Lesion size changes in osteonecrosis of the femoral head: a long-term prospective study using MRI

Feng-chao Zhao · Zi-rong Li · Nian-fei Zhang ·
Bai-liang Wang · Wei Sun · Li-ming Cheng ·
Zhao-hui Liu

Received: 20 April 2009 / Revised: 1 June 2009 / Accepted: 1 June 2009 / Published online: 17 June 2009
© Springer-Verlag 2009

Abstract Osteonecrosis of the femoral head (ONFH) is one of the intractable diseases. It is controversial whether the lesion size assessed by magnetic resonance imaging (MRI) can change over time without any operative treatment. In this study, we used MRI to observe the lesion size changes of ONFH induced by corticosteroid administration in severe acute respiratory syndrome (SARS) patients. The study included 51 SARS patients (84 hips) with early-stage ONFH who did not receive any operative treatment and were diagnosed by MRI. All of the patients underwent MRI follow-ups. Each patient was evaluated on the basis of the lesion volume on MRI at every follow-up for further comparisons. At the first MRI scan, the mean lesion volume was $10.12 \pm 8.05 \text{ cm}^3$ (range: 0.39–41.62 cm^3). At the mid-term follow-up (2.5 years), the mean lesion volume was $7.82 \pm 7.59 \text{ cm}^3$ (range: 0.11–39.65 cm^3). At the final follow-up (five years), complete regression of the lesion was observed in six hips, and the mean lesion volume was $5.67 \pm 6.58 \text{ cm}^3$ (range: 0.00–31.47 cm^3). Overall, the lesion volume was reduced by >15% in 80 hips, and only four hips with relatively larger lesion volumes showed no apparent reductions. The reduction in lesion size of ONFH observed on MRI is a slow, discontinuous and time-dependent process.

Introduction

Osteonecrosis of the femoral head (ONFH) is one of the intractable diseases that usually affect young people. Most studies have shown that the prognosis of ONFH and the outcomes of surgical treatments are associated with the lesion size [1–8]. Hence, it is very significant to establish whether the lesion size of ONFH can change over time. However, this issue currently remains controversial. Although several reports have demonstrated that it is impossible for the lesion size to change by magnetic resonance imaging (MRI) evaluation during development of the disease without any operative treatments [3, 4, 8, 9], other studies have shown that reductions, and even complete resolution, or increments in the necrotic area can occur over several years [10–15].

The lesion size changes in some of the above-described studies have been evaluated in relatively few coronal or sagittal planes. To our knowledge, MR images of lesions are affected by the hip position during the MRI scan and are also influenced by different parameters such as slice thickness and interslice gap, thereby leading to possible mismatching of the slice planes among image sets and causing inaccuracies in the lesion size changes. Therefore, it is advisable to use volume measurements for evaluating lesion size changes owing to their precision [11].

Severe acute respiratory syndrome (SARS) is a relatively newly described infectious disease caused by the SARS coronavirus (SARS-CoV), which principally damages the cells of the immune system and pulmonary epithelium [16, 17]. Treatment with a steroid is required [18, 19]. For early detection of ONFH and further treatment, 426 SARS patients who had been treated with a corticosteroid between March and May 2003 and were mostly medical staff were screened between July 2003 and January 2004. A total of

F.-c. Zhao · Z.-r. Li (✉) · N.-f. Zhang · B.-l. Wang · W. Sun ·
L.-m. Cheng · Z.-h. Liu
Osteonecrosis and Joint-Preserving and Reconstruction Center,
Department of Orthopaedic Surgery,
China-Japan Friendship Hospital,
Beijing 100029, People's Republic of China
e-mail: zhjianzh@sina.com.cn

87 patients with ONFH were diagnosed by MRI. These patients were detected at an early stage and followed up regularly at similar time intervals to provide the opportunity to study the lesion size changes by MRI.

Materials and methods

Patients

The Ethics Committee of our hospital approved the study, and all patients provided written informed consent. From March to May 2003, 426 medical staff contracted SARS and were treated with a corticosteroid. From September 2003 to January 2004, all the medical staff were screened by MRI and radiography organised by the Beijing Municipal Government, and 87 patients with ONFH were diagnosed by MRI. Subsequently, the patients with ONFH were followed annually and the latest follow-ups were carried out from October to November 2008. All of the patients underwent more than three MRI scans. Patients followed by MRI in both 2006 and 2008 and without surgical intervention were included in this study. A total of 33 patients (56 hips) who subsequently underwent surgery for discomfort during the course of the disease were excluded. Finally, 84 hips in 51 patients without smoking or alcohol abuse were included. The final patients comprised 17 men and 34 women with a mean age of 33.84 ± 9.15 years (range: 20–54 years). All 51 patients with ONFH were at the pre-collapse stage and without joint pain at the first MRI scan. According to the Association Research Circulation Osseous (ARCO) international staging system proposed in 1993 [20], 78 hips were at stage I and six hips were at stage II. The mean time from administration of the corticosteroid to the diagnosis of ONFH was 6.05 ± 1.64 months (range: 2.3–9.0 months). The mean time interval between the baseline and the latest MRI scan was 60.19 ± 1.71 months (range: 57–63.2 months). The mean time interval from the baseline to the scan in 2006 was 31.29 ± 1.85 months (range: 27.1–34.7 months). The mean time interval between the scans in 2006 and 2008 was 28.88 ± 0.67 months (range: 27.7–30.9 months, $p=0.000$). The mean sum dosage of the prednisolone-equivalent steroid was $4,124.76 \pm 2,277.10$ mg (range: 800–11,000 mg) and the mean maximum daily dosage of the steroid was 251.76 ± 175.76 mg (range: 80–820 mg).

All of the patients were treated with hyperbaric oxygen therapy after the first examination. The treatment comprised six daily sessions per week up to a total of 100 sessions. A session involved breathing 100% oxygen at 2–2.4 absolute atmospheres in a multiplace pressure chamber for 90 min using a mask breathing system [21]. Intravenous injection of prostaglandin E₁, ligustrazine and *Salvia miltiorrhiza*

was also used for ten daily sessions per month up to a total of 30 sessions. The patients were fully weight-bearing following completion of the treatment.

MRI protocol

MRI was performed with two machines using at least two protocols, i.e. coronal T1-weighted imaging and coronal short τ inversion recovery (STIR). One machine was a Signa Excite 1.5 T Imager (GE Medical Systems, Milwaukee, WI, USA). Coronal STIR images were obtained using repetition time (TR) 2,560 ms and echo time (TE) 108 ms, while coronal T1-weighted sequences (TR 400/TE 8.6/Ef) were obtained using a pelvic phased array coil. Images of 4-mm thickness with 1-mm gaps and a 34×34 -cm field of view were obtained using a 256×192 matrix and four NEX (number of excitations). The other machine was a Signa 0.5 T Imager (GE Medical Systems, Milwaukee, WI, USA). Coronal STIR images (TR 2,500/TE 80) and coronal T1-weighted sequences (TR 340/TE 15) of 5-mm thickness with 2-mm gaps were obtained.

MR image evaluation

ONFH was diagnosed using MRI by experienced radiologists and orthopaedic surgeons. MRI was diagnostic of osteonecrosis if crescentic subchondral areas demarcated by a band or ring of decreased signal intensity on T1-weighted images and increased signal intensity on the corresponding STIR images were observed [10].

Measurement of the volume of osteonecrosis

Measurement of the volume of osteonecrosis was carried out on coronal T1-weighted images. The area of osteonecrosis was considered to be the sector demarcated by the serpiginous line corresponding to the band-like hypointense margin. The outer border of this low-intensity region was assumed to represent the edge of the necrotic area. For each coronal slice, the area of osteonecrosis was outlined using an image analysis program (QWin, Leica, Heidelberg, Germany), and the volume of osteonecrosis was calculated by multiplying the area of osteonecrosis by the thickness (thickness of the slice plus the gap). The total volume of necrotic bone was the sum of the individual volumes of all slices [22].

The percentage changes in the lesion size from the baseline were calculated by dividing the differences in lesion volume between the baseline and the follow-up scans by the baseline lesion volume and multiplying by 100%. ONFH was arbitrarily estimated to be improved or worsened if there was a $>15\%$ change in the necrotic volume, while changes of $\leq 15\%$ were considered to be “no change” [12].

Statistical analysis

The volume difference between each scan was examined using one-way analysis of variance (ANOVA). When the Levene test for homogeneity of variances was significant, the Mann-Whitney U test was used to further check the results. Pearson's chi-square test or Fisher's exact test was performed to analyse the correlations of the lesion size change with time, age, ARCO stage and lesion size. For all tests, values of $p < 0.05$ were considered to be significant. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS) software (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

At the first MRI scan, 78 hips were at stage I and six hips were at stage II. Between April and July 2006, 19 hips were at stage I and 65 hips were at stage II. At the latest follow-up, six hips showed complete regression, ten hips were at stage I, 66 hips were at stage II and two hips had progressed to stage III.

At the first MRI scan, the mean volume of necrosis was $10.12 \pm 8.05 \text{ cm}^3$ (range: $0.39\text{--}41.62 \text{ cm}^3$). In 2006, the mean volume of necrosis was $7.82 \pm 7.59 \text{ cm}^3$ (range: $0.11\text{--}39.65 \text{ cm}^3$). In 2008, six hips showed complete regression, and the mean volume of necrosis was $5.67 \pm 6.58 \text{ cm}^3$ (range: $0.00\text{--}31.47 \text{ cm}^3$). The volume changes between the first MRI scan (V_{baseline}) and V_{2006} and between V_{baseline} and V_{2008} were significant ($p = 0.046$ and $p = 0.000$, respectively; Fig. 1). The volume change between V_{2006} and V_{2008} was not significant ($p = 0.062$; Fig. 1).

According to the arbitrarily defined criteria, four hips did not show a significant reduction in 2008, and their mean lesion size at the first scan of $20.37 \pm 7.41 \text{ cm}^3$ was larger than that of hips that showed a reduction ($p = 0.008$). The

average volume of the six hips that showed complete regression was $2.04 \pm 1.57 \text{ cm}^3$ (range: $0.39\text{--}4.69 \text{ cm}^3$) at the first scan and relatively smaller ($p = 0.000$; Fig. 2).

During the course of the follow-up, six patients complained of hip discomfort, although four of these patients showed lesion reductions. Their mean lesion volume at the first MRI scan was $23.97 \pm 7.71 \text{ cm}^3$ (range: $18.32\text{--}39.22 \text{ cm}^3$) and relatively larger than that of patients without symptoms ($p = 0.000$).

The lesion size changes between two intervals were evaluated. Compared with the baseline scan, 26 hips did not change and 58 hips improved in 2006. Compared with the scan in 2006, 20 hips showed no change and 64 hips improved in 2008 ($p = 0.299$).

Among the 26 hips that showed no change in 2006, six did not change and 20 improved in 2008. Among the 58 hips that improved in 2006, 14 did not change and 44 improved in 2008 ($p = 0.916$).

According to the baseline scans, we classified the hips into two groups, one containing larger lesions with necrotic volumes of $\geq 15 \text{ cm}^3$ and the other containing smaller lesions with necrotic volumes of $< 15 \text{ cm}^3$. In the larger lesion group, three hips showed no change and 15 hips improved, while in the smaller lesion group, one hip did not change and 65 hips improved in 2008 ($p = 0.029$).

Patients were classified into age groups of > 40 years and ≤ 40 years. Overall, two hips showed no change and 21 hips improved in the > 40 years group, while two hips showed no change and 59 hips improved in the ≤ 40 years group in 2008 ($p = 0.301$).

There were 27 hips in the male group and 57 hips in the female group. All of the male hips improved, while four female hips showed no change and 52 female hips improved ($p = 0.308$).

There were six hips at stage II and 78 hips at stage I at the first MRI scan. All of the stage II hips improved in 2008, while four stage I hips showed no change and 74 stage I hips improved ($p = 1.000$).

Fig. 1 Bar chart showing the mean lesion volumes at the three MRI scans ($*p < 0.05$)

Discussion

It is appropriate to establish whether ONFH can spontaneously resolve. Some researchers have reported that the lesion size is unlikely to change during the natural course of the disease [3, 4, 8, 9]. However, other researchers have observed reductions or even complete regression of lesions at the early stage of ONFH over the course of a few years [10, 13, 14]. There are some shortcomings in these studies. One is that the lesion size changes were evaluated on relatively few coronal or sagittal planes, in which the MR images can be influenced by the patient's position and the MRI protocols, and no volume measurements were carried

Fig. 2 Complete regression of a necrotic lesion. **a** Coronal T1-weighted MR image at the first MRI scan. **b** Corresponding STIR image at the first MRI scan. **c** Corresponding coronal T1-weighted MR image to that shown in **a** performed in April 2006, showing a reduction of the lesion size. **d** Corresponding coronal T1-weighted MR image to that shown in **a** performed in October 2008, showing complete regression

out. Another is that the follow-up intervals and the numbers of necrotic femoral heads included in these studies were relatively limited.

Yoshida et al. [12] calculated the necrotic volumes of 24 hips showing early-stage ONFH in 13 patients with systemic lupus erythematosus. They reported that hips with a necrotic volume of <25% showed improvement, while the mean volume of necrosis did not change in type C. Takao et al. [11] observed 31 hips with ONFH in 25 patients and found that lesions detected at less than one year after initial

steroid treatment can show size reductions using image registration as well as volume measurements.

Compared with these studies, there are some advantages in our study. First, ONFH was detected at a relatively early stage. The mean time was 6.05 ± 1.64 months (range: 2.3–9.0 months) from administration of the corticosteroid to the diagnosis of ONFH. Most of our patients were at stage I. Second, the follow-up periods with MRI were relatively similar. The mean interval from the baseline to the latest scan was 60.19 ± 1.71 months (range: 57–63.2 months).

Fig. 3 Non-necrotic femoral head with abnormal band formation. **a** Coronal T1-weighted MR image at the first MRI scan, showing irregular band formation. **b** Corresponding STIR image at the first

MRI scan, showing no abnormal signals. **c** Corresponding coronal T1-weighted MR image to that shown in **a** performed 6 months later, showing no abnormal signals

Third, our patients were generally healthy before suffering the disease and did not receive any further corticosteroid treatment.

The mean lesion volumes of ONFH were $10.12 \pm 8.05 \text{ cm}^3$ at the baseline, $7.82 \pm 7.59 \text{ cm}^3$ in 2006 and $5.67 \pm 6.58 \text{ cm}^3$ in 2008, and the overall decrease was significant. The volume changes between the first MRI scan (V_{baseline}) and V_{2006} and between V_{baseline} and V_{2008} were also significant. Although the volume change between V_{2006} and V_{2008} was not significant, the first interval was a little longer than the second interval. According to our arbitrary standard, nearly all of the lesions showed reductions and some lesions still showed reductions after 2.5 years. Therefore, there was a strong tendency for the reduction in lesion size to be time dependent. Another observed phenomenon was that the reduction was not continuous. Some lesions that showed reductions in 2006 did not reduce in 2008 and vice versa.

The ratio of the lesion size changes was lower in hips with relatively larger lesion sizes compared with hips with relatively smaller lesion sizes. One reason for this finding may be that the interface between the necrotic and normal areas is relatively smaller than the lesion size. Another reason may be that the reparative capability is limited.

There are some diagnostic criteria for ONFH, but it is hard to fulfill these criteria at the early stage (pre-radiological stage) [20, 23, 24]. If the diagnosis of ONFH is made by abnormal signals on MRI, there may be misdiagnoses [25]. During our follow-up study in SARS patients, there was an interesting finding that a few radiologically normal hips showed abnormal signals, such as band formation or decreased signal areas, on T1-weighted images and normal signals on STIR images. On the follow-up MRI, most of these abnormal signals disappeared on T1-weighted images and still showed a normal presentation on STIR images, while a few new cases occurred. We classified these hips into a non-necrotic group (Fig. 3). Since STIR is more sensitive than other protocols for detecting marrow abnormalities [26], we considered that the band or ring-like zones with decreased signal intensity on T1-weighted images and increased signal intensity on the corresponding STIR images could be used as diagnostic criteria for ONFH in the early stage. According to these diagnostic criteria, there were six hips that showed complete regression of their lesions in our study. Their initial volumes were relatively smaller. The intervals to complete resolution were >29 months.

A total of six hips with relatively larger volumes presented discomfort during the course of the disease. Among these hips, two progressed to collapse, while four hips showed lesion reductions. These results coincided with other studies in which larger lesions were found to be more likely to cause aggravation and discomfort, and therefore

early surgical intervention may be justified for these patients [1–12, 27, 28].

There were some biases in our study. One was that the patients who underwent surgical intervention for discomfort were excluded from the study. Another was that all of the patients were treated with hyperbaric oxygen therapy and administration of prostaglandin E_1 , ligustrazine and *Salvia miltiorrhiza*, which were assumed to improve the blood supply and increase bone formation and angiogenesis in necrotic lesions after the first examination [21, 29, 30]. Therefore, our results cannot be considered to reflect the natural history of ONFH. Although a few studies have reported that non-surgical treatment can reduce the lesion size, their proposals are not generally accepted [20]. The purpose of this study was simply to ascertain whether lesion reduction can occur without surgical intervention. Advanced studies are required to investigate the correlations of the lesion size changes with non-operative treatment and collapse.

Acknowledgments This work was supported by the National Natural Science Foundation of China (No. 30672117) and the Key Project of Clinical Medicine of the Public Health Ministry of China.

References

1. Cherian SF, Laorr A, Saleh KJ et al (2003) Quantifying the extent of femoral head involvement in osteonecrosis. *J Bone Joint Surg Am* 85:309–315
2. Shimizu K, Moriya H, Akita T et al (1994) Predication of collapse with magnetic resonance imaging of avascular necrosis of the femoral head. *J Bone Joint Surg Am* 76:215–223
3. Sugano N, Ohzono K, Masuhara K et al (1994) Prognostication of osteonecrosis of the femoral head in patients with systemic lupus erythematosus by magnetic resonance imaging. *Clin Orthop Relat Res* 305:190–199
4. Koo KH, Kim R (1995) Quantifying the extent of osteonecrosis of the femoral head. A new method using MRI. *J Bone Joint Surg Br* 77:875–880
5. Mont MA, Jones LC, Hungerford DS (2006) Nontraumatic osteonecrosis of the femoral head: ten years later. *J Bone Joint Surg Am* 88:1117–1132
6. Petrigliano FA, Lieberman JR (2007) Osteonecrosis of the hip: novel approaches to evaluation and treatment. *Clin Orthop Relat Res* 465:53–62
7. Hungerford DS (2007) Treatment of osteonecrosis of the femoral head: everything's new. *J Arthroplasty* 22(4):91–94
8. Zhao FC, Li ZR, Zhang NF et al (2005) Using the percentage of necrotic surface area to predict collapse of ANFH (in Chinese). *ZhongHua GuKe ZaZhi* 25(9):520–523
9. Aranow C, Zelicof S, Leslie D et al (1997) Clinically occult avascular necrosis of the hip in systemic lupus erythematosus. *J Rheumatol* 24:2318–2322
10. Sakamoto M, Shimizu K, Iida S et al (1997) Osteonecrosis of the femoral head: a prospective study with MRI. *J Bone Joint Surg Br* 79:213–219
11. Takao M, Sugano N, Nishii T et al (2006) Longitudinal quantitative evaluation of lesion size change in femoral head

- osteonecrosis using three-dimensional magnetic resonance imaging and image registration. *J Orthop Res* 24(6):1231–1239
12. Yoshida T, Kanayama Y, Okamura M et al (2002) Long-term observation of avascular necrosis of the femoral head in system lupus erythematosus: an MRI study. *Clin Exp Rheumatol* 20(4):525–530
13. Koperky KK, Braunstein EM, Brandt KD et al (1991) Apparent avascular necrosis of the hip: appearance and spontaneous resolution of MR findings in renal allograft recipients. *Radiology* 179:523–527
14. Cheng EY, Thongtrangan I, Laorr A et al (2004) Spontaneous resolution of osteonecrosis of the femoral head. *J Bone Joint Surg Am* 86:2594–2599
15. Kim YM, Rhyu KH, Lee SH et al (2003) Can osteonecrosis of the femoral head be recurrent? *Clin Orthop Relat Res* 406:123–128
16. Gu J, Korteweg C (2007) Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol* 170:1136–1147
17. Chan MH, Chan PK, Griffith JF et al (2006) Steroid-induced osteonecrosis in severe acute respiratory syndrome: a retrospective analysis of biochemical markers of bone metabolism and corticosteroid therapy. *Pathology* 38:229–235
18. Griffith JF, Antonio GE, Kumta SM et al (2005) Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. *Radiology* 235:168–175
19. Li ZR, Sun W, Qu H et al (2005) Clinical research of correlation between osteonecrosis and steroid (in Chinese). *ZhongHua WaiKe ZaZhi* 43(16):1048–1053
20. Stulberg BN (1997) Editorial comment. *Clin Orthop Relat Res* 334:2–5
21. Reis ND, Schwartz O, Militianu D et al (2003) Hyperbaric oxygen therapy as a treatment for stage-I avascular necrosis of the femoral head. *J Bone Joint Surg Br* 85:371–375
22. Hernigou P, Lambotte JC (2001) Volumetric analysis of the femur. Anatomical correlation using MRI. *J Bone Joint Surg Br* 83:672–675
23. Sternberg ME, Hayken GD, Sternberg DR (1995) A quantitative system for staging avascular necrosis. *J Bone Joint Surg Br* 77:34–41
24. Sugano N, Kubo T, Takaoka K et al (1999) Diagnostic criteria for non-traumatic osteonecrosis of the femoral head. A multicentre study. *J Bone Joint Surg Br* 81:590–595
25. Lafforgue P (2006) Pathophysiology and natural history of avascular necrosis of bone. *Joint Bone Spine* 73:500–507
26. Saini A, Saifuddin A (2004) MRI of osteonecrosis. *Clin Radiol* 59:1079–1093
27. Ito H, Matsuno T, Minami A (2006) Relationship between bone marrow edema and development of symptoms in patients with osteonecrosis of the femoral head. *AJR Am J Roentgenol* 186:1761–1770
28. Hungerford DS, Jones LC (2004) Asymptomatic osteonecrosis: should it be treated? *Clin Orthop Relat Res* 429:124–130
29. Miller SC, Marks SC Jr (1993) Alveolar bone augmentation following the local administration of prostaglandin E1 by controlled-release pellets. *Bone* 14:587–593
30. Ono I, Inoue M, Kuboki Y (1996) Promotion of the osteogenic activity of recombinant human bone morphogenetic protein by prostaglandin E1. *Bone* 19:581–588