BMC Rheumatology

RESEARCH

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Asymptomatic multifocal avascular necrosis, a commonly overlooked finding in patients with systemic lupus erythematosus

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Abstract

Background In patients with Systemic lupus erythematosus (SLE), osteonecrosis of various joints is a debilitating complication associated with the disease and its treatment, in which a considerable proportion of osteonecrosis may be asymptomatic. Recognizing the crucial role of early and timely detection, as well as appropriate management of asymptomatic osteonecrosis, in preventing joint destruction, we conducted a study to evaluate the prevalence of asymptomatic osteonecrosis in SLE patients who have already been diagnosed with symptomatic osteonecrosis. Additionally, we aimed to examine the relationship between proposed risk factors of osteonecrosis and the development of asymptomatic osteonecrosis.

Methods In this cross-sectional study, Patients with recently diagnosed symptomatic osteonecrosis of at least one joint were selected by reviewing data from the digital medical record system of the Rheumatology Research Center. The patients underwent three-phase Single Photon Emission Computed Tomography (SPECT) bone scintigraphy to screen for other asymptomatic osteonecrotic joints. MRI was subsequently performed on the asymptomatic osteonecrotic sites for further diagnostic confirmation. The study evaluated the prevalence of asymptomatic osteonecrosis, the extent of joint involvement, the specific locations of osteonecrosis, the most commonly affected joints, and the risk factors for asymptomatic osteonecrosis.

Results Eight out of the 17 patients (47%) who participated in our research were found to have asymptomatic osteonecrosis. The most commonly affected joint without symptoms was the left knee (25%), while the most frequently affected joint with symptoms was the left hip (23.07%). The only statistically significant difference observed between patients with and without asymptomatic osteonecrosis in this study was the age at which the disease first appeared ($p = 0.046$) and this age was higher among patients with asymptomatic osteonecrosis.

Conclusions Our research provides further evidence of the high incidence of asymptomatic osteonecrosis in individuals with SLE due to the nature of the disease and the frequent use of high-dose corticosteroids. It underscores the importance of early detection through whole-body SPECT bone scintigraphy and MRI, as well as prompt intervention in order to avert the incapacitating effects of osteonecrosis.

Keywords Asymptomatic osteonecrosis, Bone scintigraphy, Magnetic resonance imaging, Steroid, Systemic lupus erythematosus

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Background

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that is associated with significant morbidity and potentially fatal outcomes. The worldwide incidence of SLE ranges from 30 to 70 cases per 100,000 individuals. Timely management and treatment of various organ involvements play a vital role in enhancing results, and the administration of corticosteroids is frequently required to address different organ involvements in SLE [1].

Musculoskeletal manifestations, such as arthralgia and arthritis, are frequently observed in individuals with SLE and can notably affect their quality of life. Osteonecrosis, a recognized and incapacitating musculoskeletal complication associated with SLE, further adds to the burden experienced by patients. The occurrence of osteonecrosis in SLE is relatively common. Symptomatic osteonecrosis has been estimated to affect around 10 percent of SLE patients, while the prevalence of asymptomatic osteonecrosis is much higher, affecting more than one-third of individuals [2, 3].

Osteonecrosis, also known as avascular, aseptic, or ischemic necrosis, is a debilitating clinical condition characterized by the in-situ death of osteocytes and bone marrow. This condition occurs as a result of compromised blood supply to the affected bone and surrounding tissue, succeeding by destructive repair processes that involve the resorption of necrotic tissue and subsequent replacement with weaker osseous tissue and reduced bone formation. Osteonecrosis can result in the destruction of bone architecture, subchondral collapse of joints, and, eventually in some cases, necessitate joint replacement surgery. A combination of genetic predisposition, metabolic factors, and various local factors, including both traumatic and non-traumatic factors such as hematologic and rheumatologic diseases, and corticosteroid usage, have been suggested to play a role in the pathophysiology of osteonecrosis [4]. The clinical presentation of osteonecrosis can vary, ranging from silent or asymptomatic joint involvement to severe pain, often exacerbated by motion and weight-bearing, as well as joint deformity. Osteonecrosis predominantly affects young individuals between the ages of 30 and 60, with a male predominance observed, with a ratio of 7 to 3, except in cases of SLE. On average, patients diagnosed with osteonecrosis are in their late 30 s [5].

The femoral head and the knee joint are the most commonly affected joints, respectively [5]. In patients with SLE, osteonecrosis commonly involves joints bilaterally, and the presence of multifocal and asymptomatic osteonecrosis is frequently observed [6].

Among patients with SLE, disease activity and the administration of corticosteroids are the main risk factors for the development of osteonecrosis [3]. The management of osteonecrosis in patients with SLE is similar to that in patients with other etiologies, often necessitating total hip or knee arthroplasty [4, 7].

Various imaging modalities are utilized for the diagnosis of osteonecrosis and to assess the extent of its involvement. Plain radiographs serve as the initial evaluation in patients with suspected osteonecrosis, typically demonstrating abnormalities only during the later stages of the condition, months after the onset of symptomatic joint involvement [8].

MRI without a contrast agent is considered the gold standard for diagnosing osteonecrosis, particularly in the early stages and in asymptomatic patients, due to its high sensitivity and specificity. Characteristic MRI findings of osteonecrosis include band-like low-intensity signals in T1-weighted images that separate normal and ischemic bone, as well as pathognomonic double-line signs in T2-weighted images [9, 10].

Osteonecrosis is categorized into four stages according to the Association Research Circulation Osseous (ARCO) classification. In Stage 1, normal radiographs and show abnormal findings on MRI. Stage 2 is characterized by the absence of the crescent sign and the presence of radiographic evidence such as sclerosis, osteolysis, or focal osteoporosis. Stage 3 is marked by subchondral fracture, a fracture within the necrotic area, and/or flattening of the bone head, as observed on radiographs or CT scans. Finally, Stage 4 is distinguished by evidence of osteoarthritis, joint space narrowing, and degenerative changes [11].

Radionuclide bone scanning has a limited role in the diagnosis of osteonecrosis and is associated with a high rate of false-negative results, which can reach up to 25 percent for diagnosing hip osteonecrosis [12]. Whole-body MRI is more sensitive than a whole-body bone scan for detecting asymptomatic osteonecrosis [13]. Single photon emission computed tomography (SPECT) bone scintigraphy is a nuclear medicine imaging modality that generates cross-sectional images comparable to MRI. Unlike planar bone scintigraphy, SPECT bone scintigraphy produces three-dimensional images, which helps overcome the limitation of false-negative results. Therefore, it is recommended for screening asymptomatic osteonecrosis in high-risk patients, such as those with SLE or individuals taking corticosteroids [14].

Early detection of asymptomatic osteonecrosis plays a critical role in enabling timely intervention, preventing subchondral collapse, and ultimately reducing the need for joint replacement therapy and bone reconstruction. Therefore, maintaining a high level of suspicion and conducting thorough evaluations for osteonecrosis in high-risk patients are crucial for improving outcomes.

The objective of this study is to assess the prevalence of asymptomatic osteonecrosis among SLE patients already diagnosed with symptomatic osteonecrosis. Additionally, the study aims to investigate the association between demographic parameters and proposed risk factors for

osteonecrosis and occurrence of asymptomatic osteonecrosis, and to elucidate the characteristics of patients with asymptomatic osteonecrosis.

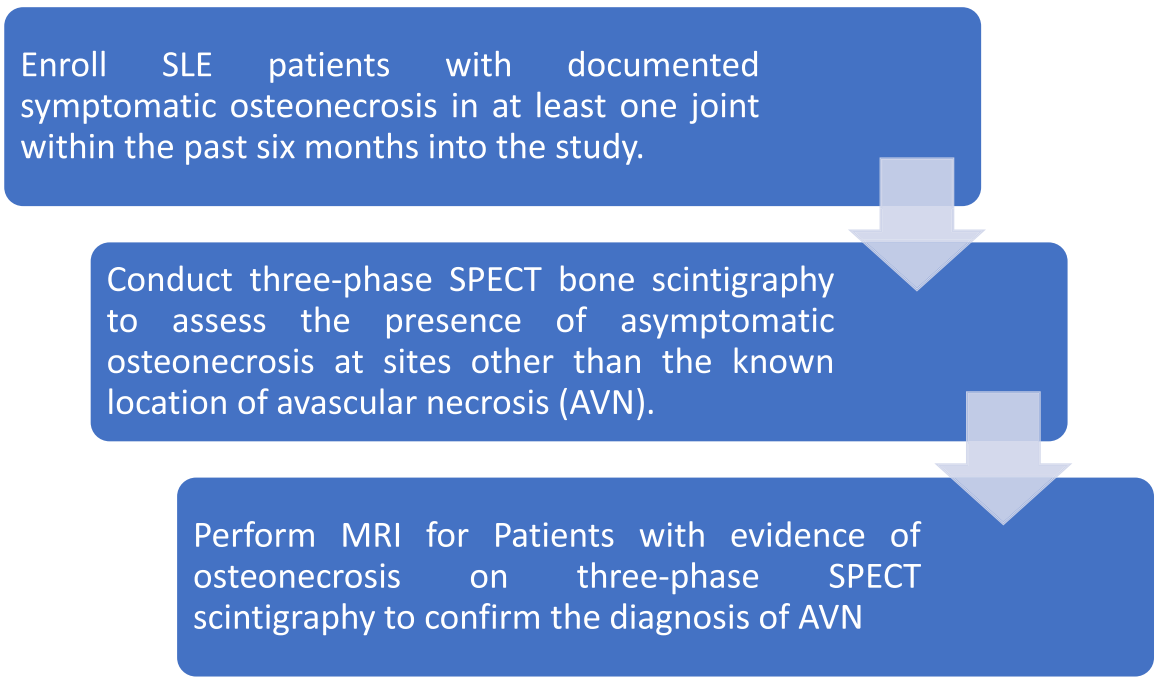
Methods

In this cross-sectional study, we reviewed the data from the digital medical record system of the Rheumatology Research Center (Rheumatry) at Shariati Hospital, Tehran University of Medical Sciences (TUMS). The study focused on identifying patients with SLE who had experienced symptomatic osteonecrosis in any joint within the previous six months. To be included, patients must have reported symptoms such as joint pain at rest or during motion, with or without limitation of range of motion. Additionally, the diagnosis of osteonecrosis had to be documented by MR imaging of the symptomatic joint.

After obtaining informed consent, patients were enrolled in the study. Patient demographic data and relevant clinical information, such as the site of documented osteonecrosis, the number of affected joints, proposed risk factors for osteonecrosis including hyperlipidemia, markers of SLE activity, organ involvement, presence of autoantibodies and antiphospholipid antibodies, and previous treatments (including corticosteroid intake history in terms of high dose, cumulative dose, route, and duration of administration, as well as the history of immunosuppressant agent use and other drug histories), were retrospectively retrieved from the database.

Patients with at least one documented symptomatic osteonecrosis were referred to the nuclear medicine department and underwent whole-body three-phase SPECT bone scintigraphy to assess the presence of asymptomatic osteonecrosis at sites other than the known location of avascular necrosis (AVN). To confirm the diagnosis, patients with evidence of osteonecrosis on three-phase SPECT scintigraphy underwent further evaluation by MR imaging. Standard protocols were followed to obtain MR images of specific sites including the pelvis, knee, shoulder, ankle, and foot.

Whole-body SPECT bone scintigraphy was chosen over whole-body MRI initially because it is more cost-effective, feasible, and has comparable sensitivity to MRI.



A flowchart outlining the workflow for detecting asymptomatic multifocal osteonecrosis

The whole-body bone scan was conducted using a variable-angle dual-head SPECT gamma camera (ECAM, MiE, Germany) in three-phase mode. For the early-phase imaging, the patient was positioned on the gamma camera so that the area of interest (the known location of avascular necrosis) was within the acquisition field. Imaging commenced immediately after the intravenous injection of 740 MBq Tc-99 m MDP (Pars Isotope Co., Tehran, Iran), and perfusion (flow phase) images were obtained in both anterior and posterior views of the

corresponding area, using a 128×128 matrix, with a dynamic imaging duration of 3 s per projection for up to 1 min. Following this step, whole-body blood pool images were obtained 5 min after the administration of the same radiotracer. Anterior and posterior projections were captured for each field of view using a 256×256 matrix. Additionally, delayed whole-body static images were acquired after a 3-h interval. If any area of abnormal radiotracer activity appeared suspicious (i.e., exhibiting increased uptake compared to background soft tissue), magnified spot views as well as SPECT-mode images were obtained from the identified region of interest. In cases where visual suspicion arose, quantitative analysis of the uptake was performed by delineating the region of interest (ROI) in the corresponding area as well as a comparable symmetrical area in the contralateral side.

The involved joints were subjected to MR imaging using a 1.5-T MRI system, specifically the Magnetom Avanto (Siemens Healthcare, Erlangen, Germany), equipped with a dedicated extremity coil. Before symptoms appear in osteonecrosis, a defining characteristic is the presence of a band-like pattern observed in T1-weighted MRI images. Additionally, distinctive double-line signs become evident in T2-weighted images during the later stages. Accordingly, T1- and T2-weighted MRI scans with fluid-sensitive fat suppression sequences were obtained in at least two planes, predominantly sagittal and coronal views, and subsequently evaluated.

Based on the signal intensity and the presence of a crescentic or band-like region or a double line sign in the bone's epiphysis, a diagnosis of osteonecrosis was established, and the extent of necrosis was determined, with staging performed according to the ARCO classification.

All SPECT bone scintigraphy images and MR images were meticulously analyzed and reported by a specialist in nuclear medicine and an experienced radiologist specialized in musculoskeletal disorders, respectively. Both specialists were blinded to the patients' clinical information.

In SLE patients with confirmed symptomatic osteonecrosis, several aspects were evaluated, including the prevalence of asymptomatic osteonecrosis, the extent of joint involvement, the specific locations of osteonecrosis, and the most commonly affected joints.

Furthermore, a comparative analysis was conducted between patients with and without asymptomatic osteonecrosis to assess the presence and potential associations with various demographic parameters and proposed risk factors for osteonecrosis. These risk factors encompassed corticosteroid utilization (including factors such as high dosage, cumulative dosage, route of administration, and treatment duration), disease activity, the presence of autoantibodies and antiphospholipid antibodies, as well as dyslipidemia.

The obtained results were analyzed using SPSS ver. 26 (SPSS Inc., Chicago, IL, USA). A significance level of $P<0.05$ was deemed statistically significant. Descriptive analysis was employed to outline the demographic characteristics of the patients and determine the prevalence of asymptomatic osteonecrosis. Due to the small sample size and the skewed nature of the quantitative data, both quantitative variables and qualitative/categorical variables were presented as frequencies and percentages. To illustrate central tendency and variability, median values along with ranges and interquartile ranges (IQR) were calculated.

Due to the limited sample size, Fisher's exact test was employed to assess the significance of the association between two categorical variables, such as determining the relationship between gender and osteonecrosis status (presence or absence of asymptomatic osteonecrosis).

Furthermore, due to the small sample size and non-normal distribution of the data, the Mann–Whitney U test was used to examine the differences in various variables between two independent groups, patients with asymptomatic necrosis and patients without asymptomatic necrosis. This included the comparison of distribution frequencies and medians of variables in the two groups.

Results

In this study, a total of 18 newly diagnosed symptomatic osteonecrosis cases in SLE patients, confirmed by MRI within the past 6 months, were enrolled between January 2022 and December 2022.

Among the 18 participants, three-phase SPECT bone scintigraphy revealed findings suggestive of asymptomatic osteonecrosis in 9 patients (50%). One patient declined to undergo an MRI and was subsequently excluded from the study. Consequently, data from 17 patients were included in the analysis, revealing asymptomatic osteonecrosis in 8 out of 17 patients (47%) based on bone scintigraphy and MRI.

Based on previous MRI evaluations, the number of previous symptomatic joint involvements ranged from one to three joints, with the same median of 2 among patients with and without asymptomatic osteonecrosis (Table 1).

In patients experiencing asymptomatic osteonecrosis, the most prevalent joints with a history of previous osteonecrosis were the left hip joints, accounting for 33.33%, while the right hip and right knee joints each accounted for 16.66%, respectively. In patients without asymptomatic osteonecrosis, the most prevalent previous joint involvements were the left knee joint (28.57%) and the right hip and right knee joints (21.42% each). Among all seventeen participants, both with and without asymptomatic osteonecrosis, the most commonly affected symptomatic joint at enrollment was the left hip (23.07%),

Table 1 Frequency of joints with osteonecrosis based on three phasic bone scintigraphy and MRI

Variables		Patients with asymptomatic osteonecrosis *n* = 8	Patients without asymptomatic osteonecrosis *n* = 9	Total *n* = 17
Number of involved Joints in bone scintigraphy	Range	1 –5	1 –5	1 –5
	Median (IQR[a])	2.5 (2.00- 4.00)	2.00 (1.00- 2.00)	2.00 (1.00—3. 0)
Number of involved joints in MRI	Range	1 – 3	Not done	1 –3
	Median (IQR)	1.00 (1.00- 2.75)	Not done	0.00 (0.00- 1.00)

[a] Interquartile range

followed by the right hip and both the right and left knees (each at 19.23%).

In the evaluation of joints using three-phase SPECT bone scintigraphy, the range of joint involvement was 1 to 5, with a median of 2. Since only joints with evidence of asymptomatic osteonecrosis in three-phase SPECT bone scintigraphy were evaluated by MRI, the range of joint involvement in MRI was 1 to 3, with a median of 1.

In the three-phase bone scintigraphy, among patients with asymptomatic osteonecrosis, the most frequently asymptomatically involved joint was the left knee, accounting for 25% of the cases, followed by the right knee and right ankle (each accounting for 16.66% of cases).

These joints were reevaluated using MRI, and osteonecrosis was confirmed in all joints that showed involvement in the bone scintigraphy. As a result, osteonecrosis in the left knee joint was found to be the most prevalent (25%) in the MRI assessment. Among the patients, 75% had osteonecrosis in stage 2, which exhibited evidence of sclerosis, osteolysis, or focal osteoporosis without a crescent sign. Additionally, 25% of the patients had osteonecrosis in stage 3, characterized by subchondral fracture, fracture in the necrotic portion, and/or flattening of the bone head.

In the evaluation of three-phase SPECT bone scintigraphy, it was observed that among patients with asymptomatic osteonecrosis, the combined occurrence of symptomatic and asymptomatic osteonecrosis was more prevalent in the left hip (20.83%), as well as the right and left knee (each at 16.66%). The asymptomatically involved joints were account for 50% of total joint involvement in patients with asymptomatic osteonecrosis. In contrast, among patients without asymptomatic osteonecrosis, the left knee joint (28.57%) along with the right hip and right knee joints (21.42% each) were the most frequently affected joints in terms of symptomatic involvement.

In the three-phase SPECT bone scan, among all seventeen participants, the left knee joint (21.05%), right knee joint, and left hip joint (each at 18.42%) were the most frequently affected joints. A detailed summary of joint involvement in the three-phase bone scan can be found in Table 2. Out of the total 17 patients, 13 patients had involvement in more than one joint, and 4 patients

Table 2 Joints with osteonecrosis in three phasic bone scintigraphy

	Patients with asymptomatic osteonecrosis (*n* = 8)		Patients without asymptomatic osteonecrosis (*n* = 9)	Total Participants	Total participants (*n* = 17)
Involved joint	Asymptomatic joints	the sum of symptomatic and asymptomatic joints	Symptomatic joints	Symptomatic joints	Total joints
Involved joints	Number (frequency)	Number (frequency)	Number (frequency)	Number (frequency)	Number (frequency)
Right hip	1 (8.33%)	3 (12.5%)	3 (21.42%)	5 (19.23%)	6 (15.78%)
Left hip	1 (8.33%)	5 (20.83%)	2 (14.28%)	6 (23.07%)	7 (18.42%)
Right knee	2 (16.66%)	4 (16.66%)	3 (21.42%)	5 (19.23%)	7 (18.42%)
Left knee	3 (25%)	4 (16.66%)	4 (28.57%)	5 (19.23%)	8 (21.05%)
Right shoulder	0 (0%)	1 (4.16%)	1 (7.14%)	2 (7.69%)	2 (5.26%)
Left shoulder	1 (8.33%)	1 (4.16%)	0 (0%)	0 (0%)	1 (2.63%)
Right ankle	2 (16.66%)	3 (12.5%)	1 (7.14%)	2 (7.69%)	4 (10.52%)
Left ankle	0 (0%)	1 (4.16%)	0 (0%)	1 (3.84%)	1 (2.63%)
Right foot	1 (8.33%)	1 (4.16%)	0 (0%)	0 (0%)	1 (2.63%)
Left foot	1 (8.33%)	1 (4.16%)	0 (0%)	0 (0%)	1 (2.63%)
Total	12 (100%)	24 (100%)	14(100%)	26 (100%)	38 (100%)

(23.52%) exhibited multifocal joint involvement, affecting three or more distinct anatomical sites.

In patients with findings related to asymptomatic osteonecrosis in the three-phase SPECT scintigraphy, six patients had involvement of only one joint. This included two left knee joints and two right ankle joints, as well as right hip and right knee joints. Additionally, two patients exhibited involvement of three joints. One patient had involvement of the right knee, left hip, and left shoulder, while another patient had involvement of the left knee and both feet's first MTP joints. These findings were confirmed by MRI.

The demographic data, as well as the clinical and laboratory characteristics of the study participants, are summarized in Table 3.

Among the participants, over 70 percent were female, and there was no significant difference observed between patients with and without asymptomatic osteonecrosis in terms of gender distribution ($p=0.583$).

The age range of the participants in the study was 22–50 years, with a median age of 39.5 years. The duration of the disease ranged from 1 to 26 years, with a median duration of 6 years. Although patients with asymptomatic osteonecrosis tended to have higher ages and longer disease durations compared to patients without asymptomatic osteonecrosis, there were no statistically significant differences observed between the two groups in terms of age ($p=0.321$) and duration of disease ($p=0.606$).

In this study, the only statistically significant difference observed between patients with and without asymptomatic osteonecrosis was the age at which the disease first appeared. The age of disease onset ranged from 22 to 46 years old, with a median of 31.5 years in patients with asymptomatic osteonecrosis, while it ranged from 15 to 40 years old, with a median of 21 years in patients without asymptomatic osteonecrosis. These differences were found to be statistically significant ($p=0.046$).

The study revealed that the number of organs affected, aside from the joints, ranged from zero to four, with a median of two organs. Among these, the kidneys and brain exhibited a higher prevalence, with frequencies of 58.82% and 17.65% respectively. This was followed by gastrointestinal, hematologic, pulmonary, and cardiac involvement, each with a frequency of 11.76%. In terms of organ involvement, it was found that the presence of two organ involvements was more prevalent overall. Specifically, patients with asymptomatic osteonecrosis demonstrated a higher prevalence of gastrointestinal,

Table 3 Demographic characteristics, clinical and laboratory findings of participants

variables		patients with asymptomatic osteonecrosis $n=8$	patients without asymptomatic osteonecrosis $n=9$	Total $n=17$	*P* value
Age	Range	27- 50	22- 46	22-50	0.321
	Median (IQR[a])	39.5 (32.00- 47.00)	31.00 (28.00- 43.00)	39.00 (29.50- 43.00)	
	Average rank	10.38	7.78		
Gender	Male[b]	2 (25.00)	3 (33.33)	5 (29.41)	0.583
	Female[b]	6 (75.00)	6 (66.67)	12 (70.59)	
Disease onset age	Range	22—46	15—40	15- 46	0.046
	Median (IQR)	31.50 (28.25- 39.50)	21.00 (18.50- 33.00)	29.00 (20.50- 35.50)	
	Average rank	11.63	6.67		
Disease duration(year)	Range	3- 10	1- 26	1 – 26	0.606
	Median (IQR)	5.50 (3.25- 8.75)	6.00 (3.50- 18.00)	6.00 (3.50- 9.50)	
	Average rank	8.25	9.67		
Organ involvement numbers	Range	0 –3	0 –4	0 – 4	0.294
	Median (IQR)	2.33 (1.00- 2.75)	2.00 (2.00- 3.00)	2.00 (1.50—3.00)	
APS	Yes[b]	0 (0)	1 (0)	1 (5.88)	0.529
Hyperlipidemia	Yes[b]	2 (25.00)	1 (11.11)	3 (17.65)	0.453
Anti-dsDNA	Positive[b]	5 (62.50)	5 (55.56)	10 (58.82)	0.581
CRP, ESR	Positive[b]	5 (62.50)	2 (22.22)	7 (41.18)	0.117
Alcohol use	Yes[b]	0 (0)	0 (0)	0 (0)	

[a] Interquartile Range

[b] frequency (%)

APS Antiphospholipid syndrome, *Anti-dsDNA* Anti double stranded DNA, *CRP* C-reactive peptide, *ESR* Erythrocyte Sedimentation Rate

pulmonary, and hematologic involvement, while kidney, brain, and cardiac involvement were more frequently observed in patients without asymptomatic osteonecrosis. Although the median number of organ involvements was higher in patients with asymptomatic osteonecrosis, no significant difference was found between the two groups in terms of the number of organs involved ($p=0.294$).

Among the participants, 58.82% of patients had a high titer of anti-double stranded DNA (anti-ds DNA) antibody, 41.18% had elevated C Reactive protein (CRP) levels and high Erythrocyte Sedimentation Rate (ESR), and 17.65% had dyslipidemia. There was no significant difference observed between patients with and without asymptomatic osteonecrosis in these factors. Only one participant had a history of previous left hip joint osteonecrosis and was diagnosed with antiphospholipid syndrome; however, asymptomatic osteonecrosis was not detected in their three-phase bone scintigraphy. None of the patients reported alcohol consumption.

The daily intake of corticosteroids ranged from 0 to 20 mg of prednisolone per day. The most common daily dose of prednisolone among patients was 10 mg/day (41.87% of patients), and 64.71% of patients consumed at least 10 mg of prednisolone per day. Interestingly one patient with previous hip joint osteonecrosis did not take prednisolone. The cumulative dose of glucocorticoid intake ranged from 3000 to 85,050 mg of prednisolone (median 13,500). Although daily prednisolone intake and cumulative dose of corticosteroids were higher, and the variability was lower in patients with asymptomatic osteonecrosis, no significant difference was found among patients with and without osteonecrosis in these measures ($p=0.131$ and $p=0.541$ respectively).

In total, 47.07% of patients received intravenous pulses of corticosteroids (37.5% in patients with asymptomatic osteonecrosis and 55.56% in patients without asymptomatic osteonecrosis). The administration of intravenous pulse corticosteroids was lower in patients with asymptomatic osteonecrosis; however, there were no significant differences between the groups ($P=0.399$). The interval between corticosteroid pulse intake and the occurrence of osteonecrosis ranged from 225 to 7300 days (median 815 days) and no significant difference was observed between groups.

There were no significant differences observed in the use of cytotoxic drugs, statins, ASA, bisphosphonates, and hydroxychloroquine intake between patients with and without asymptomatic osteonecrosis (see Table 4).

Discussion

In our evaluation, 8 out of 17 participants (47%) were found to have asymptomatic osteonecrosis. Asymptomatic osteonecrosis is highly prevalent among individuals with SLE. While the reported prevalence of symptomatic osteonecrosis ranges from 4 to 15%, the estimated prevalence of asymptomatic osteonecrosis is much higher, reaching up to 44% of patients [2, 6, 15–18].

In a study conducted by Lee et al., the prevalence of symptomatic osteonecrosis was found to be 6.9% among 1056 Korean patients with SLE during the period from 1990 to 2012 [19]. In another study conducted in Canada, the prevalence of osteonecrosis was reported to be approximately 13.5% among 1729 patients with SLE during a follow-up period of up to 40 years [2]. In a more

Table 4 Drug administration history of patients

Variables		Patients with asymptomatic osteonecrosis *n* = 8	Patients without asymptomatic osteonecrosis *n* = 9	Total *n* = 17	P value
Daily steroid use (mg)	Range	5–20	0–20	0–20	0.131
	Median (IQR[a])	10.00 (10.00—13.70)	7.50 (5.00—12.50)	10.00 (6.25—12.50)	
Cumulative steroid dose(mg)	Range	5250 – 8505	3000—80,100	3000- 85,050	0.541
	Median (IQR)	14,000.00 (10,012.50- 71,425.50)	13,150.00 (6450.00- 41,462.50	13,500.00 (9637.50- 43,127.50)	
	Average rank	9.88	8.22		
Steroid pulse use	Yes[b]	3 (37.5)	5 (55.56)	8 (47.07)	0.399
Cytotoxic drug use	Yes[b]	5 (62.50)	5 (55.56)	10 (58.82)	0.581
Statin use	Yes[b]	2 (25.00)	6 (66.67)	8 (47.07)	0.109
Aspirin use	Yes[b]	0 (0)	4 (44.44)	4 (23.53)	0.053
Bisphosphonate use	Yes[b]	4 (50.00)	5 (55.56)	9 (52.94)	0.601
Hydroxy chloroquine use	Yes[b]	5 (62.50)	5 (55.56)	10 (58.82)	0.581

[a] Interquartile Range

[b] Frequency (%)

recent study, the prevalence of symptomatic osteonecrosis among 912 SLE patients was reported to be 10.6%. The time interval between the diagnosis of SLE and the development of osteonecrosis ranged from 71.7 months to 18 years [17]. According to a study conducted by Akbarian et al., which involved the evaluation of 2,280 patients with SLE over a period of 33 years, the prevalence of symptomatic osteonecrosis was reported to be 4.6% [18].

In the study conducted by Shunichi Yokota et al., it was found that out of 152 joints with osteonecrosis detected by whole-body MRI, 60 joints (39.5%) were asymptomatic [13]. Oinuma et al. reported an incidence of osteonecrosis in SLE patients at approximately 44% within an average of three months after high-dose corticosteroid therapy, irrespective of the presence or absence of symptoms [6]. Nakamura et al. conducted a study to evaluate the occurrence of osteonecrosis in SLE patients treated with corticosteroids, and they found that osteonecrosis developed in 44% of patients who underwent periodic MRI evaluations of their hips and knees for over 10 years [20]. Another study reported a prevalence of approximately 26% for asymptomatic osteonecrosis [21]. Furthermore, in an earlier study, the prevalence of osteonecrosis detected through periodic MRI of lower limbs was found to be 37.5%, and interestingly, most of the affected patients were asymptomatic despite multiple joint involvement [22]. Our study's findings align with the literature, further confirming the significant presence of asymptomatic osteonecrosis in SLE patients.

The discrepancy in the prevalence of osteonecrosis observed in different studies can be attributed to variations in sample size, characteristics of the study population (such as age, gender, and race), and the duration of follow-up. As the follow-up period increases, the prevalence of osteonecrosis is likely to rise.

Various imaging techniques with varying sensitivity and specificity have been proposed for the diagnosis of osteonecrosis. Although MRI is the most sensitive imaging modality for detecting osteonecrosis and assessing its severity, routine use of whole-body MRI is not feasible due to its high cost. As an alternative, whole-body bone scanning, which is more sensitive than plain radiographs in diagnosing osteonecrosis, can be employed for screening asymptomatic osteonecrosis in cases of multifocal joint involvement. This screening method reveals an increased uptake of technetium-99 m methylene diphosphonate (Tc99m-MDP), aiding in the detection of asymptomatic osteonecrosis [23]. It appears that SPECT bone scintigraphy and MRI can serve as complementary imaging modalities in the diagnosis of asymptomatic osteonecrosis [24].

In our study, we initially conducted a bone scintigraphy to identify potential cases of asymptomatic osteonecrosis. To address the limitations associated with bone scintigraphy, including a higher likelihood of false negative results, we utilized three-phase SPECT bone scintigraphy. Subsequently, in the second phase, the joints exhibiting elevated Tc99m-MDP uptake in the bone scintigraphy underwent MRI for further confirmation of the diagnosis of asymptomatic osteonecrosis.

Although non-traumatic osteonecrosis commonly affects the femoral neck, tibial plateau, and femoral condyle, it can also involve additional joints, including the ankle, shoulder, foot, and wrist. In rare instances, osteonecrosis may affect joints such as the scaphoid [2, 17, 25]. In our study, the number of joints affected by osteonecrosis ranged from 1 to 5. Among the symptomatic joint involvements, osteonecrosis of the left hip was the most prevalent, with a frequency of 23.07%, followed by the right hip and both the right and left knees. Regarding asymptomatic osteonecrosis, the most frequently affected joint was the left knee (25%), followed by the right knee and right ankle, and involvement of both foot joints remaining asymptomatic. It appears that the involvement of larger joints in the lower extremities is more likely to present with symptoms.

Multifocal osteonecrosis is characterized by the simultaneous or sequential involvement of three or more anatomical sites by osteonecrosis. When multiple joints are affected by osteonecrosis, the condition becomes more complicated. Multifocal osteonecrosis has been reported in approximately 3% of patients with osteonecrosis. The most common cause of multifocal osteonecrosis is the administration of high-dose corticosteroids. Other factors such as SLE and kidney dysfunction have also been identified as contributing causes [26]. Multifocal osteonecrosis is a common finding in patients with SLE. It often manifests bilaterally and involves joints such as the hips (up to 90% of cases), knees, and shoulders. It is noteworthy that multifocal osteonecrosis is generally asymptomatic in nature [6]. In a study conducted by Young-Sil, the prevalence of multifocal osteonecrosis was reported to be 10.4% among patients with osteonecrosis, with 26 out of 254 patients presenting multifocal involvement [23]. In our study, the prevalence of multifocal osteonecrosis was observed in 4 out of 17 patients (23.52%), which is higher compared to previous studies. This higher prevalence may be attributed to the relatively small sample size and the inclusion of high-risk patients with SLE who were undergoing high-dose corticosteroid treatment. Figure 1 illustrates the bone scintigraphy and MRI of a patient with multifocal osteonecrosis.

The majority of participants were young women, with a median age of 39.5 years old. This observation aligns

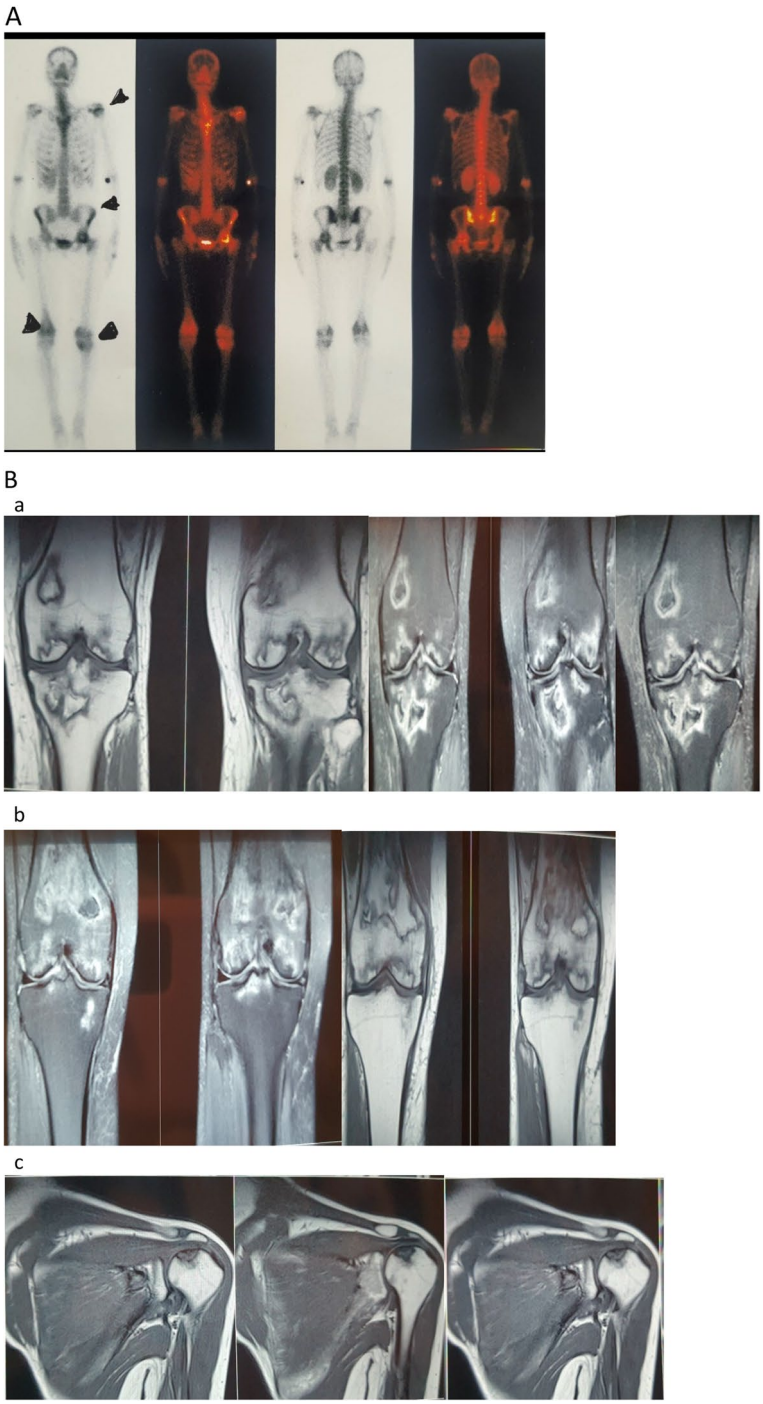


Fig. 1 The bone scintigraphy and MR images of a patient with multiple joint osteonecrosis. **A** Evidence of increased osteoblastic reaction in the left femoral head, consistent with the reparative phase of AVN, increased osteoblastic reaction in the left proximal humeral epiphysis; indicating an early phase of AVN, and increased osteoblastic reactions in the right distal femoral epiphysio-metaphyseal region and the left knee joint, suggesting an inflammatory process versus early reparative phase of AVN. **B** MRI images show AVNs in the left knee (a), right knee (b), and left shoulder (c). Bilateral Bone Infarcts and Arco Stage 2 AVNs of Femoral Condyles and left Humoral Head according to ARCO Classifications

with the global epidemiological pattern of SLE, which is known to be more prevalent in young women. Moreover, within the context of SLE, osteonecrosis demonstrates a higher occurrence in females compared to males [5].

Among patients with SLE, disease activity and organ involvement, including serositis, vasculitis, nephritis, pulmonary manifestations, cardiac complications, and central nervous system involvement, are considered

major risk factors for the occurrence of osteonecrosis [3, 26, 27]. In our study, patients with asymptomatic osteonecrosis generally had higher ages and longer durations of disease compared to patients without asymptomatic osteonecrosis. However, this finding did not reach statistical significance. Additionally, the only significant difference observed between patients with and without asymptomatic osteonecrosis was the age at which the disease first appeared, which was higher in patients with asymptomatic osteonecrosis. In contrast to our findings, a study reported that a younger age at the onset of the disease and the presence of psychosis were associated with osteonecrosis [28].

In our study, the range of organ involvement among participants varied from 0 to 4 organs. Contrary to other studies, although the median number of organ involvement was higher in patients with asymptomatic osteonecrosis, no significant difference was found between the two groups regarding the number of organs involved [3, 27].

Other known risk factors for osteonecrosis in SLE include the presence of autoantibodies, antiphospholipid syndrome, and dyslipidemia [3, 26, 29]. Our study did not find any significant difference regarding CRP level as an inflammatory marker, anti-dsDNA antibody level as an autoantibody and marker of lupus activity, the presence of antiphospholipid syndrome, and dyslipidemia between patients with symptomatic and asymptomatic osteonecrosis.

Corticosteroid utilization is the most common cause of non-traumatic osteonecrosis, and its occurrence is closely associated with the dosage and duration of corticosteroid administration [6, 30]. High-dose and long-term systemic corticosteroid treatment are strongly associated with an increased incidence of corticosteroid-associated osteonecrosis. In contrast, osteonecrosis is a rare occurrence in patients who have never received corticosteroid treatment [31]. A dose-dependent relationship has been reported between corticosteroid use and the risk of osteonecrosis development. Specifically, for each 10 mg/day increase in corticosteroid dose, there is a 3.6 percent increase in the risk of osteonecrosis. Furthermore, doses exceeding 20 mg have been associated with a higher incidence of osteonecrosis [32]. Although the pathogenesis of corticosteroid-associated osteonecrosis remains uncertain, several mechanisms have been proposed. These include abnormalities in the bone marrow stem cell pool, dyslipidemia, the presence of fat microemboli, an increase in the number and size of adipocytes within the bone marrow, vascular endothelial dysfunction, a hypercoagulable state, and apoptosis of bone cells. These factors collectively contribute to the development of marrow ischemia and subsequent osteonecrosis [33]. It appears that the initial high dose of corticosteroids plays a more significant role than the total dose and duration of corticosteroid therapy in the development of osteonecrosis. Asymptomatic osteonecrosis, in particular, can occur within a relatively short period of three months in patients with SLE following treatment with high-dose corticosteroids [34]. In addition to SLE being a recognized risk factor, frequent use of high-dose corticosteroids due to disease flares in patients with SLE may serve as a predisposing factor for osteonecrosis. It has been observed that corticosteroid-associated osteonecrosis is more prevalent among patients with SLE compared to non-SLE patients, with rates of 37% and 21%, respectively [33, 35]. Contrary to findings from other studies, our study did not identify any significant differences in the frequency of intravenously pulsed corticosteroid administration, higher dose, cumulative dose, and duration of corticosteroid intake between patients with and without asymptomatic osteonecrosis. This discrepancy may be due to our small sample size or the fact that patients who received higher doses of corticosteroids mostly presented with symptomatic osteonecrosis.

Although it has been reported that the use of cytotoxic agents is a risk factor for the occurrence of symptomatic osteonecrosis [25], In our study, there was no significant difference in the intake of cytotoxic drugs. Similarly, there were no significant differences observed in the intake of statins, ASA, bisphosphonates, and hydroxychloroquine among patients with and without asymptomatic osteonecrosis.

Limitations of the study

The low number of participants in our study can be attributed to the specific inclusion criteria we used. We enrolled only patients who had recently been diagnosed with symptomatic osteonecrosis within the last six months. This selective inclusion might account for certain discrepancies between the findings of our study and those of other researches. For instance, we found no significant differences in corticosteroid intake, disease activity, and presence of autoantibodies between patients with and without asymptomatic osteonecrosis. However, larger studies are needed to further investigate these associations.

Another limitation of our study is the use of three-phase bone scintigraphy for detecting asymptomatic osteonecrosis. It has lower sensitivity and specificity compared to whole-body MRI in detecting osteonecrosis, which is a more accurate imaging modality. This limitation should be taken into consideration when interpreting our results.

We assessed the involvement of joints at various time points from the initiation of the disease. Conducting a cohort study to screen for asymptomatic osteonecrosis in SLE patients through regular and predefined evaluations of joints after the diagnosis of symptomatic osteonecrosis could potentially provide greater value and insight.

Conclusions

Our study provides additional evidence supporting the high prevalence of asymptomatic osteonecrosis among patients with SLE. This prevalence is attributed to both the nature of the disease and the frequent use of high-dose corticosteroids in its treatment. Furthermore, our findings emphasize the importance of comprehensive screening using whole-body SPECT bone scintigraphy and MRI, as well as the necessity of timely intervention to prevent the debilitating consequences of osteonecrosis.

Acknowledgements
Not applicable.

Authors' contributions
FN played a role in data collection, EA drafted and interpreted the manuscript, BF contributed to interpreting bone scintigraphy images, LA interpreted MR images, MA was involved in patient selection, MN was involved in patient selection and STF made substantial contributions to the study's design and revised the draft. All authors reviewed the manuscript.

Funding
This study did not receive any funding.

Data availability
All data generated or analyzed during this study are incorporated in this published article.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and received approval from the ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.1003). Informed consent was obtained from all patients who participated in the study, allowing their inclusion.

Consent for publication
The informed consent included the provision for the possibility of publishing the research results.

Competing interests
The authors declare no competing interests.

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Received: 17 December 2023 Accepted: 28 November 2024
Published online: 18 December 2024

References

1. Davatchi F, Jamshidi AR, Banihashemi AT, Gholami J, Forouzanfar MH, Akhlaghi M, et al. WHO-ILAR COPCORD Study (Stage 1, Urban Study) in Iran. J Rheumatol. 2008;35(7):1384.
2. Gladman DD, Dhillon N, Su J, Urowitz MB. Osteonecrosis in SLE: prevalence, patterns, outcomes and predictors. Lupus. 2018;27(1):76–81.
3. Kallas R, Li J, Petri M. Predictors of Osteonecrosis in Systemic Lupus Erythematosus: A Prospective Cohort Study. Arthritis Care Res (Hoboken). 2022;74(7):1122–32.
4. Shah UH, Mandl LA, Mertelsmann-Voss C, Lee YY, Alexiades MM, Figgie MP, Goodman SM. Systemic lupus erythematosus is not a risk factor for poor outcomes after total hip and total knee arthroplasty. Lupus. 2015;24(9):900–8.
5. Assouline-Dayan Y, Chang C, Greenspan A, Shoenfeld Y, Gershwin ME. Pathogenesis and natural history of osteonecrosis. Semin Arthritis Rheum. 2002;32(2):94–124.
6. Oinuma K, Harada Y, Nawata Y, Takabayashi K, 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(12):1145–8.
7. Kasturi S, Goodman S. Current Perspectives on Arthroplasty in Systemic Lupus Erythematosus: Rates, Outcomes, and Adverse Events. Curr Rheumatol Rep. 2016;18(9):59.
8. Murphey MD, Roberts CC, Bencardino JT, Appel M, Arnold E, Chang EY, et al. ACR Appropriateness Criteria Osteonecrosis of the Hip. J Am Coll Radiol. 2016;13(2):147–55.
9. Amanatullah DF, Strauss EJ, Di Cesare PE. Current management options for osteonecrosis of the femoral head: part 1, diagnosis and nonoperative management. Am J Orthop (Belle Mead NJ). 2011;40(9):E186–92.
10. Zibis AH, Varitimidis SE, Dailiana ZH, Karantanas AH, Arvanitis DL, Malizos KN. Fast sequences MR imaging at the investigation of painful skeletal sites in patients with hip osteonecrosis. Springerplus. 2015;4(1):3.
11. Yoon BH, Mont MA, Koo KH, Chen CH, Cheng EY, Cui Q, et al. The 2019 Revised Version of Association Research Circulation Osseous Staging System of Osteonecrosis of the Femoral Head. J Arthroplasty. 2020;35(4):933–40.
12. Mont MA, Ulrich SD, Seyler TM, Smith JM, Marker DR, McGrath MS, et al. Bone scanning of limited value for diagnosis of symptomatic oligofocal and multifocal osteonecrosis. J Rheumatol. 2008;35(8):1629–34.
13. Yokota S, Sakamoto K, Shimizu Y, Asano T, Takahashi D, Kudo K, et al. Evaluation of whole-body modalities for diagnosis of multifocal osteonecrosis-a pilot study. Arthritis Res Ther. 2021;23(1):83.
14. Murphey MD, Foreman KL, Klassen-Fischer MK, Fox MG, Chung EM, Kransdorf MJ. From the radiologic pathology archives imaging of osteonecrosis: radiologic-pathologic correlation. Radiographics. 2014;34(4):1003–28.
15. Ehmke TA, Cherian JJ, Wu ES, Jauregui JJ, Banerjee S, Mont MA. Treatment of osteonecrosis in systemic lupus erythematosus: a review. Curr Rheumatol Rep. 2014;16(9):441.
16. Nevskaya T, Gamble MP, Pope JE. A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors. Clin Exp Rheumatol. 2017;35(4):700–10.
17. Ersin M, Demirel M, Ekinci M, Mert L, Çetin Ç, Artım Esen B, et al. Symptomatic osteonecrosis of the hip and knee in patients with systemic lupus erythematosus: Prevalence, pattern, and comparison of natural course. Lupus. 2021;30(10):1603–8.
18. Akbarian M, Faezi ST, Gharibdoost F, Shahram F, Nadji A, Jamshidi AR, et al. Systemic lupus erythematosus in Iran: a study of 2280 patients over 33 years. Int J Rheum Dis. 2010;13(4):374–9.
19. Lee J, Kwok SK, Jung SM, Min HK, Nam HC, Seo JH, et al. Osteonecrosis of the hip in Korean patients with systemic lupus erythematosus: risk factors and clinical outcome. Lupus. 2014;23(1):39–45.
20. 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(11):1307–14.
21. Abu-Shakra M, Buskila D, Shoenfeld Y. Osteonecrosis in patients with SLE. Clin Rev Allergy Immunol. 2003;25(1):13–24.
22. Houssiau FA, N'Zeusseu Toukap A, Depresseux G, Maldague BE, Malghem J, Devogelaer JP, Vande Berg BC. Magnetic resonance imaging-detected avascular osteonecrosis in systemic lupus erythematosus: lack of correlation with antiphospholipid antibodies. Br J Rheumatol. 1998;37(4):448–53.

23. An YS, Park S, Jung JY, Suh CH, Kim HA. Clinical characteristics and role of whole-body bone scan in multifocal osteonecrosis. BMC Musculoskelet Disord. 2019;20(1):23.
24. Agrawal K, Tripathy SK, Sen RK, Santhosh S, Bhattacharya A. Nuclear medicine imaging in osteonecrosis of hip: Old and current concepts. World J Orthop. 2017;8(10):747–53.
25. Calvo-Alén J, McGwin G, Toloza S, Fernández M, Roseman JM, Bastian HM, et al. 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. 2006;65(6):785–90.
26. Sun W, Shi Z, Gao F, Wang B, Li Z. The pathogenesis of multifocal osteonecrosis. Sci Rep. 2016;6:29576.
27. Fialho SC, Bonfá E, Vitule LF, D'Amico E, Caparbo V, Gualandro S, Pereira RM. Disease activity as a major risk factor for osteonecrosis in early systemic lupus erythematosus. Lupus. 2007;16(4):239–44.
28. Faezi ST, Hoseinian AS, Paragomi P, Akbarian M, Esfahanian F, Gharibdoost F, et al. Non-corticosteroid risk factors of symptomatic avascular necrosis of bone in systemic lupus erythematosus: A retrospective case-control study. Mod Rheumatol. 2015;25(4):590–4.
29. Wei Q, Zhou M, Liu J, Zhang S, Gao F, Lin H, Chen Z. Relationship between osteonecrosis and antiphospholipid antibodies in patients with systemic lupus erythematosus: a systematic review protocol. BMJ Open. 2021;11(7): e046163.
30. Hussein S, Suitner M, Béland-Bonenfant S, Baril-Dionne A, Vandermeer B, Santesso N, et al. Monitoring of Osteonecrosis in Systemic Lupus Erythematosus: A Systematic Review and Metaanalysis. J Rheumatol. 2018;45(10):1462–76.
31. Liu LH, Zhang QY, Sun W, Li ZR, Gao FQ. Corticosteroid-induced Osteonecrosis of the Femoral Head: Detection, Diagnosis, and Treatment in Earlier Stages. Chin Med J (Engl). 2017;130(21):2601–7.
32. Mont MA, Pivec R, Banerjee S, Issa K, Elmallah RK, Jones LC. High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: Meta-Analysis and Systematic Literature Review. J Arthroplasty. 2015;30(9):1506-12.e5.
33. Shigemura T, Nakamura J, Kishida S, Harada Y, Ohtori S, Kamikawa K, et al. Incidence of osteonecrosis associated with corticosteroid therapy among different underlying diseases: prospective MRI study. Rheumatology (Oxford). 2011;50(11):2023–8.
34. Nagasawa K, Tada Y, Koarada S, Horiuchi T, Tsukamoto H, Murai K, et al. Very early development of steroid-associated osteonecrosis of femoral head in systemic lupus erythematosus: prospective study by MRI. Lupus. 2005;14(5):385–90.
35. Xie XH, Wang XL, Yang HL, Zhao DW, Qin L. Steroid-associated osteonecrosis: Epidemiology, pathophysiology, animal model, prevention, and potential treatments (an overview). J Orthop Translat. 2015;3(2):58–70.

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