patients were followed up every 6 months for the first 2 years and then annually. They could also ask for examination at any time if they experienced discomfort. Until the latest follow-up performed in October 2011, there were more than 7 years after they were diagnosed with this intractable disease. The results of 7 years follow-up can gave us valuable information about the prognosis of ONFH and factors which affected it, especially in these special population.

## Patients and methods

### Patients

The ethics committee of our hospital approved the study, and all patients provided written informed consent. From June 2003 to January 2004, 127 patients (211 hips) developed osteonecrosis of the femoral head (ONFH). These patients were followed up every 6 months for the first 2 years and then annually. MRI, CT, radiography or all three examinations were performed as required. The patients also could ask for an examination at any time if

they experienced discomfort. The end-point was the collapse of the femoral head as shown by plain radiography or CT. Hips that did not collapse required follow-up for more than 7 years. Eleven hips in eight patients were excluded from the study because they underwent surgery and had no symptoms. Ten hips in six patients were lost to follow-up. One-hundred and ninety hips in 117 patients were studied. The mean patient age was 32.10 ± 9.03 years (range 19–59 years). There were 39 men (61 hips) with a mean age 31.94 ± 9.49 years and 78 women (129 hips) with a mean age 32.18 ± 8.85 years, $p = 0.897$. The total dose of prednisolone-equivalent steroid was 4,903.62 ± 3,092.15 mg (range 800–16,600 mg), 5,248.20 ± 3,323.55 mg in men and 4,731.32 ± 2,977.02 mg in women ($p = 0.396$). Ninety-two right hips were affected and 98 left hips. The mean time from the administration of corticosteroid to diagnosis of ONFH was 6.26 ± 1.71 months (range 2.2–10.0 months). According to the international Association Research Circulation Osseous (ARCO) classification, 168 hips were at stage I and 22 hips at stage II at the first follow-up visit.

## MRI protocol

MRI was performed using a Signa Excite 1.5 T imager (GE Medical Systems, Milwaukee WI, USA) with at least two protocols: coronal T1-weighted imaging and coronal short time inversion recovery (STIR). Coronal T1-weighted sequences (TR 400 ms/TE 8.6 ms/Ef) used a pelvic phased-array coil. Images of 3-mm thickness with a 0.3-mm gap and 34 × 34 cm field of view were obtained using a 256 × 192 matrix and four excitations. Coronal STIR images were obtained with TR 2,560 ms and TE 108 ms.

ONFH was defined as the presence of a crescent-shaped area of subchondral bone marrow with high or partially high signal intensity circumscribed by a low-signal-intensity rim on T1-weighted images. The rim of low signal intensity had to completely circumscribe the marrow and show increased signal intensity on the corresponding STIR images [1]. Bone marrow edema (BME) was considered to be an ill-defined area of low signal intensity on T1-weighted images with a corresponding high signal intensity on STIR images that involved the femoral head and neck beyond the necrotic zone and extended to the intertrochanteric regions [3].

According to Sugano et al. [4], necrotic lesions are classified into four types, based on their location on coronal midsection T1-weighted images: type A lesions occupy the medial one-third or less of the weight-bearing portion; type B lesions occupy the medial two-thirds or less of the weight-bearing portion; type C1 lesions occupy more than the medial two-thirds of the weight-bearing portion but do not extend laterally to the acetabular edge; and type C2 lesions occupy more than the medial two-thirds of the weight-bearing portion and extend laterally to the acetabular edge.

The volume of the osteonecrosis was measured on T1-weighted images. For each coronal slice, the area of necrosis was outlined using an image analysis program (Leica QWIN, Germany) and the volume calculated by multiplying the area of necrosis by the thickness of the slice plus the gap. The total volume of necrotic bone was the sum of the individual volumes for each slice [1, 5].

The arc of the lateral viable portion of the femoral head on coronal T1-weighted images was measured on six central slices. The extent of viable lateral column (VLC) was defined by the formula $VLC = (A_1/180 + \ldots + A_6/180)/6 \times 100$ (Fig. 1) and classified into four groups: group a, VLC ≤ 25 %; group b, VLC > 25 to ≤50 %; group c, VLC > 50 to ≤75 %; and group d, VLC > 75 %.

## Treatments

Thirty-eight symptomatic hips that had not collapsed were treated with impacted bone graft through a femoral neck window.

## Statistical analysis

Differences between age, total steroid dose, volume of necrosis, modified necrotic index and VLC were examined using nonparametric tests. Pearson's chi-square test or Fisher's exact test was used to correlate pain or collapse

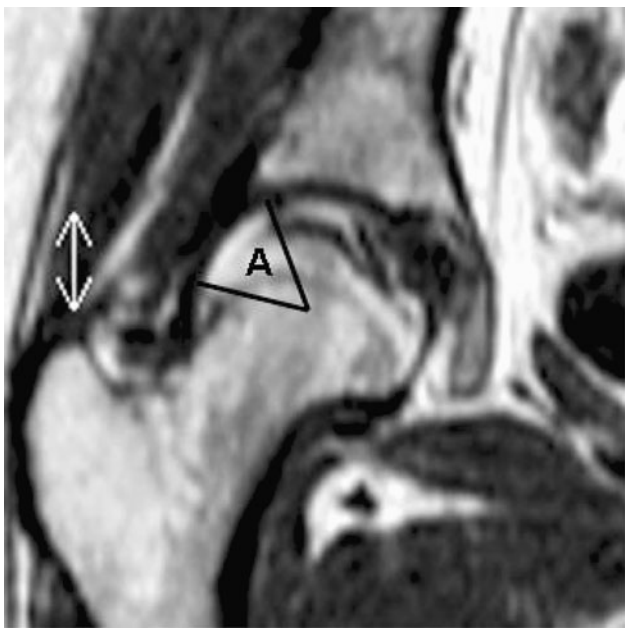


**Fig. 1** Measurement of viable lateral column. *A* is the angle between the viable lateral column (from the head–neck junction to lateral margin of necrosis) on a coronal image

with gender, side, stage and location of necrosis. For all tests, $p < 0.05$ was considered to be significant. Statistical analysis was conducted using the Statistical Package for the Social Sciences software version 13.0 (SPSS, Chicago, IL, USA).

## Results

### Progression of ARCO stage

By January 2011, 50 hips had collapsed. Twenty-three hips collapsed after head-preserving surgery. Signs of necrosis disappeared in 10 hips over the seven years of follow-up, these hips having progressed through stage I and stage II to stage 0 (Fig. 2). The progression of ARCO stage is illustrated in Table 1.

### Time of onset of pain

Sixty-six hips (34.74 %) developed pain during the 7 years of follow-up. The mean interval from steroid administration to onset of pain was 18.39 ± 17.73 months (range 2–73 months). Thirty-three hips (50.00 %) developed pain within 12 months of steroid administration, 18 (27.27 %) within 12–24 months and six (9.09 %) within 24–36 months; only nine hips (13.64 %) developed pain more than 36 months after steroid administration. Four hips were in ARCO stage I, 54 in stage II and eight in stage III when the pain began.

### Risk factors for pain

Gender, total steroid dose and side affected were not associated with the development of pain. Patients with larger ONFH lesions and less VLC were most likely to complain of pain. ONFH with bone marrow edema (BME) or collapse was significantly associated with pain (Table 2).

### Time of collapse

Fifty hips collapsed during the 7 years of follow-up, including 32 hips (64.00 %) during the first three years. The mean time from steroid administration to collapse was 37.27 ± 22.11 months (range 5–90 months); the duration from the onset of pain to collapse was 16.03 ± 15.61 months (range 0–59 months).

### Risk factors for collapse

Age, gender, total steroid dose, side affected and the initial stage were not associated with collapse. Hips with larger lesions or less VLC were most likely to collapse. ONFH

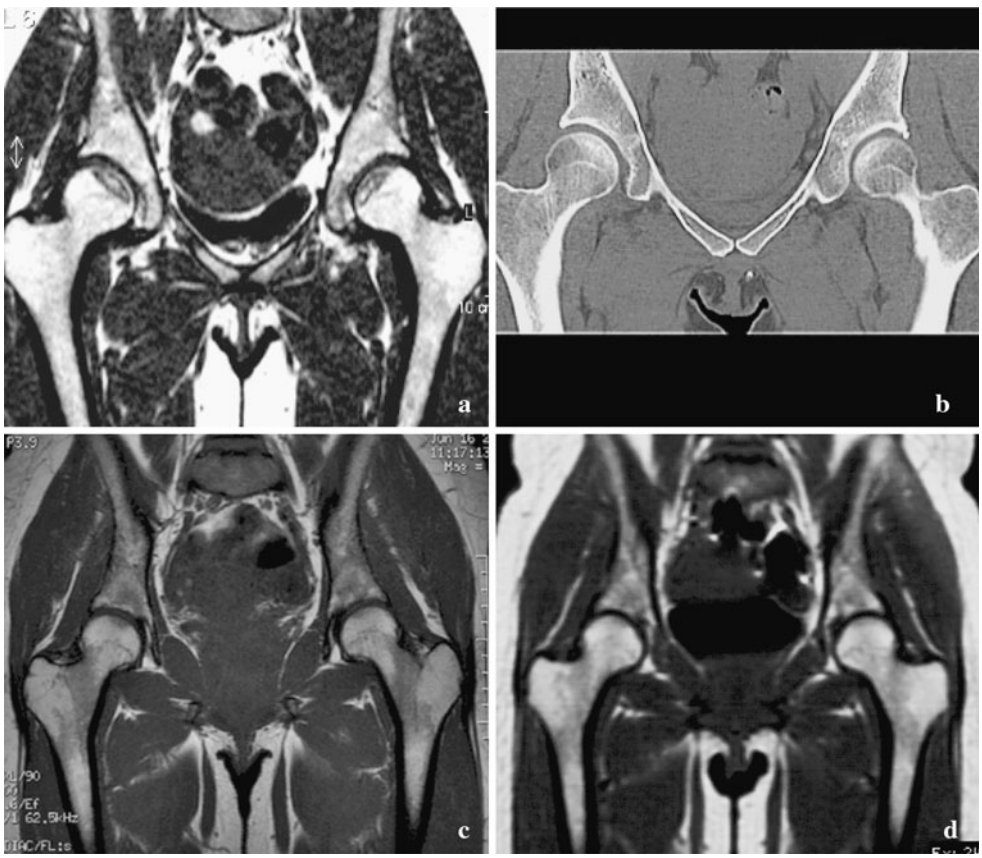


**Fig. 2** Complete regression of a necrotic lesion. **a** Coronal T1-weighted MRI shows typical bilateral necrosis of the femoral head. **b** Coronal CT that performed two years later shows that the osteonecrosis has progressed to ARCO stage II. **c** Corresponding coronal T1-weighted MRI obtained in June 2006, showing marked reduction in lesion size. **d** Corresponding coronal T1-weighted MRI obtained in 2009, showing complete regression

**Table 1** Progression of the ARCO stage

| Initial stage | Surgery | Final stage | | | |
|---|---|---|---|---|---|
| | | 0 | I | II | III |
| I | Yes | | | 11 | 21 |
| | No | 10 | 1 | 105 | 21 |
| II | Yes | | | 4 | 2 |
| | No | | | 10 | 6 |

**Table 2** Comparison between hips that remained painless for more than 7 years and hips that became symptomatic

| Variable | Pain ($N = 66$) | Painless ($N = 124$) | $p$ |
|---|---|---|---|
| Age (years) | 30.09 ± 7.88 | 34.35 ± 9.92 | 0.001 |
| Male/female | 22/44 | 39/85 | 0.791 |
| Total steroid dose (mg) | 5136.59 ± 2819.50 | 4846.22 ± 3164.10 | 0.533 |
| Side affected (R/L) | 36/30 | 62/62 | 0.551 |
| Initial ARCO stage (I/II) | 54/12 | 114/10 | 0.038 |
| Location (A/B/C1/C2) | 2/5/27/32 | 39/38/39/8 | 0.000 |
| Volume of necrosis, range ($mm^3$) | 19.30 ± 6.41, 0.39–39.22 | 9.74 ± 6.69, 5.47–41.62 | 0.000 |
| VLC, range (%) | 15.9669 ± 14.69, 1.04–100 | 40.45 ± 25.72, 0.67–72.87 | 0.000 |
| VLC (a/b/c/d) | 56/7/3/0 | 41/49/17/17 | 0.000 |
| Edema (Y/N) | 49/17 | 0/124 | 0.000 |
| Collapse (Y/N) | 50/16 | 0/124 | 0.000 |

with pain or bone marrow edema was significantly associated with collapse (Table 3).

In 66 symptomatic hips, the lesion in the collapsed hip was larger than that in the hip that had not collapsed. The VLC in the collapsed hip was less than that in the uncollapsed hip (Table 4).

In 38 hips treated with a head-preserving procedure, hips with larger lesions or less VLC were most likely to collapse. ONFH with bone marrow edema (BME) was significantly associated with collapse (Table 5).

**Table 3** Comparison between hips that collapsed and those that did not

| Variable | Collapsed ($N = 50$) | Uncollapsed ($N = 140$) | $p$ |
|---|---|---|---|
| Age (years) | 31.24 ± 8.39 | 33.45 ± 9.77 | 0.157 |
| Male/female | 17/33 | 44/96 | 0.738 |
| Total steroid dose (mg) | 5498.70 ± 3026.89 | 4750.08 ± 3037.16 | 0.136 |
| Side affected (R/L) | 27/23 | 71/69 | 0.690 |
| Initial ARCO stage (I/II) | 42/8 | 126/14 | 0.255 |
| Location (A/B/C1/C2) | 0/1/17/32 | 41/42/49/8 | 0.000 |
| Surgery (Y/N) | 23/27 | 15/125 | 0.000 |
| Pain (Y/N) | 50/0 | 16/124 | 0.000 |
| Edema (Y/N) | 49/1 | 0/140 | 0.000 |
| Volume of necrosis, range ($mm^3$) | 21.38 ± 5.35, 0.39–39.22 | 10.09 ± 6.58, 10.89–41.62 | 0.000 |
| VLC, range (%) | 9.82 ± 5.50 1.04–100 | 39.84 ± 24.95 0.67–24.72 | 0.000 |
| VLC (a/b/c/d) | 50/0/0/0 | 47/56/20/17 | 0.000 |

**Table 4** Comparison between hips that collapsed and those that had not collapsed in symptomatic hips

| Variable | Collapsed ($N = 50$) | Uncollapsed ($N = 16$) | $p$ |
|---|---|---|---|
| Age (years) | 31.24 ± 8.39 | 26.50 ± 4.41 | 0.035 |
| Male/female | 17/33 | 5/11 | 0.839 |
| Total steroid dose (mg) | 5498.70 ± 3026.89 | 4005.00 ± 1647.97 | 0.065 |
| Side (R/L) | 27/23 | 9/7 | 0.875 |
| Initial ARCO stage (I/II) | 42/8 | 12/4 | 0.417 |
| Location (A/B/C1/C2) | 0/1/17/32 | 2/4/10/0 | 0.000 |
| Operation (Y/N) | 23/27 | 15/1 | 0.001 |
| Edema (Y/N) | 49/1 | 0/16 | 0.000 |
| Volume of necrosis ($mm^3$) | 21.38 ± 5.35 | 12.83 ± 5.04 | 0.000 |
| VLC (%) | 9.82 ± 5.50 | 35.13 ± 17.85 | 0.000 |
| VLC (a/b/c/d) | 50/0/0/0 | 6/7/3/0 | 0.000 |

## Discussion

The administration of steroids is a major cause of ONFH [6–10]. Knowledge of the natural history of osteonecrosis associated with steroid is very meaningful. Many studies have focused on the prognosis of this intractable disease. In the pre-MRI era, ONFH was diagnosed by CT or radiography only when the patient presented with discomfort [11, 12]. It has been difficult to determine the complete natural history of ONFH, as most symptomatic hips have collapsed or will collapse soon [13]. With the advent of MRI, it became possible to make an early diagnosis of osteonecrosis and particularly to detect asymptomatic ONFH lesions. Most asymptomatic lesions are not apparent

**Table 5** Results for 38 symptomatic hips treated with head-preserving surgery

| Variable | Collapsed ($N = 23$) | Uncollapsed ($N = 15$) | $p$ |
|---|---|---|---|
| Age (years) | 32.13 ± 6.75 | 26.60 ± 4.55 | 0.009 |
| Male/female | 4/19 | 4/11 | 0.687 |
| Total steroid dose (mg) | 5014.78 ± 2314.16 | 3905.33 ± 1655.15 | 0.117 |
| Side (R/L) | 15/8 | 9/6 | 0.744 |
| Initial ARCO stage (I/II) | 21/2 | 11/4 | 0.188 |
| Location (A/B/C1/C2) | 0/0/10/13 | 2/3/10/0 | 0.001 |
| Edema (Y/N) | 23/0 | 0/15 | 0.000 |
| Volume of necrosis ($mm^3$) | 20.30 ± 4.01 | 13.08 ± 5.11 | 0.000 |
| VLC (%) | 10.21 ± 5.65 | 32.62 ± 15.25 | 0.000 |
| VLC(a/b/c/d) | 23/0/0/0 | 6/9/0/0 | 0.000 |

on radiographs. Many researchers have used MRI to explore the natural history of ONFH by focusing on the asymptomatic side in patients with confirmed osteonecrosis, but these studies have shortcomings [1, 14]. Firstly, the contralateral hip may not progress in the same manner as the symptomatic side; for example, weight-bearing and/or pain onset after diagnosis may differ. Secondly, the progression of the asymptomatic side cannot represent the natural history of ONFH, because the time between necrosis and onset of pain is different to that on the symptomatic side. Thirdly, most of the patients in these studies had an underlying disease, such as systemic lupus erythematosus, sickle cell disease or rheumatoid arthritis, and these may have effects on hip pain.

Compared with previous research, our study has some advantages. All of the patients had the same primary disease SARS, and the patients were generally healthy before developing SARS and were not receiving corticosteroids. Thirdly, osteonecrosis was detected relatively early. The mean time between the administration of corticosteroid and diagnosis of ONFH was 6.26 ± 1.71 months (range 2.2–10.0 months); 88.42 % of hips were at ARCO stage I and 11.58 % at stage II. Fourth, the duration of follow-up was relatively similar between the patients. With these advantages, an analysis of the follow-up of SARS patients treated with steroids can provide valuable information regarding the natural history of osteonecrosis of the femoral head.

Firstly, in agreement with previous studies, the extent of the necrotic lesion was an important determinant of prognosis. The volume and surface area of necrosis have been shown to be larger in symptomatic or collapsed hips [1, 6–10, 14–18]. According to the classification of Sugano, 2/41 hips with type A disease, 5/43 hips with type B, 27/66 hips with type C1 and 32/40 hips with type C2 complained of pain. Furthermore, 0/41 type A, 1/43 type B, 17/66 type C1 and 32/40 type C2 diseased hips collapsed. In 38 hips treated with head-preserving surgery (impacted bone graft through a femoral neck window), 0/2 type A, 0/3 type B, 10/20 type C1 and 13/13 type C2 diseased hips collapsed. Most femoral heads with large necrotic areas will collapse, even when treated with head-preserving procedures. Gender, total steroid dose, side affected and initial stage were not correlated with pain or subsequent collapse.

Secondly, the follow-up of SARS patients and previous studies show that, at all sites, osteonecrosis develops within 6 months of steroid administration, especially within 2–3 months, even in patients on long-term glucocorticoid therapy [13, 19]. The time of steroid administration can serve as a beginning point to observe the natural history of ONFH induced by steroid. In our study, the mean interval from steroid administration to onset of pain was 18.39 ± 17.73 months, 86.36 % of patients with ONFH complained of pain within three years of steroid administration; only 13.64 % complained of pain after more than three years. Of hips that collapsed, the mean time from steroid administration to collapse was 37.27 ± 22.11 months, 64.00 % did so within 3 years of steroid administration. In a retrospective study, the median incubation period (time interval between the commencement of steroid therapy and the onset of pain) was 18 months [20]. Pain onset is often the consequence of mechanical failure and can frequently be combined with bone marrow edema [21]. This irreversible change predicts a poor outcome, even when the radiological abnormalities are minimal. In this study, 75.76 % of symptomatic hips progressed to collapse, especially those with bone marrow edema (100 %). The results showed that the period 3 years after the initial administration of steroids was the main period during which mechanical failure of the necrotic segment occurred.

Thirdly, it was previously believed that the size of necrotic lesions remained unchanged over time [16, 17, 22]. Theoretically, this was illogical. A few days or weeks after the death of all cell types in the bone and marrow, vascular connective tissue (granulation tissue) develops at the interface between viable bone and necrotic bone; this is a physiological response that contains the lesion and promotes healing. Our follow-up of these SARS patients showed that repair is a slow, discontinuous and time-dependent process, and the results have been published [1]. When neovascularization is inadequate, and bone remodeling is limited and ill-adapted to local constraints, stress fracture occurs, causing incapacitating pain and irreversible epiphyseal deformity. Collapse is not only correlated with lesion size, but also with repair capacity. There are three

types of repair: limited, reconstructive and destructive [23]. Depending on the type of repair, necrotic femoral heads with lesions of similar size can collapse at different times. In the present study, the shortest time between steroid administration and collapse was 5 months and the longest was 90 months; the shortest and longest times to onset of pain were 2 and 73 months, respectively. Repair capacity plays an important role in the time between pain onset and collapse and should be considered when we try to preserve the necrotic head. Methods that can promote repair capacity, such as concentrated autologous bone marrow mononuclear cells and growth factor, should be studied to improve the results of head-preserving procedures [24, 25]. The relationship between the incubation period (time interval between the commencement of steroid therapy and the onset of pain) and repair capacity, as well as the outcomes of head-preserving procedures, should be further investigated.

Fourthly, in 40 patients with a small, asymptomatic osteonecrotic lesion (<10 % of the femoral head) was in one hip and symptomatic disease in the contralateral hip. Hernigou et al. [26] found progression to symptomatic disease in 88 % of hips, with collapse occurring in 73 %, at a mean of 92 months (range 72–140 months) after diagnosis. On the basis of these findings, the authors recommended prophylactic joint-preserving surgical treatment of asymptomatic hips, regardless of lesion size or location. Our findings differed from this. According to Sugano's classification, 0/40 hips with small lesions and 1/43 hips with medium-sized lesions collapsed during the 7 years of follow-up. Of hips with VLC > 25 %, 0/93 collapsed. Ten hips with small lesions showed complete regression. The results of our study suggest that nonoperative treatment may be suitable for small and/or medially located lesions.

**Conflict of interest** We did not receive any benefits directly or indirectly from commercial parties.

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