# Prevalence and risk factor for symptomatic avascular necrosis development in Thai systemic lupus erythematosus patients

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## Summary

***Background:*** **Avascular necrosis (AVN) has been reported in systemic lupus erythematosus (SLE) and most SLE patients suffer from this problem.**

***Objectives:*** **To study the prevalence of AVN in Thai SLE patients and to determine the risk factors for developing AVN.**

***Methods:*** **A retrospective study was performed, between January 1, 1995 and August 31, 2005, on patients over 15 years of age in Khon Kaen, Thailand.**

***Results:*** **The medical records of 736 SLE patients were reviewed. The female to male ratio was 15.4:1. The prevalence of AVN was 8.8%. The average age at the time of AVN detection was 27 years (range, 18-54) and the average duration of disease 69 months (range, 12-112). All cases were AVN of the hip joint. The factors correlated with AVN included: long duration of disease, history of previous septic arthritis in the ipsilateral hip to the AVN development, hematological involvement, gastrointestinal involvement, arthritis and cutaneous vasculitis. After regression analysis, hematological involvement and long duration of disease were associated with AVN with a respective odds ratio of 3.13 (95%CI 1.13-8.54) and 1.01 (95%CI 1.00-1.02). Neither high-dose steroid nor antimalarial treatment were correlated with AVN in our study and 4.6% (n=3) of patients had never received steroid therapy during the follow-up period.**

***Conclusion:*** **Prevalence of symptomatic AVN was 8.8% in our SLE patients. A longer duration of disease and hematological involvement were associated with AVN development.** ***(Asian Pac J Allergy Immunol 2012;30:152-7)***


***Key words:*** *systemic lupus erythematosus, avascular necrosis, osteonecrosis, arthritis, autoimmune disease*

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## Introduction

Systemic lupus erythematosus (SLE) is a serious autoimmune disease which commonly occurs among women of childbearing age.[1-3] The disease may cause organ inflammation and permanent structural damage. Patients can suffer from complications of the disease or the side effects of its treatment. Avascular necrosis (AVN) is not an uncommon complication in SLE. The prevalence varies between 4 and 27%.[4-7] AVN is characterized by death of the bone marrow and trabecular bone due to disruption of the blood supply.[8] The femoral head is the most commonly affected bone and bilateral AVN has been documented.[4,6,9] The other affected sites include the knee, ankle, shoulder, elbow and wrist.[9]

The etiopathogenesis of AVN in SLE is not clear but it is likely caused by multiple factors such as high-dose or long-duration steroid therapy,[6,7,9-11] immunosuppressant therapy,[6,9,10] positivity for anti-phospholipid antibody,[7] lupus nephritis,[5] neuropsychiatric lupus[6] and Cushingoid status.[6] By contrast, anti-malarials seem to be a protective factor against developing AVN.[5,6] Steroid use is an important risk factor of AVN; some reports indicate a negative association between steroid treatment and AVN development[4,5] while others show a positive association between steroid treatment and the presence of the anti-phospholipid antibody,[4,5,9,10] lupus nephritis[6,7,9] and neuropsychiatric lupus,[5,7,9] respectively. Moreover, some patients developed AVN without any history of steroid therapy.[12] Since

**Table 1.** Clinical differences between the AVN and no AVN groups.

| Clinical characteristics | AVN group N = 65 | No AVN group N = 671 | Odds ratio (95%CI) | *p*-value |
|---|---|---|---|---|
| Age at onset of disease (years) (median, range) | 27 (12-54) | 27 (14-67) | | 0.90 |
| Duration of disease (months) (median, range) | 69.1 (12-112) | 61.2 (0.25-158) | | <0.001* |
| Gender | | | | |
| Male | 7.7% | 5.8% | 1 | |
| Female | 92.3% | 94.2% | 1.28 (0.54-3.03) | 0.578 |
| Coexisting diseases | | | | |
| Diabetes mellitus | 69.8% | 60.8% | 1.49 (0.83-2.76) | 0.159 |
| Hypertension | 18.5% | 14.3% | 1.35 (0.64-2.69) | 0.366 |
| Dyslipidemia | 14.9% | 9.2% | 1.71 (0.61-4.24) | 0.218 |
| History of ipsilateral septic arthritis | 15.6% | 8.1% | 6.02 (2.38-14.24) | <0.001* |
| Organ involvement | | | | |
| Pulmonary involvement | 0 | 10.0% | - | 0.158 |
| Cutaneous vasculitis | 20% | 3.0% | 6.51 (1.76-19.8) | 0.045* |
| Gastrointestinal involvement | 20.3% | 9.1% | 5.44 (0.85-26.13) | 0.008** |
| Neuropsychiatric lupus | 18.8% | 11.2% | 1.54 (0.67-3.23) | 0.234 |
| Lupus nephritis | 40.6% | 34.6% | 1.29 (0.73-2.25) | 0.333 |
| Synovitis | 28.1% | 14.0% | 2.40 (1.25-4.23) | 0.003* |
| Skin rash | 32.8% | 22.5% | 1.68 (0.92-2.99) | 0.064 |
| Hematologic involvement | 35.9% | 17.0% | 2.73 (1.50-4.87) | <0.001* |
| Serositis | 4.7% | 3.1% | 1.51 (0.28-5.30) | 0.506 |
| Treatment | | | | |
| High dose steroid | 66.2% | 61.5% | 1.07 (0.61-1.89) | 0.809 |
| Immunosuppressive agent[1] | 50.8% | 44.6% | 1.30 (0.76-2.21) | 0.337 |
| Antimalarial drug[2] | 21.0% | 31.9% | 0.57 (0.28-1.07) | 0.076 |

*statistical significant

**no statistical significant by 95%CI but *p*-value <0.05

[1]included cyclophosphamide, azathioprine, cyclosporine and mycophenolate mofetil

[2]included chloroquine and hydroxychloroquine

the trends are unclear and most of studies include a low number of SLE patients, we decided to investigate the prevalence of AVN and to assess the risk of AVN development among SLE patients in a large population.

## Methods

All of the medical records—between January 1, 1995 and August 31, 2005—from the Department of Medical Records and Registration were searched for patients over 15 in Khon Kaen, (northeastern) Thailand, with a diagnosis of SLE. All of the patients fulfilled the American College of Rheumatology 1997 revised criteria for SLE.[13] We reviewed and recorded their chronological data, clinical data indicating arthritis, disease duration, laboratory data, radiographic data, medical treatment and outcomes.

The categorical data were reported as percentages and the continuous data as a mean ± SD. The odds ratio was calculated to compare the outcomes among the categorical data. The Student *t* test was used for comparisons of the continuous data with a normal distribution while the Wilcoxon-Rank sum or Kruskal-Wallis test was used for those with a non-normal distribution. All of the statistical tests were two-tailed and a p-value < 0.05 was considered statistically significant. All of the data analyses were performed using STATA version 11.0 (StataCorp Inc., College Station, Texas, USA).

**Table 2.** Multivariate analysis of clinical predictors of AVN development.

| Clinical characteristics | Crude odds ratio (95%CI) | Adjusted odds ratio (95%CI) | *p*-value |
|---|---|---|---|
| Duration of disease (months) | | 1.01 (1.00-1.02) | 0.001* |
| History of ipsilateral septic arthritis | 6.02 (2.38-14.24) | 1.30 (0.89-1.90) | 0.170 |
| Coexisting diabetes mellitus | 1.49 (0.83-2.76) | 0.58 (0.18-1.82) | 0.345 |
| Cutaneous vasculitis | 6.51 (1.76-19.8) | 1.78 (0.19-16.31) | 0.608 |
| Synovitis | 2.40 (1.25-4.23) | 1.42 (0.48-4.26) | 0.520 |
| Hematologic involvement | 2.73 (1.50-4.87) | 3.13 (1.13-8.54) | 0.026* |
| Antimalarial treatment | 0.57 (0.28-1.07) | 0.58 (0.18-1.81) | 0.345 |

*Statistically significant

AVN was diagnosed when the patient was symptomatic and the presence of AVN had been confirmed by conventional radiography or magnetic resonance imaging. The date of SLE diagnosis was the time that SLE was diagnosed. If the patient was diagnosed with SLE before being referred to our hospital, the date of SLE diagnosis at the local hospital was entered as the date of SLE diagnosis. The date of AVN diagnosis was the time that AVN was detected. Duration of disease at the time of AVN diagnosis was calculated by subtracting the date of AVN diagnosis from the date of SLE diagnosis. The duration of disease in patients who had no AVN was calculated by subtraction between the date of study and the date of SLE diagnosis.

Major organ exacerbations was defined as organ involvement that needed high-dose steroid treatment. Any pulmonary disease associated with SLE (*i.e.*, pulmonary haemorrhage, pneumonitis or interstitial lung disease) constituted pulmonary involvement. Any gastrointestinal disease associated with SLE (*e.g.*, gastrointestinal vasculitis) constituted gastrointestinal involvement. Hematologic involvement was defined as any hematologic problem associated with SLE (*e.g.*, lymphopenia, haemolytic anemia or thrombocytopenia). Serositis included pleuritis and pericarditis. Skin involvement was defined by any dermatologic problem associated with SLE; such as malar rash, oral ulcer, discoid lupus or photosensitivity rash. High-dose steroid therapy was defined as a steroid dosage equivalent to prednisolone > 30 mg/day at any time during follow-up. The maximum dose of steroid therapy was the highest dose of steroid therapy at any time during the disease and the dosage was calculated to the equivalent dose of prednisolone.

## Results

The study included 736 patients, mostly female (691 cases). AVN was identified in 65 cases. The prevalence of symptomatic AVN in our study was 8.8% (95%CI 6.8-10.9). Median age and median duration of disease at the time of AVN diagnosis was 27 years (interquartile range; IQR 18-54) and 69 months (IQR 12-112), respectively. All were AVN of the femoral head. Bilateral AVN was recorded in 21 cases (32.3%)

Long duration of disease, history of ipsilateral septic arthritis of the hip joint, cutaneous vasculitis, gastrointestinal involvement, synovitis and hematologic involvement were significantly more frequently found in the AVN group than in the non-AVN group (Table 1). After performing multivariate analysis, only hematologic involvements and long duration of disease were related to diagnosis of AVN with an odds ratio (OR) of 3.13 (95%CI 1.13-8.54) and 1.01 (1.00-1.02), respectively (Table 2).

Three of the AVN patients (4.6%) had never received any steroid treatment during the follow-up period and none had history of alcohol intake, septic arthritis or trauma of the involved joint.

Core decompression and prosthetic joint replacement was performed in 2 (3%) and 35 of our 65 AVN patients (53.8%), respectively. Two patients initially had core decompression and their clinical condition temporarily improved but later prosthetic joint replacement was needed.

## Discussion

The prevalence of symptomatic AVN in our study was not different from that in previous reports (Table 3). Interestingly, however, AVN was detected following ipsilateral septic arthritis of hip in 15% of our AVN patients. According to anatomical vascular structure, the ligamentum teres artery, medial circumflex artery and lateral circumflex artery are the main blood supply to the femoral head. Nonetheless, there are few areas of vascular anatomosis[14] and whenever a blood vessel is disrupted, there is a risk of developing AVN. An abrupt increase in intra-articular pressure due to septic

**Table 3.** Comparison of clinical predictors of AVN development with data from previous studies.

| Data | Our study | Gladman DD. | Mok CC. | Mok MY. | Nagasawa K. | Calvo-Alén J. | Uea-areewongsa P. |
|---|---|---|---|---|---|---|---|
| Years | 1995-2005 | 1970-1995 | 1971-1997 | 1978-1998 | 1980-1987 | 2005 | 1992-2008 |
| Number of SLE patients | 736 | 744 | 320 | 265 | 111 | 571 | 186 |
| Number of AVN (%) | 65 (8.8%) | AVN 70 cases control 70 cases | 38 (12%) | 11 (4%) | 24 (21.6%) | AVN 39 cases Control 59 cases | 41 (22%) AVN 20 cases Control 20 cases |
| Age at SLE onset (years) (mean, range) | | 29.8 (8.8-55) | 26.6 (10-54) | 21.3 (17-28) | 24.1 (10-42.3) | | 28.7 |
| Age at presentation of AVN (years) (mean, range) | 27 (18-54) # | - | | 30.5 (21-40) | - | | 32.7 |
| Disease duration at presentation of AVN (years) (mean, range) | 5.8 (1-9.3) # | 7.9 (0.3-33.2) | 6.0 | 9.2 (2-23) | 4.1 (1.2-13) | 3.9 | 4.4 |
| Site of AVN | Hip 100% | Hip 54.2%, Knee 24.8% Ankle 5.9%, Shoulder 11.8%, Elbow 2.0%, Wrist 1.3% | Hip 95%, knee 13%, humerus 3%, carpal bone 3% | Hip 91% | Mostly Hip | - | Hip 100% |
| Bilateral AVN | 32.3% | 38.6% | 72% | 70% (hip) | 83.3% (hip) | - | 100% |
| Factors associated with AVN | | | | | | | |
| Longer duration of disease | OR 1.01 (1.00-1.02)* | - | Not related | - | - | Not related | Not related |
| Coexisting disease | | | | | | | |
| Diabetes mellitus | Not related* | - | Not related | - | - | Not related | NA |
| Hypertension | Not related | - | Not related | - | Not related | Not related | Not related |
| Dyslipidemia | Not related | Not related | - | - | Not related | Not related* | - |
| History of ipsilateral septic arthritis | OR 1.30 (0.89-1.90) | - | - | - | - | - | - |
| Organ involvement | | | | | | | |
| Pulmonary involvement | NA | - | - | - | - | - | - |
| Cutaneous vasculitis | OR 1.78 (0.19-16.31)* | Not related | Not related | - | - | - | - |
| Gastrointestinal involvement | Not related | - | - | - | - | - | - |
| Neuropsychiatric lupus | Not related | Not related | Related§ | - | Not related | - | Not related |
| Lupus nephritis | Not related | Not related | Related§ | - | Not related | - | OR 7.8 (1.25-48.75)* |
| Synovitis | Not related* | OR 4.2 (1.6-13.7)* | Not related | - | - | - | - |
| Skin rash | Not related | - | Related to photosensitivity rash§ | - | - | - | - |
| Hematologic involvement | OR 3.13 (1.13-8.54)* | - | Not related | - | Not related | - | - |
| Serositis | Not related | - | Not related | - | - | - | - |
| Anti-phospholipid antibody | - | Not related | Related to lupus anticoagulant§ | Not related | Related to lupus anticoagulant§ | Not related | Not related |
| Treatment | | | | | | | |
| Steroid | Not related | OR 18.5 (3.2-359.6)* | Related to mean daily dose§ | - | Related to maximal daily dose§ | Related to average dailay dose and highest dose§ | Not related* |
| Cumulative dose of steroid | - | Not related* | Not related | Not related | - | - | Not related |
| Immunosuppressive agent | Not related | OR 2.7 (1.02-8.8)* | Related to cyclophophamide§ | - | Not related | OR 3.89 (1.39-10.93) | Not related |
| Antimalarial drug | Not related* | Not related* | Related (negative relationship) § | - | - | Not related | OR 0.09 (0.01-0.96)* |

#median (interquartile range)
*multivariate analysis
§Odds ratio was not available.
NA: data could not be analyzed
SLE; systemic lupus erythematosus, AVN; avascular necrosis, SD; standard deviation, OR; Odds ratio

arthritis can result in disruption of the blood supply to the femoral head and the bone becomes ischemic[15]. Although there was no statistical support for this after performing a multivariate analysis to define the association between AVN development and the history of ipsilateral septic arthritis, practitioners should be aware that early recognition of septic arthritis of the hip joint might help to prevent the sequelae of AVN development.

According to our observations, the duration of disease was related to AVN diagnosis: (a) the longer the duration of the disease the greater the risk of lupus exacerbation and (b) the longer the exposure to high-dose steroid (and/or immunosuppressant therapy) the greater the immune suppression and predisposition to infection.

Septic arthritis of the hip joint was slightly more frequently found in patients who received high-dose steroid or immunosuppressant therapy than in those who received low-dose steroid therapy (8% vs. 2%, $p$ =0.24). Therefore, it is possible that the longer the duration of disease, the higher the risk of having AVN develop because this indirectly predisposes the hip joint to septic arthritis. The exact reason for this remains unknown.

Hematological involvement was the only clinical parameter related to the development of AVN in our SLE patients, particularly, among patients with hemolytic anemia. This result might be explained by the low oxygen-carrying capacity of red blood cells to the target tissue. The hip joint—*which is sensitive to ischemia*—might be affected by tissue hypoxia, which ultimately lead to AVN.

High-dose steroid therapy has been reported to be a predictor of AVN development. In our large series, however, there was no association between steroid therapy and AVN development. Moreover, 3 of our 65 AVN patients had no history of steroid use during the follow-up period. Our results, therefore, do not support the role of steroids in the development of AVN.

The limitations of our study include: (a) financial limitations for doing some tests (*i.e.,* lupus anti-coagulant, anti-cardiolipin antibody); (b) no record of the SLE disease activity index, so we were unable to define the associations between AVN and anti-phospholipid syndrome or SLE disease activity; (c) the inability to get an early diagnosis of AVN, so that we were not able to determine the true prevalence of AVN in SLE, which in the end includes asymptomatic patients; (d) the difficulty in defining the mean or median dose of steroid therapy because various steroid dosages were used during the follow up period based on organ involvement. We therefore did not investigate the association between AVN development and the mean or median dose of steroid treatment and, (e) the retrospective collection of data. However, due to our large cohort, the preliminary data may provide some baseline information to assist in the evaluation of SLE patients and could be used for better care of SLE patients in daily practice.

## Conclusion

The etiology of AVN in SLE patients is multifactorial. Practitioners should suspect AVN in patients who have (a) a longer of duration of disease or (b) hematological involvement. Importantly, AVN can be diagnosed early by using sensitive techniques.

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