RHEUMATOLOGY

Rheumatology 2011;50:2023–2028
doi:10.1093/rheumatology/ker277
Advance Access publication 24 August 2011

Original article

Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: prospective MRI study

Tomonori Shigemura[1], Junichi Nakamura[1], Shunji Kishida[1], Yoshitada Harada[2], Seiji Ohtori[1], Koya Kamikawa[3], Nobuyasu Ochiai[1] and Kazuhisa Takahashi[1]

Abstract

Objectives. The purpose of this study was to clarify the incidence of (CS)-associated osteonecrosis among different underlying diseases and to evaluate the risk factors for steroid-associated osteonecrosis in a prospective MRI study.

Methods. We prospectively used MRI to study 337 eligible underlying disease patients requiring CS therapy and succeeded in examining 1199 joints (hips and knees) in 302 patients with MRI for at least 1 year starting immediately after the onset of CS therapy (1-year follow-up rate of 90%). The underlying diseases included SLE in 687 joints (173 patients) and a variety of other rheumatological disorders in 512 joints (129 patients).

Results. The incidence of osteonecrosis was significantly higher in SLE patients than in non-SLE patients (37 *vs* 21%, $P = 0.001$). Logistic regression analysis revealed that adolescent and adult patients had a significantly higher risk of osteonecrosis compared with paediatric patients [odds ratio (OR) = 13.2], that high daily CS dosage (>40 mg/day) entailed a significantly higher risk of osteonecrosis compared with the dosage of <40 mg/day (OR = 4.2), that SLE patients had a significantly higher risk of osteonecrosis compared with non-SLE patients (OR = 2.6) and that male patients had a significantly higher risk of osteonecrosis compared with female patients (OR = 1.6).

Conclusion. These findings suggest that the incidence of CS-associated osteonecrosis varies among different underlying diseases.

Key words: Corticosteroid, Osteonecrosis, Systemic lupus erythematosus, Prospective study, Magnetic resonance imaging.

Introduction

Although high-dose CS therapy is regarded as a risk factor for osteonecrosis, the pathogenesis of steroid-associated osteonecrosis remains unknown. Sakamoto *et al.* [1] observed initial abnormal findings of osteonecrosis during high-dose CS therapy in their MRI prospective study. Nakamura *et al.* [2] reported that increasing CS doses at the recurrence of SLE was a risk factor for development of new osteonecrosis. On the other hand, neither total cumulative dose of CSs nor long-term CS therapy appears to be a risk factor, as evidenced by another study observing no new cases of osteonecrosis during long-term, low-dose CS therapy [2]. Indeed, a study observed spontaneous repair of osteonecrotic lesions during long-term, low-dose CS therapy [3].

Another risk factor for CS-associated osteonecrosis appears to be age at the time of CS administration. Nakamura *et al.* [4] reported a lower incidence of steroid-associated osteonecrosis in paediatric SLE patients than in adult SLE patients. Using dynamic MRI, Nakamura *et al.* [5] identified significantly more blood

[1]Department of Orthopaedic Surgery, Graduate school of Medicine, Chiba University, Chiba City, [2]Department of Orthopaedic Surgery, Chibaken Saiseikai Narashino Hospital, Narashino City and [3]Department of Orthopaedic Surgery, Teikyo University Chiba Medical Center, Ichihara City, Chiba, Japan.

Submitted 17 April 2011; revised version accepted 4 July 2011.

Correspondence to: Junichi Nakamura, Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba City, Chiba 260-0856, Japan.
E-mail: njonedr@yahoo.co.jp

CLINICAL SCIENCE

supply to the femoral head (especially to the growth plate) in paediatric SLE patients than in adult SLE patients after CS administration.

CSs are prescribed for the treatment of several diseases. In a prospective MRI study, Oinuma *et al.* [6] reported an incidence of osteonecrosis in 44% of adult patients with SLE. However, to our knowledge, the incidence of osteonecrosis associated with CS treatment of other underlying diseases remains unknown. The purpose of this study was to clarify the incidence of steroid-associated osteonecrosis among different underlying diseases and to evaluate the risk factors for steroid-associated osteonecrosis in a prospective MRI study.

Materials and methods

We prospectively registered 668 patients who received CS therapy from 1986 to 2009. The inclusion criteria were as follows: (i) MRI screening of their hips and knees within the first year following the initiation of CS administration and (ii) MRI follow-up for at least 1 year thereafter. With respect to MRI screening, Sakamoto *et al*. [7] reported that the incidence of steroid-associated osteonecrosis as observed with MRI was the highest in the hip (63%), followed by the knee (51%), ankle (16%) and shoulder joints (16%), and the incidence of osteonecrosis in the ankle and shoulder was 0% in a patient without osteonecrosis in both the hips and knees. Based on his report, we considered MRI screening of bilateral hips and knees to be both sufficient and cost-effective. We excluded from this initial group those patients who received CSs for the treatment of organ transplantation or malignant tumour because of the degree of variation in patient conditions and the survival rates associated with these diseases. We also excluded one hip because it had been treated for femoral neck fracture and two knees because they evidenced OA at the initial presentation. After these exclusions, 337 patients remained, who had received MRI evaluation of their hips and knees following the initiation of CS administration. Of these 337 patients, 302 (1199 joints) were followed with MRI for at least 1 year, constituting a 1-year follow-up rate of 90%. These 1199 joints (302 patients) comprised the study group for our subsequent analyses.

The underlying diseases diagnosed in these 1199 joints (302 patients) were as follows: SLE in 687 joints (173 patients), PM/DM in 108 joints (27 patients), pemphigus/bullous pemphigoid in 82 joints (21 patients), vasculitis syndrome (PAN or Takayasu's arteritis) in 56 joints (14 patients), uveitis in 56 joints (14 patients), respiratory disease (idiopathic pulmonary fibrosis, diffuse panbronchiolitis or idiopathic pulmonary haemosiderosis) in 24 joints (6 patients), neuromuscular disease (myasthenia gravis or multiple sclerosis) in 20 joints (5 patients), adult-onset Still's disease in 20 joints (5 patients), RA in 20 joints (5 patients), liver disease (autoimmune hepatitis or primary biliary cirrhosis) in 18 joints (5 patients), SS in 16 joints (4 patients), nephrosis in 16 joints (4 patients), ITP in 12 joints (3 patients), SSc in 12 joints (3 patients), granulomatosis with polyangitiis (Wegener's) in 12 joints (3 patients), sarcoidosis in 12 joints (3 patients), hyperthyroidism in 12 joints (3 patients), Behçet's disease in 8 joints (2 patients) and ulcerative colitis (UC) in 8 joints (2 patients). Due to the great variety of underlying diseases, and because more than half of the joints had SLE and the number of joints with each of the remaining underlying diseases was relatively small by comparison, we divided the joints into two groups: an SLE group and a non-SLE group (Table 1). We also divided patients into the following three age groups: paediatric (<15 years old), adolescent (15–20 years old) and adult (>20 years old). The paediatric group comprised 72 joints (18 patients) in the SLE group and 32 joints (8 patients) in the non-SLE group. The adolescent group comprised 96 joints (24 patients) in the SLE group and 36 joints (9 patients) in the non-SLE group. The adult group comprised 519 joints (131 patients) in the SLE group and 444 joints (112 patients) in the non-SLE group.

Incidence of osteonecrosis

The diagnosis of osteonecrosis was based on the 2001 revised criteria for classification of osteonecrosis of the femoral head from the Japanese Ministry of Health, Labor and Welfare (JMHLW classification) [8, 9]. The boundary of a necrotic lesion is defined as a low-intensity band (band-like pattern) on the central coronal section of the femoral head on T_1-weighted images. MRI screening methods for CS-associated osteonecrosis have been established [1–7]. The incidences of osteonecrosis of the hip and knee joints were compared between the SLE group and the non-SLE group as a function of the patient's age at the time of initiation of CS therapy, using Fisher's exact test and SPSS version 16.0 software (SPSS; Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Table 1 Patient's characteristics in the SLE and non-SLE groups

Characteristic	SLE group (687 joints)	Non-SLE group (512 joints)	*P*-value
Female, %	94 (644 joints)	70 (360 joints)	0.001*
Age at initial CS administration, years	30.9 (13.6)	45.1 (18.2)	0.001**
Highest daily CS dose, mg/day	56.4 (11.1)	52.2 (15.5)	0.001**

Values are expressed as mean (S.D.) unless otherwise specified. *Fisher's exact probability test, **Mann–Whitney's U-test.

Risk factors for osteonecrosis

The hip and knee joints were divided into the following two groups: those with osteonecrosis and those without osteonecrosis. The proportions of female patients (percentage) were compared in paediatric, adolescent and adult patients between the SLE group and the non-SLE group using Fisher's exact test. The patient's age at the time of initiation of CS therapy, the highest daily CS dosage (mg/day) and the highest daily CS dosage per weight (mg/day/kg) were compared in paediatric, adolescent and adult patients between the SLE and the non-SLE group using the Mann–Whitney U-test. CS dosages were converted into equivalent prednisone dosages based upon the method described by Felson and Anderson [10]. Risk factors for CS-associated osteonecrosis were calculated using a logistic regression analysis.

The research was in compliance with the Helsinki Declaration. It was approved by the institutional review board of the Graduate School of Medicine, Chiba University, and registered with the University Hospital Medical Information Network. All participants gave written informed consent.

Results

Incidence of osteonecrosis

The incidence of osteonecrosis was significantly higher in the SLE group than in the non-SLE group ($P = 0.001$): osteonecrosis developed in 255 (37%) of 687 joints in the SLE group (Table 2) *vs* 107 (21%) of 512 joints in the non-SLE group (Table 3). Within the non-SLE group, the incidence of osteonecrosis was as follows: 27% (29 joints in 13 patients) in PM/DM, 23% (19 joints in 10 patients) in pemphigus/bullous pemphigoid, 14% (8 joints in 5 patients) in vasculitis syndrome, 5% (3 joints in 3 patients) in uveitis, 21% (5 joints in 2 patients) in respiratory disease, 25% (5 joints in 2 patients) in neuromuscular disease, 45% (9 joints in 3 patients) in adult-onset Still's disease, 0% (none) in RA, 28% (5 joints in 3 patients) in liver diseases, 0% (none) in SS, 25% (4 joints in 1 patient) in nephrosis, 50% (6 joints in 2 patients) in ITP, 33% (4 joints in 1 patient) in SSc, 25% (3 joints in 1 patient) in granulomatosis with polyangitiis, 0% (none) in sarcoidosis, 25% (3 joints in 2 patients) in hyperthyroidism, 0% (none) in Behçet's disease and 50% (4 joints in 1 patient) in UC.

The incidence of osteonecrosis did not significantly differ between the SLE and the non-SLE group among the paediatric patients [3% (2 joints in 1 patient) *vs* 6% (2 joints in 1 patient), $P = 0.585$, Table 4]. However, the incidence of osteonecrosis was significantly higher in the SLE group than in the non-SLE group among the adolescent patients [51% (49 joints in 19 patients) *vs* 25% (9 joints in 3 patients), $P = 0.010$, Table 5] and among the adult patients [39% (204 joints in 75 patients) *vs* 22% (96 joints in 45 patients), $P = 0.001$, Table 6].

Regarding disease location, osteonecrosis of the femoral head occurred at a significantly higher rate in the non-SLE group than in the SLE group ($P = 0.001$). Specifically, of the 255 joints in the SLE group that developed osteonecrosis, 114 of these cases were hip joints (45%) *vs* 141 knee joints. In contrast, of the 107 joints in the non-SLE group that developed osteonecrosis, 71 of these cases were hip joints (66%) *vs* 36 knee joints.

Risk factors for osteonecrosis

The most frequent highest daily CS dosage was between 60 and 70 mg/day, occurring in 742 (62%) of the 1199 joints (188 of the 302 patients) studied. Figure 1 illustrates the incidence of osteonecrosis as a function of highest daily CS dosage (segmented into 10-mg-wide bands). The incidence of osteonecrosis was significantly higher in the joints exposed to high CS dosages of 40 mg/day compared with joints exposed to <40 mg/day (8 *vs* 33%,

Table 2 Comparison between joints with and without osteonecrosis in the SLE group

Characteristic	With osteonecrosis (255 joints)	Without osteonecrosis (432 joints)	*P*-value
Female, %	92 (235 joints)	95 (409 joints)	0.195*
Age at initial CS administration, years	31.9 (12.6)	30.2 (14.1)	0.116**
Highest daily CS dose, mg/day	58.3 (9.2)	55.3 (11.9)	0.001**

Values are expressed as mean (S.D.) unless otherwise specified. *Fisher's exact probability test, **Mann–Whitney U-test.

Table 3 Comparison between joints with and without osteonecrosis in the non-SLE group

Characteristic	With osteonecrosis (107 joints)	Without osteonecrosis (405 joints)	*P*-value
Female, %	62 (66 joints)	73 (294 joints)	0.032*
Age at initial CS administration, years	46.4 (14.7)	44.8 (19.0)	0.751**
Highest daily CS dose, mg/day	56.0 (13.5)	51.3 (15.9)	0.009**

Values are expressed as mean (S.D.) unless otherwise specified. *Fisher's exact probability test, **Mann–Whitney U-test.

Table 4 Comparison between joints with and without osteonecrosis in SLE and non-SLE groups in paediatric patients (<15 years of age)

Characteristic	SLE group (72 joints)		Non-SLE group (32 joints)	
	With osteonecrosis (2 joints)	Without osteonecrosis (70 joints)	With osteonecrosis (2 joints)	Without osteonecrosis (30 joints)
Female, %	100	83	100	87
Age at initial CS administration, years	14.9	11.3	13.8	9.1
Highest daily CS dose, mg/day	60.0	51.1	60.0	50.0
Highest daily CS dose per weight, mg/kg/day	1.0	1.4	1.3	1.7

Table 5 Comparison between joints with and without osteonecrosis in SLE and non-SLE groups in adolescent patients (between 15 and 20 years of age)

Characteristic	SLE group (96 joints)		Non-SLE group (36 joints)	
	With osteonecrosis (49 joints)	Without osteonecrosis (47 joints)	With osteonecrosis (9 joints)	Without osteonecrosis (27 joints)
Female, %	92	100	100	85
Age at initial CS administration, years	17.4	17.3	17.9	18.1
Highest daily CS dose, mg/day	60.8	58.3	65.6	52.2
Highest daily CS dose per weight, mg/kg/day	1.1	1.2	1.3*	1.0*

Mann–Whitney U-test, *$P = 0.011$.

Table 6 Comparison between joints with and without osteonecrosis in SLE and non-SLE groups in adult patients (>20 years of age)

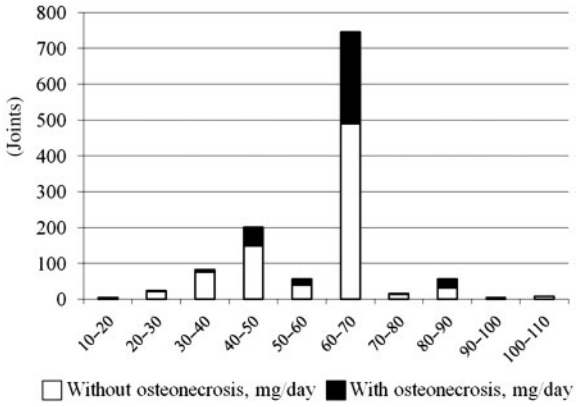
Characteristic	SLE group (519 joints)		Non-SLE group (444 joints)	
	With osteonecrosis (208 joints)	Without osteonecrosis (318 joints)	With osteonecrosis (96 joints)	Without osteonecrosis (348 joints)
Female, %	92*	97*	57**	70**
Age at initial CS administration, years	35.6	36.4	49.7	50.0
Highest daily CS dose, mg/day	57.7	55.8	55.1	51.3
Highest daily CS dose per weight, mg/kg/day	1.1	1.1	1.0***	0.9***

Fisher's exact probability test, *$P = 0.041$, **$P = 0.019$; Mann–Whitney U-test, ***$P = 0.032$.

$P = 0.001$). Among adolescent non-SLE patients, the highest daily CS dosage per weight was significantly higher for those with osteonecrosis than for those without osteonecrosis ($P = 0.011$, Table 5). In the adult SLE and adult non-SLE patient groups, the percentage of females was significantly lower among those with osteonecrosis than among those without osteonecrosis ($P = 0.041$, $P = 0.019$, respectively; Table 6). In the adult non-SLE patient group, the highest daily CS dosage per weight was significantly higher among those with osteonecrosis than among those without osteonecrosis ($P = 0.032$).

Logistic regression analysis revealed the following: (i) adolescent and adult patients had a significantly higher risk of osteonecrosis compared with paediatric patients, with an odds ratio (OR) of 13.2 ($P = 0.001$); (ii) higher daily CS dosage (>40 mg/day) entailed a significantly higher risk of osteonecrosis compared with dosage <40 mg/day, with an OR of 4.2 ($P = 0.001$); (iii) SLE patients had a significantly higher risk of osteonecrosis compared with non-SLE patients, with an OR of 2.6 ($P = 0.001$); and (iv) male patients had a significantly higher risk of osteonecrosis compared with female patients, with an OR of 1.6 ($P = 0.010$). In brief, age, CS dosage, underlying disease, and sex were significant risk factors for osteonecrosis.

FIG. 1 Incidence of osteonecrosis as a function of the highest daily CS dosage.



Discussion

Osteonecrosis occurred more frequently in knee joints than in hip joints in SLE patients. MRI screening of knee joints is known to be as important as that of the hips; however, to our knowledge, few studies about the incidence of CS-associated osteonecrosis of knee joints have been reported [7]. The present study was the first prospective MRI study about the incidence of CS-associated osteonecrosis among different underlying diseases. MRI is useful for accurate diagnosis of osteonecrosis, since it can detect asymptomatic osteonecrosis. MRI was first applied for the diagnosis of osteonecrosis in 1983 [11]. MRI is currently the gold standard for early diagnosis of osteonecrosis. Iida *et al*. [12] reported that the only initial finding of early osteonecrosis was a band-like pattern on MRI. The band-like pattern reflects tissue repair around the necrotic bone [13]. Only following the collapse of osteonecrosis are the onset of pain and some deformities observed [12]. Klippel *et al.* [14] studied the incidence of osteonecrosis in a series of patients with various collagen diseases and reported the following percentages: 8.3% in 375 SLE patients, 3.7% in 81 granulomatosis with polyangitiis patients, 3.2% in 94 PM/DM patients, 2.3% in 43 idiopathic cryoglobulinaemia patients, 2.1% in 46 PAN patients, 0.7% in 137 JRA patients, 0.4% in 710 RA patients and 0.4% in 238 Behçet's syndrome patients. Since his study evaluated symptomatic osteonecrosis after articular collapse with plain X-ray images, his results almost certainly underestimated the true incidence of osteonecrosis.

Regarding risk factors for CS-associated osteonecrosis, our study indicated that SLE was a relative risk factor for osteonecrosis with an OR of 2.6 compared with the other collagen diseases in aggregate. All the patients underwent MRI screening before CS therapy by MRI screening. All the osteonecrosis developed after CS therapy. Published studies have also provided evidence that SLE patients may be at higher risk of developing osteonecrosis. Dubois *et al.* [15] reported a case of osteonecrosis developing in an SLE patient who was not receiving CS therapy. Tektonidou *et al.* [16] reported a case of osteonecrosis developing in a patient with APS who also was not being treated with CSs. APS is an autoimmune disorder characterized by recurrent thrombotic episodes that in some patients is associated with SLE or other autoimmune diseases. Although the pathogenesis of steroid-associated osteonecrosis remains unknown, several studies indicate that haemostatic abnormalities caused by CS administration are related to the development of osteonecrosis. Oinuma *et al.* [17] identified a significant correlation between the development of a sustained haemostatic abnormality following the onset of high-dose CS therapy and the subsequent development of osteonecrosis. Nagasawa *et al.* [18] reported a lower incidence of osteonecrosis in SLE patients on warfarin than in SLE patients not being treated with warfarin. Motomura *et al.* [19] reported that warfarin and probocol were associated with a decrease in the incidence of osteonecrosis from 70 to 5% in a rabbit model.

Moreover, our study indicated that high-dose CS administration was also considered to be a risk factor for osteonecrosis. Highest daily CS dosage, mean CS dosage, highest daily CS dosage per weight, cumulative CS dosage, duration of CS therapy and/or pulse therapy were all evaluated as possible indices of CS dosage. Since the protocol of CS therapy was dictated by the disease activity or by the preferences of the chief physician, it was challenging to prove a pathogenic mechanism linking CS therapy to osteonecrosis. However, the substantial numbers of reports of osteonecrosis developing within a few months after the onset of CS administration indicates that CS dosage during this period should be analysed in detail. Le Parc *et al.* [20] reported that the incidence of osteonecrosis after renal transplantation declined from 29% in 1960 to 5% in 1996 owing to improvements in immunosuppressant therapy. Sakai *et al.* [21] also reported that the incidence of osteonecrosis after renal transplantation declined from 16% in a group receiving CSA to 0% in a group receiving FK506 (tacrolimus), observing that FK506 enabled reductions in the quantity of CSs that the patients required, which in turn enabled the patients to avoid increases in their cholesterol levels and thrombosis. These reports indicate that high-dose CS therapy in the short term is related to osteonecrosis and that continuing advances in immunosuppressive therapy may lead to reductions in the incidence of CS-associated osteonecrosis.

One limitation of this study was that all the other underlying diseases apart from SLE were grouped together into a single, non-SLE group. Since the resultant set of underlying diseases is heterogeneous, ideally the incidence of CS-associated osteonecrosis should be analysed individually for each of these diseases. Unfortunately the small numbers of the patients affected by these other diseases in our study population precluded such an analysis. Thus, further study is needed to clarify to what extent

these other diseases may be risk factors for osteonecrosis.

Rheumatology key message

- The incidence of CS-associated osteonecrosis was different among different underlying diseases.

Acknowledgements

We appreciated the cooperation of all of the members of the Hip group at Chiba University for the prospective MRI study: Keishi Yamashita, MD, Kazuhiro Oinuma, MD, Satoshi Iida, MD, Koh Shimizu, MD, Masaaki Sakamoto, MD, Atsushi Chuma, MD, Sumio Ikenoue, MD, Isao Abe, MD, Shigeru Mitsuhashi, MD, Hitoshi Watanabe, MD, Chiho Suzuki, MD, Yasuyuki Takamori, MD, Makoto Otsuka, MD, Chikashi Shirai, MD, Takeshi Miyasaka, MD, Yoko Miura, MD, Shinji Yamamoto, MD, Takayuki Nakajima, MD, Munenori Takeshita, MD and Makoto Takazawa, MD.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Sakamoto M, Shimizu K, Iida S, Akita T, Moriya H, Nawata Y. Osteonecrosis of the femoral head. A prospective study with MRI. J Bone Joint Surg Br 1997;79:213–9.

2 Nakamura J, Ohtori S, Sakamoto M, Chuma A, Abe I, Shimizu K. Development of new osteonecrosis in systemic lupus erythematosus patients in association with long-term corticosteroid therapy after disease recurrence. Clin Exp Rheumatol 2010;28:13–8.

3 Nakamura J, Harada Y, Oinuma K, Iida S, Kishida S, Takahashi K. Spontaneous repair of asymptomatic osteonecrosis associated with corticosteroid therapy in systemic lupus erythematosus: 10-year minimum follow-up with MRI. Lupus 2010;19:1307–14.

4 Nakamura J, Saisu T, Yamashita K, Suzuki C, Kamegaya M, Takahashi K. Age at time of corticosteroid administration is a risk factor for osteonecrosis in pediatric patients with systemic lupus erythematosus. A prospective magnetic resonace imaging study. Arthritis Rheum 2010;62:609–15.

5 Nakamura J, Miura Y, Ikenoue S *et al*. Blood supply of proximal femur during steroid therapy in SLE patients using dynamic MRI. In: *Proceedings of the 77th Annual Meeting of the American Academy of Orthopaedic Surgeons, New Orleans, LA, 9–13 March 2010*. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2010, 542.

6 Oinuma K, Harada Y, Abe I, Kamikawa K, Moriya H. Osteonecrosis in patients with systemic lupus erythematosus develops very early after starting high dose corticosteroid treatment. Ann Rheum Dis 2001;60:1145–8.

7 Sakamoto M. A prospective study of steroid-induced osteonecrosis by MRI screening [in Japanese]. J Jpn Orthop Assoc 1994;68:367–78.

8 Sugano N, Atsumi T, Ohzono K, Kubo T, Hotokebuchi T, Takaoka K. The 2001 revised criteria for diagnosis, classification, and staging of idiopathic osteonecrosis of the femoral head. J Orthop Sci 2002;7:601–5.

9 Nakamura J, Kishida S, Harada Y *et al*. Inter-observer and intra-observer reliabilities of the Japanese Ministry of Health, Labor and Welfare type classification system for osteonecrosis of the femoral head. Mod Rheumatol. Advance access published February 24, 2011, doi:10.1007/s10165-011-0430-y.

10 Felson DT, Anderson JJ. A cross-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. Lancet 1987;1:902–5.

11 Moon KL Jr, Genant HK, Helms CA, Chafetz NI, Crooks LE, Kaufman L. Musculoskeletal applications of nuclear magnetic resonance. Radiology 1983;147:161–71.

12 Iida S, Harada Y, Shimizu K *et al*. Correlation between bone marrow edema and collapse of the femoral head in steroid-induced osteonecrosis. Am J Roentgenol 2000;174:735–43.

13 Lang P, Jergesen HE, Moseley ME, Block JE, Chafetz NI, Genant HK. Avascular necrosis of the femoral head: high-field-strength MR imaging with histologic correlation. Radiology 1988;169:517–24.

14 Klippel JH, Gerber LH, Pollak L, Decker JL. Avascular necrosis in systemic lupus erythematosus. Silent symmetric osteonecroses. Am J Med 1979;67:83–7.

15 Dubois EL, Cozen L. Avascular (aseptic) bone necrosis associated with systemic lupus erythematosus. JAMA 1960;22:966–71.

16 Tektonidou MG, Malagari K, Vlachoyiannopoulos PG, Kelekis DA, Moutsopoulos HM. Asymptomatic avascular necrosis in patients with primary antiphospholipid syndrome in the absence of corticosteroid use: a prospective study by magnetic resonance imaging. Arthritis Rheum 2003;48:732–6.

17 Oinuma K, Harada Y, Nawata Y *et al*. Sustained hemostatic abnormality in patients with steroid-induced osteonecrosis in the early period after high-dose corticosteroid therapy. J Orthop Sci 2000;5:374–9.

18 Nagasawa K, Tada Y, Koarada S *et al*. Prevention of steroid-induced osteonecrosis of femoral head in systemic lupus erythematosus by anti-coagulant. Lupus 2006;15:354–7.

19 Motomura G, Yamamoto T, Miyanishi K, Jingushi S, Iwamoto Y. Combined effects of an anticoagulant and a lipid-lowering agent on the prevention of steroid-induced osteonecrosis in rabbits. Arthritis Rheum 2004;50:3387–91.

20 Le Parc JM, André T, Helenon O, Benoit J, Paolaggi JB, Kreis H. Osteonecrosis of the hip in renal transplant recipients. Changes in functional status and magnetic resonance imaging findings over three years in three hundred five patients. Rev Rheum Engl Ed 1996;63:413–20.

21 Sakai T, Sugano N, Kokado Y, Takahara S, Ohzono K, Yoshikawa H. Tacrolimus may be associated with lower osteonecrosis rates after renal transplantation. Clin Orthop Relat Res 2003;415:163–70.