Outcomes of Symptomatic Osteonecrosis in 95 Patients with Systemic Lupus Erythematosus

DAFNA D. GLADMAN, VANDANA CHAUDHRY-AHLUWALIA, DOMINIQUE IBAÑEZ, EARL BOGOCH, and MURRAY B. UROWITZ

ABSTRACT. ***Objective.*** To describe the frequency and type of symptomatic osteonecrosis (ON) in a large cohort of patients with systemic lupus erythematosus (SLE) followed in a single center and to describe the outcome in terms of mortality and disability compared to SLE patients without ON.

Methods. Patients with ON were identified from the University of Toronto Lupus Clinic Database. The diagnosis of ON was confirmed by radiographs, bone scans, tomograms, or magnetic resonance images. A comparison group of patients with SLE without ON was selected from the same database, matched by year of birth, sex, and year of entry to the clinic. Mortality, disability, and health related quality of life were compared between patients with and without ON.

Results. Ninety-nine patients with ON were identified with 217 affected joints, the majority hips and knees, often in a bilateral distribution. There was no increase in mortality. Patients with ON had higher Health Assessment Questionnaire scores and lower SF-20 scores of physical functioning, suggesting increased disability. Hip joints that underwent surgery were more likely to have higher grades of ON at diagnosis.

Conclusion. Symptomatic ON occurred in 12.8% of 744 patients with SLE and often involved multiple joints. ON was not associated with increased mortality but was associated with physical disability. Radiological class of the hip joints at diagnosis of ON was predictive of subsequent surgery. (J Rheumatol 2001;28:2226–9)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
AVASCULAR NECROSIS
PROGNOSIS
OUTCOMES

Osteonecrosis (ON) is a frequently seen complication in systemic lupus erythematosus (SLE). It was initially described by Dubois and Cozen in 11 of 400 patients with SLE[1]. Subsequent reports describe an occurrence of ON in 5–40% of patients with SLE[2-12]. Symptomatic ON has been reported in 10–12% of patients with SLE. Higher prevalences have been reported in series in which magnetic resonance imaging (MRI) was used for its detection[6].

From the University of Toronto Lupus Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, University Health Network, Toronto Western Hospital, and the Department of Orthopedics, St. Michael's Hospital, Toronto, Ontario, Canada.

Supported by The Arthritis Society, The Ontario Lupus Association, and The Lupus Databank Research Program.

D.D. Gladman MD, FRCPC, Professor of Medicine, University of Toronto, Deputy Director, Centre for Prognosis Studies in the Rheumatic Diseases; V. Chaudhry-Ahluwalia, MD, FRCPC, Geoff Carr Ontario Lupus Association Lupus Fellow; D. Ibanez, MSc, Biostatistician, Centre for Prognosis Studies in the Rheumatic Diseases; E. Bogoch, MD, FRCPC, Associate Professor of Surgery, University of Toronto, Department of Orthopedics, St. Michael's Hospital; M.B. Urowitz, MD, FRCPC, Professor of Medicine, University of Toronto, Director, Centre for Prognosis Studies in the Rheumatic Diseases.

Address reprint requests to Dr. D. Gladman, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, 399 Bathurst Street, MP 1-318, Toronto, Ontario, Canada, M5T 2S8.
E-mail:dafna.gladman@utoronto.ca

Submitted October 19, 2000; revision accepted April 27, 2001.

Studies to date have reported on small numbers of patients with ON varying from 7 to 40 per study. Several studies included only patients with ON of the hips. The consequence of ON with regards to mortality and disability has not been described. The aims of our investigation were: (1) to describe the frequency and distribution of ON in a large cohort of patients with SLE followed in a single center; (2) to analyze the outcomes in terms of joint surgery in patients with ON; and (3) to analyze mortality and disability in patients with ON compared to age, sex, and year of entry matched SLE patients without ON from the same cohort.

MATERIALS AND METHODS

The University of Toronto Lupus Clinic Cohort. A total of 744 patients with SLE were registered and followed at the University of Toronto Lupus Clinic between 1970 and 1995. The patient population is similar to other large series[13]. Patients are followed at the clinic at 2–6 month intervals. At each visit a complete history, physical examination, and laboratory evaluation are carried out, including a history of avascular necrosis and appropriate radiographs where applicable. All information collected on these patients is entered into a computer database.

Patients with ON. A search of the Lupus Clinic Database identified 95 patients with ON. The diagnosis of ON was suspected clinically and confirmed by radiographic evaluation. A modification of the Marcus and Enneking staging system was used for the diagnosis of ON by radiographs[14]. When radiographs were unavailable we were still able to grade the severity of ON based on the radiologic report, a system we demon-

strated as valid[14]. If radiographs were normal, but the clinical suspicion was still present, other imaging techniques such as bone scans, tomograms, or MRI were utilized.

Comparison group. For each patient with ON, a control was chosen from the same database matched for year of birth, sex, and year of entry to the clinic. These controls did not have evidence of ON in the course of followup at our clinic.

Outcome measures. Surgery for the affected joints for the patients with ON was recorded. Patients completed health assessment instruments including the Health Assessment Questionnaire (HAQ) and the Medical Outcome Trust Short Form 20 (SF-20)[15-17]. All-cause mortality was calculated for patients with ON and the controls.

Statistical analysis. Simple statistics were calculated for demographic information. One way analysis of variance and chi-square tests of association were used to examine the HAQ and SF-20 scores. Kaplan-Meier survival curves with log rank test were used to compare survival rates in patients and controls.

RESULTS

Of the 744 patients recorded in the Lupus Clinic database, 95 (12.8%) were documented with sustained osteonecrosis. There were 78 women and 17 men, mostly Caucasian, with a mean age at diagnosis of 28.4 years and a mean age at diagnosis of ON of 36.7 years, and a mean disease duration of 8.29 years (Table 1). The control group was well matched to the patient group (Table 1). Of note, the degree of disease activity at presentation to the clinic as measured by the SLE Disease Activity Index (SLEDAI)[18] was similar in both groups. Overall, 217 joints were involved with ON in the 95 patients (Table 2). The majority (184) were identified by radiographs and reports. Twenty-two joints were identified by bone scan, 8 by MRI, and one by tomogram. The joints most commonly affected were the hips and knees, often in a bilateral distribution. Shoulders, ankles, elbows, and wrists were also involved but in a lower frequency. Table 3 outlines the number of joints affected per patient. The majority of the patients (70.5%) had 2 or more joints affected, while less than a third of the patients had ON in only one joint. Of the 28 patients who had a single joint affected with ON, 13 had ON of the hip, 9 had ON of a knee, 2 each had isolated wrist and shoulder involvement, and one each had ankle and elbow.

Table 1. Demographics for patients with ON and controls.

Feature	Patients with ON	Controls
No. of patients	95	95
Female/Male	78/17	78/17
Caucasian/black/other	77/9/9	79/8/8
Alive/dead	83/12	82/13
Age at diagnosis of SLE*, yrs	28.4 (8.8–55)	32.7 (14–73.6)
Age at presentation to Clinic*, yrs	32.5 (17.2–69.9)	35.1 (15.4–73.9)
Age at diagnosis of ON*, yrs	36.7 (17.2–66.4)	NA
Disease duration at ON*, yrs	8.29 (0–33.5)	NA
SLEDAI at presentation**	12.0 (0–51)	11.7 (0–56)
SLEDAI score at ON*	6.7 (0–32)	NA

* Mean (range) in years; ** mean score (range); NA: not available.

Table 2. Pattern of ON in 95 patients with SLE.

Sites Affected	No. of Patients		No. of Joints
	Unilateral	Bilateral	
Hips	16	52	120
Knees	16	18	52
Shoulders	5	9	23
Ankles	5	5	15
Elbows	2	1	4
Wrists	3	0	3
Total	47	85	217

Table 3. Number of joints involved per patients in 95 patients with ON.

Joint Count	Frequency (%)
1	28 (29.5)
2	43 (45.3)
3	10 (10.5)
4	9 (9.5)
5	1 (1.1)
6	1 (1.1)
8	2 (2.1)
10	1 (1.1)

Total joints affected 217.

Eighty-four of the 217 joints underwent surgical procedures. Of those, 70 were prosthetic joints and 14 nonprosthetic procedures, including 2 joint fusions, 3 osteotomies, one core biopsy with vascular graft, 5 arthroscopies, and 3 allografts. Sixty-seven of the 120 hips (56%) were surgically treated at last followup and 53 (44%) were not. There was no difference in disease duration at the time of diagnosis of ON between patients who did and did not have surgical intervention for ON of the hip (disease duration 7.35 ± 6.7 vs 6.89 ± 5.4 years, respectively). Moreover, patients who had a surgical intervention, had it within 3.1 years of diagnosis of ON, while those who did not have surgery were followed for a mean of 7.17 ± 5.5 years following the diagnosis of ON. Radiologic grading at the time of diagnosis of ON was available for 58 of the 67 hip joints that underwent surgery, and of those, 62% had grade 3 or 4 ON at diagnosis. Of the 53 hips that did not have surgery, 51 had radiological grading at diagnosis, and only 13 (25.5%) of those were graded as Marcus-Enneking grade ≥ 3 at diagnosis. Thus, a higher radiological grade at diagnosis was predictive of surgery for ON of the hip ($p \leq 0.001$; Table 4).

There was no difference in mortality between patients with ON and their controls. Twelve of the 95 patients with ON and 14 of the 95 controls have died. Kaplan-Meier survival curves showed no difference in the survival rates in both groups ($p = 0.27$) (Figure 1). The curve remains the same if we use duration of followup as the time line. Causes of death were similar in the 2 groups. Causes of death

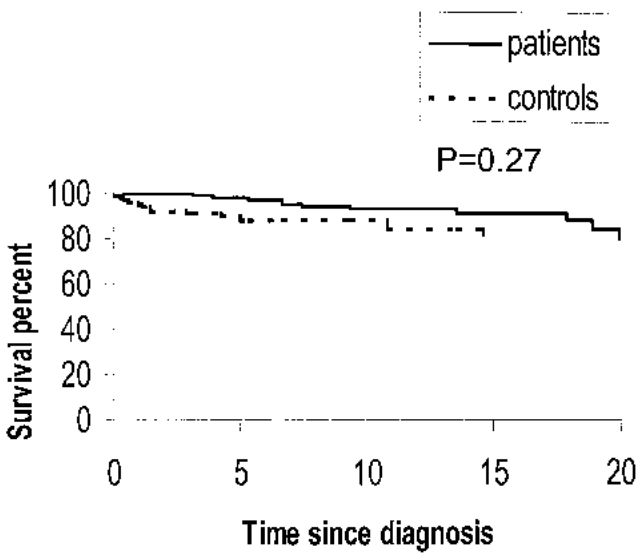

Figure 1. Kaplan-Meier survival curves for SLE patients with osteonecrosis and matched controls.

among the ON patients and controls included: active lupus: 5 and 6, respectively; infection: 3 and 5, respectively; myocardial infarction: 2 and one, respectively, and one patient in each group died of a malignancy and another died of unknown cause.

The degree of disability as measured by the HAQ and health related quality of life measured by the SF-20 in 65 patients with ON were compared to those of the 53 control group who completed these measures. As shown in Table 5, the total HAQ score, excluding pain, was significantly higher in the patients with ON compared to their controls, although there was no difference in the pain score. The physical functioning domain of the SF-20 also revealed impairment in the ON patient group compared to the control group. Patients who underwent surgery did not differ from patients who did not undergo surgery with regards to their HAQ or SF-20 scores.

Table 4. Radiologic grade at diagnosis and surgery for ON of the hip in SLE.

Radiologic Grade at Diagnosis	Surgery, n = 58 n = 58 (%)	No Surgery, n = 51 (%)
Grade 1 or 2	22 (37.9)	38 (74.5)
Grade 3 or more	36 (62.1)	13 (25.5)

$p \leq 0.001$

Table 5. Disability and Health Related Quality of Life scores in patients with ON compared to controls.

	Patients with ON, n = 65	Controls, n = 53	p*
HAQ (excluding pain)	0.7	0.4	0.012
HAQ pain score	1.1	0.9	0.39
Physical functioning	52.4	72.1	0.0023
Role functioning	44.0	50.9	0.40
Social functioning	75.2	78.8	0.47
Mental health	70.2	68.6	0.69
Pain	50.5	56.4	0.24
Health perception	47.1	48.4	0.80

* One-way analysis of variance.

DISCUSSION

ON is a frequent complication in patients with SLE, and has been recognized as a feature of the accumulated damage in SLE[19]. Its frequency has varied in the literature, and has largely depended on the method used to identify the ON. The frequency of symptomatic ON varies from 5 to 12%. However, if newer modalities are used to make the diagnosis, the frequency increases to 30–52%[2,6,10,20,21]. Thus, there is a population of patients with SLE who have asymptomatic ON. It has been suggested that early surgical therapy is indicated to prevent morbidity in patients with ON[22]. However, Aranow, *et al*[12] found that only one of their patients with clinically occult MRI detected ON of the hip developed symptoms at one year. Similarly, only a small proportion (2 of 8) of the patients who demonstrated ON by MRI went on to develop any clinical or radiological abnormalities after 3 years of followup in the study of Nagasawa, *et al*[21].

Our study of 744 patients followed since 1970 revealed that the frequency of symptomatic ON is 12.8%. While we do not perform radiographs routinely on all our patients, we do assess them regularly for any indication of lupus activity or its complications. Thus we are confident that we were able to document the frequency of symptomatic ON accurately in our patient population. This large cohort of patients with ON allowed us to evaluate the frequency of the joints affected by ON in patients with SLE, as well as to document the occurrence of multiple joint involvement in the same patient. In our 95 patients we documented ON in 217 joints. The majority of the patients had ON of the hips or knees, most with bilateral involvement. Of the 217 joints that had ON, 84 were surgically treated, 70 with joint replacement and 14 with other procedures. Hips that were graded high (≥ 3) on the Modified Marcus-Enneking classification at diagnosis of ON were more likely to require surgery. It is possible that in these patients the progression of ON was more aggressive, as joint destruction occurred early. However, it should be noted that 44% of the hips with ON clinically and radiologically were not treated surgically. Indeed, of the patients with ON grade 3 or higher, 25.5% did not undergo a surgical procedure at the time of the study. This suggests that not all joints affected by ON result in complete joint destruction. Moreover, some joints with ON become asymptomatic and do not require further intervention.

This is the first study to document outcomes in patients with SLE who develop ON. We investigated whether the presence of ON was associated with increased mortality and found that mortality was the same in both patients and controls and that the survival curves were similar, suggesting that there was no effect of the ON process on survival. However, ON clearly affects quality of life of patients with SLE, particularly their physical function. Both the HAQ and the physical functioning domain of the SF-20 showed significant impairment among patients with ON compared to the SLE patients who did not have ON. This was not related solely to pain, since both the HAQ pain score and the pain domain of the SF-20 were similar among patients with and without ON. The results were unaffected by surgery, as patients with or without surgery had similar scores for both the HAQ and the SF-20.

Thus, ON is common among patients with SLE, occurring in 12.8% of our patients, a frequency in keeping with previous reports. ON results in disability and reduced physical function, but has no effect on mortality. Some patients with SLE and ON can manage without surgical procedures. While we have shown that the presence of previously documented arthritis, and use and dose of corticosteroids and immunosuppressive medications are predictive for the development of ON[23], further studies are necessary to clarify the factors that lead to the impaired quality of life and reduced physical function.

REFERENCES

1. Dubois EL, Cozen L. Avascular (aseptic) bone necrosis associated with systemic lupus erythematosus. JAMA 1960;174:966-71.
2. Zizic TM, Marcoux C, Hungerford DS, Dansereau JV, Stevens MB. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. Am J Med 1985;79:596-604.
3. Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. J Rheumatol 1987;14 Suppl 13:223-6.
4. Weiner ES, Abeles M. Aseptic necrosis and glucocorticosteroids in systemic lupus erythematosus: a reevaluation. J Rheumatol 1989;16:604-8.
5. Massardo L, Jacobelli S, Leissner M, Gonzalez M, Villarroel L, Rivero S. High-dose intravenous methylprednisolone therapy associated with osteonecrosis in patients with systemic lupus erythematosus. Lupus 1992;1:401-5.
6. Halland AM, Klemp P, Botes D, Van Heerden BB, Loxton A, Scher AT. Avascular necrosis of the hip in systemic lupus erythematosus: the role of magnetic resonance imaging. Br J Rheumatol 1993;32:972-6.
7. Migliaresi S, Picillo U, Ambrosone L, et al. Avascular osteonecrosis in patients with SLE: relation to corticosteroid therapy and anticardiolipin antibodies. Lupus 1994;31:37-41.
8. Watanabe T, Tsuchida T, Kanda N, Tamaki K. Avascular necrosis of bone in systemic lupus erythematosus. The predictive role of precipitating autoantibodies. Scand J Rheumatol 1997;26:184-7.
9. Mont MA, Glueck CJ, Pacheco IH, Wang P, Hungerford DS, Petri M. Risk factors for osteonecrosis in systemic lupus erythematosus. J Rheumatol 1997;24:654-62.
10. Houssiau FA, N'Zeusseu Toukap A, Depresseux G, et al. Magnetic resonance imaging-detected avascular osteonecrosis in systemic lupus erythematosus: lack of correlation with antiphospholipid antibodies. Br J Rheumatol 1998;37:448-53.
11. Mok CC, Lau CS, Wong RW. Risk factors for avascular bone necrosis in systemic lupus erythematosus. Br J Rheumatol 1998;37:895-900.
12. Aranow C, Zelicof S, Leslie D, et al. Clinically occult avascular necrosis of the hip in systemic lupus erythematosus. J Rheumatol 1997;24:2318-22.
13. Gladman DD, Urowitz MB. Systemic lupus erythematous — clinical features. In: Klippel JH, Dieppe PA, editors. Rheumatology. St. Louis: Mosby; 1997:711-18.
14. Chaudhry-Ahluwalia V, Gladman DD, Urowitz MB, Bogoch E, Farewell VT. Radiographic reports in osteonecrosis of the hip in systemic lupus erythematosus. Clin Orthop 1998;352:131-6.
15. Fries JF, Spitz P, Kraines RG, Holman HH. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:127-45.
16. Stewart AL, Hays RD, Ware JE. The MOS Short-form General Health Survey. Medical Care 1988;26:724-34.
17. Gladman D, Urowitz M, Ong A, Gough J. A comparison of five health status instruments in patients with systemic lupus erythematosus (SLE). Lupus 1996;5:190-5.
18. Bombardier C, Gladman DD, Urowitz MB, Charron D, Chang CH, and The Committee on Prognosis Studies in SLE. The development and validation of the SLE Disease Activity Index (SLEDAI). Arthritis Rheum 1992;35:630-40.
19. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the SLICC/ACR damage index for SLE. Arthritis Rheum 1996;39:363-9.
20. Zizic TM, Hungerford DS, Stevens MB. Ischemic bone necrosis in systemic lupus erythematosus. I. The early diagnosis of ischemic necrosis of bone. Medicine 1980;59:134-42.
21. Nagasawa K, Tsukamoto H, Tada Y, et al. Imaging study on the mode of development and changes in avascular necrosis of the femoral head in systemic lupus erythematosus: long-term observations. Br J Rheumatol 1994;33:343-7.
22. Hungerford DS, Zizic TM. The treatment of ischemic necrosis of bone in systemic lupus erythematosus. II. Medicine 1980;56:143-8.
23. Gladman DD, Urowitz MB, Chaudhry-Ahluwalia V, Hallett D, Cook RJ. Predictive factors for symptomatic osteonecrosis in systemic lupus erythematosus. J Rheumatol 2001;28:761-5.