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ORIGINAL PAPER

The natural history of asymptomatic osteonecrosis of the femoral head

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Abstract
Purpose To observe the natural history of asymptomatic osteonecrosis of the femoral head, and to analyse the associations between the subsequent development of symptoms, epidemiological risk factors and the character of the lesions.
Methods Sixty-eight patients were diagnosed with asymptomatic osteonecrosis of the femoral head. The patients were classified based on the development of symptoms. Relations were sought between symptom development and epidemiological risk factors, and the size and location of the necrotic lesions.
Results Thirty-eight patients developed symptoms (55.9 %) at a mean 2.27 years after diagnosis. Symptoms developed in 18 of 28 patients with alcohol-related necrosis (64.3 %), in eight of 14 patients with steroid-related necrosis (57.1 %), and in 12 of 26 patients with idiopathic necrosis (46.2 %). None of the following: gender, age, body mass index (BMI), smoking status, or cholesterol level, was found to be significantly associated with the development of symtoms in asymptomatic osteonecrosis of femoral head (ONFH). Duration and amount of exposure to steroid were not significantly associated with symptom development. In the groups of heavy alcohol drinkers, large necrotic lesions and laterally located lesions showed a higher prevalence of symptom development.
Conclusion Symptoms developed in 55.9 % of asymptomatic osteonecrosis of the femoral head. Prevalence of symptom development was significantly higher in heavy alcohol drinkers and large-sized lateral lesions.

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Introduction

An asymptomatic osteonecrosis of femoral head (ONFH) is typically discovered as the contralateral hip of a patient with one symptomatic joint. Treatment of the asymptomatic hip is controversial. While some authors claim a benign natural history, others have reported a rate of femoral head collapse exceeding 50 %.

Symptomatic ONFH generally progresses to joint collapse and the only definite treatment option is total hip arthroplasty [1–3]. However, a variety of joint-preserving operative treatment methods have been introduced because ONFH occurs predominantly in the young, and these treatment options produce promising results when the procedure is implemented before joint deterioration [4–6]. The advent of magnetic resonance imaging (MRI) has facilitated the diagnosis of asymptomatic ONFH; however, the natural history of asymptomatic ONFH is not yet understood. Furthermore, guidelines for the treatment of this condition have not been well defined [5–7].

The purpose of this study was to analyse the asymptomatic osteonecrosis of the femoral head, to evaluate the overall prevalence of progression to symptomatic disease and to determine whether various radiographic and demographic factors influence progression of the disorder.

Methods

Sixty-eight patients with asymptomatic ONFH were enrolled in this study. Twenty- four patients were diagnosed as an incidental finding and 44 patients with bilateral ONFH had unilateral hip pain. Of 44 symptomatic hips that were contralateral to asymptomatic hips, 41 hips were treated by total hip arthroplasty or joint-preserving procedure such as core decompression or stem cell transplantation. Plain

radiographs in pelvic anteroposterior view and in the frog leg view were obtained. Diagnosis by simple radiography was based on the presence of increased opacity due to the presence of a necrotic lesion, the presence of sclerotic or cystic lesions, or the crescent sign. Twenty-two hips showed a cold spot in femoral head by Tc-99 m bone scan. Diagnosis by MRI was based on the presence of a double line sign or a low signal intensity band in axial and coronal planes. Forty-six hips were diagnosed by MRI. Cases with a femoral fracture or femoral head dislocation were excluded.

The cohort comprised 45 men and 23 women of mean age 49.6 years (range 24 to 82 years). Patients were followed up for an average of 6.6 years (range 2.0–10.6 years). The epidemiological risk factors for ONFH were: alcohol drinking in 28 (41.2 %) and steroid administration in 14 (20.6 %). Steroid administration was defined as the use of 1,800 mg of prednisolone or another steroid of equivalent potency for four weeks or more or the continuous intake of corticosteroids for at least two months [8]. The alcohol drinking was classified by drinking habit as social drinking or heavy drinking. Social drinking was defined as the consumption of 400 to 1,000 ml of ethyl alcohol per week (about 5.5 bottles of soju weekly) and heavy drinking was defined as the consumption of 1,000 ml or more of ethyl alcohol weekly (about 14 bottles of soju per week) [8, 9]. Relations with symptom development were sought for the duration of steroid administration, the continuance of steroid administration after a diagnosis of ONFH, and duration and amount of alcohol consumed.

Lesion locations were classified as medial, central, and lateral, where a medial lesion was defined as a lesion involving less than the medial one-third of the weight-bearing area, a central lesion as a lesion involving between the medial one-third and two-thirds of the weight-bearing area, and a lateral lesion as a lesion involving the lateral one-third of the weight-bearing area [10, 11]. Lesion sizes were classified as small (< 30 % of the area of the femoral head), medium (30 to 50 % of the femoral head), and large (> 50 % of the femoral head) [12–14]. MR images were used to measure lesion sizes using the equation $((A' \times B'/A \times B) \times 100)$, where A = the largest diameter of the femoral head in the axial plane, A′ = the longest anteroposterior length of a necrotic lesion in the axial plane, B = largest diameter of the femoral head in the coronal plane, and B′ = longest mediolateral length of the necrotic lesion in the coronal plane. When MR images were not available, frog leg view and pelvis AP view radiographs were used to measure lesion sizes.

Largest femoral head diameter (A) and longest anteroposterior length of lesion (A′) were measured in frog leg lateral view, and largest femoral head diameter (B) and longest mediolateral length of lesion (B′) were measured in pelvis anteroposterior view [12, 15] (Fig. 1). The locations and sizes of the necrotic lesion were measured after three orthopaedic surgeons had reached consensus on measurement methods. Furthermore, all measurements were made without knowledge of any patient information.

The chi-square test was used to compare risk factor frequencies (sex, alcohol, cholesterol level, etc.) for asymptomatic ONFH (osteonecrosis of femoral head) and symptomatic ONFH, and to determine relations between symptom development and BMI, steroid use, smoking status, alcohol consumption, lesion size and location. Fisher's exact test was used to compare smoking status and steroid use in the asymptomatic ONFH and symptomatic ONFH groups. The Student's *T*-test was used compare continuous variables between these two groups, and Kappa statistics were used to calculate intra-observer and inter-observer reliabilities for the determination lesion location and size. Intra-observer reliability was determined by performing measurements twice with an interval of four weeks. Kappa statistics were defined as follows: poor 0.00–0.20; fair 0.21–0.40; moderate 0.41–0.60; substantial 0.61–0.80, and almost perfect 0.81–1.00.

The statistical analysis was performed using SPSS version 15.0 (SPSS, Chicago, Illinois), and p values of < 0.05 were regarded as significant.

Results

During follow-up, 38 of the 68 asymptomatic patients (55.9 %) developed symptoms. The average time between diagnosis and symptom development was 2.27 years (range 0.5–6.5 years).

Inter-observer reliability regarding lesion locations agreed significantly; kappa values ranged from 0.612 to 0.841. There were ten medial lesions, 21 central lesions, and 37 lateral lesions. Inter-observer reliability regarding lesion sizes also agreed significantly; kappa values ranged from 0.471 to 0.824. There were 19 large lesions, 29 medium lesions, and 20 small lesions. Intra-observer agreements for lesion locations and sizes had kappa values of 0.879 and 0.729, respectively.

None of the following: gender, age, body mass index (BMI), smoking status, or cholesterol level, was found to be significantly associated with the development of symptoms in asymptomatic ONFH (Table 1). Regarding symptom development with respect to risk factors, symptoms developed in 18 of 28 patients with alcohol-related necrosis (64.3 %), in eight of 14 patients with steroid-related necrosis (57.1 %), and in 12 of 26 patients with patients with idiopathic necrosis (46.2 %). No significant association was found between the presence of risk factors and symptom development (Table 2). Furthermore, duration of exposure to risk factors, such as to steroid administration and alcohol

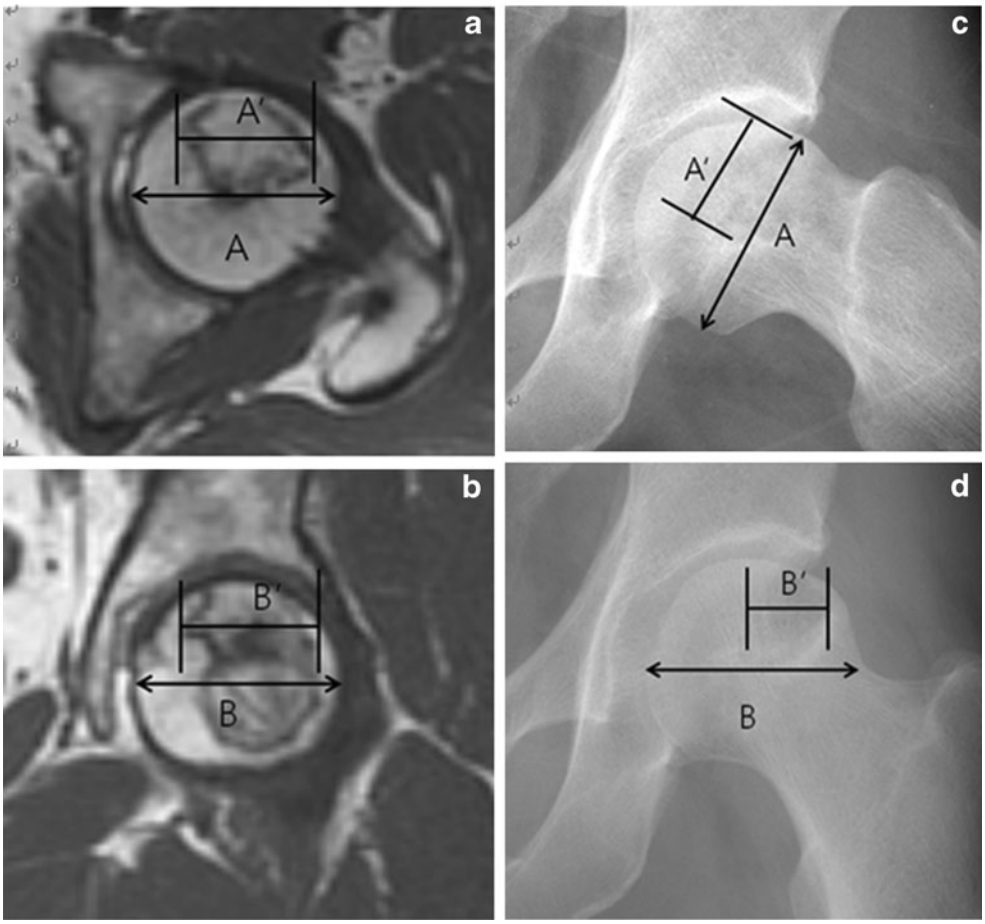

Fig. 1 **a**, **b** The method of measurement of the size of necrotic lesion on the axial image (**a**) and the coronal image (**b**) of MRI. **c**, **d** The method of measurement on the frogleg lateral (**c**) and the anteroposterior (**d**) radiographs

drinking, was found to have no significant association with symptom development (Table 3). Steroid was continued in all eight patients on steroid at diagnosis, and five developed symptoms. In six patients, steroid was withdrawn after diagnosis, and three developed symptoms. The development of symptoms and steroid continuance after diagnosis were not related (P=0.738).

On the other hand, for alcohol drinking, symptoms developed in ten of 19 social drinkers, but in eight of nine heavy drinkers, and this difference was significant (P=0.043). Furthermore, lesion size was found to be significantly associated with symptom development. Of 20 hips with a small lesion, two became symptomatic (10.0 %), but of 29 hips with a medium lesion, 20 became symptomatic (69.0 %), and of the 19 hips with a large lesion, 16 became symptomatic (84.2 %) (Table 4). In addition, lesion location was also found to be significantly associated with symptom development. Symptoms developed in 29 of 37 patients with a lateral lesion (76.3 %), eight of 21 with a central lesion (38.1 %), and in one of ten with medial lesion (10.0 %) (Table 5). The results show that symptom development is significantly more likely for large lesions and lesions with a lateral location.

Table 1 Comparison of demographic data between the patients with development of symptoms and the patients that remained asymtomatic

	Symptomatic (n=38)	Asymptomatic (n=30)	P value
Sex (male:female)	23:15	22:8	0.082
Age (years)	50.6±12.2	48.4±12.7	0.584
SLE	1	2	0.436
Smoking	10	8	0.693
Cholesterol	182.8±45.8	166.9±50.0	0.304
Body mass index	23.52±3.3	22.48±3.5	0.485

SLE Systemic lupus erythematosus

Table 2 Comparison of symptom development between the patients with risk factors and the patients with idiopathic ONFH

	Symptom development	Percentage of symptom development	*P* value versus idiopathic ONFH
Idiopathic (*n*=26)	12	46.2 %	
Alcohol (*n*=28)	18	64.3 %	0.827
Steroid (*n*=14)	8	57.1 %	0.521

ONFH osteonecrosis of femoral head

Discussion

The treatment of asymptomatic ONFH remains controversal [4, 5]. According to our findings, the most important factors of prognosis are lesion size and location; that is, large laterally disposed lesions are significantly more likely to become symptomatic.

Nam et. al. [12] found no significant relationship between symptom development in asymptomatic ONFH and risk factors, such as, alcohol drinking, steroid administration, or with age, BMI, and sex. In this study, no significant relation was found between the factors examined and symptom development, and thus, no guidance was given regarding the need for surgical treatment based on considerations of causative factors.

Nakamura et al. [16] observed asymptomatic ONFH in systemic lupus erythematosus (SLE) patients administered steroids, and concluded that both duration and degree of steroid use are more related to symptom development and lesion progression. However, in the study, no significant relation was found between symptom development and duration or degree of exposure to steroid. We found no significant difference between symptom development in the symptomatic and asymptomatic groups with respect to drinking duration, but a significant difference in terms of the amount of consumed. Matsuo et al. [9] found nine and 18 fold higher risks for the development of femoral head necrosis among those consuming 400 to 1,000 ml and more than 1,000 ml of alcohol per week, respectively. Hirota et al. [17, 18] found that annual alcohol consumptions of over 4,000 ml, 4,000–10,000 ml, and 10,000 ml or more increase the risk of ONFH by 3.2–2.2, 8.3–9.7, and 3.1–12.9-fold, respectively. They concluded that the alcohol intake has a cumulative effect to the development of ONFH, on the basis of the relation between drinking duration and development of ONFH. In our study, no significant correlation was found between symptomatic progression of asymptomatic ONFH and drinking duration. On the other hand, drinking habit was significantly related to symptom development. The result of our analysis suggests that heavy alcohol drinking habit should be considered as high risk for symptomatic progression of asymptomatic ONFH. This study had a strength that suggested the relationship between symptom development of asymptomatic ONFH and alcohol, which was not mentioned in the previous studies.

Table 3 The duration of exposure to risk factors in the patients with development of symptoms and the patients that remained asymptomatic

	Symptomatic	Asymptomatic	*P* value
Alcohol (year)	33.2±13.0	22.8±10.4	0.057
Steroid (month)	22.6±16.8	36.8±39.1	0.487

Table 4 Comparison of symptom development between the sizes of lesion

	Small (*n*=20)	Medium (*n*=29)	Large (*n*=19)	*P* value
Symptom development	2	20	16	< 0.0001
Percentage of symptom development	10.0 %	69.0 %	84.2 %	

Nevertheless, the most important factors of ONFH prognosis are lesion location and size [7, 11–15, 19–28]. Sugano et al. [28] reported an extensive progression of femoral head collapse, usually when the necrotic lesion invades the inner one-third of the weight bearing region on anteroposterior view of plain radiographs and when the necrotic lesion involves more than 43 % of the femoral head on lateral view. Similarly, Mont et al. [23] found that more invasion of the weight bearing region and a larger lesion size increased the probability of femoral head collapse. Nam et al. [12] suggested that the most important factor is lesion size. Our study analysed the lesion size and location with respect to symptomatic development, and demonstrated that greater invasion of the weight-bearing region, a lateral disposition, and lesion size significantly affect symptomatic development.

Based on these findings, considerations of lesion size and location are important when making decisions regarding surgical treatment. Hungerford et al. [5] advocated core decompression for patients with a necrotic lesion involving 15 to 30 % percent of femoral head, and Mont et al. [23] concluded that lesions invading the lateral two-thirds of the

Table 5 Comparison of symptom development between the locations of lesion

	Medial (*n*=10)	Centre (*n*=21)	Lateral (*n*=37)	*P* value
Symptom development	1	8	29	0.002
Percentage of symptom development	10.0 %	38.1 %	76.3 %	

weight-bearing region and more than 25 % of the femoral head require early treatment.

In our study, 84.2 % of large asymptomatic ONFH progressed to symptomatic hips and only 10 % of small asymptomatic ONFH developed symptoms. These results are consistent with previous studies [12, 23]. Therefore, this study strongly suggests that the size of the lesion should be considered as most reliable risk factor for disease progression. Furthermore, the prevalence of symptom development was high for lateral necrosis (76.3 %) and even higher for laterally disposed large lesions (91.6 %). These findings indicate that large necrotic lesions involving more than 50 % of the femoral head and lateral necrotic lesions involving more than the medial two-thirds of the weight-bearing region should be considered for early joint-preserving operative treatment even though the patients were asymptomatic.

The limitations of this study are that MRI was performed in only 46 cases, and thus, 22 cases were diagnosed using plain radiographs and bone scan. Therefore, in the study, osteonecrosis tended to be advanced enough to be visualised in plain radiographs, which explains the higher percentage of symptom development and the shorter time to symptom onset in our study as compared to previous studies. However, Hernigou et al. [22] also evaluated femoral head osteonecrosis using only plain radiographs, and reported a higher rate of femoral head collapse than other studies. On the other hand, the benefits of our study are: It was based on national data, the course of asymptomatic ONFH was analysed in terms of symptom development, and a standard set of surgical indications was used throughout.

Conclusion

No significant association was found between symptom development and the presence of risk factors such as gender, BMI, smoking status, cholesterol level and steroid administration. Significant relations were found between alcohol consumption, a lateral lesion (prevalence 76.3 %), and a large lesion (prevalence 84.2 %); and the prevalence for a laterally located large lesion was 91.6 %.

Therefore, the size and location of the lesion are the most important risk factors for symptom development. Alcohol consumption habit is another significant risk factor for symptom development.

We recommend that joint-preserving operative treatment be considered in such cases to preserve the native hip joint and to forestall the need for total hip arthroplasty.

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References

1. Meyers MH (1988) Osteonecrosis of the femoral head. Pathogenesis and long-term results of treatment. Clin Orthop Relat Res 231:51–61
2. Hungerford DS (2002) Osteonecrosis: avoiding total hip arthroplasty. J Arthroplasty 17(4 Suppl 1):121–124
3. Belmar CJ, Steinberg ME, Hartman-Sloan KM (2004) Does pain predict outcome in hips with osteonecrosis? Clin Orthop Relat Res 425:158–162
4. Mont MA, Hungerford DS (1995) Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 77:459–474
5. Hungerford DS, Jones LC (2004) Asymptomatic osteonecrosis: should it be treated? Clin Orthop Relat Res 429:124–130
6. Jin H, Xia B, Yu N, He B, Shen Y, Xiao L, Tong P (2012) The effects of autologous bone marrow mesenchymal stem cell arterial perfusion on vascular repair and angiogenesis in osteonecrosis of the femoral head in dogs. Int Orthop 36(12):2589–2596
7. Takatori Y, Kokubo T, Ninomiya S, Nakamura S, Morimoto S, Kusaba I (1993) Avascular necrosis of the femoral head. Natural history and magnetic resonance imaging. J Bone Joint Surg Br 75:217–221
8. Fukushima W, Fujioka M, Kubo T, Tamakoshi A, Nagai M, Hirota Y (2010) Nationwide epidemiologic survey of idiopathic osteonecrosis of the femoral head. Clin Orthop Relat Res 468(10):2715–2724
9. Matsuo K, Hirohata T, Sugioka Y, Ikeda M, Fukuda A (1988) Influence of alcohol intake, cigarette smoking and occupational status on idiopathic osteonecrosis of the femoral head. Clin Orthop 234:115–123
10. Sugano N, Atsumi T, Ohzono K, Kubo T, Hotokebuchi T, Takaoka K (2002) The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. J Orthop Sci 7:601–605
11. Sakamoto M, Shimizu K, Iida S, Akita T, Moriya H, Nawata Y (1997) Osteonecrosis of the femoral head: a prospective study with MRI. J Bone Joint Surg Br 79:213–219
12. Nam KW, Kim YL, Yoo JJ, Koo KH, Yoon KS, Kim HJ (2008) Fate of untreated asymptomatic osteonecrosis of the femoral head. J Bone Joint Surg Am 90:477–484
13. Morse CG, Mican JM, Jones EC et al (2007) The incidence and natural history of osteonecrosis in HIV-infected adults. Clin Infect Dis 44:739–748
14. Yoshida T, Kanayama Y, Okamura M, Negoro N, Inoue T, Yoshikawa J (2002) Long-term observation of avascular necrosis of the femoral head in systemic lupus erythematosus: an MRI study. Clin Exp Rheumatol 20:525–530
15. Kim YM, Ahn JH, Kang HS, Kim HJ (1998) Estimation of the extent of osteonecrosis of the femoral head using MRI. J Bone Joint Surg Br 80:954–958
16. Nakamura J, Harada Y, Oinuma K, Iida S, Kishida S, Takahashi K (2010) Spontaneous repair of asymptomatic osteonecrosis associated with corticosteroid therapy in systemic lupus erythematosus: 10-year minimum follow-up with MRI. Lupus 19: 1307–1314
17. Hirota Y, Hirohata T, Fukuda K et al (1993) Association of alcohol intake, cigarette smoking, and occupational status with the risk of idiopathic osteonecrosis of the femoral head. Am J Epidemiol 137:530–538
18. Hirota Y, Hotokebuchi T, Sugioka Y (1997) Idiopathic osteonecrosis of the femoral head: Nationwide Epidemiologic Studies in Japan. In: Urbaniak JR (ed) Osteonecrosis: Etiology, diagnosis, and treatment. The American Orthopaedic association, Rosemont, pp 51–58
19. 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

20. Jergesen HE, Khan AS (1997) The natural history of untreated asymptomatic hips in patients who have non-traumatic osteonecrosis. J Bone Joint Surg Am 79:359–363
21. Cheng EY, Thongtrangan I, Laorr A, Saleh KJ (2004) Spontaneous resolution of oste-onecrosis of the femoral head. J Bone Joint Surg Am 86:2594–2599
22. Hernigou P, Poignard A, Nogier A, Manicom O (2004) Fate of very small asymptomatic stage-I osteonecrotic lesions of the hip. J Bone Joint Surg Am 86:2589–2593
23. Mont MA, Zywiel MG, Marker DR, McGrath MS, Delanois RE (2010) The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. J Bone Joint Surg Am 92:2165–2170
24. Min BW, Song KS, Cho CH, Lee SM, Lee KJ (2008) Untreated asymptomatic hips in patients with osteonecrosis of the femoral head. Clin Orthop Relat Res 466:1087–1092
25. Kubo T, Yamazoe S, Sugano N et al (1997) Initial MRI findings of non-traumatic osteonecrosis of the femoral head in renal allograft recipients. Magn Reson Imaging 15:1017–1023
26. Shimizu K, Moriya H, Akita T, Sakamoto M, Suguro T (1994) Prediction of collapse with magnetic resonance imaging of avascular necrosis of the femoral head. J Bone Joint Surg Am 76:215–223
27. Sugano N, Ohzono K, Masuhara K, Takaoka K, Ono K (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
28. Sugano N, Ohzono K, Masuhara K, Takaoka K, Ono K (1994) Prognostication of nontraumatic avascular necrosis of the femoral head. Significance of location and size of the necrotic lesion. Clin Orthop Relat Res 303:155–164