Non-corticosteroid risk factors of symptomatic avascular necrosis of bone in systemic lupus erythematosus: A retrospective case-control study

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Abstract

Objective. Avascular necrosis of bone (AVN) is an important complication of systemic lupus erythematosus (SLE). Corticosteroid therapy has been underlined as a main risk factor for osteonecrosis. However, AVN development in patients who have never received corticosteroid and the absence of AVN in the majority of the patients, who received corticosteroid, propose a role for non-corticosteroid risk factors in AVN development.

Methods. This case-control study included two subsets: oral corticosteroid (66 AVN and 248 non-AVN patients) and pulse-therapy subset (39 AVN and 312 non-AVN patients) who have attended our Lupus clinic from 1979 to 2009. Patients received similar cumulative dose corticosteroid, equal maximum dose and 1-year maximum dose of corticosteroid. The demographic data (including sex, age of disease onset, age at the diagnosis of AVN, organs involvement, SLIDE Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics/ American College of Rheumatology-Damage index (SLICC/ACR-DI), number of disease flare ups were compared between two subsets.

Results. The mean age of SLE onset was younger (P value = 0.04) in the AVN patients. In oral corticosteroid subset, malar rash (P value < 0.001) and oral ulcer (P value = 0.003) were seen more frequently in non-AVN patients, whereas psychosis (P value = 0.03) was significantly more prevalent AVN subset in oral corticosteroid subset. In corticosteroid pulse subset, no significant difference in clinical features was noted.

Conclusion. In oral corticosteroid subset, younger age of disease onset and psychosis were significantly associated with AVN, whereas malar rash and oral ulcer showed negative association AVN.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that more frequently affects young women [1,2]. Avascular necrosis of bone (AVN) is a well-known complication of SLE that occurs in about 4–15% of patients which is the highest rate among rheumatological conditions [3–5]. AVN is considered a major link between SLE and orthopedic surgery [6]. Study by Mertelsmann-Voss et al. reported AVN subset constituted 24% of total SLE patients who had undergone arthroplasty [7]. Various underlying mechanisms have been implicated in AVN such as marrow cell hypertrophy, lipid-induced osteocyte necrosis, and microemboli formation [8]. Segmental subchondral bone necrosis is followed by marginal demarcation of the infected area by reactive bone formation or fibrotic tissue [9]. Osteonecrosis predisposes the bone to fracture and leads to secondary degenerative changes of the joint. These changes result in significant pain and limitation of motion, and affecting the quality of life [10]. Several risk factors as male sex, antiphospholipid (APS) antibodies, and corticosteroid therapy have been associated with increased susceptibility to AVN [5,11–15]. High dose prednisolone treatment (> 40 mg/d) is considered as a main parameter which predisposes toward osteonecrosis [13,15–23]. However, there are a considerable proportion of SLE patients with AVN complications that have no history of corticosteroid treatment [3,24–25]. On the other hand, most SLE patients who receive corticosteroid do not develop AVN in the course of disease [4]. The aim of our study was to evaluate the impact of non-corticosteroid factors in development of symptomatic AVN. The cumulative dose of corticosteroid and its route of administration were matched between cases and controls; hence we removed the presence of corticosteroid as a risk factor.

Patients and methods

Selection of patients and control groups

Medical records of SLE patients who have attended our Lupus clinic at Rheumatology Research Center (RRC), Tehran University of Medical Science (TUMS), were studied retrospectively. All patients fulfilled the 1982 or 1997 revised American College of Rheumatology (ACR) criteria for the classification of SLE [26–27]. From 1979 to 2009, 2280 SLE patients were registered in our database [28]. Among these studied patients, 105 cases have
been complicated by AVN, which were confirmed via clinical and radiologic (plain radiographs, bone scans, or MRI) assessments [28]. Thirty-nine SLE patients with positive history of corticosteroid pulse therapy were categorized separately as pulse-therapy subgroup compared with a control group consisting of 312 non-AVN SLE patients. Medical records of AVN and non-AVN subsets were studied. The cumulative dose of oral corticosteroid or pulse therapy was measured from SLE onset to AVN diagnosis. The controls comprised 248 (oral subgroup) and 312 (pulse-therapy subgroup) matched SLE patients without AVN, who had received the same cumulative corticosteroid dose via similar route of administration. The cumulative dose of corticosteroid, maximum dose, and 1-year maximum dose were matched between cases and controls. The patients who had received pulse corticosteroid doses were excluded from both case and control groups. The clinical, laboratory, and therapeutic differences between cases and controls were compared.

Demographic data and clinical features

The demographic data (including sex, age of disease onset, age at the diagnosis of AVN), clinical features including organs involvement, SLE Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage index (SLICC/ACR-DI), number of disease flare ups, overlap syndromes with other autoimmune disease, ischemic heart disease, fatty liver (confirmed by ultrasonography), osteoporosis ($T$ score $< -2.5$), and fragility fractures were recorded from patient’s file.

Laboratory tests

The laboratory tests performed included autoantibodies profile including antinuclear antibodies that was detected by an indirect immunofluorescence, anti-double-strand (ds) DNA antibodies (ELISA and Critidia luciliae), anticitrullinated antibodies (aCL) (ELISA), and lupus anticoagulant (LAC), Complete Blood Count (CBC), lipids profile (including triglyceride, cholesterol, LDL, HDL), and urinalysis. The laboratory data were collected from patient’s file.

Statistical analysis

Data were analyzed using SPSS V.20 software (Chicago, IL, USA). The normality of distribution of continuous data was checked, and compared between two groups by unpaired t-test. Categorical variables were compared by chi-square test or Fishers exact test. The binary logistic regression backward stepwise model was applied for eligible variables with $P$ value $< 0.1$, to determine the independent risk factors of AVN.

Results

Among 2280 patients who registered between 1979 and 2009, 105 patients (4.6%) have developed symptomatic AVN. We studied 66 cases with AVN who received oral corticosteroid and 39 AVN cases who had received pulse therapy. The controls were 560 matched SLE patients without AVN who had received the same cumulative corticosteroid dose.

Oral corticosteroid subset

AVN cases comprised 55 female (83.4%) and 11 male patients (16.6%) while controls consisted of 174 females (87.0%) and 26 males (13.0%). Age of SLE onset among the case groups was 24.3 ± 7.1 years. The mean age of SLE onset did not show significant difference between cases and controls (24.3 ± 7.1 vs. 26.87 ± 7.6 years, $P$ value = 0.47). The mean time interval between disease onset and diagnosis of AVN was 4.7 ± 5.7 years. The mean cumulative dose of corticosteroid in AVN cases was 17989 ± 13506 mg.

In AVN cases, 62 cases (93.9%) had a single joint involvement. The hip was the most commonly affected joint (91%), of which 55% of them had bilateral hip involvement. Four patients (6.1%) had multiple joint involvements. The mean of SLEDAI at the disease onset was 18.3 ± 14.2 in cases and 17.1 ± 6.3 in controls ($P$ value = 0.6). At the study end, the mean of SLEDAI was 2.8 ± 3.4 in cases and 4.8 ± 3.1 in controls ($P$ value = 0.006). Thirty-four patients (51.5%) in the AVN group and hundred and thirty patients (65.0%) in the controls group had episodes of SLE flare up during the course of disease ($P$ value = 0.78). The SLICC/ACR damage index (without the AVN item from the musculoskeletal component) at the time of AVN diagnosis was 1.3 ± 1.3 in cases group, and it was 0.8 ± 0.6 at study end in controls group ($P$ value = 0.021).

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Among clinical manifestations, malar rash (92.3% vs. 65.1%; $P$ value < 0.001) and oral ulcer (76.2% vs. 49.0%; $P$ value = 0.003) were significantly more prevalent in controls than cases. On the contrary, psychosis (12.1% vs. 3.0%; $P$ value = 0.04) and polyarthritis (10.6% vs. 0%; $P$ value = 0.006) were significantly more frequent in cases than controls. There was no significant difference between cases and controls in the other clinical manifestations in oral corticosteroid subset (Table 1).

The cumulative doses of corticosteroid were matched between cases and controls groups. The mean time to achieve equivalent cumulative corticosteroid doses was 4.7 ± 5.7 years in cases and 3.7 ± 2.4 years ($P$ value = 0.196) in controls. The maximum daily dose of corticosteroid was higher in cases than controls (78.5 ± 14.57 mg vs. 50.4 ± 16.8 mg; $P$ value = 0.1). Aspirin was more frequently administered in cases than controls (27% vs. 13%; $P$ value = 0.05) but its impact was not statistically significant in multivariate logistic regression model. There was no significant difference in the use of anti-malarial drugs, immunosuppressive drugs, and statins between two subsets (Table 2).

The binary logistic regression backward stepwise model was used for variables with $P$ value $< 0.1$, to determine the independent risk factors of AVN. Table 3 shows the results of binary logistic regression analysis. In oral corticosteroid subset, the age of SLE onset ($P$ value: 0.031), malar rash incidence ($P$ value = 0.002), oral ulcer incidence ($P$ value = 0.015), and psychosis ($P$ value = 0.013) were significantly different between cases and controls (Table 3).

Corticosteroid pulse subset

AVN cases comprised 34 female (87.2%) and 5 male patients (12.8%) while controls consisted of 259 females (83.0%) and 53 males (17.0%). Age of SLE onset among the AVN cases was 24.6 ± 7.6 years. The mean age of SLE onset did not show significant difference between cases and controls in pulse corticosteroid group (24.6 ± 7.6 vs. 25.8 ± 7.3 years, $P$ value = 0.42). The mean time interval between disease onset and diagnosis of AVN was 4.9 ± 6.5 years. The mean cumulative dose of corticosteroid in AVN cases was 19689 ± 12206 mg.

In AVN subgroup, 37 cases (94.9%) had a single joint involvement. The hip was the most commonly affected joint (91.8%), of which 61.7% had bilateral hip involvement. Two patients (5.1%) had multiple joint involvements. The mean of SLEDAI at the disease onset was 18.6 ± 13.3 in AVN cases and 18.2 ± 8.3 in controls ($P$ value = 0.8). At the study end, the mean of SLEDAI was 6.7 ± 4.4 in cases and 7.8 ± 3.5 in controls ($P$ value = 0.61). Seventeen AVN patients (43.6%) and hundred and fifty-nine non-AVN patients (51.0%) in corticosteroid pulse subset experienced SLE flare up ($P$ value = 0.08). The SLICC/ACR damage index (without the AVN item from the musculoskeletal component) at
the time of AVN diagnosis was 1.5 ± 1.2 in cases group, and it was 0.7 ± 0.8 at study end in controls group (P value = 0.011).

In AVN cases, oral ulcer (P value = 0.04) and malar rash (P value = 0.01) were more commonly observed. There was no significant difference between AVN cases and non-AVN controls in the other clinical manifestations in pulse-therapy subset. The clinical manifestations of patients are tabulated in Table 1.

Similar to oral corticosteroid subset, in pulse-therapy subset, younger age of onset (P value = 0.03), malar rash (P value = 0.01), and oral ulcer (P value = 0.01) were associated with osteonecrosis. However, in contrast with oral corticosteroid subset, psychosis did not show significant association with AVN development.

None of the laboratory features was significantly different between the cases and controls groups in both oral and pulse corticosteroid subsets. The laboratory features of patients are tabulated in Table 4.

Discussion

AVN is a well-documented complication of SLE [21]. There are several factors associated with AVN in SLE, including corticosteroid therapy, Raynaud’s phenomenon [11,14,29], vasculitis [22], presence of arthritis [4], Cushingoid features [19,22], cytotoxic therapy [4,30], and APS antibodies [14,22]. Mechanisms that may be responsible for development of osteonecrosis include vasculopathy and vascular occlusion, abnormal endothelial function, abnormal lipid metabolism, fat emboli, and microfracture [29].

Corticosteroid is known as an important risk factor of AVN development [13,15–23]. Glucocorticoids contribute to expansion of osteoclasts lifespan while suppress osteoblasts and osteocytes [31]. Furthermore, glucocorticoids regulate blood flow in bone arteries by modulating vasoactive agents such as endothelin-1 or bradykinin [31]. However, in contrast with the patients who undergo corticosteroid treatment, do not develop AVN in the course of disease [4], and some SLE patients with osteonecrosis have never been on corticosteroid [3,24–25]. Thus corticosteroid-independent factors are involved in AVN pathology.

The mean age of SLE onset in AVN cases in both oral corticosteroid and corticosteroid pulse were significantly younger than in controls. This finding was in accordance to a study by Sayarioglu et al. [30]. The AVN subset in our study achieved the determined cumulative dose of corticosteroid over a longer time than controls.

Table 1. Clinical manifestations of AVN and non-AVN subsets.

<table>
<thead>
<tr>
<th>Oral corticosteroid subset</th>
<th>Corticosteroid pulse subset</th>
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<tr>
<td>AVN group (cases)</td>
<td>Non-AVN group (cases)</td>
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<tr>
<td>AVN group (cases)</td>
<td>Non-AVN group (cases)</td>
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<tr>
<td>Mean SLEDAI at disease onset</td>
<td>18.3 ± 14.2</td>
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<tr>
<td>Mean SLEDAI at study end</td>
<td>2.8 ± 3.4</td>
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<tr>
<td>SLICC/ACR-DI at study end</td>
<td>1.3 ± 1.3</td>
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<tr>
<td>Malar rash, N(%)</td>
<td>43 (65.1%)</td>
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<tr>
<td>Discoid rash, N(%)</td>
<td>14 (21.2%)</td>
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<tr>
<td>Oral ulcer, N(%)</td>
<td>32 (49.0%)</td>
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<tr>
<td>Arthritis, N(%)</td>
<td>51 (77.3%)</td>
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<tr>
<td>Raynaud’s phenomenon, N(%)</td>
<td>11 (16.7%)</td>
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<tr>
<td>Livedo reticularis, N(%)</td>
<td>5 (7.6%)</td>
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<tr>
<td>Psychosis, N(%)</td>
<td>8 (12.1%)</td>
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<tr>
<td>Seizure, N(%)</td>
<td>14 (21.2%)</td>
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<tr>
<td>Renal involvement, N(%)</td>
<td>60 (90.1%)</td>
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<tr>
<td>Nephrotic syndrome, N(%)</td>
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<td>APS syndrome, N(%)</td>
<td>7 (10.6%)</td>
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<tr>
<td>Dermatomyositis, N(%)</td>
<td>2 (3.0%)</td>
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<tr>
<td>Scleroderma, N(%)</td>
<td>6 (9.1%)</td>
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<tr>
<td>Osteoporosis, N(%)</td>
<td>24 (36.4%)</td>
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<tr>
<td>Frailty fracture, N(%)</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>Fatty liver, N(%)</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>Ischemic heart disease, N(%)</td>
<td>3 (4.5%)</td>
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N the number of patient, SLEDAI Systemic Lupus Erythematosus Disease Activity Index, SLICC/ACR-DI Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage index, APS Anti-phospholipid syndrome.
corticosteroid doses in a shorter time [32]. The difference may be partly due to the difference in clinical status of AVN subsets of the two studies. The SLEDAI score at disease onset was similar between cases and controls groups in both oral corticosteroid and pulse-therapy subsets. At the study end, mean SLEDAI was lower in cases than in controls; however, the difference was not statistically significant. Previous studies have underlined the correlation between SLE disease activity and osteonecrosis [13]. However, study by Fialho et al. contradicted this notion and underlined disease activity as a predictor of AVN development [33]. It is noteworthy that this study focused on SLE patients in early stage of disease. Disease activity might lose the meaningful correlation with AVN incidence in long term follow-ups. In our study the number of flare-ups during the study period was higher in controls than in cases. However, the difference was not statistically significant.

The time span between AVN occurrence and diagnosis of AVN via imaging can play a confounding role in our analysis. The SLICC/ACR damage index (without the AVN item from the musculoskeletal component) at the time of AVN was higher in cases than in controls group, but it was not statistically significant in multivariate analysis. This means that patients with AVN have a higher damage index in other organs in addition to musculoskeletal system. This issue has not been evaluated in previous studies. According to our results, no significant association between Raynaud’s phenomenon, livedo reticularis, or vasculitis with AVN existed. Vasculopathy and vasculitis may have a role in the pathogenesis of AVN although there are some controversial evidence. A number studies have unraveled the relationship between Raynaud’s phenomenon [11,14,30,34], livedo reticularis [14,35], and vasculitis [10,14,22,24,29–30,36] with osteonecrosis. On the contrary, a body of evidence has denied the correlation between AVN and vasculopathy and vasculitis in SLE [13–15,32,35].

APS antibodies as a prothrombotic factor might predispose to AVN by causing microvascular thrombosis. There have been controversial results regarding the link between APS antibodies and AVN [14,22]. In our study, no significant association between APS antibody level and AVN was noted. Tektonidou et al. showed that patients with APS syndrome who never received corticosteroid were predisposed to AVN [35], which indicates the important role of APS in the pathogenesis of AVN. A study by Yang et al. has reported that nephrotic syndrome as a prothrombotic condition had association with AVN [36]. However, our study did not detect any meaningful association between nephritic syndrome and AVN which was in accordance with a number of studies [15,30,32]. Moreover, no significant association between vascular thrombosis and AVN was noted, which was similar to the report of Sayarlioglu et al. [30].

Association between hyperlipidemia and AVN has been the subject of ongoing dispute [32,37–39]. According to our dataset no significant association between hyperlipidemia and AVN existed. Calvo-Alen et al. reported a protective effect for hyperlipidemia in development of osteonecrosis [39]. Although some reports have suggested that fatty liver probably via asymptomatic fat emboli counts as a risk factor for AVN [40], we did not detect a significant association. It is noteworthy that liver sonography is not a routine component of work up in our SLE patients; therefore fatty liver may have been underdiagnosed.

Among clinical manifestations malar rash and oral ulcer had a protective role in AVN development, which was statistically significant. Sayarlioglu et al. [30] reported that oral ulcer was more common in patients with AVN. Among CNS manifestations just psychosis had significant association with AVN, which was in accordance with some previous reports [21,36]. However, a number of studies did not find any association between CNS manifestations and AVN [30,32]. Arthritis was more common in cases than controls, but it was not statistically significant, which supports the results of other studies [30,32]. Polymyositis as an overlap syndrome with SLE had a relationship with AVN that was not statistically significant in multivariate analysis. It has not been evaluated by previous studies and needs to be addressed in more scrutinized investigations. Only Javier Cavallasca et al. have reported a SLE case with scleroderma and AVN [41].

In contrast with our results, Klipper et al. [11] found a significant association between hematologic features (leucopenia and thrombocytopenia) and AVN development. Prasad et al. [32] showed that osteoporosis, as a possible cause of microfractures (predisposing to AVN), was less frequent in the cases than controls, but there was no difference in osteoporosis between cases and controls in our study. We did not detect any protective effect of antimalarials or aspirin in development of AVN. This finding was in accordance with study of Prasad et al. [32]. Aspirin was used significantly more frequently in cases group but multivariate logistic regression model ruled out its significant influence. Aspirin was used for ischemic heart disease, scleroderma, and APS syndrome in AVN subset. There was no association between cytotoxic therapy and statins administration with osteonecrosis in our study, which was in contrast with a number of previous studies [4,39]. Moreover Belmont et al. unraveled protective effect for atorvastatin in development of AVN [42]. The controversial results may be due to the inclusion criteria of these studies. Future studies are warranted to examine the association between lipid profile and osteonecrosis.

**Conclusion**

In our patients, younger age of disease onset and psychosis were significantly associated with development of AVN, whereas...
malar rash and oral ulcer were negatively associated with AVN in multivariate analysis.

**Conflict of interest**

None.

**References**