Clin Rheumatol (2015) 34:2071–2077
DOI 10.1007/s10067-015-3075-y

ORIGINAL ARTICLE

High triglyceride is a risk factor for silent osteonecrosis of the femoral head in systemic lupus erythematosus

Takeshi Kuroda[1] · Naohito Tanabe[2] · Ayako Wakamatsu[1] · Chinatsu Takai[1] · Hiroe Sato[1] · Takeshi Nakatsue[1] · Yoko Wada[1] · Masaaki Nakano[3] · Ichiei Narita[1]

Received: 16 July 2015 / Revised: 7 September 2015 / Accepted: 7 September 2015 / Published online: 18 September 2015

Abstract The purpose of this study was to clarify the factors related to silent osteonecrosis of the femoral head (ONFH) in patients with systemic lupus erythematosus (SLE). Seventy-eight patients with SLE were selected on the basis of having been newly diagnosed and requiring high-dose prednisolone, including pulse therapy with methylprednisolone, as the initial treatment. All the patients initially underwent MRI at 3 months after the start of corticosteroid treatment to detect any early changes in the femoral head. These examinations were then performed again 3 months later. Laboratory parameters were evaluated at the start of steroid treatment and at 1 month thereafter. By 3 months after the start of corticosteroid treatment, silent ONFH was diagnosed by MRI in 21 patients (26.9 %), being bilateral in 11 patients and unilateral in 10. The occurrence of silent ONFH was not related to SLE disease activity index, serological activity, or renal function; it was also unrelated to body mass index (BMI), body surface area (BSA), and the initial dose of prednisolone per unit body weight. However, the total cholesterol level at 4 weeks after the start of steroid treatment tended to be higher in patients with silent ONFH. Patients with a higher triglyceride level showed a significantly higher frequency of silent ONFH both before (p=0.002) and 4 weeks after (p=0.036) steroid initiation.

A high triglyceride level is an important risk factor for silent ONFH in patients with SLE, and large-scale epidemiologic surveys of such early events are needed in this patient population.

Keywords Magnetic resonance imaging · Osteonecrosis of the femoral head · Steroid · Systemic lupus erythematosus · Triglyceride

Introduction

Osteonecrosis of the femoral head (ONFH) occurs frequently (3–40 %) in patients receiving corticosteroids for underlying conditions such as systemic lupus erythematosus (SLE),

✉ Takeshi Kuroda
kurodat@med.niigata-u.ac.jp

Naohito Tanabe
tanabena@gmail.com

Ayako Wakamatsu
a.sohma0@gmail.com

Chinatsu Takai
chinatsunachi.89@gmail.com

Hiroe Sato
hiroe77212@hotmail.com

Takeshi Nakatsue
takeshinakatsue@gmail.com

Yoko Wada
yoko.wada@gmail.com

Masaaki Nakano
manakano@clg.niigata-u.ac.jp

Ichiei Narita
naritai@med.niigata-u.ac.jp

[1] Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Chuo-ku, Niigata City 951-8510, Japan

[2] Department of Health and Nutrition, Faculty of Human Life Studies, University of Niigata Prefecture, 471 Ebigase, Higashi-ku, Niigata 950-8680, Japan

[3] Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, 2-746 Asahimachi-Dori, Chuo-ku, Niigata City 951-8518, Japan

nephrotic syndrome, and renal transplantation [1–4]. The etiology of this disorder has not been clarified, and no prophylaxis has been established to date. Although the pathogenesis remains unclear, involvement of lipid metabolism abnormality [5], hypercoagulability [6], oxidative stress [7], and vascular endothelial dysfunction [8] has been suggested.

To analyze the risk factors associated with steroid-induced ONFH, it seems important to detect early changes in the femoral head by MRI and early clinical events caused by steroid therapy. Meanwhile, for treatment of SLE, several strategies have been selected according to the clinical conditions of affected patients, and there are a number of differences among multicenter hospitals, such as the indications for use of immunosuppressants. However, in previous studies performed at single institutions, the treatment strategy, the steroid selected, the initial dose of steroid, and the drugs used concomitantly have been quite similar. In addition, the speed at which the steroid has been tapered off has been quite uniform. Therefore, it should be possible to clarify the background factors associated with ONFH. On the basis of this idea, in a cohort of strictly selected SLE patients, we investigated the early development of ONFH using MRI and the early changes in laboratory parameters associated with steroid therapy.

Materials and methods

Selection of patients

Seventy-seven patients (8 males and 70 females) with SLE classified according to the 1982 revised American Rheumatology Association criteria were analyzed prospectively. Their ages at onset of SLE ranged from 15 to 69 years with a mean of 33.8 years. All of the patients were selected on the basis of having been newly diagnosed as having SLE and requiring a high dose (more than 30 mg/day or more than 0.5 mg/kg body weight) of prednisolone (PSL), including pulse therapy with 1000 mg/day methylprednisolone, for 3 days as the initial treatment. They were followed consecutively at our hospital.

The study protocol was approved by the institutional review board of Niigata University Medical and Dental Hospital and executed according to the Declaration of Helsinki. Written informed consent to participate in the study was obtained from all patients. In addition, we obtained written informed consent from the next to kin, caregivers, or guardians of minors/children enrolled in this study.

Evaluation of the femoral head

All of the patients underwent plain radiography and MRI initially at 3 months after the start of treatment with corticosteroids to detect any early changes in the femoral head. Subsequently these examinations were performed 3 months thereafter. Plain radiography consisted of antero-posterior pelvic and lateral projections of individual hips. ONFH was diagnosed to have occurred when a band-like low-signal area was seen in the femoral head on MRI T1-weighted images, which was confirmed by a radiology specialist interpreting the image. Conventional symptomatic ONFH was diagnosed when such MRI abnormalities plus continuous hip pain and/or radiographic abnormalities appeared.

Laboratory examinations

Routine laboratory examinations were performed for all of the patients. For analysis of clinical and laboratory features that seemed to contribute to the induction of ONFH, the patients were divided into two groups; one consisted of patients who showed abnormalities on MRI (silent ONFH), and the other group included patients without any sign of ONFH on MRI. In order to analyze the early effect of high-dose corticosteroid, the data were obtained at the start of steroid treatment and at 1 month thereafter. The extent of sequential differences in the levels of laboratory parameters between the baseline and 1 month after the start of treatment was compared between the two groups. The parameters were selected on the basis that their levels were related to the SLE Disease Activity Index (SLEDAI) [9]. Patients who had a high level of cholesterol were treated with statins at the discretion of the attending physician. Laboratory indices and clinical evaluations of disease activity included determinations of C3, C4, CH50, anti-dsDNA antibody, anti-phospholipid antibodies including IgM and IgG, anti-cardiolipin antibodies and lupus anticoagulant, the serum creatinine level, and 24-h proteinuria, which were assessed using routine laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the formula described previously [10]. The body weight (BW), body mass index (BMI), and body surface area (BSA) of each patient were also recorded at the time of steroid initiation. BSA was calculated using the Du Bois and Du Bois formula [11].

Statistical analysis

Differences in continuous variables between the groups were analyzed using Fisher's exact test, and Student's t test and Mann-Whitney U test were also where appropriate. In order to confirm whether a specific variable was associated with silent ONFH independently of the initial dose of PSL, multivariate logistic regression analysis was performed by including these two variables simultaneously in a model. Thereafter, the interaction of the effects of these two variables on silent ONFH was assessed by adding an interaction term to the model. All statistical tests were two-tailed. Differences at $p<0.05$ were deemed to be statistically significant.

Results

Clinical features of SLE patients

A total of 78 patients (8 men and 70 women) participated in this study, and the male to female ratio was 1:8.8. The age at onset of SLE ranged from 15 to 69 years (average 33.8 years).

Development of ONFH

All of the enrolled patients were followed consecutively at our hospital for at least 6 months and completed the study. All of the patients who underwent MRI and radiographic examinations at the baseline showed no abnormalities in the femoral head. By 3 months of corticosteroid treatment, silent ONFH diagnosed by MRI had developed in 21 patients (26.9 %), being bilateral in 11 patients and unilateral in 10.

Table 1 shows the clinical characteristics and laboratory findings of these patients at the time of steroid initiation for SLE. The most common clinical feature was malar rash, and *musculoskeletal* manifestations and renal disease were also frequent. The SLEDAI score was 17.2, and high activity (SLEDAI =11–19) was most frequent (42.3 %), followed by very high disease activity (SLEDAI ≥20) (37.2 %). Anti-phospholipid antibodies were detected in 21 patients (26.9 %). Thirteen patients (16.7 %) were cigarette smokers and 28 (35.9 %) were alcohol drinkers. The relationships between clinical features and silent ONFH are also shown in Table 1. Characteristics such as patient sex, age at onset, several symptoms, mean initial dose of PSL, steroid pulse therapy, anti-phospholipid antibodies, habitual cigarette smoking, habitual alcohol drinking, and treatment with statins showed no significant correlation with silent ONFH. The SLEDAI score, an indicator of SLE disease activity, was not significantly correlated with ONFH. As for the relationship between serological activity, renal function, and silent ONFH, none of the parameters such as C3, C4, CH50, and anti-dsDNA antibody showed any significant correlation with silent ONFH. In addition, renal function parameters such as serum creatinine, eGFR, and urinary protein were not correlated with silent ONFH.

Relationships between BMI, BSA and the initial dose of prednisolone per unit BW, BMI, and BSA, and silent ONFH

As shown in Table 2, relationships between BMI, BSA and the initial dose of steroid per BW, BMI and BSA, and silent ONFH were evaluated. For initial treatment, 16.7 % of the patients received a mean PSL dose of 47.4 mg and corticosteroid pulse therapy. None of the parameters showed any significant correlation with silent ONFH.

Early changes in total cholesterol and triglyceride after steroid therapy

Table 3 shows the relationship between total cholesterol and triglyceride and silent ONFH. The total cholesterol level at 4 weeks after the start of steroid treatment tended to be higher in patients with silent ONFH. Before the start of steroid treatment, the level of triglyceride was significantly correlated with the incidence of silent ONFH (p=0.002), and 4 weeks after the start of steroid treatment, the level of triglyceride was also significantly correlated with the incidence of silent ONFH (p= 0.036).

Patients with a lower triglyceride level showed a significantly lower incidence of silent ONFH. In order to assess whether the triglyceride level was associated with silent ONFH independently of the initial dose of PSL, multivariate logistic regression analyses were performed, and the results are shown in Table 4. The triglyceride level before steroid therapy was significantly associated with silent ONFH, even after adjustment for the effect of initial PSL dose. The interaction between triglyceride before PSL therapy and the initial dose of PSL was not significant (P for interaction=0.807).

Discussion

ONFH is known to occur as one of the serious complications of corticosteroid treatment in patients with SLE. Among several factors associated with ONFH, corticosteroid therapy is considered to be one of critical importance. There have been many reports of ONFH onset in SLE patients to date, but the precise incidence of ONFH in this group of patients is unknown. The reported frequency of symptomatic ONFH in patients with SLE has ranged from 3 to 40 % [1–4]. It is now possible to detect osteonecrotic change soon after administration of corticosteroid, thanks to the widespread use of magnetic resonance imaging (MRI) making early diagnosis possible. Nagasawa et al. described that 33 % of patients developed ONFH within 3 months after the start of corticosteroid treatment and that symptomatic ONFH became apparent at 2 years and beyond [12]. That study was a multicenter one, and several strategies were selected for treatment of SLE according to the clinical conditions of the patients, resulting in slight differences among the participating hospitals. However, in studies performed at a single institution, the treatment strategy, selection of steroid, initial dose of steroid, speed of steroid tapering, and drugs used together with steroid have been quite similar. Therefore, we investigated the very early development of ONFH at 3 months after the start of steroid therapy using MRI imaging to clarify the background factors associated with ONFH. We found that the prevalence of silent ONFH among our patients was 26.9 %, similar to that described previously.

Table 1 Relationship between clinical features and silent osteonecrosis of the femoral head in patients with SLE

	Silent ONFH(+)	Silent ONFH(−)	*P* value*
Characteristic	(*n*=21)	(*n*=57)	
	n (%)	*n* (%)	
Male/female, *n*	2/19	6/51	1.000
Mean age at SLE onset, year (SD) (range)	31.9 (14.5) (15–60)	34.6 (12.2) (15–69)	0.430
Body length, cm (SD)	159.5 (6.7)	158.1 (6.5)	0.398
Body weight, kg (SD)	56.3 (11.0)	53.5 (13.0)	0.371
Clinical features			
Musculoskeletal manifestations	11 (52.4 %)	32 (56.1 %)	0.802
Malar rash	12 (57.1 %)	38 (66.7 %)	0.435
Alopecia	4 (19.0 %)	6 (10.5 %)	0.445
Oral ulcer	0 (0 %)	7 (12.3 %)	0.180
CNS disease	1 (4.8 %)	6 (10.5 %)	0.667
Renal disease	11 (54.2 %)	32 (56.1 %)	0.802
Serositis	3 (14.3 %)	8 (14.0 %)	1.000
SLEDAI (SD) (range)	17.0 (5.2) (8–26)	17.3 (6.8) (8–32)	0.896
Moderate activity (SLEDAI=6–10)	2 (9.5 %)	14 (24.6 %)	
High activity (SLEDAI=11–19)	10 (47.6 %)	23 (40.3 %)	0.257
Very high activity (SLEDAI ≥20)	9 (42.9 %)	20 (35.1 %)	
Anti-phospholipid antibodies	4 (19.0 %)	17 (29.8 %)	0.402
Cigarette smoking	6 (28.6 %)	7 (12.2 %)	0.100
Habitual alcohol drinking	8 (38.1 %)	20 (35.1 %)	0.797
Statins[a]	5 (23.8 %)	24(42.1 %)	0.189
C3 (mg/dl) (SD)	54.2 (28.1)	56.5 (29.5)	0.753
C4 (mg/dl) (SD)	13.1 (9.7)	12.5 (8.6)	0.779
CH50 (U/ml) (SD)	24.6 (14.0)	23.9 (13.1)	0.832
Anti-dsDNA antibody (IU/ml)(SD)	127.9 (177.0)	97.7 (128.9)	0.412
Serum creatinine level (mg/dl)(SD)	1.08 (1.29)	1.31 (4.19)	0.813
eGFR (ml/min/m^2)(SD)	85.0 (35.0)	100.7 (46.9)	0.167
Urinary protein (g/day)(SD)	1.11 (1.38)	1.08 (1.95)	0.932

Values are mean (SD) or percentage

ONFH osteonecrosis of the femoral head, *SLEDAI* systemic lupus erythematosus disease activity index, *eGFR* estimated glomerular filtration rate

*Fisher's exact test, Student's *t* test, and Mann-Whitney *U* test

[a] Statins (pravastatin, atorvastatin, pitavastatin, and rosuvastatin)

Table 2 Relationship between body mass index, body surface area and initial dose of steroid per body weight, body mass index and body surface area, and osteonecrosis of the femoral head in patients with SLE

	Silent ONFH (+)	Silent ONFH (−)	*P* value*
BMI (kg/m^2)	22.2 (4.6)	21.3 (4.5)	0.430
BSA (m^2)	1.57 (0.14)	1.52 (0.17)	0.280
Mean initial dose of PSL, mg/day (range)	51.0 (11.2) (40–80)	46.1 (9.6) (30–60)	0.065
Steroid pulse therapy	2 (9.5 %)	11 (19.3 %)	0.495
PSL/BW (mg/kg)	0.94 (0.30)	0.89 (0.21)	0.401
PSL/BMI (mg/kg/m^2)	2.4 (0.77)	2.2 (0.53)	0.247
PSL/BSA (mg/m^2)	32.7 (8.2)	30.4 (6.0)	0.166

Values are mean (SD)

ONFH osteonecrosis of the femoral head, *BMI* body mass index, *BSA* body surface area, *PSL* prednisolone, *PSL/BW* initial prednisolone dose per body weight, *PSL/BMI* initial prednisolone dose per body mass index, *PSL/BSA* initial prednisolone dose per body surface area

*Student's *t* test

Table 3 Early changes in total cholesterol and triglyceride after steroid therapy in patients with SLE

	Silent ONFH (+)	Silent ONFH (−)	*P* value*
TG (before steroid therapy) (mg/dl)	212.3 (142.3)	134.9 (52.0)	0.002
TG (4 weeks after starting steroid therapy) (mg/dl)	234.0 (137.8)	168.0 (98.9)	0.036
TC (before steroid therapy) (mg/dl)	214.9 (76.4)	189.9 (95.2)	0.364
TC (4 weeks after starting steroid therapy) (mg/dl)	279.9 (99.5)	229.9 (76.8)	0.062
LDL-C (before steroid therapy) (mg/dl)	99.1 (12.9)	110.3 (97.2)	0.769
LDL-C (4 weeks after starting steroid therapy) (mg/dl)	122.3 (47.3)	150.7 (90.6)	0.476
HDL-C (before steroid therapy) (mg/dl)	40.4 (20.2)	42.3 (20.6)	0.792
HDH-C (4 weeks after starting steroid therapy) (mg/dl)	74.5 (18.1)	70.4 (21.3)	0.580

Values are mean (SD)

ONFH osteonecrosis of the femoral head, *TG* triglyceride, *TC* total cholesterol, *LDL-C* LDL-cholesterol, *HDL-C* HDL-cholesterol

*Student's *t* test

We found no differences in the clinical characteristics of the patients, such as sex, age, height, and body weight and clinical features. The SLEDAI is a validated tool for global assessment of SLE disease activity by experienced clinicians. The SLEDAI score includes disease activity, damage due to disease, and health status and is widely used as a comprehensive index of disease activity. Almost all of our patients showed high or very high disease activity at the time of steroid initiation. However, the SLEDAI score was not correlated with silent ONFH.

In addition, we found no evidence that anti-phospholipid antibodies were correlated with silent ONFH. ONFH has been identified in patients with primary anti-phospholipid syndrome (APS), suggesting a role of lupus anticoagulant and anti-cardiolipin antibodies in the pathogenesis of ONFH [13]. In primary APS, hypercoagulopathy can trigger osteonecrosis in SLE patients. However, in secondary APS, several reports have found no relationship between ONFH and APS [14]. In the early state investigated in the present study, there was no relationship between anti-phospholipid antibodies and silent ONFH.

In Japan, cigarette smoking and habitual alcohol consumption are independent risk factors for ONFH [15]. In our study, both cigarette smoking and habitual alcohol consumption were not correlated with ONFH. In our patients, alcohol consumption seemed to be lower than in series reported previously. HMG-CoA reductase inhibitors (statins) have been widely used for treatment of dyslipidemia as well as for preventing coronary artery disease. On the basis of a chicken model, Wang et al. suggested that lovastatin prevented steroid-induced ONFH [16], and a study by Nishida et al. using a rabbit model also suggested that pitavastatin had a similar effect [17]. We used pravastatin, pitavastatin, lovastatin, and atorvastatin for prevention of ONFH, but no such preventive effect was observed.

We also investigated serological parameters such as C3, C4, CH50, and anti-ds DNA antibody, as well as renal function parameters such as the serum creatinine level, eGFR, and daily urinary protein. However, none of these factors were correlated with ONFH. Thus, both serological activity and renal function, as the most common forms of organ involvement, were not correlated with ONFH. Therefore, initial serological activity in SLE and renal function might not be related to silent ONFH.

Moreover, our study showed that the initial dose of PSL, steroid pulse therapy, BMI, and BSA were not correlated with silent ONFH, being similar to the results obtained by Sekiya et al. [18]. Corticosteroid is considered to be the main risk

Table 4 Independent relationship of triglyceride and initial dose of prednisolone to occurrence of silent osteonecrosis of the femoral head in patients with SLE

	OR	(95 % CI)	*P* value
Model 1			
TG (before steroid therapy)(per every +10 mg/dL)	1.09	(1.01–1.17)	0.022
Initial dose of PSL (per every +10 mg/day)	1.49	(0.81–2.74)	0.198
Model 2			
TG (4 weeks after starting steroid therapy)(per every +10 mg/dL)	1.05	(1.00–1.10)	0.062
Initial dose of PSL (per every +10 mg/day)	1.68	(0.94–3.00)	0.081

Both variables in each model were included in a multivariate logistic regression model simultaneously. *P* for interaction was 0.807 for model 1 and 0.842 for model 2 when an interaction term was added to each model

TG triglyceride, *PSL* prednisolone, *OR* odds ratio, *CI* confidence interval

factor for ONFH in SLE. Studies investigating the association of ONFH and steroid treatment have yielded conflicting results with regard to the cumulative steroid dosage, maximum steroid dose, route of steroid administration, and duration of steroid treatment. ONFH may develop in patients who have received high-dose, short-term, or long-term steroids. In our present study, however, the patients were treated with steroid for the first time, and our observation period was short. This may partly explain why our results were different from those of previous studies.

Recently, the initial dose of PSL has sometimes been determined according to the patient's weight or BSA [19]. Therefore, we investigated the relationship of BMI and BSA with the initial dose of PSL. However, we failed to identify any relationship between BMI, BSA, the initial dose of PSL per unit BW, the initial dose of PSL per BMI, or the initial dose of PSL per BSA. None of the factors evaluated were associated with silent ONFH.

Our data revealed that the level of triglyceride both before and after the start of steroid treatment was significantly higher in patients with ONFH. The level of triglyceride before PSL therapy, rather than that after PSL therapy, might therefore be a more reliable predictor of silent ONFH. As the interaction between triglyceride before PSL therapy and initial dose of PSL was not significant, the effect of triglyceride before PSL therapy on silent ONFH would not have been modified by the initial dose of subsequent PSL. Several studies have revealed that a high triglyceride level is a risk factor for ischemic heart disease and stroke [20–22]. ONFH is caused by partial or total disruption of blood flow to the femoral head, and SLE patients tend to develop silent ONFH through a similar mechanism. In addition, it is well known that steroid treatment induces iatrogenic metabolic syndrome, and in view of this, a high triglyceride level is considered to be an important risk factor for silent ONFH.

Furthermore, the level of total cholesterol after steroid treatment tended to be higher in patients with silent ONFH. Nevertheless, the levels of HDL-C and LDL-C were not correlated with silent ONFH. As described previously, the total cholesterol level after 1 month of steroid treatment was significantly higher in the silent ONFH group than that in the non-ONFH group. Our data are similar to those reported previously [12].

In conclusion, we studied 78 SLE patients, including 32 femoral joints in 21 patients, using MRI for 3 months after initial corticosteroid administration. The incidence of silent ONFH was 26.9 %. The level of triglyceride was significantly higher in patients with silent ONFH, both before treatment and 4 weeks after steroid initiation. In addition, hypercholesterolemia 4 weeks after steroid initiation tended to be predictive of silent ONFH. Large epidemiologic surveys of early events such as silent ONFH in this patient population will be necessary.

Acknowledgments This study was supported by a research grant from the Research Committee on Idiopathic Osteonecrosis of the Femoral Head of the Ministry of Health, Labour, and Welfare of Japan.

Disclosures None.

References

1. Abeles M, Urman JD, Rothfield NF (1978) Aseptic necrosis of bone in systemic lupus erythematosus. Relationship to corticosteroid therapy. Arch Intern Med 138:750–754
2. 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
3. Landmann J, Renner N, Gächter A, Thiel G, Harder F (1978) Cyclosporin A and osteonecrosis of the femoral head. J Bone Joint Surg Am 69:1226–1228
4. Mont MA, Hungerford DS (1995) Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 77:459–474
5. Moskal JT, Topping RE, Franklin LL (1997) Hypercholesterolemia: an association with osteonecrosis of the femoral head. Am J Orthop 26:609–612
6. Oinuma K, Harada Y, Nawata Y, Kobayashi K, Abe I, Kamikawa K, Moriya H (2000) Sustained hemostatic abnormality in patients with steroid-induced osteonecrosis in the early period after high-dose corticosteroid therapy. J Orthop Sci 5:374–379
7. Ichiseki T, Matsumoto T, Nishino M, Kaneuji A, Katsuda S (2004) Oxidative stress and vascular permeability in steroid-induced osteonecrosis model. J Orthop Sci 9:509–515
8. Iuchi T, Akaike M, Mitsui T, Ohshima Y, Shintani Y, Azuma H, Matsumoto T (2003) Glucocorticoid excess induces superoxide production in vascular endothelial cells and elicits vascular endothelial dysfunction. Circ Res 92:81–87
9. Bombardier C, Gladman DD, Urowitz MB, Carton D, Chang CH (1992) Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum 35:630–640
10. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Modification of the modification of diet in renal disease (MDRD) study equation for Japan. Am J Kidney Dis 50:927–937
11. DuBois D, DuBois EF (1989) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871
12. Nagasawa K, Tada Y, Koarada S, Horiuchi T, Tsukamoto H, Murai K, Ueda A, Yoshizawa S, Ohta A (2005) Very early development of steroid-associated osteonecrosis of femoral head in systemic lupus erythematosus: prospective study by MRI. Lupus 14:385–390
13. Seleznick MJ, Silveira LH, Espinoza LR (1991) Avascular necrosis associated with anticardiolipin antibodies. J Rheumatol 18:1416–1417
14. Calvo-Alén J, McGwin G, Toloza S, Fernández M, Roseman JM, Bastian HM, Cepeda EJ, González EB, Baethge BA, Fessler BJ, Vilá LM, Reveille JD, Alarcón GS, LUMINA Study Group (2006) Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXIV. Cytotoxic treatment is an additional risk factor for the development of symptomatic osteonecrosis in lupus patients: results of a nested matched case-control study. Ann Rheum Dis 65:785–790
15. Takahashi S, Fukushima W, Kubo T, Iwamoto Y, Hirota Y, Nakamura H (2012) Pronounced risk of nontraumatic osteonecrosis of the femoral head among cigarette smokers who

have never used oral corticosteroids: a multicenter case-control study in Japan. J Orthop Sci 17:730–736
16. Wang GJ, Cui Q, Balian G (2000) The pathogenesis and prevention of steroid-induced osteonecrosis. Clin Orthop Relat Res 370:295–310
17. Nishida K, Yamamoto T, Motomura G, Jingushi S, Iwamoto Y (2008) Pitavastatin may reduce risk of steroid-induced osteonecrosis in rabbits. Clin Orthop Relat Res 466:1054–1058
18. Sekiya F, Yamaji K, Yang K, Tsuda H, Takasaki Y (2010) Investigation of occurrence of osteonecrosis of the femoral head after increasing corticosteroids in patients with recurring systemic lupus erythematosus. Rheumatol Int 30:1587–1593
19. Fesslar BJ, Boumpas DT (1995) Severe major organ involvement in systemic lupus erythematosus. Diagnosis and management. Rheum Sis Clin North Am 21:81–98
20. Noda H, Iso H, Saito I, Konishi M, Inoue M, Tsugane S, JPHC Study Group (2009) The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. Hypertens Res 32:289–298
21. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M, Asia Pacific Cohort Studies Collaboration (2004) Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. Circulation 110:2678–2686
22. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V (2007) Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 115:450–458