

Original article

Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus

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Abstract

Objectives. To assess the prevalence and severity of inflammatory abnormalities of the hand, wrist and foot joints in SLE patients by US and to correlate them with clinical, laboratory and disease activity score parameters.

Methods. Sixty-two consecutive SLE patients were enrolled in the present study and underwent clinical evaluation, laboratory tests and bilateral high-resolution US of the hand, wrist and foot joints. Joint effusion (JE), synovial hypertrophy (SH) and local pathological vascularization [power Doppler (PD)] were evaluated according to both a dichotomous score and a semi-quantitative (0–3) grading system. In addition, a global US score was calculated by summing the values given to each elementary lesion for every single joint and every joint group. US findings were correlated with physical examination, serological parameters (CRP, ANA, anti-dsDNA, ENA, aPL, C3 and C4 serum levels) and disease activity indexes (SLEDAI-2K, ECLAM).

Results. US detected inflammatory joint abnormalities in 54/62 patients (87.1%); 72.6% presented involvement of the MTP joints, 46.7% the MCP joints, 19.3% the PIP joints and 53% the wrists. A total of 1984 joints were examined highlighting JE in 19.1% of cases, SH in 6.9% and positive PD in 1.1%. The global US inflammatory score had a mean value of 10.9 (s.d. 15.2). No correlations were found between US findings and SLE disease activity parameters.

Conclusion. US demonstrated a high prevalence of inflammatory joint abnormalities in SLE that were also present in asymptomatic patients. Interestingly, the foot joints were the most frequently involved. US is a valuable tool for detecting subclinical synovitis in SLE.

Key words: ultrasound, synovitis, SLE.

Introduction

SLE is a chronic inflammatory disorder with a multifactorial aetiology in which genetic and environmental factors interact in disease susceptibility [1, 2]. Key features of the disease are autoimmunity alterations, characterized by the production of a wide range of autoantibodies [3–5]. SLE mainly affects women of reproductive age

and every organ and/or system can be involved in the pathological process [1, 6]. Among them, involvement of the musculoskeletal system is most frequent and often the earliest manifestation of SLE, occurring in up to the 94% of patients during the course of the disease [7]. The joint involvement is characterized by heterogenic features such as arthralgia, arthritis and, more rarely, as deforming arthropathy, known as Jaccoud arthropathy [7]. In recent years, the monitoring of disease activity by using specific composite indices has become an important aspect in the management of patients affected by SLE [8]. Moreover, new therapeutic approaches have been introduced, further highlighting the need for different tools able to evaluate disease activity and treatment efficacy [9].

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In view of the high frequency of joint involvement in SLE patients, the application of specific instruments to assess this feature is recommended. Musculoskeletal US has been proven to be a useful imaging technique that helps in correlating clinical and anatomical findings, providing relevant information that might influence management of the disease [10, 11]. US is able to depict synovial and tenosynovial inflammation as well as structural damage lesions [10]. Moreover, the application of power Doppler (PD) has improved the sensitivity of US in detecting active inflammation through the identification of pathologically increased haematic perfusion [12]. US has been applied in several rheumatic inflammatory diseases [13–18]. However, only a few studies have been focused on the assessment of SLE patients using US [19–23].

The aim of the present study was to evaluate joint inflammatory abnormalities of the hand, wrist and foot joints in SLE patients using US and PD. Imaging findings were correlated with clinical, laboratory and disease activity score parameters.

Patients and methods

Patients affected by SLE, diagnosed according to the 1997 revised ACR criteria, were consecutively enrolled in the study [24]. All of them were in the in- and outpatient population attending the Lupus Clinic of the Rheumatology Unit of Sapienza Università di Roma, Italy. The study was conducted according to the protocol and good clinical practice principles and Declaration of Helsinki statements. All patients gave their informed consent and the study was approved by the Comitato Etico Sapienza Università di Roma, Policlinico Umberto I, Rome, Italy.

The study protocol included complete physical examination, blood draws and ultrasonographic assessment. The clinical and laboratory data were collected in a standardized computerized electronically filled form, including demographics, past medical history with date of diagnosis, co-morbidities and previous and concomitant treatments. In particular, joint involvement of the wrists, hands and feet was defined as the presence of pain and/or swelling and/or functional impairment in the reported medical history or at the physical examination. Clinical activity was assessed using the SLEDAI 2000 (SLEDAI-2K) and the ECLAM [8, 25]. Each subject underwent peripheral blood sample collection. The sera recovered were then stored at -20°C until assayed. CRP was assessed by nephelometry (mg/l). ANA was determined by means of IIF on HEp-2 and anti-dsDNA by IIF on *Crithidia luciliae* in accordance with the manufacturer's instructions (Orgentec Diagnostika, Mainz, Germany). ENA (anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP) anti-CL (IgG and IgM isotype) and anti- β 2GPI (IgG and IgM isotype) were determined by ELISA (Diamedix, Miami, FL, USA), and LA was assessed according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on LA/phospholipid-dependent antibodies). In all patients, C3 and C4

serum levels (mg/dl) were studied by using radial immunodiffusion.

On the same day as the clinical evaluation, all patients underwent an ultrasonographic assessment at the US unit of the same department. A single rheumatologist, expert in musculoskeletal US, who was blinded to clinical and laboratory data, performed the examination and scored the static images. A MyLab70 XVision Gold (Esaote, Genova, Italy) machine equipped with a multifrequency linear array transducer (6–18 MHz) was used. PD settings were PD pulse repetition frequency 750 Hz, Doppler frequency 11.1 MHz, gain 50% and low filters. A systematic bilateral multiplanar grey-scale and PD examination, including both dorsal and palmar scans, of the hand (MCP and PIP joints), wrist and foot joints (MTP joints), was performed according to international guidelines for musculoskeletal US in rheumatology [26]. Specifically, at the wrist level, the radiocarpal and ulnocarpal joints were evaluated, performing longitudinal and transverse scans over the dorsal and volar aspects of the joints. Both joints were scored and the one that presented the highest score was considered for final radioulnocarpal (RUC) joint score at the wrist level.

Every joint was examined in order to identify signs of synovitis, i.e. joint effusion, synovial hypertrophy and PD signal. All abnormalities were defined according to the OMERACT definitions for ultrasonographic pathology [27]. US-detected elementary lesions were primary evaluated with a dichotomous score (absence or presence) and then graded according to a semi-quantitative scale ranging from 0 to 3 (0 = absent, 1 = mild, 2 = moderate and 3 = severe). Then, ultrasonographic inflammatory scores, calculated by adding the values given to each elementary lesion, were elaborated for every single joint and every joint group (MTP, MCP, PIP wrist joints). Finally, a global score was obtained by adding together the scores for all joint groups. All data were reported on the electronic database.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 13.0; SPSS, Chicago, IL, USA). Chi-square and Fisher's exact test were used to compare qualitative differences between joint groups, while Wilcoxon's test (Mann-Whitney *U*-test) was performed to compare parametric variables. The findings were expressed as the mean (s.d.). Values of $P < 0.05$ were considered to be statistically significant.

Results

Sixty-two consecutive patients (58 females and 4 males) were included in the study. The demographic, clinical, laboratory and therapeutic parameters of the enrolled subjects are reported in Table 1.

Ultrasonographic findings

The US findings related to joint inflammatory abnormalities (joint effusion and/or synovial hypertrophy and/or PD)

TABLE 1 Demographic, clinical, laboratory and therapeutic characteristics of SLE patients: cumulative and at the time of US evaluation

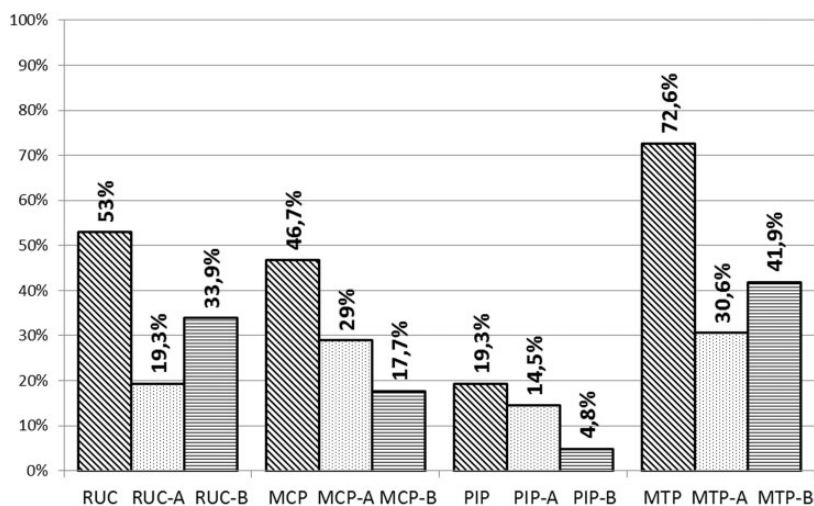
	Cumulative	At the time of the US evaluation
Female/male, <i>n</i>		58/4
Age, mean (s.d.), years	—	42.8 (12.9)
Disease duration, mean (s.d.), months	—	134.7 (112.5)
Joint involvement, <i>n</i> (%)	56 (90.3)	25 (40)
Skin involvement, <i>n</i> (%)	50 (80.6)	8 (12.9)
Renal involvement, <i>n</i> (%)	21 (33.8)	8 (12.9)
Serositis, <i>n</i> (%)	14 (22.6)	0 (0)
Neuropsychiatric involvement, <i>n</i> (%)	9 (14.5)	1 (1.6)
Cytopenia, <i>n</i> (%)	40 (64.5)	10 (16.1)
Laboratory parameters		
CRP, mean (s.d.), mg/l		5.2 (4.7)
ANA, <i>n</i> (%)	51 (82.2)	44 (70.9)
Anti-dsDNA, <i>n</i> (%)	43 (69.3)	15 (24.2)
Anti-Sm, <i>n</i> (%)	15 (24.2)	4 (6.4)
Anti-SSA, <i>n</i> (%)	23 (37.1)	12 (19.3)
Anti-SSB, <i>n</i> (%)	13 (20.9)	5 (8.1)
Anti-RNP, <i>n</i> (%)	14 (22.6)	6 (9.7)
Anti-cardiolipin IgG and/or IgM, <i>n</i> (%)	31 (50.0)	3 (4.8)
Anti-β2GPI IgG and/or IgM, <i>n</i> (%)	9 (14.5)	1 (1.6)
LA, <i>n</i> (%)	14 (22.6)	1 (1.6)
Low C3 and/or C4 levels, <i>n</i> (%)	28 (45.2)	22 (35.5)
C3, mean (s.d.), mg/dl	—	65.5 (47.5)
C4, mean (s.d.), mg/dl	—	12.3 (10.8)
Treatment		
Glucocorticoids, <i>n</i> (%)	57 (91.9)	46 (74)
Glucocorticoids, mean weekly dosage (s.d.), mg	—	51.3 (34.8)
HCQ, <i>n</i> (%)	55 (90.1)	42 (67.7)
MTX, <i>n</i> (%)	22 (35.5)	7 (11.3)
AZA, <i>n</i> (%)	16 (25.8)	5 (8.1)
Mycophenolate, <i>n</i> (%)	20 (32.2)	10 (16.1)
Ciclosporin A, <i>n</i> (%)	20 (32.2)	7 (11.3)
CYC, <i>n</i> (%)	11 (17.7)	1 (1.6)
Rituximab, <i>n</i> (%)	3 (4.8)	1 (2)
SLEDAI-2K, mean (s.d.)	—	2.3 (2.9)
ECLAM, mean (s.d.)	—	0.9 (1)

were observed in 54 of 62 (87.1%) patients. Only 25 patients of these 54 presented articular involvement at the clinical examination and 29 of these showed US signs of inflammation in the absence of clinical joint disease. In particular, US inflammatory changes were at least detected in a single RUC in 33/62 (53%) patients, in an MCP in 29/62 (46.7%), in a PIP in 12/62 (19.3%) and in an MTP in 45/62 (72.6%), as shown in Fig. 1. According to these findings, MTP joints were the most frequently involved site, with statistically significant differences with respect to RUC ($P=0.005$), MCP ($P=0.0003$) and PIP ($P<0.000001$) joints. In the MCP group the most commonly involved joint was the second MCP, presenting at least one US alteration in 20/62 (32.2%) patients, followed in descending order by the third MCP, which showed US inflammatory signs in 30.6% of patients, the first MCP in 20.9%, the fifth MCP in 22.6% and the fourth MCP in 19.3%. In the PIP joints, the third PIP was the most frequently involved (12.9% patients). The first and second

PIP joints showed US abnormalities each in 11% of patients, the fifth PIP in 9.6% and the fourth PIP in 8.1%. In the MTP joints, the second MTP had US-detected involvement in 61.3% patients, the third MTP in 51.6%, the first MTP in 45.2%, the fourth MTP in 40.3% and the fifth MTP in 17.7% (Fig. 2).

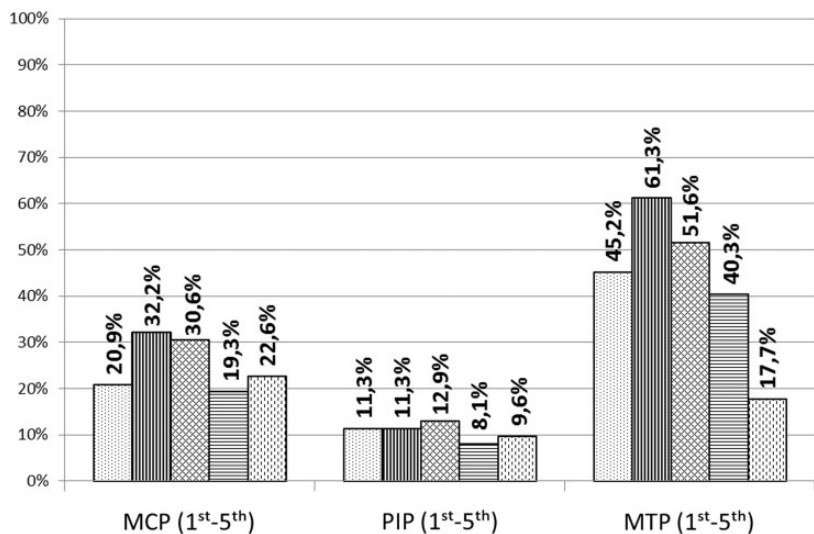
A total of 1984 joints were studied by US. The most prevalent abnormal US finding was joint effusion, which was detected in 378/1984 joints (19.1%). Synovial hypertrophy was demonstrated in 138/1984 joints (6.9%) and PD signal was positive in 22/1984 joints (1.1%). The global US inflammatory score had a mean value of 10.9 (s.d. 15.2). The analysis of each articular group showed that the MTP joints presented the highest US score, followed by the MCP, RUC and PIP joints, as shown in Table 2. Specifically, the mean RUC score was 1.8 (s.d. 2.6), the mean MCP was 3.3 (s.d. 7.4), the mean PIP was 1.24 (s.d. 5.3) and the mean MTP was 4.5 (s.d. 5.2).

Fig. 1 Histograms representing the frequency of joint inflammatory involvement detected by US in the four articular groups (RUC, MCP, PIP and MTP).



The 62 SLE patients included in the study were subgrouped according to the presence or absence of clinical manifestations (Group A and Group B, respectively). RUC-A, radioulnocarpal joints Group A; RUC-B, radioulnocarpal joints Group B; MCP-A, metacarpophalangeal joints Group A; MCP-B, metacarpophalangeal joints Group B; PIP-A, proximal interphalangeal joints Group A; PIP-B, proximal interphalangeal joints Group B; MTP-A, metatarsophalangeal joints Group A; MTP-B, metatarsophalangeal joints Group B.

Fig. 2 Histogram showing the frequency of inflammatory involvement detected by US at different joint sites.



The MCP joints (1st-5th), PIP joints (1st-5th) and MTP joints (1st-5th) were assessed in the 62 patients affected by SLE included in the study.

The US score was significantly higher in MTP joints than in MCP ($P=0.0029$) and PIP ($P=0.0001$) joints, showing that MTP joints were the most severely involved articular site (Fig. 3). In particular, among the 620 MTP joints evaluated, 160/620 (25.8%) presented only joint effusion and 41/620 (46.6%) presented both joint effusion and synovitis. Supplementary Fig. S1, available at *Rheumatology*

Online, illustrates examples of grey-scale and PD US synovitis in the MTP and RUC joints of patients with SLE.

At the patient level, RUC joint effusion was detected in 14/62 (22.6%) patients, RUC joint synovial hypertrophy without PD in 11/62 (17.7%) and RUC joint synovial hypertrophy with PD in 7/62 (11.3%). In the MCP joints, 15/62 patients (24.2%) presented only joint effusion, 6/62 (9.7%)

synovial hypertrophy without PD and 6/62 (9.7%) synovial hypertrophy with PD. In the PIP joints, 6/62 (9.7%) patients presented only joint effusion, 4/62 (6.5%) synovial hypertrophy without PD and 2/62 (3.2%) synovial hypertrophy with PD. Finally, in the MTP joints, 31/62 (50%)

patients presented only joint effusion, 10/62 (16%) synovial hypertrophy without PD and 3/62 (4.8%) synovial hypertrophy with PD.

The possible presence of a concomitant condition of OA was evaluated. The US signs of initial OA (mild osteophytes) at the PIP, first MCP and first MTP joints were detected in only 4/62 patients (6.5%) and in these joints there was no effusion or synovial hypertrophy.

TABLE 2 Global ultrasonographic inflammatory scores calculated for the RUC, MCP, PIP and MTP^a joints after the US evaluation

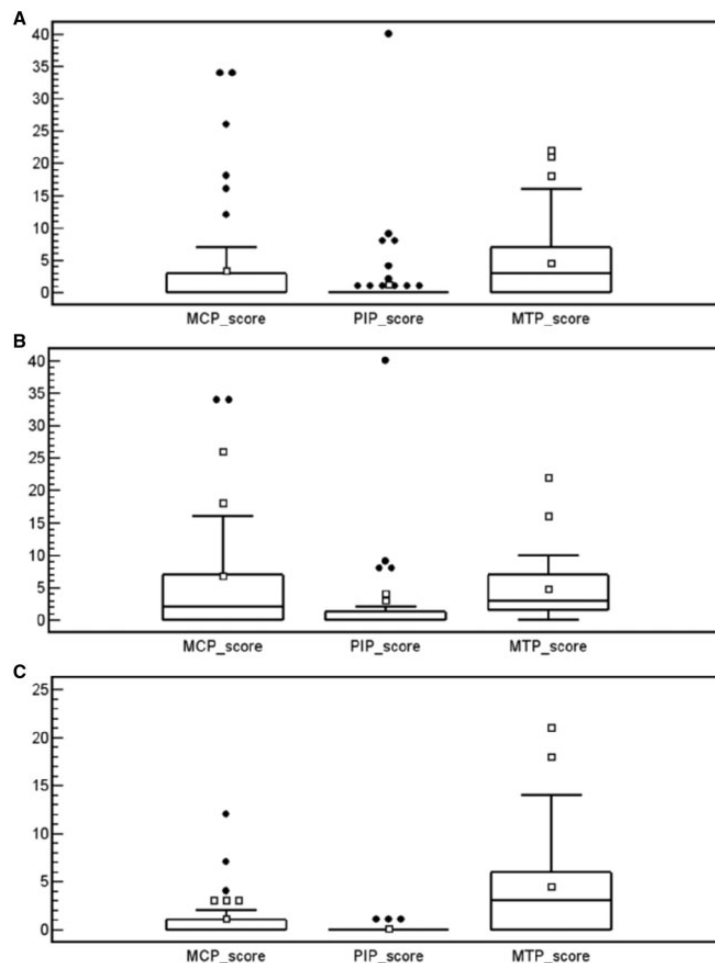
Joint	US inflammatory scores, mean (s.d.)
RUC	1.8 (2.6)
MCP	3.3 (7.4)
PIP	1.24 (5.3)
MTP	4.5 (5.2)

^aThe MTP joints presented the highest US score, followed by the MCP, RUC and PIP joints.

Correlation between clinical/laboratory and ultrasonographic data

For the analysis of the correlations between clinical data and ultrasonographic findings of joint involvement, patients were divided into two subgroups, according to the presence or absence of clinical joint involvement, considered as the presence of joint pain associated or not with articular swelling at examination time. The first subgroup included 40.3% patients showing a clinical joint involvement (Group A) and the second group was

Fig. 3 Mean ultrasonographic inflammatory score at different joint sites.



The scores were calculated at the MCP, PIP and MTP joints in (A) the group of SLE patients, (B) patients in Group A and (C) patients in Group B.

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TABLE 3 Correlations between clinical and ultrasonographic findings

	Presence of clinical joint involvement (Group A, <i>n</i> = 25)	Absence of clinical joint involvement (Group B, <i>n</i> = 37)	<i>P</i> -value
Total score, mean (s.d.)	17.5 (20.8)	6.6 (7.2)	0.009
RUC score, mean (s.d.)	3 (2.8)	1.02 (2.2)	0.0003
MCP score, mean (s.d.)	2 (10.4)	1.1 (2.4)	0.002
PIP score, mean (s.d.)	2.9 (8.2)	0 (0.3)	0.06
MTP score, mean (s.d.)	4.8 (5.3)	4.4 (5.3)	0.09

composed of 59.7% patients without joint manifestations (Group B).

The global US inflammatory score obtained in Group A presented a mean value of 17.5 (s.d. 20.8), which was significantly higher than the score obtained in Group B ($P=0.009$). Similarly, US inflammatory scores calculated for the RUC and MCP joints were significantly higher in Group A than in Group B ($P=0.0003$ and $P=0.002$, respectively). No significant differences were found among US inflammatory scores of the PIP and MTP joints (Table 3). The analysis of the correlations between CRP levels and US total score found significant results ($R=0.3$, $P=0.01$).

Finally, no correlations were highlighted between US findings and SLEDAI-2K and ECLAM. Similarly, no correlation was demonstrated between US findings and the autoantibodies tested (data not shown).

Discussion

Several studies have demonstrated that ultrasonography is a useful imaging modality in the assessment of a wide range of abnormalities in rheumatic diseases [28–32]. In particular, RA and SpA have been extensively investigated by musculoskeletal US, mostly for the analysis of US-detected inflammatory lesions [33, 34]. However, very few US studies have focused on the assessment of musculoskeletal abnormalities in SLE, even though joint involvement is the most common feature in SLE patients [11, 19–22].

To the best of our knowledge, this is the first US study aimed at analysing inflammatory changes in the foot (MTP) joints in SLE patients. We found that MTP joints were the most frequently involved site (72.6% of patients) compared with the wrist, MCP and PIP joints. The MTP joints are considered a target joint in RA and their assessment by US has been extensively investigated in a number of studies that demonstrated its sensitivity in detecting joint inflammation, even when compared with other imaging techniques such as magnetic resonance [35–37]. The evidence of high US inflammatory scores for joint lesions in the presence of bony erosions involving, in particular, the fifth MTP has been described as a suggestive element for RA [38]. In the present study, US inflammatory scores calculated to quantify the severity of local joint inflammation presented the highest values for the MTP joints, with

statistically significant differences with respect to the MCP and PIP joints. These innovative results seem to indicate that, as well as in RA, the MTP joints may be a target area of inflammation in SLE and might be suggestive of similar inflammatory features at the joint level in the two diseases. However, these findings need further investigation.

At the hand and wrist joint level, our results are essentially in agreement with those obtained by previous researchers [11, 20–23]. In particular, different aspects of US synovitis have been previously reported in the RUC, MCP and PIP joints of SLE patients [20, 21]. Our results confirmed that, in the hand and wrist, the RUC joints are the most commonly involved site in SLE patients, followed by the MCP and PIP joints. US-detected abnormalities at this level, including signs of mild synovitis, were seen in a large number of patients in our study and, as recently reported, may be related to conditions of wrist arthralgia [39].

SLE is a prototype of systemic autoimmune diseases with a wide range of clinical features and serum autoantibodies [1, 40]. The disease is characterized by heterogeneous degrees of severity as well as unpredictable disease flares and remissions [40–42]. Overall, the musculoskeletal system is the most common and often the earliest manifestation of SLE. In our study, the presence of at least a single US abnormality was detected in the majority of patients (87.1%), supporting the concept of a high prevalence of joint involvement in SLE. However, only 40% of our patients presented clinical features of joint involvement at the time of evaluation, and in all of them US confirmed the presence of inflammatory joint conditions. This dissociation between clinical and US imaging findings is suggestive of a condition of subclinical synovitis and has already been reported in several studies performed in different rheumatic diseases, stressing the concept of a greater sensitivity of US in detecting inflammation when compared with clinical evaluation [43–45].

The lack of correlation between US findings and the SLEDAI-2K and ECLAM, as highlighted in the present study, suggests the need for a global assessment of SLE patients that might even include imaging modalities, such as US, in order to better classify joint inflammatory conditions and avoid the risk of underestimating subclinical inflammatory abnormalities. SLEDAI-2K and ECLAM

lack the sensitivity to identify local disease inflammation activity at the joint level because the presence of joint disease without signs of systemic or major organ involvement is not systematically analysed in these composite indices.

Additional applications of musculoskeletal US to SLE patients have been recently developed, using this imaging technique in paediatric patients and to monitor biologic therapy [46, 47].

US has many advantages over other imaging modalities, as it is safe, inexpensive and well accepted by patients. In the future, further development of US technologies might broaden the potential uses of this imaging technique, adding relevant information to the diagnostics and monitoring of rheumatic diseases such as SLE [48–50].

In conclusion, three key points emerge from the present study: the unexpected involvement of the MTP joints in SLE patients, the demonstration of subclinical articular abnormalities in a consistent percentage of SLE patients and the absence of correlation between US and SLE disease activity scores. The results presented in this study suggest the inclusion of US in the assessment of SLE patients in order to better assess joint pathology, adding useful information not easily gained by clinical examination.

Rheumatology key messages

- Unexpected involvement of the MTP joints in SLE patients was found by US.
- Subclinical articular abnormalities were seen in a consistent percentage of SLE patients.
- The absence of correlations between US and SLE disease activity scores was demonstrated.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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