

Is joint involvement in systemic lupus erythematosus always inflammatory?

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Cite this article as: Özsoy Z, Bulat B, Sandal Uzun G, et al. Is joint involvement in systemic lupus erythematosus always inflammatory? *J Health Sci Med.* 2025;8(6):953-958.

Received: 21.08.2025

Accepted: 07.09.2025

Published: 25.10.2025

ABSTRACT

Aims: Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease that can affect multiple organs and systems. Arthralgia and myalgia are common symptoms in patients with SLE, and their etiology may be inflammatory or may result from joint hypermobility or fibromyalgia. This study aimed to investigate whether musculoskeletal complaints in SLE patients are attributable solely to inflammatory activity or whether they may also be associated with hypermobility or fibromyalgia.

Methods: Patients who fulfilled the 2012 SLE classification criteria were included. Patients who had undergone surgical procedures affecting joint mobility within the last 6 months, or those with concomitant diseases such as rheumatoid arthritis or inflammatory myositis that may present with inflammatory arthritis, were excluded from the study. Disease activity at the time of examination was assessed using the SLE Disease Activity Index-2000 (SLEDAI-2K). Hypermobility was evaluated using the Beighton Hypermobility Score, and fibromyalgia was assessed according to the 2016 Fibromyalgia Diagnostic Criteria. Patients were divided into three groups: those with hypermobility, those with fibromyalgia, and those with neither condition. Demographic characteristics, comorbidities, medications, disease activity, and pain scores were analyzed.

Results: Six patients with both fibromyalgia and hypermobility were excluded. A total of 120 patients were analyzed, of whom 104 (86.7%) were female. The median (min-max) disease duration was 12 (1-38) years. Hypermobility was detected in 25 patients (20.8%) and fibromyalgia in 28 patients (23.3%). Overall, 44.1% of the cohort had either hypermobility or fibromyalgia. No significant differences were found between groups in terms of comorbidities. Patients with fibromyalgia had higher median patient VAS and pain scores compared with the other two groups, while their SLEDAI-2K activity scores were lower. Arthritis, according to SLEDAI-2K, was more frequent in the group without hypermobility or fibromyalgia. A significant difference in pulse-steroid use was found between the hypermobility and fibromyalgia groups ($p=0.01$) and between the fibromyalgia and neither group ($p=0.02$).

Conclusion: Severe musculoskeletal pain due to hypermobility may mimic arthralgia or arthritis and may be misinterpreted by clinicians as disease progression. This could lead to unnecessary immunosuppressive therapy (risk of overtreatment), which could lead to increased risk of infection and liver and kidney dysfunction. Therefore, hypermobility and fibromyalgia, which may coexist in the course of SLE, should be thoroughly evaluated. In our study, a significant frequency (almost half of the patients) of pain was due to non-inflammatory causes.

Keywords: Systemic lupus erythematosus, inflammation, hypermobility, fibromyalgia, arthritis

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease that can affect multiple organs and systems. Genetic, environmental, and hormonal factors play a role in its etiology.¹ The prevalence of joint involvement in patients with SLE ranges from 69% to 95%. Unlike inflammatory arthritides such as rheumatoid arthritis, joint involvement in SLE typically follows a non-erosive course. Limitation of range of motion is uncommon; however, subluxations and laxity may occur.² Joint hypermobility is defined as the extension of joint range of motion beyond the normal limits established for

age, sex, and ethnicity during passive movement. It may occur as an isolated condition or in association with rheumatologic diseases. Benign joint hypermobility syndrome (BJHS) is characterized by widespread joint laxity and musculoskeletal pain in the absence of an associated rheumatologic disease.³

The most widely used method for assessing hypermobility is the five-item criterion set developed by Beighton et al.⁴ Each extremity is evaluated separately, and the patient receives a score ranging from 0 to 9. A score of ≥ 4 is considered indicative

of joint hypermobility. Arthralgia and myalgia are common symptoms in both SLE and BJHS. Joint hypermobility has been reported in approximately 25% of SLE patients in the literature.⁵ Another condition characterized by widespread musculoskeletal pain is fibromyalgia. The diagnosis of fibromyalgia requires fulfillment of all the items outlined in the 2016 American College of Rheumatology (ACR) diagnostic criteria.⁶ The prevalence of fibromyalgia in SLE patients has been reported to reach as high as 60% in some studies.⁷

Arthralgia and myalgia are frequent symptoms in SLE patients. While these symptoms may arise from SLE disease activity, they may also be due to underlying joint hypermobility and/or fibromyalgia. This study aimed to determine the prevalence of hypermobility and fibromyalgia in patients with SLE and to investigate their impact on disease activity.

METHODS

This study was conducted in accordance with the 2013 revision of the Declaration of Helsinki and was approved by the Hacettepe University Health Sciences Researches Ethics Committee (Date: 03.09.2024, Decision No: 2024/15-41).

This study included 120 patients followed at the Hacettepe University Department of Rheumatology between 10 September 2024, and 15 June 2025, who fulfilled the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. Patients who had undergone surgical procedures affecting joint mobility in the previous 6 months or who had comorbid diagnoses that could present with inflammatory arthritis, such as rheumatoid arthritis or inflammatory myositis, were excluded. Our study was conducted as a prospective cohort.

Hypermobility was assessed in SLE patients using the Beighton Hypermobility Score,⁴ and fibromyalgia was defined according to the ACR 2016 fibromyalgia diagnostic criteria.⁶ Disease activity at the time of examination was determined using the SLE Disease Activity Index-2000 (SLEDAI-2K) assessment form.⁸ Hypermobility, fibromyalgia, and disease activity were assessed by the same rheumatologist at the same visit. Clinical and laboratory data of the included patients were retrieved from the hospital automation system and patient files.

Six patients with both fibromyalgia and hypermobility were excluded from the study and not included in the analysis to avoid diagnostic overlap. Patients were divided into three groups: those with hypermobility, those with fibromyalgia, and those with neither condition. Demographic characteristics (age, sex), presenting symptoms, comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, COPD, asthma), medications (mycophenolate mofetil, azathioprine, methotrexate, leflunomide, cyclosporine, cyclophosphamide, rituximab, IVIG, glucocorticoids, hydroxychloroquine), SLEDAI-2K activity scores, and pain assessments (pain score and VAS) were compared.

Statistical Analysis

Patient data were analyzed using the IBM SPSS Statistics version 23 biostatistics software. The normality of distribution

for numerical variables was assessed both visually (histograms and probability plots) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were presented as mean±standard deviation for normally distributed variables, and as median and interquartile range for non-normally distributed variables. Likewise, categorical and non-numerical variables were presented as frequency table. For comparisons of means between two independent groups with normal distribution, the student's T test was used, whereas for non-normally distributed data the Mann-Whitney U test was applied. For dependent two-group comparisons, the paired sample t-test and Wilcoxon signed-rank test were used for normally and non-normally distributed variables, respectively. In analyses involving more than two groups, one-way ANOVA or Kruskal-Wallis test was performed for independent groups depending on distributional assumptions, while repeated measures ANOVA or the Friedman test was applied for dependent groups. For categorical variables or frequency comparisons, the Chi-square or Fisher's exact test was employed, depending on sample distribution. A p-value <0.05 was considered statistically significant. The effects of hypermobility and fibromyalgia on disease activity were analyzed by logistic regression.

RESULTS

Baseline Characteristics

At baseline, six patients with both fibromyalgia and hypermobility were excluded, and the remaining 120 patients were included in the analysis, of whom 104 (86.7%) were female. The median (min-max) age was 40 (18-77) years. The median (min-max) disease duration was 12 (1-38) years. Hypermobility was detected in 25 patients (20.8%) and fibromyalgia in 28 patients (23.3%). Overall, 44.1% of the cohort had either hypermobility or fibromyalgia.

Clinical Outcomes

Patients with hypermobility were younger compared with those with fibromyalgia or those without either condition. Patients with fibromyalgia had higher median patient VAS and pain scores compared with the other two groups, while their SLEDAI-2K activity scores were lower ([Table 1](#)). Arthritis, according to SLEDAI-2K, was more frequent in the group without hypermobility or fibromyalgia. There was no difference between the groups in terms of organ/system involvement at the time of study inclusion. However, hypocomplementemia were more common in the hypermobility group. In addition, CRP levels were higher in the group without hypermobility or fibromyalgia ([Table 1](#)). No difference was found between the groups in terms of comorbidities ([Table 2](#)). When immunosuppressive treatments received at any time were analyzed, there was no difference between groups except for history of pulse-steroid therapy (p=0.02) ([Table 2](#)). Pairwise comparisons of pulse-steroid history revealed significant differences between the hypermobility and fibromyalgia groups (p=0.01) and between the fibromyalgia and neither group (p=0.02).

In baseline analyses, hypermobility was present in 24.3% of patients with active disease (SLEDAI ≥3) compared to 16.0%

Table 1. Comparison of patient groups with hypermobility only, fibromyalgia only, and neither

	Hypermobility n (%) 25 (20.8)	Those with fibromyalgia n (%) 28 (23.3)	Without hypermobility and fibromyalgia n (%): 67 (55.9)	p
Female	23 (92)	27 (96.4)	54 (80.6)	0.08
Age	27 (19-58)	49.5 (18-77)	41 (18-73)	<0.001
Disease duration (years)	9 (2-26)	13 (1-31)	11 (1-38)	0.34
Patient VAS	20 (0-90)	40 (20-80)	20 (0-100)	<0.001
Pain assessment	0 (0-3)	2 (0-4)	0 (0-4)	<0.001
SLEDAI-2K activity score	4 (0-35)	2 (0-12)	4 (0-36)	0.02
The organ/system involvements at the time of inclusion n (%)				
Arthritis	5 (20)	1 (3.6)	17 (25.4)	0.04
Fever	9 (36)	13 (46.4)	32 (47.8)	0.59
Hematopoietic system involvement	16 (64)	11 (39.3)	33 (49.3)	0.19
Central nervous system involvement	4 (16)	2 (7.1)	12 (17.9)	0.4
Skin involvement	21 (84)	23 (82.1)	50 (74.6)	0.53
Renal involvement	11 (44)	7 (25)	27 (40.3)	0.28
Cardiac involvement	3 (12)	2 (7.1)	9 (13.4)	0.68
Pleural effusion	3 (12)	1 (3.6)	10 (14.9)	0.29
Laboratory findings at the time of inclusion				
Anti-ds DNA positivity	20 (80)	21 (75)	58 (86.6)	0.37
Complement deficiency	24 (96)	20 (71.4)	57 (85.1)	0.04
CRP levels, mg/dl	2 (1-7)	2 (1-4)	8 (1-26)	<0.001
AFAS antibody positivity	15 (60)	10 (37)	29 (45.3)	0.24
RF positivity	5 (27.8)	3 (12)	10 (16.9)	0.39
CCP positivity	0 (0)	2 (12.5)	2 (4.1)	0.27

When the three groups were compared, the significant parameters were compared in paired groups. There was a difference in median age between the group with hypermobility and fibromyalgia ($p<0.001$), between the group with hypermobility and neither group ($p<0.001$), and between the group with fibromyalgia and neither group ($p: 0.028$). There was a difference in the median patient VAS value between the groups with hypermobility and fibromyalgia ($p: 0.003$), and between the groups with fibromyalgia and neither ($p<0.001$). There was a difference in pain assessment between the groups with hypermobility and fibromyalgia ($p: 0.002$), between the groups with fibromyalgia and neither ($p<0.001$). There was a difference in the median SLEDAI-2K Activity Score between the groups with hypermobility and fibromyalgia ($p: 0.01$), and between the groups with fibromyalgia and neither ($p: 0.01$). There was a difference in the frequency of arthritis according to the SLEDAI-2K Activity Score between the groups with fibromyalgia and neither ($p<0.01$). There was a difference in hypocomplementemia between the hypermobility and fibromyalgia groups ($p: 0.01$). There was a difference in the median patient CRP value between the groups with hypermobility and neither ($p<0.001$), and between the groups with fibromyalgia and neither ($p<0.001$).

VAS: Visual Analog Scale, SLEDAI-2K: SLE Disease Activity Index-2000, DNA: Deoxyribose nucleic acid, CRP: C-reactive protein, AFAS: Antiphospholipid syndrome, RF: Rheumatoid factor, CCP: Cyclic citrullinated peptide

Table 2. Comparison of comorbidities and treatments according to patient groups with hypermobility only, fibromyalgia only, and neither

		Hypermobility n (%) 25 (20.8)	Those with fibromyalgia n (%) 28 (23.3)	Without hypermobility and fibromyalgia n (%): 67 (55.9)	p
Comorbidities	Hypertension	1 (4)	8 (28.6)	13 (19.4)	0.06
	Diabetes mellitus	0 (0)	3 (10.7)	2 (3)	0.11
	Coronary artery disease	0 (0)	1 (3.6)	4 (6)	0.43
	Chronic renal failure	5 (20)	5 (17.9)	6 (9)	0.27
	Antiphospholipid antibody syndrome	3 (12)	3 (10.7)	5 (7.5)	0.75
Treatments	Mycophenolate mofetil	11 (44)	11 (39.3)	31 (46.2)	0.82
	Azathioprine	13 (52)	14 (50)	26 (38.8)	0.4
	Cyclosporine	2 (8)	1 (3.6)	3 (4.5)	0.72
	Cyclophosphamide	6 (24)	3 (10.7)	21 (31.3)	0.1
	Rituximab	3 (12)	5 (17.9)	14 (21.2)	0.59
	Methotrexate	1 (4)	0 (0)	7 (10.4)	0.14
	Leflunomide	0 (0)	2 (7.1)	3 (4.5)	0.42
	IVIg	5 (20)	2 (7.1)	14 (20.9)	0.25
	Daily corticosteroid use	21 (84)	25 (89.3)	56 (83.6)	0.76
	History of pulse-steroid therapy	16 (64)	8 (28.6)	36 (53.7)	0.02

Pairwise comparisons of pulse-steroid history revealed significant differences between the hypermobility and fibromyalgia groups ($p=0.01$) and between the fibromyalgia and neither group ($p=0.02$).

IVIg: Intravenous immunoglobulin

of those without activity ($p=0.271$), indicating no significant difference. In contrast, fibromyalgia was observed more frequently among patients without active disease (34.0% vs. 15.7%, $p=0.020$). Consistently, univariate logistic regression demonstrated that fibromyalgia was associated with a lower likelihood of active disease (OR=0.362, 95% CI 0.152-0.864, $p=0.022$), whereas hypermobility showed no significant association (OR=1.684, 95% CI 0.663-4.280, $p=0.274$).

DISCUSSION

In our study, the majority of patients were female. Hypermobility was present in 20.8% of patients, and fibromyalgia in 23.3%. Patients with hypermobility were younger compared with the other groups. Patients with fibromyalgia had higher patient VAS and pain scores compared with the other two groups, while their SLEDAI-2K activity scores were lower. According to the SLEDAI-2K, arthritis was more frequent in patients without hypermobility or fibromyalgia, whereas, hypocomplementemia were more common in the hypermobility group. A history of pulse-steroid therapy was less frequent among patients with fibromyalgia.

Joint involvement is one of the most common manifestations in patients with SLE and may occur in up to 90% of cases. According to the 2012 SLICC criteria, joint involvement in SLE is defined as “synovitis involving two or more joints, characterized by swelling or effusion, or tenderness in two or more joints with morning stiffness lasting at least 30 minutes”.⁸ Although not life-threatening, joint involvement significantly impairs quality of life, leading to functional limitations and even disability. The frequency of work loss in SLE patients during the first 5 years of disease onset ranges between 15% and 40%.^{9,10} Joint involvement may occur at any stage of the disease. It is characterized by wide heterogeneity in phenotype and severity, ranging from minor arthralgia to erosive arthritis.^{11,12} Arthralgia most frequently involves the hand joints and may sometimes be associated with morning stiffness.¹¹ In a study of 1000 patients, Cervera et al.¹³ reported arthritis in 84% of the cohort. Similarly, in a more recent lupus cohort, musculoskeletal involvement was reported in 80% of patients.¹⁴ In our study, arthritis was present in 19.2% according to the SLEDAI-2K, and was more frequent in the group without hypermobility or fibromyalgia. SLE-related arthritis is typically characterized by symmetric involvement of small joints. In most patients, bone erosions are absent.¹¹ In long-standing disease, however, severe joint laxity and deformities may develop, a condition referred to as Jaccoud’s arthropathy (JA).¹⁵ JA affects approximately 3-13% of patients and may result in joint subluxation.^{16,17} When evaluating patients with SLE, rheumatologists should consider the possibility of hypermobility and fibromyalgia in the presence of arthralgia without specific signs of arthritis, such as joint swelling, redness, or warmth. Systematic screening for fibromyalgia and hypermobility should be performed in SLE patients with persistent joint pain.

The gold standard for assessing SLE disease activity has not yet been established. An ideal activity index should reflect both improvement and deterioration across the different systems involved during the disease course, and should distinguish

activity from chronic damage. Among the available indices, SLEDAI, revised in 2002, is the most commonly used in observational and randomized controlled studies. It consists of 24 objective variables, including 16 clinical and 8 laboratory items, related to disease activity within the previous 28 days.^{18,19} However, this tool may not capture all possible features of joint involvement in SLE patients, such as inflammatory arthralgia or monoarthritis. In our cohort, disease activity was assessed using the SLEDAI-2K, and when groups were compared, it was revealed that patients with fibromyalgia had lower disease activity scores. In addition, univariate logistic regression demonstrated that fibromyalgia was associated with a lower likelihood of active disease. Overall, there is a strong scientific consensus that FM does not directly increase SLE activity but negatively impacts symptom burden and quality of life.²⁰ While there is no definitive explanation for this, patients with higher disease activity likely experience symptoms related to disease burden. Additionally, it may be difficult to diagnose fibromyalgia in someone with active disease due to the disease burden. Considering that fibromyalgia patients focus more on their perception of pain and therefore make more hospital admissions, these patients may have lower disease activity because they are under more doctor’s care.

Joint laxity in rheumatic diseases has been investigated in various studies over the years. Benign joint hypermobility syndrome (BJHS) has been reported in 5-57% of young women and in 2-35% of men in the general population.²¹ Although BEHS historically considered to be benign, one study reported that the percentage of patients with BEHS who had at least one rheumatologic disease was 67.1% in those who were medically examined, 33.3% in those with limited examination, and 9.2% in those who were not examined at all, when comprehensive serologic and radiographic studies were performed for musculoskeletal complaints in addition to physical examination (MAK6- 11). The five most common rheumatologic diseases in BJHS patients were fibromyalgia (22 cases), psoriasis (22 cases), ankylosing spondylitis (11 cases), psoriatic arthritis (11 cases), and rheumatoid arthritis (9 cases).²² These findings highlight the need for thorough clinical assessment in BJHS patients to ensure timely diagnosis of coexisting rheumatologic diseases.

In a study examining 378 patients referred to a rheumatology clinic, hypermobility was identified in 50 patients (13.2%). Compared to controls without hypermobility, the most frequent clinical diagnosis in hypermobile patients was soft tissue rheumatism, observed in 67% versus 25% ($p<0.001$). Fibromyalgia syndrome was present in 30% of hypermobile patients compared to 8% of non-hypermobile patients ($p<0.001$), whereas the least common diagnosis was inflammatory arthritis, observed in 4% versus 32% ($p<0.001$).²³ These results suggest a relationship between hypermobility and soft tissue rheumatic complaints, which may be clinically useful for rheumatologists. In our study, six patients with both fibromyalgia and hypermobility were excluded from the study and not included in the analysis to avoid diagnostic overlap.

Although there are few studies on the relationship between SLE and hypermobility in the literature, it has been shown that hypermobility is associated with inflammatory

arthropathies, particularly SLE.²⁴ In one study, 10 of 59 patients with SLE (17%) were found to be hypermobile.²⁵ Studies conducted in Iraq in 2018 and in Türkiye in 2024 reported a hypermobility prevalence of 52.8% and 50%, respectively.^{26,27} Another study conducted with 81 patients found a statistically significant difference in hypermobility between SLE patients and healthy populations.²⁸ whereas Bleifeld and Inglis²⁹ described localized hand hypermobility in half of SLE patients. In addition to Bridges et al.'s²⁴ findings that 25% of SLE patients are hypermobile, another study with 16 SLE patients and 19 healthy controls, as well as Klemp et al.'s³⁰ study, found hypermobility to be more common in SLE; however, no statistically significant difference between groups was reported.⁵ In our cohort, 20.8% of patients exhibited hypermobility.

As expected from the literature, rheumatology patients are predominantly female (66.9% female, 33.1% male), and the BEHS patient population was also predominantly female (84.4%).²² A similar female-to-male ratio (89% female, 11% male) has been reported in an Italian BEHS cohort.³¹ Differences in muscle structure, sex hormones, and pain perception between males and females have been suggested, although genetic causes remain largely unknown,^{31,32} and further genetic studies are needed to determine whether it is an X-linked condition. Consistent with the literature, 92% of patients with hypermobility in our study were female. Interestingly, in a controlled study of SLE patients with severe disease requiring long-term corticosteroid therapy, hypermobility was not associated with age at disease onset, disease duration, or corticosteroid treatment.³⁰ In our study, 64% of hypermobile patients had a history of pulse steroid therapy, while disease duration was similar across all three groups. Wallace et al.³³ reported a fibromyalgia prevalence of 22% in 464 SLE patients, and Morand et al.³⁴ reported 25.3% in a cohort of 87 SLE patients. Another study found fibromyalgia prevalence in SLE to be as high as 61%.³⁵ In our cohort, consistent with the literature, the prevalence of fibromyalgia was 23.3%.

Limitations

The absence of a control group in our study is a significant limitation. Multicenter studies including control groups are needed to better elucidate the relationship between hypermobility and lupus and to provide guidance in clinical practice.

CONCLUSION

There are insufficient studies in the literature regarding our cohort. Although our study's primary strength is its single-center presence, we contribute to the literature with our substantial patient population. We believe that clinicians should be aware of the importance of considering the diagnoses of hypermobility and fibromyalgia, in addition to disease activation, when managing arthralgia in SLE patients. This will prevent unnecessary immunosuppressive therapy, which can result in complications such as unnecessary infection and organ dysfunction, and which also carries additional financial costs. In conclusion, musculoskeletal symptoms are common in most SLE patients. While many of these symptoms are related to disease activity, some may

be associated with hypermobility or fibromyalgia. Detecting these conditions is essential for disease management. The high prevalence of joint involvement in SLE patients and the clinical heterogeneity require increased awareness and thorough evaluation. Hypermobility disorder can cause severe musculoskeletal pain, which may be mistaken for disease-related arthralgia or arthritis in SLE and perceived by clinicians as disease progression, potentially leading to unnecessary immunosuppressive therapy or escalation of treatment. Therefore, hypermobility and fibromyalgia, which may coexist in the course of SLE, should be thoroughly evaluated. Although arthralgia is a complaint shared across different diseases, applying diagnostic criteria minimizes uncertainty in diagnosis. Distinctions should be made between complaints associated with fibromyalgia and HEDS. However, any clinical diagnosis is subject to inter-clinician variability, highlighting the need for further clinical studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Hacettepe University Health Sciences Researches Ethics Committee (Date: 03.09.2024, Decision No: 2024/15-41).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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