TITLE : **Predictors of musculoskeletal flares and Jaccoud's arthropathy in patients with Systemic Lupus Erythematosus: a 5-year prospective study.**

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ABSTRACT

Objective

To investigate the prognostic value of US in predicting musculoskeletal flares and Jaccoud's arthropathy (JA) in Systemic Lupus Erythematosus (SLE).

Methods

Eighty out of 94 patients (76 female; age 45.5±13.2 years) with non-deforming non-erosive (NDNE) arthritis and 48/60 healthy controls (42 female; age 49.6±11.6 years) completed the 5-year follow-up study. Each patient was prospectively assessed for the occurrence of musculoskeletal flares using BILAG2004 and hand deformities according to Jaccoud's articular index. Baseline clinical, serological, semi-quantitative (0 – 3 scale) ultrasound (US) findings, PD-synovitis and PD-tenosynovitis scores were used as covariates to identify predictors of study outcomes. Short Form 36 v2 (SF36v2) health survey questionnaire was administered.

Results

Twelve MS flares in 10 (12.5%) patients were recorded and the incidence rate was 3.0 per 100 patient-year. Baseline PD-synovitis score independently predicted MS flare (p<0.001; RR 2.0; 95% CI 1.4 – 3.0) within 2 years since US examination. Five (6.2%) patients developed JA whose incidence rate was 1.25 per 100 patient-year. Independent risk factors for development of JA were higher longitudinal BILAG score in the musculoskeletal domain (p=0.005; RR 2.4 95% CI 1.3 - 4.6) and longer disease duration (p=0.013; RR 1.2; 95% CI 1.1-1.3). JA and active musculoskeletal inflammation (BILAG≥C), but not US erosions, were associated with lower results in SF36v2 physical and mental summary components.

Conclusions

Performing musculoskeletal US can be useful in order to predict MS flares. Jaccoud's deformities may arise in patients with long-standing SLE and prolonged, even subclinical, joint and tendon inflammation.

1. Introduction

Musculoskeletal (MS) complaints are very common in Systemic Lupus Erythematosus (SLE) affecting 70-95% of patients (1-3). They represent the heralding symptom in 60-80% of cases and are reported in up to 60% of disease flares (3, 4). Inflammatory MS manifestations are described as a major cause of pain and compromised hand function, interfering with daily activities in 73% of SLE patients and causing low productivity or work disability in 49% and 17% of them, respectively (5-8). In particular, impairment of patients' health related quality of life (HRQoL) is mostly associated with MS flares (9, 10). Inflammatory joint involvement in SLE primarily affects the hands and clinically occurs as transient and migratory arthralgia (30-50%), or fleeting (25-40%) or persistent (10-15%) arthritis but tenosynovitis could also be present (11). SLE arthritis is often classified as non-deforming and non-erosive (NDNE) on X-ray (12), but hands and feet deformities may arise in 5-15% of cases as hallmarks of Jaccoud's Arthropathy (JA) (12, 13). Radiographic erosions may be detected in less than 5% of patients showing persistent arthritis, sometimes deformities, high prevalence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (aCCP), thus referred as rhupus syndrome (RS) to indicate an overlap between Rheumatoid Arthritis (RA) and SLE (12, 14). This classification has been recently questioned by ultrasound (US) studies that showed an unexpected burden of erosive damage in up to 41% of patients as well as a surprisingly high prevalence of synovitis (25-94%) and tenosynovitis (28-65%) (15)..

These data challenge the belief that lupus arthritis is a benign entity and suggest that the burden of joint damage in SLE may be underestimated (15, 16), Identifying factors associated with MS flares and development of joint damage, such as deformities, would help preventing a major cause of disability for SLE patients. In particular, unveiling the progression and predictive values of synovitis, tenosynovitis and erosions detected by high-resolution US, which prognostic properties have not been addressed by longitudinal studies, can be crucial in facilitating targeted therapies and measuring response (15, 16). US was proved to be more sensitive than clinical examination in

detecting joint ad tendon inflammation (17-21), which even subclinical has been reported as predictive of MS flare (22) and responsible for future development of JA (23). This prospective study was planned with the aim to clarify whether and which high-resolution US findings are associated with an increased risk of MS flares and JA. As secondary aims we would estimate their prevalence and incidence, highlighting their impact on patients HRQoL and identifying other relevant clinical or serological predictive factors.

2. Patients and methods

2.1. Study design

Ninety-four consecutive Caucasian patients fulfilling at least 4 of the 1997 ACR criteria for SLE (24) were recruited between January 2010 and April 2010 in a 5-year prospective study. Follow-up visits were scheduled every 6 months (figure 1). In order to assure complete capturing of clinically significant data, patients were asked to refer to the clinic in case of symptoms suggestive of disease flare or drug adverse event and both patients and healthy controls were solicited by phone call to attend the scheduled visits. Those who failed to attend the scheduled visits were excluded from the study in order to minimize data loss.

Inclusion criteria were: a) past or present joint and/or tendons inflammatory involvement, b) having not taken NSAIDs in the 5 days prior to baseline, c) having been on stable corticosteroids dose over previous 4 weeks, d) having been on stable antimalarial and immunosuppressive therapy over previous 3 months. Exclusion criteria were: i) RS defined by the presence of X-ray erosions or fulfilment of both SLE and RA classification criteria (25), ii) hand and feet deformities, iii) avascular necrosis or iv) myositis. Sixty age- and gender-matched volunteers were recruited from healthy hospital staff as controls.

Ethical approval for the study was obtained from the local Ethics Committee (references 111/10/CE and 224/11/CE) and all participants gave their written informed consent.

2.2.Study outcomes

The British Isles Lupus Assessment Group (BILAG) 2004 disease activity index is sensitive to change and suitable for use in longitudinal studies of SLE if the outcome of interest is worsening of disease activity (26). MS flares were defined as any increase in activity to grade A (severe) or B (moderate) in the MS-BILAG domain. Any increase in activity to grade C was defined as minimal change and not included in flare definition (26).

Development of JA was defined as any increase (≥1) in JA index (table 1) calculated according to Spronk *et al.* (23).

2.3.Clinical assessment

At every visits, patients and controls underwent detailed standardized joints and tendons examination according to EULAR recommendations (27). A bilateral examination for tenderness and swelling of the following joints was performed: shoulder, elbow, wrist, metacarpophalangeal (MCP) , proximal inter-phalangeal (PIP) of the hand, knee, ankle and metatarsophalangeal (MTP). Fixed or reducible MCP subluxation, ulnar drift, swan neck or boutonniere deformities of the fingers and Z thumbs were also evaluated. A bilateral examination for tenderness and swelling of the following tendons or group of tendons was performed: flexor pollicis longus tendon, flexor carpi radialis tendon, flexor digitorum tendons of the second, third, fourth and fifth fingers (at both common tendon sheath and finger tendon sheath level), extensor tendons of the first, second, third, fourth, fifth, and sixth compartments.

SLEDAI was used to assess global disease activity and BILAG was applied to evaluate disease activity in individual organ systems. A mean longitudinal MS-BILAG score was calculated by assigning at each visit result an additive numerical scoring scheme as follows: A = 12 (very

active disease), B = 8 (moderate activity), C = 1 (mild stable disease) and D = 0 (inactive but previously involved) (28). According to inclusion criteria no patient scored E (no current or previous disease activity). Cumulative organ damage was calculated using the ACR/Systemic Lupus International Collaborating Clinics Damage Index (SDI).

Medications ongoing at baseline, classified as immunosuppressant, antimalarial, low dose prednisone (<10 mg daily or equivalent) or high dose prednisone (≥10 mg daily or equivalent) were categorized as present/absent. Modifications of treatment, defined as increased (introduction of new agent or increased dose) or lowered (withdrawal or dose reduction) immunosuppressive, antimalarial or corticosteroids therapy, were recorded. The scheduled switch from induction (i.e. cyclophosphamide or mycophenolate) to maintenance therapy (i.e. azathioprine or other immunosuppressant) in management of renal or central nervous system involvement were not considered as modifications of treatment.

At the end of follow-up, the Short Form 36 v2 (SF36v2) health survey questionnaire was administered to assess HRQoL.

Clinical assessment and indices calculation were performed by a trained rheumatologist blind to serologic, ultrasonographic and radiologic findings.

2.4. Serologic assessment

At baseline, each patient was tested for ANAs (IF Hep-2), anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-Sm (ELISA; Normal Value (NV) <10 IU/dl), RF (ELISA; NV<14 IU/dl) anti-CCP (ELISA; NV<25 IU/dl) and HLA-DR1/DR4 status. Anti-dsDNA (Farr assay; NV<7 IU/dl), CRP (NV<0.5 mg/dl), C3 (NV 90-180 mg/dl) and C4 (NV 10-40 mg/dl) complement fraction levels was tested at baseline and prior to each follow-up visit.

2.5. Ultrasound and radiographic assessment

Patients (baseline, flare-up and final visits) and healthy controls (baseline and final visits) underwent the same high-resolution US examination protocol performed by an experienced rheumatologist, blind to clinical data, using a Logiq9 (GE, Medical Systems, Wisconsin, USA) with an 8-15 MHz linear array probe. On the basis of previous studies that identified the most frequently affected joints and tendons in SLE (18-20, 29) the following anatomic sites were bilaterally evaluated using a multi-planar scanning technique: second and third MCP and wrist joints, flexor pollicis longus tendon, flexor carpi radialis tendon, flexor digitorum superficialis and profundus tendons of the 2nd to the 5th fingers (at both carpal tunnel and finger levels) and extensor tendons of the 1st to the 6th compartments at the dorsal aspect of the wrist. All the tendon or group of tendons surrounded by a single tendon sheath, were scanned in transverse view from the most proximal to the most distal portion at the tracts surrounded by synovial sheath. All findings were also documented in the corresponding perpendicular longitudinal view. Values of grey-scale (GS) setting parameters were fixed before the study to obtain maximal contrast of different soft tissues examined. Power-Doppler (PD) settings were adjusted according to Torp-Pedersen's recommendations (30). Bone erosion, tenosynovitis and synovitis were scored as present/absent according to OMERACT definitions (31). GS-tenosynovitis and GS-synovitis as well as PD-tenosynovitis and PD-synovitis (figure 2) were further semi-quantitatively graded from 0 to 3 (0=normal; 1=mild; 2=moderate; 3=severe) as described elsewhere (31-33). PD-synovitis (range 0-18) and PD-tenosynovitis (range 0- 74) scores were the sum of the grades of all PD signal on the targeted joints and tendons, respectively.

Inter-observer agreement rates (*k* values) with another sonographer was evaluated in half of patients and healthy controls and resulted good-to-excellent for qualitative assessment (0.68 - 0.96), for GS-synovitis (0.71 – 0.93), GS-tenosynovitis (0.64 – 0.83), PD-synovitis (0.76 – 0.84) and PD-tenosynovitis (0.78 – 0.91) semi-quantitative assessment. Patients underwent plain radiography of the hands and wrists at baseline and final assessment with the aim to identify any erosive pattern related to inflammatory arthritis in this cohort. An expert rheumatologist, blind to clinical and US

results, evaluated X-ray looking for presence/absence of erosions defined as breaks in the cortical bone surface with or without new bone formation.

2.6. Statistical analysis

The characteristics of interest were reported as mean ± standard deviation (S.D.) or median (25th - 75th percentiles) for normal or non-normal distributed variables, according to Kolmogorov-Smirnov test, and number with corresponding percentage.

The search for independent predictive factors of MS flares (present/absent at any time point) and JA (present/absent at the end of follow-up) included univariate analyses and stepwise Cox proportional hazard models. Explanatory baseline variables tested were: age, disease duration, CRP, positivity for anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-Sm, RF, anti-CCP, C3, C4, anti-dsDNA, SLEDAI, SDI, MS-BILAG score, ongoing medication, US erosions, GS-synovitis ≥ 2, GS-tenosynovitis≥ 2, PD-synovitis≥ 1, PD-tenosynovitis≥ 1, PD-synovitis score, PD-tenosynovitis score. Considering the long observation time, in order to minimize any possible bias effect, we included longitudinal MS-BILAG score, occurrence and number of MS flare (only for JA as outcome), and modifications of treatment with antimalarial, immunosuppressant, corticosteroids as time-varying explanatory variables. For same reason, the time-varying effect of US baseline findings in predicting MS flare at each year of follow-up was tested. Student's t-test, or Mann-Whitney test if necessary, and Chi-square test were used for quantitative and qualitative variables, respectively. Stepwise Cox proportional hazard models were fitted with covariates with $p<0.1$ to predict outcomes. Specificity and sensitivity of predictive factors was calculated by mean of ROC curve. Two-tailed p values less than 0.05 were considered significant. Relative Risk (RR) with 95% Confidence Interval (CI) were calculated. Statistical analyses were performed using the software package MedCalc 15.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1 Study population

Eighty patients (76 female; age 45.5±13.2 years) and 48 healthy controls (42 female; age 49.6±11.6 years) completed the 5-year follow-up (Table 2). Reasons for drop-out of 14 SLE patients and 12 healthy controls were: outmigration, change of address or phone number, withdrawal of consent and death. No major differences between groups were detected.

At baseline, 9/80 (11.2%) patients reported arthritis in the past month but only 7/80 (8.7%) had swollen joints (median count 0; range 0 - 10) at clinical examination, 19/80 (23.7%) complained of inflammatory arthralgia in the past month but only 10/80 (12.5%) of them had tender joints (median count 0; range 0 -22) at the time of visit. Six/80 (7.5%) patients had tenderness along the path of a tendon or group of tendons (median 0; range 0 -3) but none of them had swelling. In order to score for MS-BILAG, MS manifestations occurred in the 4 weeks prior to baseline were compared with those of the 4 weeks before resulting in 1/80 (1.3%) patients scoring A on MS-BILAG, 6/80 (7.5%) scoring B, 21/80 (26.2%) scoring C and 52/80 (65.0%) scoring D. The overall disease activity according to SLEDAI score was 3.2±2.1, thus representative of longstanding Caucasian SLE cohorts according to Urowitz et al. (34) and only in a small part related to joint activity.

US detected a higher number of inflamed joints and tendons than clinical examination (supplementary file 1). US synovitis and tenosynovitis with GS≥2 and PD≥1 were more frequent in patients with higher MS-BILAG score, but were also detected in 5 out of 21 (23.8%) patients scoring C and were almost absent (1.9%) in those scoring D (Table 3). In particular, GS-synovitis≥2 was found in 25 (5.2%) out of 480 scanned joints (10 were not clinically tender or swollen) from 6/80 (7.5%) patients of whom 3 scored C on MS-BILAG. PD-synovitis≥1 was detected in 32/480 (6.7%) joints (11 without clinical synovitis), from 10/80 (12.5%) patients of whom 4 scored C on MS-BILAG. GS-tenosynovitis≥2 was found in 10 (0.5%) out of 1920 scanned tendon sites (8 were not clinically tender nor swollen) from 4/80 (5.0%) patients of whom 3 scored C on MS-BILAG.

PD-tenosynovitis≥1 was detected in 19/1920 (1.0%) tendon sites (13 with no sign of tenosynovitis) from 9/80 (11.2%) patients of whom 5 scored C and 1 scored D on MS-BILAG.

Considering US as the gold standard for joints and tendons assessment, a low sensitivity (31.6% for tendons, 65.6% for joints) with high specificity (96.7% for joints, 99.0% for tendons) of the clinical assessment was found.

3.2 Musculoskeletal flares at patient level

During follow-up in 3 (0.4%) out of 855 visits a MS-BILAG score of A was recorded, in 20/855 (2.3%) it was B, in 108/855 (12.6%) it was C and in 724/855 (84.7%) it was D, confirming that disease activity in this cohort was only in a small part related to the joint. The distribution of longitudinal mean MS-BILAG score was highly skewed (median 0; IR 0 – 0.22; 95% CI 0 – 0.65).

Twelve/855 (1.4%) MS flares (3 A severe and 9 B moderate) in 10/80 (12.5%) patients (median 0; range 0 - 2) and 40/855 (4.6%) minimal change in activity (any increase to C) in 31/80 (38.8%) patients were recorded with complete capturing of clinically significant flares in patients included in the analysis. Mean time to MS flare occurrence was 29.0±19.0 months and annual incidence rate was 3.0 per 100 patient-year. Among patients who developed MS flare, 2/10 (20.0%) scored B at baseline, 4/10 (40%) C and 4/10 (40%) D on MS-BILAG (figure 3). Flares isolated to the musculoskeletal domain occurred in 4 (33.3%) cases. Major reasons for introduction of new medication or increased dose of ongoing treatment in 17/80 patients (21.2%) were flares, while for drug withdrawal or reduced dose in 29/80 patients (36.2%) were adverse events (n=12; 15.0%) and scheduled steroids tapering (n=20; 25.0%).

On univariate analysis, CRP higher than upper normal limit (70.0% vs 24.3%; p=0.003), GS-synovitis≥2 (50.0% vs 1.4%; p<0.001), GS-tenosynovitis≥2 (20% vs 2.8%; p=0.020), PD-synovitis≥1 (50% vs 7.1%; p<0.001), PD-tenosynovitis≥1 (60.0% vs 4.3%; p<0.001) and PD-synovitis score [1 (0 - 4) vs 0 (0 -0); p<0.001; (figure 4A)] registered at baseline were associated with development of MS flare. When all US findings were entered in the multivariate model, after

adjusting for baseline and time varying explanatory variables, baseline PD-synovitis score resulted the only independent predictors (p<0.001; RR 2.0; 95%CI 1.4 – 3.0) of MS-flares within 24 months since US examination . Baseline PD-synovitis score >2 was associated with a 2-year risk of MS flare with a sensitivity of 66.7% and a specificity of 97.3% (AUC=0.804; 95% CI 0.699 – 0.886) (Figure 4B).

3.3 Musculoskeletal flares at joint level

At the time of MS flare, tender joint count was 7.7 (±4.4) and swollen joint count was 5.5 (±3.0). MCP were involved in 11 out of 12 (91.7%) flares (9 bilaterally, 2 unilaterally) and in the only case without inflamed MCP there was PIP, wrists and elbows involvement. The PIP showed inflammatory signs (swelling or tenderness) in 6/12 (50.0%) cases, wrist in 4/12 (33.3%), elbow, knee, ankle, and MTP in 1/12 (8.3%). Three/10 patients (33.3%) in 5/12 flares (41.6%) showed a clinically relevant tendonitis of the finger flexor tendons. US showed PD-synovitis≥1 in 12/12 flares (100%) and PD-tenosynovitis≥1 in 8/12 (66.7%) (see supplementary file 2).

Forty-four (9.2%) out of 480 joints scanned by US examination at baseline showed swelling and/or tenderness during flare; 20/44 (45.4%) flared joint and 5/436 (1.1%) non-flared joints had baseline GS-synovitis≥2 (p<0.001) whereas 24/44 (54.5%) flared joints and 8/436 (1.8%) non-flared joints (p<0.001) showed baseline PD-synovitis≥1.

Baseline detection of US erosions was not associated with increased risk of MS-flare either at patient level nor at joint level.

3.4 Hand deformities

Five (6.2%) patients developed hand deformities (Table 4). The estimated incidence rate of JA was 1.25 per 100 patient-year. On univariate analysis longer disease duration (25.9±10.4 vs.

14.2±6.3 years; p<0.001) and CRP higher than upper normal limit (80% vs. 26.1%; p=0.026) at baseline or having suffered from MS flares (40.0% vs 10.7%; p=0.014), lack of immunosuppressive treatment (100% vs 22%; p<0.001) and higher longitudinal MS-BILAG score [0.1 (0 − 1.8) vs 0 (0 − 0.3); p=0.001] during follow-up were associated with development of hand deformities. However, after adjusting for baseline and time varying confounding factors, only longer disease duration (p=0.013; RR 1.2; 95%CI 1.1-1.3) and higher longitudinal MS-BILAG (p=0.005; RR 2.4 95%CI 1.3 - 4.6) were retained in the multivariate model as predictors of hand deformities. None of the baseline US abnormalities, including joint erosions, was associated with development of deformities.

3.5 US erosions

At final visit, new US erosions were revealed in 13/80 (16.3%) patients of whom 4 had US erosions at baseline, but none showed erosion on X-ray. Major accrual of US erosions was detected at second MCP level bilaterally (see supplementary file 3). The incidence of new US erosions was significantly higher (p=0.022) in SLE patients compared with healthy controls (n=1; 2.0%).

3.6 Patient Reported Outcomes

Patients who developed JA had worse results in both physical and mental health components of the SF36v2 than NDNE, and both scored worse than healthy controls (figure 5A), at the end of follow-up. In NDNE patients, SF36v2 mental and physical domains were mostly influenced by high MS-BILAG score (figure 5B) rather than by the evidence of US joint erosions (figure 5C). In particular, patients who scored ≥ C on MS-BILAG had statistically significant lower results in bodily pain (p=0.004) and global health (p=0.019) components of the SF36v2 questionnaire than patients who scored D.

4. Discussion

This study identified a risk profile for musculoskeletal flares and Jaccoud's deformities, reported the incidence of these two complications and depicted them as determinants of impaired HRQoL in a large prospectively followed-up and representative cohort of SLE patients with NDNE arthritis. Moreover, it provided valuable insights into the progression and predictive value of abnormalities detected by high-resolution US in SLE and supported previous observations highlighting that US is more accurate than physical examination in detecting joint and tendon inflammation in symptomatic SLE patients without clinical joint swelling or tendonitis (17-21).

We firstly demonstrated that, although frequently detected in patients, baseline subclinical synovitis or tenosynovitis (GS=1 without PD signal) are also observed in healthy controls and had no prognostic or predictive value. However, the most significant and innovative finding to emerge from this study is that, after correction for the potential confounding effect of disease activity and treatment changes, a higher PD-synovitis score at baseline was independently predictive of MS flare within 24 months since US examination. The time-restricted effect of PD-synovitis score suggests that, rather than be a marker for a more aggressive (e.g. deforming) subtype of SLE arthritis, it recognized patients with residual or subclinical disease activity not detectable on clinical examination and, if not properly treated, at risk for flare. Therefore, this marker can help the clinician in the decision making process for starting or enhancing immunosuppressive therapy in order to prevent MS flare. In this scenario, performing US could be useful in clinical practice for symptomatic patients without synovitis on physical examination, scoring C on MS-BILAG, who do not deserve increased immunosuppression for high disease activity in other organs or systems.

Along with this novel observation, we longitudinally estimated the incidence and prevalence of JA as 1.2 per 100 patient-year and 6.2%, respectively. To the best of our knowledge this is the first report on the incidence of JA in SLE patients, whereas previous cross-sectional study reported the prevalence of Jaccoud's deformities as 3.5-13.3% (13, 35). The risk profile for development of JA was characterized by prolonged even subclinical joint and tendon inflammation, according to longitudinal MS-BILAG activity score, and longer disease duration. Baseline US findings were not

associated with development of JA probably because the long time needed for appearance of deformities and the transient nature of joint and tendon inflammation; the latter is supported by the relatively low incidence and severity of inflammatory abnormalities detected by US (18) and histopathology (36) in these patients. Subclinical inflammation in joints and tendons was addressed as responsible for accrual of soft tissue damage resulting in JA (36, 37), however it cannot satisfactorily explain why only a relatively small proportion of patients develops deformities. Previous cross-sectional studies (13, 18, 23, 35) identified longer disease duration as a risk factors for JA, but the mechanisms underlying this association are unclear. Higher cumulative dose of corticosteroids may be partly responsible for impaired soft tissue healing and remodeling in susceptible individuals (38, 39) resulting in joint laxity and loss of articular stabilizing mechanisms. Although we did not look at cumulative steroids dose in our cohort, patients developing Jaccoud's deformities were all treated with long-standing low dose steroids and lack in immunosuppressants. In light of these observations we would suggest to consider JA as a late complication of NDNE, consequent to treatment failure, and not a distinct subtype of SLE arthritis. Further prospective studies are needed to evaluate the potential effect of targeted strategies, based on ultrasonographic tight control of MS disease activity and steroid-sparing agents, in preventing development of hand deformities.

We also showed that the burden of US erosions slightly progressed over time in patients with NDNE but, unlike erosions seen in RA (40), they were not predictive of deformities or accrual of erosive damage. Moreover, it is noteworthy that US erosions were not a cause of worse HRQoL in NDNE patients whereas active MS activity and Jaccoud's deformities resulted major determinants for low HRQoL. In the light of this evidence a patient should not be classified as suffering from RS relying solely on isolated US findings. In the absence of X-rays erosions, RA-like synovitis and persistently high anti-CCP and RF should raise suspicion of pre-radiographic form of RS and must suggest a more aggressive treatment (41).

This study have some limitations. First, although we made an effort in order to minimize the effect of treatment confounding factors, further studies based on targeted therapy in naïve patients are needed to confirm these data. Nevertheless, this could be particularly difficult as lupus is a systemic disease and patients need different therapeutic approaches tailored according to severity of symptoms and occurrence of life-threatening manifestations. Second, this study was not specifically designed to assess the effect of different MS manifestation on HRQoL, thus our results should be confirmed by future studies. Third, we recorded a 14.8% and 20.0% drop-out rate in SLE patients and healthy controls, respectively. However, in observational studies conducted over a lengthy period of time a high drop-out rate is to be expected and, conventionally, a 20% drop-out rate is regarded as acceptable (42). Moreover, drop-out rates were comparable in the two groups and by assuring the complete capturing of clinically significant data we minimized concerns in interpretation of study results.

In conclusion, high-resolution US could be an effective response to the unmet need for a more sensitive and specific tool for assessing joint and tendons in SLE patients, especially those scoring C on MS-BILAG complaining of inflammatory joint pain but without clinical synovitis or tenosynovitis. US could be clinically useful in order to identify those patients at risk for MS flare and consequently institute the most appropriate treatment to prevent hand deformities and deterioration of HRQoL. Further studies combining histopathology and imaging tools, including CT and MRI, are needed to shed some light on their potential clinical implications and therapeutic targets for preventing MS inflammation and damage in SLE patients.

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APPENDIX

Supplementary data are available at Seminars in Arthritis and Rheumatisms Online.

Table 1. Description of the Jaccoud's articular index according to Spronk et al (23).

Jaccoud's articular index		
Deformities	**Number of affected index**	*Assigned points*
MCP subluxation with limited extension	1-4	1
	5-8	2
Ulnar drift (>20°)	1-4	2
	5-8	3
Swan neck deformities	1-4	2
	5-8	3
Boutonniere deformities	1-4	2
	5-8	3
Z-thumb deformity	1	2
	2	3

MCP: metacarpophalangeal

Table 2. Baseline demographic, clinical and serological feature of the 80 patients who completed the follow-up.

Age at onset (years)	30.7 (±11.6)
Disease duration at enrollment (years)	10.5 (±7.1)
Follow-up (months)	56.6 (±6.7)
Cumulative 1997 ACR criteria	
Malar rash	27 (33.8)
Discoid rash	7 (8.8)
Photosensitivity	17 (21.3)
Oral/nasopharyngeal ulcers	10 (12.5)
Non-erosive arthritis	80 (100)
Pleuritis or pericarditis	30 (37.5)
Renal disorders	23 (28.8)
Neurologic disorders	3 (3.8)
Laboratory findings	
C-reactive protein	24 (30.0)
Low C3 Complement	36 (45)
Low C4 Complement	28 (35)
ANA	80 (100)
Anti-dsDNA	34 (42.5)
Anti-Ro/SSA	28 (35.0)
Anti-La/SSB	9 (11.2)
Anti-RNP	16 (20.0)
Anti-Sm	9 (11.2)
Rheumatoid Factor	11 (13.7)
Anti-CCP	4 (5.0)
HLA-DR1 or DR4	29 (36.2)
SLEDAI	3 (±2.1)
SLICC/Damage Index	0.9 (±1.4)
Ongoing Medication	80 (100%)
Prednisone >10mg/day	13 (16.3)
Prednisone<10mg/day	53 (66.3)
Antimalarial agents	56 (70.0)
Immunosuppressant	54 (67.4)
Methotrexate	23 (28.8)
Azathioprine	22 (27.5)
Cyclophoshamide	2 (2.5)
Mycophenolate Mophetil	11 (13.8)
Rituximab	2 (2.5)

Quantitative variables are expressed as mean ± standard deviation. Values are the number of patients, values in brackets are percentage. MS-BILAG: musculoskeletal domain of BILG2004. ANA: antinuclear antibodies (tested by IIF, using Hep2 cell substrate, positivity was defined as a titre ≥ 1:320).Anti-dsDNA antibodies (tested by Farr assay). Anti-extractable nuclear antigens (SSA, SSB, Sm, RNP), Rheumatoid Factor, antiCCP (anti-cyclic citrullinated peptide antibodies) tested by ELISA.

Table 3. Distribution of baseline ultrasound findings in healthy controls and in patients according to categorical musculoskeletal BILAG score.

Baseline US findings	Healthy controls (n=48)	SLE (n=80)	BILAG A/B (n=7)	BILAG C (n=21)	BILAG D (n=52)
GS-synovitis = 0	45 (93.7)	65 (81.2)	1 (14.3)	16 (76.2)	48 (92.3)
GS-synovitis = 1	3 (6.3)	9 (11.2)	3 (42.8)	2 (9.5)	4 (7.7)
GS-synovitis = 2	0	3 (3.8)	1 (14.3)	2 (9.5)	0
GS-synovitis= 3	0	3 (3.8)	2 (28.6)	1 (4.8)	0
PD-synovitis = 0	48 (100)	70 (87.4)	1 (14.3)	17 (81.0)	52 (100)
PD-synovitis = 1	0	5 (6.3)	3 (42.8)	2 (9.5)	0
PD-synovitis = 2	0	5 (6.3)	3 (42.8)	2 (9.5)	0
PD-synovitis = 3	0	0	0	0	0
PD-synovitis score[a] (range 0-18)	0	0 (0 – 8)	1 (0 – 8)	0 (0 – 4)	0 (0 – 0)
GS-tenosynovitis = 0	43 (89.6)	50 (62.5)	2 (28.6)	10 (47.6)	38 (73.1)
GS-tenosynovitis = 1	5 (10.4)	26 (32.5)	4 (57.1)	8 (38.1)	14 (26.9)
GS-tenosynovitis = 2	0	4 (5.0)	1 (14.3)	3 (14.3)	0
GS-tenosynovitis= 3	0	0	0	0	0
PD-tenosynovitis = 0	48 (100)	71 (88.7)	4 (57.1)	16 (76.2)	51 (98.1)
PD-tenosynovitis = 1	0	4 (5.0)	0	3 (14.3)	1 (1.9)
PD-tenosynovitis = 2	0	5 (6.3)	3 (42.8)	2 (9.5)	0
PD-tenosynovitis = 3	0	0	0	0	0
PD-tenosynovitis score[a] (range 0-78)	0	0 (0 – 8)	0 (0 - 8)	0 (0 – 4)	0 (0 – 1)
Bone erosions	2 (4.1)	13 (16.2)	1 (14.3)	3 (14.3)	9 (17.3)

Unless otherwise indicated values are the number of patients, values in brackets are percentage.

a: values are median (range) GS: gray-scale. PD: power-Doppler.

Table 4. Characteristics of patients who developed deformity during follow-up.

Age (Gender)	Disease Duration	Main clinical manifestations[a]	Serologic findings	Baseline MS-BILAG	Baseline US findings	Treatment	Number of MS-Flare	JAI deformities	JAI score
42 yrs (F)	14 yrs	Malar rash, photosensitivity, serositis, TVP in APS.	ANA, CRP.	C	GS-S=2, PD-S=1 GS-T=2, PD-T=1	HCQ, PDN	2	MCP sub-luxation, swan neck deformities, Z thumbs.	8
57 yrs (F)	15 yrs	Lupus nephritis, leukopenia, lymphopenia.	ANA, anti-dsDNA.	D	GS-S=1, GS-T=1.	HCQ	0	Ulnar drift	3
57 yrs (F)	31 yrs	Lupus nephritis, serositis, stroke in APS	ANA, SSA, RNP, CRP.	D	Erosions.	HCQ, PDN	0	Ulnar drift, MCP sub-luxation, boutonniere deformities,	5
69 yrs (F)	36 yrs	Discoid rash, leukopenia, lymphopenia.	ANA, anti-dsDNA, CRP.	D	Erosions	HCQ, PDN	1	Ulnar drift, swan neck deformities.	4
65 yrs (F)	32 yrs	Serositis, leukopenia, lymphopenia.	ANA, SSA, CRP.	C	GS-T=1.	HCQ, PDN	0	Ulnar Drift, MCP sub-luxation.	5

a: other than arthritis. APS: antiphospholipid syndrome. JAI: Jaccoud's articular index. HCQ: Hydroxychloroquine. PDN: prednisone. MCP: metacarpophalangeal. GS-S: grey-scale synovitis. GS-T: grey-scale tenosynovitis. PD-S: power-Doppler synovitis. PD-T: power-Doppler tenosynovitis

ANA: antinuclear antibodies (tested by IIF, using Hep2 cell substrate, positivity was defined as a titre ≥ 1:320). Anti-dsDNA antibodies (tested by Farr assay). CRP: c-reactive protein.

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Figure legends

Figure 1. Study design overview.

Figure 2. (A) Baseline longitudinal dorsal scan of a second MCP joint, in a patient scoring B on MS-BILAG, showing grade 2 grey-scale synovitis (*) with **(B)** grade 2 power-Doppler signal (arrow). **(C)** Longitudinal volar scan of the third digit flexor tendon (t), during a severe flare, showing grade 2 grey-scale tenosynovitis (*) with **(D)** grade 2 power-Doppler signal (arrow). m: metacarpal head. pp: proximal phalanx.

Figure 3. Distribution of MS flare over the 5-year follow-up period according to baseline MS-BILAG score and baseline PD-synovitis score >2 (black) or ≤2 (dark grey).

Figure 4. (A) Box and whisker graph showing different distribution of baseline PD-synovitis score in patients who and who not developed flares during follow-up. **(B)** Receiver operating characteristic curve showing association of baseline PD-synovitis score and development of MS flare within 2 years since US examination.

Figure 5. (A) Spider plot resuming how each component of the SF36v2 varies in healthy controls and in patients with NDNE or Jaccoud's arthritis. Spider-plots resuming how each component of the SF36v2 in SLE patients suffering with NDNE varies according to the presence of **(B)** active MS symptoms classified as MS-BILAG ≥ C and **(C)** US erosions. BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role emotional RF, role physical; SF, social functioning; VT, vitality. NDNE, non-deforming non-erosive.