Ultrasonographic abnormalities of wrist and metacarpophalangeal joints in a cohort of Egyptian patients with systemic lupus erythematosus

Noha H. Shedid[a], Eman A. Hafez[a], Safa A. Akram[c], Hossam M. Sakr[b], Elham S. Mohamed[a]

Departments of [a]Internal Medicine and Rheumatology, [b]Radiodiagnosis, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [c]Department of Rheumatology and Rehabilitation, Faculty of Medicine, Baghdad University, Baghdad, Iraq

Correspondence to Elham S. Mohamed, MD, Department of Internal Medicine and Rheumatology, Faculty of medicine, Ain Shams University, Cairo, Egypt.
E-mail: drelhamshabaan@hotmail.com

Received: 9 December 2019
Accepted: 29 December 2019
Published: 18 August 2020

The Egyptian Journal of Internal Medicine
2019, 31:951–957

Background
Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by chronic inflammation and autoantibodies, affecting different organs. Musculoskeletal manifestations are one of the most common manifestations in SLE, usually nonerosive and nondeforming. Musculoskeletal ultrasonography (US) can detect synovial inflammation and structural damage lesions.

Aim
The aim was to detect ultrasound abnormalities of the wrist and metacarpophalangeal (MCP) joints in a cohort of Egyptian patients with SLE and their relation to disease activity.

Patients and methods
A total of 80 female patients with SLE and 10 age-matched apparently healthy controls were enrolled. Clinical examination and laboratory investigations were done for all patients. US examinations of both wrists and second to fifth MCP joints were done for all participants. Patients were divided according to clinical and US assessments.

Results
US detected synovitis of MCPs and/or wrist in 63.75% patients compared with 10% of healthy control ($P<0.01$). Synovitis was identified in most of the patients with SLE who had hand arthralgia when compared with patients without ($P<0.01$). Conversely, 18.3% of patients had wrist joints tenderness on physical examination with no sonographic abnormalities. Systemic Lupus Erythematosus Disease Activity Index score and dsDNA antibodies were associated with the presence of synovitis.

Conclusion
US is a valuable tool for assessment of joints in patients with SLE. It helps in detection of inflammation when compared with clinical examination and monitoring disease activity.

Keywords:
anti-DNA, arthralgia, musculoskeletal ultrasound, synovitis, systemic lupus erythematosus, Systemic Lupus Erythematosus Disease Activity Index

Egypt J Intern Med 31:951–957

1110-7782

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous auto-immune disease characterized by chronic inflammation and autoantibodies that may affect different organs and have a variable clinical course [1,2]. Musculoskeletal involvement is one of the most common clinical manifestations of SLE, and the published series report musculoskeletal involvement in up to 95% of patients, with joint pain being the initial presenting manifestation in 50% of SLE cases [3–5]. In most cases, the patients have symmetrical, inflammatory polyarthritis, especially in hand and wrist joints, but sometimes patients experience arthralgia without evident arthritis on physical examination [6]. Joint involvement has been reported from joint SLE studies as nonerosive, erosive, and deforming arthropathy [7].

Early diagnosis and monitoring of disease activity using specific indices have become a major aspect in the management of patients with SLE. Considering the frequent affection of joints in those patients, the need of a certain tool to evaluate this feature is encouraged. Musculoskeletal ultrasonography (MSKUS) has been considered as a useful tool for assessment [8] and defining complications in patients with SLE with articular involvement [9]. Ultrasonography (US) can detect synovitis in various joints such as the wrists, metacarpophalangeal (MCPs), and metatarsophalangeal

by demonstrating effusion, synovial hypertrophy, and using Doppler ultrasound for demonstrating vascularity [10–12]. MSKUS has been used in several rheumatic inflammatory diseases other than SLE [13–18]. Although there are a growing number of studies on the application of MSKUS in SLE [6,8,10–12,19], the interpretation of these findings in relation to clinical presentation of patients remains to be elucidated.

Aim

The present study aimed at describing the US findings of wrist and MCP joints in a cohort of Egyptian patients with SLE and assessment of their relation to clinical evaluation and disease activity.

Patients and methods

Patients and study design

This was a cross-sectional case–control study that included 80 consecutive female patients with SLE diagnosed according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [20] and 10 age-matched apparently healthy female patients as healthy controls. Patients were recruited from Rheumatology Outpatient Clinics and the Inpatient Department at Ain Shams University Hospital. Patients with other connective tissue diseases, trauma to the hand and/or wrist, diabetes mellitus, and other diseases that affect the musculoskeletal system of the hand were excluded. The study was approved by the Local Research Ethical Committee of Ain Shams University and conforms to the provisions of the Declaration of Helsinki in 1995. All participants gave informed consent to participate after explaining the nature of the study.

Clinical assessment

All patients were subjected to detailed history taking and full clinical examination including rheumatological evaluation. Assessment of disease activity was done using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [21]. Patients were divided according to the presence or absence of hand arthralgia or arthritis into two groups: group I included patients with hand arthralgia or arthritis (45 patients), and group II included asymptomatic patients without hand arthralgia (35 patients) as a control group.

Laboratory assessment

Laboratory investigations included complete blood count, erythrocyte sedimentation rate, C-reactive protein, complement 3 (C3) and complement 4 (C4) level, urinalysis, 24 h urinary proteins, antinuclear antibody determined by indirect immunofluorescence assay, anti-double-stranded DNA (anti-dsDNA) determined by indirect immunofluorescence, anticyclic citrullinated peptide by enzyme-linked immunosorbent assay with titer, and rheumatoid factor (immunoglobulin M) measured by biotec RA factor latex agglutination.

Diagnostic imaging evaluation

US and power Doppler (PD) assessment were done by a trained radiologist in MSKUS who was blinded to the clinical and laboratory data. The second to fifth MCP and the wrist joints were examined bilaterally from the dorsal and palmar aspects through both volar and dorsal recesses. We counted on the more affected recess in the longitudinal and transverse planes. US was performed using LOGIQ P7 ultrasound machine (Innovative Ultrasound imaging. Rancho Santa Margarita, Canada), equipped with a 7.5–12 MHz linear probe working at a Doppler frequency of 6.7 MHz. The first MCP joints were excluded to avoid bias of possible associated osteoarthritis. The mentioned joints were assessed for synovitis. Synovitis is defined according to the OMERACT definitions as presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal [22]. Synovitis was graded using a semiquantitative four-point scale (0–3) as follows: grade 0=absence of visible synovial hypertrophy, grade 1=mild hypoechoic synovial hypertrophy, grade 2=moderate hypoechoic synovial hypertrophy (with some amending to a hypoechoic bulge above the line of the adjacent bones), and grade 3=marked hypoechoic synovial hypertrophy (with some amending that this is extension to one of the two diaphyses or more).

A score ranging from 0 to 3 for PD of small joint inflammation was used as follows: grade 0=absence of signal; grade 1=up to three single vessel signals or two single vessels plus one confluent signal; grade 2=moderate, signal occupying less than 50% of the synovium; and grade 3=marked, vessel signals more than 50% of the synovial area. [23,24]. Erosion is defined as intra-articular and/or extra-articular discontinuity of bone surface (visible in two perpendicular planes) [22].

Patients were also divided according to presence or absence of sonographic evidence of synovitis into two groups.

Statistical methods

Data were analyzed using statistical program for the social sciences (SPSS) version 17.0 (IBM Company,

New York City, US). Data were expressed as mean±SD for quantitative parametric measures in addition to median percentiles for quantitative nonparametric measures and both number and percentage for categorized data. For the comparison between the two groups regarding quantitative data, we performed the independent *t*-test when the data were parametric and the Mann–Whitney test when the data were nonparametric. The comparison between the two groups of patients regarding the qualitative data were done using the χ^2-test, and/or Fisher exact test was used instead of the χ^2-test when the anticipated count in any cell was found to be less than 5. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. The probability of error at 0.05 was considered significant, whereas at 0.01 is highly significant.

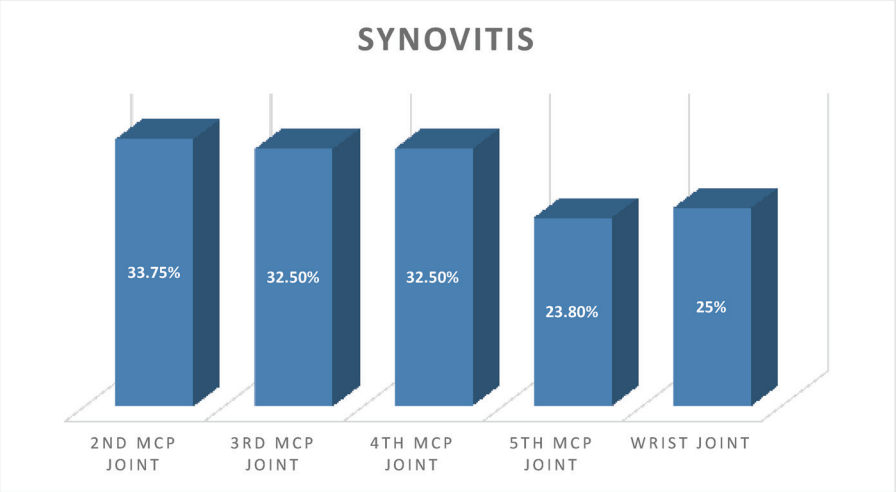
Results

A total of 80 consecutive female patients with SLE were enrolled in this study, with a mean age of 33.93 ±6.87 years (range=18–50) and mean disease duration of 6.36±3.21 years (range=1–18) and 10 healthy women as a control group, with a mean age of 30.3 ±7.33 years. Overall, 45 (56.2%) patients complained of arthralgia. On clinical examination, average 17 (21.2%) patients had tenderness over one or more joints of the hand, whereas six (7.5%) patients had swelling of one or more joints of the hand by clinical examination. Antinuclear antibody was positive in all patients (100%), anti-dsDNA was positive in 54 (68.4%) patients, RF was positive in 30 (37.5%) patients, whereas anticyclic citrullinated peptide was negative in all patients. A total of 78 (97%) patients were treated with corticosteroids, 73 (91.3%) on hydroxychloroquine, 60 (75%) on azathioprine, six (7.5%) on mycophenolate mofetil, and two (2.5%) on cyclophosphamide.

Among the patients with SLE, 51 (63.75%) patients had sonographic evidence of hand (MCPs and/or wrist) synovitis (grade ≥1), which was only observed in one healthy (10%) control ($P<0.01$) and it was grade 1. A total of 12 (15%) patients had positive PD signals (grade 1) and three (3.8%) patients had bone erosions (in third and fourth MCP joints compared with none of healthy control ($P<0.01$). Synovitis (grade ≥1) in patient with SLE was most frequently detected through the dorsal recesses in the second MCP joints (33.75%) followed by third and fourth MCP joints (32.5%), wrist joints (25%). and lastly. Fifth MCP joints (23.8%) (Fig. 1). Most synovitis in patient with SLE was grade I in 50 (62.5%) patients and grade 2 was identified in four (5%) patients, whereas grade 3 was not detected in the examined patients.

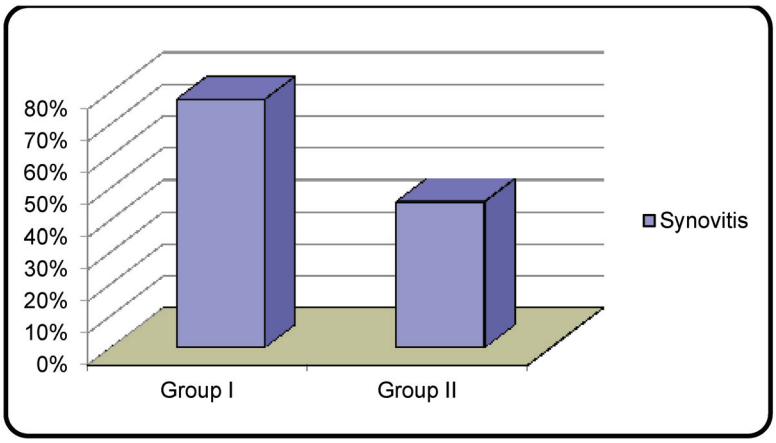
Patients were divided into group I, comprising patients with arthralgia or arthritis (45 patients), and group II, comprising patients without arthralgia (35 patients). Synovitis of wrist and/or MCP joints was detected by US in 35/45 (77.7%) of patient with SLE with hand arthralgia (group I) compared with 16/35 (45.7%) patients without hand arthralgia (group II) ($P<0.01$) (Fig. 2). Positive PD signals in the previous joints were identified in 10/45 (22.2%) patients of group I compared with 2/35(5.7%) patients of group II ($P<0.01$). Bone erosions were found in 2/45 (4.4%) patients of group compared with 1/35 (2.9%) patients of group II ($P>0.05$). SLEDAI score was significantly higher in group I compared with group II [median 6.0

Figure 1



Distribution of ultrasonography-detected synovitis in the joint dorsal recesses of wrist and metacarpophalangeal joints in 80 patient with systemic lupus erythematosus.

Figure 2



Comparison between group I patient with systemic lupus erythematosus with hand arthralgia and/arthritis and group II without arthralgia regarding frequency of patients with synovitis.

(interquartile range: 4.0–8.0) vs 3.0 (2.0–6.0); $P>0.05$]. Comparison between both groups concerning demographic and clinical data is shown in Table 1.

Synovitis by MSKUS was observed in wrists of eight (40%) patients without tenderness at clinical examination and in wrists of 12 (60%) patients without swelling. Corresponding percentages for second MCP joints were 51.9 and 77.8%, third MCP joints were 46.2 and 76.9%, fourth MCP were 69.2 and 84.6%, and fifth MCP were 68.4 and 89.5%. Conversely, 11 (18.3%) patients had wrist joint tenderness on physical examination with no sonographic abnormalities. Corresponding percentage for second MCP joints was 5.7%, third MCP joints 18.5%, fourth MCP 7.4%, and fifth MCP 4.9% (Table 2).

Patients with sonographic evidence of synovitis were associated significantly with a higher SLEDAI score, anti-dsDNA antibodies titer, erythrocyte sedimentation rate ($P<0.05$), and lower C3 and C4 levels than patients without ($P<0.01$). Table 3 shows this significant comparison between patient with SLE with and without synovitis regarding parameters of disease activity.

Discussion

MSKUS has been rarely applied for assessment of joint manifestations and activity in patients with SLE [25]. The present study describes MSKUS findings of wrists and MCP joints of a population of Egyptian patients with SLE in relation to clinical presentation. Overall, sonography-detected synovitis was found in more than half of patient with SLE (nearly 64%), with involvement of MCP joints more frequently (nearly 33%) than wrist joints (25%). Our results are in agreement with those obtained by previous researchers. Previous studies reported synovitis in 25–94% of patient with SLE, with MCP joints involvement in 11–84% and wrist joints involvement in 22–94% [6,10,12,26–28]. PD-positive signals and erosions were identified in 15% and 4% of examined patients with SLE, respectively. In the previous studies, they were reported in 10–82% and 2–41%, respectively [10,12,27,29,30]. These wide variations may be owing to different sample sizes, number of joints examined per patient (e.g. 10 joints in this study, three joints in study by Gabba *et al.* [29], and 32 joints by Iagnocco *et al.* [12]), patients inclusion criteria [some studies included patients with rheumatoid arthritis and lupus overlap (Rhupus) [11,26–28]], or previous treatments before sonographic evaluation [30].

Many studies, including the present study, distinctly separated rhupus from nonrhupus patients and documented presence of erosions in patient with SLE by MSKUS [10,29,31,32]. Zayat *et al.* [33] have previously used US to show that bone erosion is not as specific for rheumatoid arthritis as once thought, and these erosions may have different pathogenesis and clinical importance than they do in RA for further researches to understand their nature and progression with help of MSKUS and MRI.

In this study, we found MSKUS abnormalities with increased disease activity in most of the patients with SLE who had hand arthralgia at the time of examination, when compared with patients with SLE without. This is in harmony with other studies [6,34] in which one of them documented worsened

Table 1 Comparison between group I symptomatic patients and group II asymptomatic patients regarding demographic, clinical, and laboratory features of all 80 patients with systemic lupus erythematosus

Variables	Group I patients (symptomatic) (arthralgia or arthritis) (*n*=45)	Group II (asymptomatic) (without arthralgia) (*n*=35)	$t/\chi^2/z^*$	*P* value
Age (years)	33.47±6.90 (18–49)	34.51±6.89 (19–50)	–0.67	>0.05.
Disease duration (years)	6.04±3.15 (1–15)	6.77±3.28 (1–18)	–1.00	>0.05
Malar rash	13 (28.90)	9 (25.70)	0.1	>0.05
Photosensitivity	12 (26.70)	11 (31.40)	0.218	>0.05
Oral ulcer	20 (44.40)	11 (31.40)	1.405	>0.05
Alopecia	19 (42.20)	15 (42.90)	0.003	>0.05
Serositis	6 (13.30)	3 (8.60)	0.447	>0.05
Neuropsychiatric	0	0	NA	NA
Lupus nephritis	17 (37.78)	13 (37.14)	0.004	>0.05
Laboratory parameters				
WBC (10^3/l)	5.5±2.3 (3– 12)	6.52±2.5 (3.2–12)	–1.86	>0.05
Lymphocytes (10^3/l)	1.70±0.86 (0.51–4.2)	1.88±0.63 (0.8–3.4)	–1.03	>0.05
Platelet (10^3/l)	224,8±80.5 (96–390)	229,9±67,7 (4,8–375)	–0.29	>0.05
Hg (g/dl)	10.44±1.44 (7.3–13.1)	11.05±1.50 (7.3–14.9)	–1.83	>0.05
ESR (mm/h)	33.89±16.85 (10–95)	27.46±15.12 (8–60)	1.77	>0.05
CRP (μl/ml)	4.02±2.66 (0–15)	3.86±2.65 (0–12)	0.27	>0.05
24 h urinary protein (mg/24 h)	223.29±179.27 (25–631)	228.43±277.06 (43– 1500)	–0.10	>0.05
C3 (mg/dl)	91.12±11.84 (65–120)	98.77±13.38 (78–145)	–2.70	<**0.01**
C4 (mg/dl)	19.66±9.77 (11–44)	22.42±10.09 (11–45)	–1.23	>0.05
ANA	45 (100)	35 (100)	NA	NA
Anti-dsDNA	35 (77.8)	19 (55.9)	4.3	<**0.05**
Titer	44.67±40.20 (10–120)	32.00±30.37 (10–180)	1.55	>0.05
Anti-CCP	0	0	NA	NA
Titer (μl/ml)	10.63±6.21 (1–20)	8.30±4.89 (0–20)	1.81	>0.05
RF	19 (42.2)	11 (31.4)	0.97	>0.05
Titer (μl/ml)	9.19±5.85 (2–32)	11.31±6.98 (3–32)	1.45	>0.05
SLEDAI	6.0, 4.0–8.0 (0–16)	3.0, 2.0–6.0 (0–12)	–3.74	<**0.01**

Data are represented as mean±SD (range) and *n* (%). ANA, antinuclear antibody; anti-CCP, anti-citrullinated peptide antibody; anti-dsDNA, anti-double-stranded DNA antibody; C3, C3 complement fraction; C4, C4 complement fraction; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NA, nonapplicable; RF, rheumatoid factor; SLEDAI, SLE disease activity index. *Student-*t* test, χ^2 test, Mann–Whitney test.

Table 2 Comparison between patient with systemic lupus erythematosus with and without individual ultrasonography detected joint synovitis regarding presence or absence of joint tenderness and swelling

Clinical examination joint synovitis	Joint tenderness [*n* (%)]		χ^2	*P* value	Joint swelling [*n* (%)]		χ^{2*}	*P* value
	Yes	No			Yes	No		
Wrist								
Yes (20 patients)	12 (60)	8 (40)	13.54	<**0.01**	8 (40)	12 (60)	25.87	<**0.01**
No (60 patients)	11(18.3)	49 (81.7)			0	59 (98.3)		
Second MCP								
Yes (27 patients)	13 (48.1)	14 (51.9)	21.93	<**0.01**	6 (22.2)	21 (77.8)	21.79	<**0.01**
No (53 patients)	3 (5.7)	50 (94.3)			0	53 (100.0)		
Third MCP								
Yes (26 patients)	14 (53.8)	12 (46.2)	10.43	<**0.01**	6 (23.1)	20 (76.9)	13.47	<**0.01**
No (54 patients)	10 (18.5)	44 (81.5)			0	54 (100.0)		
Fourth MCP								
Yes (26 patients)	8 (30.8)	18 (69.2)	11.42	<**0.01**	4 (15.4)	22 (84.6)	24.42	<**0.01**
No (54 patients)	4 (7.4)	50 (92.6)			0	54 (100.0)		
Fifth MCP								
Yes (19 patients)	6 (31.6)	13 (68.4)	10.31	<**0.01**	2 (10.5)	17 (89.5)	3.17	>0.05
No (61 patients)	3 (4.9)	58 (95.1)			0	60 (98.4)		

MCP, metacarpophalangeal. *χ^2 test.

Table 3 Comparison between patient with systemic lupus erythematosus with and without ultrasonography detected joint synovitis regarding disease activity parameters

Variables	Synovitis (51 patients)	No synovitis (29 patients)	t/z^*	*P* value
ESR (mm/h)				
Mean±SD	35.27±16.96	26.67±14.60	2.426	<**0.05**
Range	10–95	8–51		
Anti-ds DNA				
Mean±SD	53.08±43.61	32.41±30.89	2.441	<**0.05**
Range	10–160	10–180		
C3 (mg/dl)				
Mean±SD	85.56±10.18	97.44±12.57	-3.826	<**0.01**
Range	65–100	70–145		
C4 (mg/dl)				
Mean±SD	15.06±3.61	22.80±10.63	-3.187	<**0.01**
Range	11.3–23	11–45		
SLEDAI				
Median (IQR)	8 (4–10)	4 (2–6)	8.646	<**0.05**
Range	0–16	0–12		

ESR, erythrocyte sedimentation rate; IQR, interquartile range; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. *Student's *t*-test, Mann–Whitney test.

functional ability and a lower quality of life in the group of hand arthralgia [6]. Another study assessed long-term (nearly 6 years) patient outcome after sonographic baseline assessment of patients with arthralgia and joint MSKUS abnormalities [35]. They found that these symptomatic patients with MSKUS abnormalities received more methotrexate and hydroxychloroquine, essentially for treatment of persistent musculoskeletal activity in comparison with asymptomatic patient with SLE with normal MSKUS and that may be an indicator for the importance of MSKUS as a prognostic tool for worse musculoskeletal affection.

In this study, there were a considerable number of asymptomatic patients with no hand arthralgia who showed MSKUS abnormalities (46%). In the earlier studies, they varied from 3 to 58% [6,29,34,36,37], although a more recent one reported unexplained higher frequency of MSKUS abnormalities in asymptomatic patients, reaching 85% [28]. Similarly, on physical examination of joints, a significant number of patients with US-detected synovitis did not show either swelling or tenderness. The actual significance of these abnormalities in asymptomatic patients is needed to be clarified with long-term follow-up to see if it will continue to be silent or it will progress to become clinically detectable with possibility of chronic deformities occurrence as Jaccoud's arthropathy. In addition, we need to know if this subclinical US-detected synovitis will be an indication of immunosuppressive treatment. On the contrary, the presence of a percentage of patients (reaching 18% in wrist and third MCP joints) with joint tenderness on clinical examination but with no MSKUS abnormalities was recorded, which was also reported by Lins *et al*. [38], who found 111/896 (12%) joints with tenderness on physical examination had no sonographic abnormalities. Ours and theirs study concluded that these clinical findings may be linked to some reasons that cannot be interpreted using US. So the unnecessary intensification of treatment of those patients with immunosuppressive glucocorticoids exposes them to adverse effects and organ damage [39]. MSKUS will be more efficient in assessment of joint activity, therefore assist in reducing overtreatment with glucocorticoids [32].Some studies have pointed out to an association between presence of MSKUS abnormalities and SLE disease activity measures [6,31]. In the current study, patients with US-detected synovitis showed higher SLEDAI score and anti-dsDNA titer with other parameters that favors increased disease activity than patients without US findings. Nevertheless, there were other studies that found the opposite [8,12,40], and they suggested that comprehensive assessment of patients with SLE should be completed by imaging modalities, such as US for a better estimation of joint inflammation.

Conclusion

In conclusion, MSKUS appears to be a valuable tool for assessment of joints in patient with SLE especially with hand arthralgia. It has a greater ability in detection of inflammation when compared with clinical examination. It can help in monitoring of joint disease activity and in treatment decision.

Limitation of the study

Males were not included in the present study, which was not intended.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 George C, Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011; 365:2110–2121.

2 Wu T, Ding H, Han J, Arriens C, Wei C, Han W, *et al.* Antibody array based proteomic screening of serum markers in systemic lupus erythematosus: a discovery study. J Proteome Res 2016; 15:2102–2114.

3 Cipriano E, Ceccarelli F, Massaro L, Spinelli FR, Alessandri C, Perricone C, *et al.* Joint involvement in patients affected by systemic lupus erythematosus: application of the swollen to tender joint count ratio. Rheumatismo 2015; 67:62–67.

4 Grossman JM. Lupus arthritis. Best Pract Res Clin Rheumatol 2009; 23:495–506.

5 Santiago MB, Galvão V. Jaccoud arthropathy in systemic lupus erythematosus: analysis of clinical characteristics and review of the literature. Medicine (Baltimore) 2008; 87:37–44.

6 Torrente-Segarra V, Lisbona MP, Rotés-Sala D, *et al.* Hand and wrist arthralgia in systemic lupus erythematosus is associated to ultrasonographic abnormalities. Jt Bone Spine 2013; 80:402–406.

7 Ball EM, Bell AL. Lupus arthritis-do we have a clinically useful classification? Rheumatology (Oxford) 2012; 51:771–779.

8 Ossandon A, Iagnocco A, Alessandri C, Priori R, Conti F, Valesini G. Ultrasonograph ic depiction of knee joint alterations in systemic lupus erythematosus. Clin Exp Rheumatol 2009; 27:329–332.

9 Piga M, Gabba A, Vacca A, Porru G. Multiple septic bursitis and spontaneous Achilles tendon tear in systemic lupus erythematosus. J Rheumatol 2010; 37:2438–2440.

10 Wright S, Filippucci E, Grassi W, Grey A, Bell A. Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. Lupus 2006; 15:501–506.

11 Delle Sedie A, Riente L, Scire CA, Iagnocco A, Filippucci E, Meenagh G, *et al.* Ultrasound imaging for the rheumatologist, sonographic evaluation of wrist and hand joint and tendon involvement in systemic lupus erythematosus. Clin Exp Rheumatol 2009; 27:897–901.

12 Iagnocco A, Ceccarelli F, Rizzo C, Truglia S, Massaro L, Spinelli FR, *et al.* Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology 2014; 53:465–472.

13 Meenagh G, Filippucci E, Iagnocco A, *et al.* Ultrasound imaging for the rheumatologist VIII. Ultrasound imaging in osteoarthritis. Clin Exp Rheumatol 2007; 25:172–175.

14 Delle Sedie A, Riente L, Iagnocco A, *et al.* Ultrasound imaging for the rheumatologist X. Ultrasound imaging in crystal-related arthropathies. Clin Exp Rheumatol 2007; 25:513–517.

15 Riente L, Delle Sedie A, Filippucci E, *et al.* Ultrasound imaging for the rheumatologist IX. Ultrasound imaging in spondyloarthritis. Clin Exp Rheumatol 2007; 25:349–353.

16 Meenagh G, Filippucci E, Delle Sedie A, *et al.* Ultrasound imaging for the rheumatologist XIX. Imaging modalities in rheumatoid arthritis. Clin Exp Rheumatol 2009; 27:3–6.

17 Delle Sedie A, Riente L, Filippucci E, *et al.* Ultrasound imaging for the rheumatologist XXXII. Sonographic as- sessment of the foot in patients with psoriatic arthritis. Clin Exp Rheumatol 2011; 29:217–222.

18 Riente L, Delle Sedie A, Filippucci E, *et al.* Ultrasound imaging for the rheumatologist XIV. Ultrasound imaging in connective tissue diseases. Clin Exp Rheumatol 2008; 26:2303.

19 Yoon HS, Kim KJ, Baek IW, Park YJ, Kim WU, Yoon CH, *et al.* Ultrasonography is useful to detect subclinical synovitis in SLE patients without musculoskeletal involvement before symptoms appear. J Clin Rheumatol 2014; 33:341–348.

20 Petri M, Orabi AM, Alarcon GS, Gorden C, Merill JT, Fortin PR, *et al.* Derivation and validation of the systemic lupus international collaboration clinics classification criteria for systemic lupus erythematosus. Arthritis Rheumatol 2012; 64:2677–2686.

21 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheumatol 1992; 35:630–640.

22 Bruyn GA, Iagnocco A, Naredo E, Balint P, Gutierrez M, Hammer HB, *et al.* OMERACT definitions for ultrasonographic pathology and elementary lesions of rheumatic disorders fifteen years on. J Rheumatol 2019; 46:1–20.

23 D'Agostino MA, Terslev L, Aegerter P, *et al.* Scoring ultrasound synovitis in rheumatoid arthritis: a EULAROMERACT ultrasound taskforce – Part 1: definition and development of a standardised, consensus-based scoring system. RMD Open 2017; 3:e000428.

24 Terslev L, Naredo E, Aegerter P, *et al.* Scoring ultrasound synovitis in rheumatoid arthritis: a EULAROMERACT ultrasound taskforce-Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. RMD Open 2017; 3:e000427.

25 Torrente-Segarra V, Salman-Monte TC, Corominas H. Musculoskeletal involvement and ultrasonography update in systemic lupus erythematosus: new insights and review. Eur J Rheumatol 2018; 5:127–130.

26 Iagnocco A, Ossandon A, Coari G, *et al.* Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. Clin Exp Rheumatol 2004; 22:621–624.

27 Buosi AL, Natour J, Machado FS, Takahashi RD, Furtado RN. Hand ultrasound: comparative study between 'no rhupus' lupus erythematosus and rheumatoid arthritis. Mod Rheumatol 2014; 24:599–605.

28 Salliot C, Denis A, Dernis E, Andre V, Perdriger A, Albert JD, *et al.* Ultrasonography and detection of subclinical joints and tendons involvements in systemic lupus erythematosus (SLE) patients: a cross-sectional multicenter study. Joint Bone Spine 2018; 85:741–745.

29 Gabba A, Piga M, Vacca A, *et al.* Joint and tendon involvement in systemic lupus erythematosus: an ultrasound study of hands and wrists in 108 patients. Rheumatology 2012; 51:2278–2285.

30 Zayat AS, Conaghan PG, Sharif M, Freeston JE, Wenham C, Hensor EM, *et al.* Do non-steroidal anti-inflammatory drugs have a significant effect on detection and grading of ultrasound-detected synovitis in patients with rheumatoid arthritis? Results from a randomised study. Ann Rheum Dis 2011; 70:1746–1751.

31 Ball E, Gibson D, Bell A, Rooney M. Plasma IL-6 levels correlate with clinical and ultrasound measures of arthritis in patients with systemic lupus erythematosus. Lupus 2014; 23:46–56.

32 Zayat AS, Mahmoud K, Yusof MYM, *et al.* Defining inflammatory musculoskeletal manifestations in systemic lupus erythematosus. Rheumatology 2019; 58:304–312.

33 Zayat AS, Ellegaard K, Conaghan PG, *et al.* The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. Ann Rheum Dis 2015; 74:897–903.

34 Dreyer L, Jacobsen S, Juul L, Terslev L. Ultrasonographic abnormalities and inter-reader reliability in Danish patients with systemic lupus erythematosus – a comparison with clinical examination of wrist and metacarpophalangeal joints. Lupus 2015; 24:712–719.

35 Corzo P, Salman-Monte TC, Torrente-Segarra V, Polino L, Mojal S, Carbonell-Abelló J. Joint ultrasound baseline abnormalities predict a specific long-term clinical outcome in systemic lupus erythematosus patients. Lupus 2017; 26:729–733.

36 Zayat AS, Md Yusof MY, Wakefield RJ, *et al.* The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology (Oxford) 2016; 55:485–494.

37 Mosca M, Tani C, Carli L, *et al.* The role of imaging in the evaluation of joint involvement in 102 consecutive patients with systemic lupus erythematosus. Autoimmun Rev 2015; 14:10–15.

38 Lins CF, Lima de Sá Ribeiro D, Dourado Santos WG, Rosa G, Machicado V, Pedreira AL, *et al.* Ultrasound findings on hands and wrists of patients with systemic lupus erythematosus: relationship with physical examination. Ultrasound Med Biol 2017; 43:1764–1768.

39 Thamer M, Hernán MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. J Rheumatol 2009; 36:560–564.

40 Ruano CA, Malheiro R, Oliveira JF, *et al.* Ultrasound detects subclinical joint inflammation in the hands and wrists of patients with systemic lupus erythematosus without musculoskeletal symptoms. Lupus Sci Med 2017; 3: e000184.