Title: Comparative assessment of hand joint ultrasound findings in symptomatic patients with systemic lupus erythematosus and Sjögren’s syndrome – a pilot study

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Abstract:

Systemic lupus erythematosus (SLE) and primary Sjögren’s syndrome (SS) can be associated with inflammatory arthritis, which is underdiagnosed by clinical examination. This study aimed to compare for the first time the ultrasound (US) - detected joint abnormalities in these two diseases, and to define the role of US in patients’ management.

A cross-sectional, observational study was conducted in patients with SLE (n=18) and SS (n=23) and symptoms of hand joint pain and no previous diagnosis of arthritis. Data related to disease activity, duration, damage scores, inflammatory and serological markers, treatment, and clinical and ultrasound parameters (derived from the assessment of 902 joints) were analysed and correlated using descriptive statistics, correlation tests and regression models.

Subclinical synovitis/tenosynovitis was found in 44.4% SLE patients and 21.7% SS patients (p=0.23). There was no significant correlation between either the total Power Doppler (PD) score or the total Grey Scale (GS) score and disease activity scores (British Isles Lupus Assessment Group BILAG index and European League Against Rheumatism Sjögren’s syndrome disease activity ESSDAI index). Both damage scores (Systemic Lupus International Collaborating Clinics index - SLICC and Sjögren’s syndrome disease damage index - SSDDI) correlated with the GS synovitis score. A significant proportion of patients with SLE and SS had erosions (55.6% and 34.8%, respectively, p=0.184) and osteophytes (61.1 vs. 60.9, p=0.98) in at least one joint.

Lack of correlation between disease activity scores and US outcome measures showed their limitations in diagnosing subclinical synovitis in SLE and SS patients. Future research is needed to establish if the development of erosions could be prevented by early diagnosis and prompt treatment of inflammatory arthritis associated with SLE and SS.
Key words: ultrasound, arthritis, systemic lupus erythematosus (SLE), Sjögren’s syndrome (SS), erosions, Power Doppler signal.

Introduction

Musculoskeletal system involvement is a frequent and often early manifestation of the disease pathology, occurring in up to 94% of systemic lupus erythematosus (SLE) patients, and in up to 60% of Sjögren’s syndrome (SS) patients during the disease course (Fauchais, et al. 2010, Pipili, et al. 2008). However, there is controversy as to the nature of the arthritis associated with these two conditions, as to whether it is a non-erosive and non-aggressive arthritis. A few recent studies have found the evidence of a severe deforming erosive polyarthritis, with several features consistent with rheumatoid arthritis in both SLE and SS patients (Amezcua-Guerra, et al. 2013, Wright, et al. 2006) and established that Jaccoud’s arthropathy is an erosive form of arthritis (Ceccarelli, et al. 2017). It should be noted that these more recent studies used ultrasound (US) or MRI examination as the main tool to assess for the joint inflammatory changes and damage (Ball, et al. 2014, Di Matteo, et al. 2018), compared to older studies, which were based on clinical examinations and x-rays (Scutellari, et al. 1987). This is due to the increased sensitivity of US in detecting subclinical inflammation and bone erosive changes (Kane, et al. 2004, Klauser, et al. 2012, Riente, et al. 2010). US has been proven to be a useful imaging technique in various rheumatologic conditions associated with musculoskeletal symptoms. Although previous studies could not reach a consensus regarding the correlation of US-detected active synovitis in SLE with the disease activity scores (BILAG) (Gabba, et al. 2012, Ruano, et al. 2017), there is evidence that SLE patients with abnormalities at the US examination of their hands were more likely to
receive immunosuppressive therapy compared to SLE patients with a normal US scan (Corzo, et al. 2017).

The hypothesis of this pilot study was that US could facilitate the diagnosis of inflammatory arthritis in patients with SLE and SS and hand joint pain. There is limited knowledge regarding the utility of hand US examination in SLE and SS patients, as different sets of joints were assessed in various studies (Amezcua-Guerra, et al. 2013, Iagnocco, et al. 2014, Iagnocco, et al. 2002, Iagnocco, et al. 2004). There are no previous studies evaluating both inflammatory and degenerative US outcome measures or assessing these two patient populations in parallel.

This study also explored correlations between US outcome measures and disease activity and damage scores, as well as clinical and serological parameters. In addition, we assessed the proportion of patients who had their treatment optimised as a result of the US scan, who would not have had their treatment changed based on routine clinical and laboratory examinations alone.

**Materials and methods:**

**Ethical issues**

The data was collected as routine standard of care in the evaluation of patients referred to the US service. The study was approved by the local ethics committee (ref. 13/LO/0999). Patients were consented to take part in the study.

**Patients**

This was a cross-sectional study of patients with SLE and SS, referred with symptoms of hand pain by their clinicians, who underwent US examination of their hands to assess for features of joint inflammatory changes. None of the patients had previous diagnoses of any type of inflammatory arthritis. Patients with rheumatoid arthritis/SLE overlap (Rhupus) or Jaccoud’s arthropathy, joint replacement, recent trauma, concomitant diagnosis of hand
osteoarthritis (OA) or positive serology for anti CCP antibodies were excluded from this pilot study. All patients were already diagnosed as either having SLE based on the 2012 American College of Rheumatology Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE or as having primary SS based on the American-European Consensus Criteria for Sjögren’s Syndrome. 69.56% (16/23) SS patients had a diagnostic salivary gland biopsy, 56.5% (13/23) have been tested positive for anti-Ro antibodies and 26.08% (6/23) had both positive salivary gland biopsy and serology.

Patients’ disease severity was assessed using either the global BILAG (British Isles Lupus Assessment Group) or ESSDAI (EULAR Sjögren’s syndrome disease activity index) scores (Gordon, et al. 2003, Seror, et al. 2015); patients’ damage scores were evaluated using SLICC (Systemic Lupus International Collaborating Clinics) and SSDDI (Sjögren’s syndrome disease damage index) scores (Dayal, et al. 2002, Vitali, et al. 2007), while the musculoskeletal symptoms were assessed through clinical examination and by using the musculoskeletal domains of the above mentioned disease activity scores. The numerical BILAG scores were calculated as previously described (Yee, et al. 2010). Information about age, gender, disease duration, treatment regimen (steroids, disease modifying anti-rheumatic drugs - DMARDs, biologic treatments - rituximab), immunological profile (antinuclear antibodies - ANA, anti-double stranded DNA antibodies - dsDNA, anti-extractable nuclear antigen antibodies – ENA (Ro and La), anti-cyclic citrullinated peptide antibodies - CCP, rheumatoid factor - RF were assessed using routine methods using in house clinical laboratory protocols) and inflammatory markers (erythrocyte sedimentation rate - ESR, C - reactive protein - CRP) were also recorded at the time of US examination. On clinical examination, tender joint count (TJC), swollen joint count (SJC) and pain scores using visual analogue scores (VAS) were also assessed and recorded.
US examination

The joints in the hand were scanned using the US machine, Logiq S8 (GE Medical Systems Ultrasound and Primary Care Diagnostics, Wauwatosa, WI, USA) equipped with a multi-frequency linear matrix array transducer (8-22 MHz). B-mode and conventional Power Doppler (PD) machine settings were optimised for all US examinations. We used the US settings recommended by the EULRA/OMERACT task force for hand US examination (Doppler frequency of 10.3 MHz, pulse repetition frequency of 750 Hz and Doppler gain of 50–53 dB) (D'Agostino, et al. 2017). These settings were optimised by decreasing the pulse repetition frequency and wall filter, and adjusting the Doppler gain to the level just below random noise. The examination was performed by one rheumatology consultant with 8 years of experience in musculoskeletal US. The mean intra-observer agreement calculated on 22 patients was 92% (k=0.67).

The European League Against Rheumatism (EULAR) guidelines for musculoskeletal US assessment in rheumatology diseases were followed. At the time of scanning, the ultrasonographer was blinded to the disease activity scores and serological markers of patients included in the study. The images were obtained in two (dorsal and volar, and transverse and longitudinal) planes of 22 joints: metacarpophalangeal (MCP) joints 1-5, proximal interphalangeal (PIP) joints 1-5, and intercarpal, radial and ulnar aspects of the wrists bilaterally, as well as flexor and extensor tendons. Information about individual joint synovial hypertrophy (SH) grade and total Grey Scale (GS) score for 22 hand joints, as well as joint individual and total PD, osteophytes and erosions scores were collected for each patient. The presence of active joint inflammation was defined as PD signal within a region of GS synovitis, which was graded 1-3; synovial thickening - GS synovitis was graded 1-3; and joint effusion as present/absent, as per the Outcome Measures in Rheumatoid Arthritis
Clinical Trials (OMERACT) definitions developed for RA (Wakefield, et al. 2005). Erosions were defined as an intra-articular discontinuity of the bone surface that is assessed in two perpendicular planes (Wakefield, et al. 2005).

The GS synovitis score and PD score/joint were scored as previously described (D'Agostino, et al. 2017). The total GS synovitis and PD scores were calculated as the sum of the individual joint scores. The erosion score was calculated as the total number of erosions per patient (as all the joints have been scored in a binary manner; 1 - present, 0 - absent). Only joints without osteophytes on US were taken into consideration when calculating the total PD score (to minimise the risk of miss-interpreting active synovitis associated with osteophytes as manifestation of inflammatory arthritis associated with SLE or SS).

Assessment of active inflammation or chronic inflammatory changes affecting the extensor and flexor tendons overlying the above-mentioned joints was performed using the scoring system previously described (Naredo, et al. 2013). In this study, we analysed only on the proportion of patients with signs of active and chronic tenosynovitis.

The duration of US examination, including scoring of US parameters was approximately 20-25 min/patient. Figures 1-3 provide examples of US abnormalities found in patients with SLE and SS.

Hand radiography

All patients underwent a posterior-anterior radiography of their hands.

Treatment optimisation

All patients with active synovitis (defined as presence of PD signal) found at the US examination of their hands had their treatment optimised. This optimisation included
Statistical analysis
Analysis was conducted using IBM SPSS Statistics (IBM 2013. Armonk, New York, USA). Outcome measures with normal distribution such as age, CRP, ESR, SJC, TJC, total PD score, were expressed as mean ± standard deviation (SD). Certain results were expressed as a percentage of the total of that group. Median and interquartile range (IQR) were used to characterize variables with skewed distribution (such as disease activity scores and US scores), while Mann Whitney U test was used to compare them between the two patient groups. In this study, we assessed correlations between disease duration, clinical joint examination (SJC, TJC) and disease activity scores with US outcome measures using Spearman’s correlation test for continuous variables and logistic regression for the binary outcome measures. For all statistical tests, p<0.05 was considered significant.

RESULTS
Clinical and laboratory findings
Eighteen SLE patients and twenty-three SS patients who attended the US outpatient clinic between 2014-2017 were included in this study, which represented only 41/503 (8.15%) from all the patients referred to the rheumatologist-led US clinic for the suspicion of inflammatory arthritis or assessment of their disease control in the case of a previous diagnosis of an inflammatory arthritis. All patients apart from one SLE patient were female. The age of patients ranged from 24 to 68 years old. There was no statistically significant difference regarding age or disease duration between the two patient groups (Table 1).
The clinical parameters recorded at the time of US examination did not show any statistically significant difference between SLE and SS patients. The clinical examination revealed a small number of swollen finger joints (3.29 +/- 4.29 vs. 2.24 +/- 6.11, p=0.58). This was concordant with the clinical assessment of the referring clinicians who interpreted finger joint swelling as potentially related to Raynaud’s phenomenon, inflamed finger skin lesions or possible OA; therefore referring these patients to have a confirmatory US scan.

In terms of serological differences, ANA seropositivity was more frequently encountered in the SLE group compared to SS (p=0.006). Although all SLE patients were ANA positive at the time of diagnosis and at many other assessments during their disease course, only 77.8% SLE patients were positive at the time of the US scan, findings that suggested well-controlled disease and concordant with patients’ numerical BILAG scores, which were low (4.4 +/- 5.02).

Similarly, the ESSDAI score of the SS group was also low (2.31 +/- 1.58). In this study sample, more patients with SLE were treated with oral steroids at the time of US examination compared to patients with SS (p=0.02). There were no significant differences in disease duration, clinical examination, patient reported outcome (global VAS) and treatments between the two patient groups, with the exception of treatment with steroids, which was more frequently used in patients with SLE (Table 1).

US Findings

Despite having equivocal clinical examination for the presence of active synovitis in their hands and wrists, we found active subclinical synovitis on US in 27.8% of SLE patients and 21.7% of SS patients (p=0.653). Patients with SLE had a higher overall median GS score compared to SS (p=0.012). A large proportion of patients (61.1% and 60.9% for SLE and SS respectively) had osteophytes in at least one hand joint (p=0.984). Unexpectedly, 55.6% of SLE patients (10/18) included in the study also had erosions, despite no previous diagnosis of
Arthritis associated with SLE, while a lower proportion (34.8%, 8/23) had erosions in the SS patient group, without reaching statistical significance (p=0.184). Erosions were found in four of the SLE patients at the wrist level alone, while the other six patients had erosions in various joints, including wrists, metacarpophalangeal and interphalangeal joints (median erosion score/patient was 2, IQR-3.5). In contrast, the majority of the erosions were found at the wrist level in SS patients (7/8 patients, 87.5%). The number of erosions per patient in the SS group was lower than in the SLE group (median erosion score/patient was 0, IQR-1).

The majority of SLE patients (55.6%) had at least one joint with moderate SH (grade 2), while patients with SS had predominantly mild SH (grade1), which was detected in 40.7%. Active tenosynovitis was found in at least one tendon in 27.8% patients with SLE and 8.69% patients with SS (p=0.653). Eight patients with SLE (44.4%) and five patients with SS (21.7%) had active inflammation in either their joints and/or tendons.

A higher proportion of patients in both groups had osteophytes in at least one joint (61.1% SLE patients vs. 60.9% SS patients, p=0.98).

**Hand radiography**

All patients had hand radiography organised by their clinicians for the suspicion of associated inflammatory arthropathy (in the last 12 months), and none had erosions on radiography. Osteophytes were found on X-rays in 33.3% (6/18) SLE patients and 30.4% (7/23) SS patients.

**Correlations between US outcome measures and clinical outcomes and treatment at the time of the scan**
We explored the association between different treatments (conventional and biologic DMARDs or steroids) and various US outcome measures, such as PD score, GS score, GS and PD scores for tenosynovitis (Table 2).

GS score correlated with the disease duration in the SS patient group (r=0.61, p=0.0038). From all treatments, only the use of conventional DMARDs (hydroxychloroquine and methotrexate) correlated with the osteophyte score and only in the SS patient group as assessed by a logistic regression analysis model (p=0.0079). As expected, there was a moderate positive correlation between the erosion score and duration of disease in the SLE group (r=0.48, p=0.049), but no correlation with any of the treatments used. In the SS group, treatment with biologics (rituximab) correlated significantly with the erosion score in a logistic regression model (p=0.002), despite the limitation posed by the very low number of patients treated with rituximab in this group.

In addition, the association between disease duration and musculoskeletal domain of disease activity scores (BILAG and ESSDAI), damage indexes (SLICC and SSDDI), and US outcome measures were also explored (Table 3). We highlight the lack of relationship between various US outcome measures (total GS, PD, and erosions scores) with the disease severity scores (BILAG or ESSDAI) in both disease groups. The only statistically significant correlations identified were between SJC and both osteophyte and GS scores; and between TJC and both PD and erosion scores in the SLE group, while SJC correlated significantly with both GS and PD scores in the SS group (Table 3). In the SS group we also identified positive correlations between GVAS and both GS and osteophyte scores.

The disease damage scores (SLICC or SSDDI) showed a strong correlation with the GS score in both patient groups. In addition, SLICC also correlated significantly with the PD score in SLE patients and the SSDDI score correlated with the erosion score in SS patients.
Discussion


The results of this study highlighted that the presence of both active synovitis and erosions in SLE and SS patients was not reflected by the parameters commonly used in clinical practice (TJC, SJC, serological markers or disease activity scores). This observation was similar to other US studies in SLE (Iagnocco, et al. 2014, Ruano, et al. 2017), while discordant to another one, which found good correlation between US detected synovitis and BILAG score (Gabba, et al. 2012).

The present report identified a slightly lower proportion of patients active synovitis/tenosynovitis at the time of the scan than studies which included patients with Rhupus, Jaccoud’s arthropathy or CCP positive joint pain associated with SLE (Iagnocco, et al. 2014), but more than found in asymptomatic SLE patients (Ruano, et al. 2017). This suggests that patient heterogeneity in clinical presentation is likely to influence significantly the US findings in SLE.

Although the proportion of SLE patients with erosions was higher in this study compared to other studies (Ball, et al. 2014, Mosca, et al. 2015, Piga, et al. 2016), this can be explained by the concomitant detection of erosions and osteophytes in our study. As none of the previous studies reported on the presence of osteophytes a direct comparison cannot be made. We can
conclude that in our study, SLE patients had erosions due to an inflammatory arthropathy (in a similar proportion to the previous reported figures), while a small proportion also had concomitant erosive OA changes.

The utility of US in assessing the joint abnormalities associated with symptomatic SS was explored using various US protocols (Amezcua-Guerra, et al. 2013, Iagnocco, et al. 2002, Iagnocco, et al. 2010); however, none of the previous studies reported data on the prevalence of US-detected osteophytes in SS patients.

Inflammatory arthritis associated with SS is less well characterised and considered to be non-erosive and a rare clinical occurrence. In our SS patient group, approximately one in three patients had at least one joint with erosions, while previous studies found erosions in 3.12% and 18% respectively (Amezcua-Guerra, et al. 2013, Iagnocco, et al. 2010). The higher prevalence of erosions in our SS patient group might be explained by additional subclinical erosive OA identified in our SS patient group, while the other studies did not comment on the presence of erosive OA features. In addition, the above mentioned studies investigated different patient groups (Italian versus Mexican population) and used different US examination protocols (wrist assessment for erosions in the study by Iagnocco et al. 2010, and assessment of hands, wrists, ankles, elbows and knees in the study by Amezcua-Guerra et al. 2013). In addition, both studies included a relatively small number of SS patients (32 and 17 patients respectively).

The significant proportion of SLE and SS patients found with osteophytes in at least one joint in our study (approximately 2/3) is not surprising, considering the patients’ mean age. A recent study found hand OA in 45.5% SS patients compared to 14.7% SLE patients on hand radiography (Aksoy, et al. 2016), which is recognised as being less sensitive than US (Hussain, et al. 2018). Unfortunately, none of the previous US studies in SLE or SS reported data about the presence of osteophytes to enable a comparison.
Obvious limitations of this study are the low sample size and the use of only one ultrasonographer; therefore, the results cannot be generalised or used to guide treatment or make patient management recommendations.

Conclusion:

This study explored for the first time in parallel clinical, serological and US outcome measures in two groups of patients (SLE and SS) who have overlapping clinical and serological features, and found that the two groups of patients are not very dissimilar. The main finding (undoubtedly associated clinical implications) was the lack of correlation between US parameters and disease activity or damage scores in both diseases, raising clinician awareness of an unmet need for better characterisation of subclinical synovitis and joint damage that could be responsible for symptoms in patients with SLE and SS. This disparity between the US detected active synovitis and disease activity scores suggests that patients with SLE and SS might have active arthritis even if their disease is not active in other organs and systems in the same time, or could be explained by the small sample size.

Although the increased sensitivity of US examination compared to clinical examination or validated outcome measure was established in various clinical studies in RA (Ciurtin, et al. 2016, Ten Cate, et al. 2013), future research is needed to identify the clinical relevance of the US findings for the management of patients with SLE and SS.

References


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**Figure legends:**

**Figure 1** – Chronic tenosynovitis of the flexor tendon of the index finger: tendon irregularity – white arrow; synovial hypertrophy – open arrow; and fluid within the tendon sheath – white star) in a patient with systemic lupus erythematosus (SLE).

**Figure 2** – Established erosions (white arrow) affecting a proximal interphalangeal joint in a patient with Sjögren’s syndrome (SS).

**Figure 3** – Various degrees of active synovitis affecting proximal interphalangeal joints in a patient with systemic lupus erythematosus (SLE).

A – synovial hypertrophy grade 3 (synovial thickening significantly bulging over the line linking tops of the periarticular bones with extension), PD grade 1 (single vessels)
B – synovial hypertrophy grade 2 (synovial thickening bulging over the line linking tops of the periarticular bones with extension one side of the joint), PD grade 3 (confluent vessels, >50% of joint area)

C – synovial hypertrophy grade 2 (synovial thickening minimally bulging over the line linking tops of the periarticular bones, but with extension one side of the joint), PD grade 2 (confluent vessels, <50% of joint area)
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The European League Against Rheumatism (EULAR) guidelines for musculoskeletal US assessment in rheumatology diseases were followed. At the time of scanning, the ultrasonographer was blinded to the disease activity scores and serological markers of patients included in the study. The images were obtained in two (dorsal and volar, and transverse and longitudinal) planes of 22 joints: metacarpophalangeal (MCP) joints 1-5, proximal interphalangeal (PIP) joints 1-5, and intercarpal, radial and ulnar aspects of the wrists bilaterally, as well as flexor and extensor tendons. Information about individual joint synovial hypertrophy (SH) grade and total Grey Scale (GS) score for 22 hand joints, as well as joint individual and total PD, osteophytes and erosions scores were collected for each patient. The presence of active joint inflammation was defined as PD signal within a region of GS synovitis, which was graded 1-3; synovial thickening - GS synovitis was graded 1-3; and joint effusion as present/absent, as per the Outcome Measures in Rheumatoid Arthritis
Clinical Trials (OMERACT) definitions developed for RA (Wakefield, et al. 2005). Erosions were defined as an intra-articular discontinuity of the bone surface that is assessed in two perpendicular planes (Wakefield, et al. 2005).

The GS synovitis score and PD score/joint were scored as previously described (D'Agostino, et al. 2017). The total GS synovitis and PD scores were calculated as the sum of the individual joint scores. The erosion score was calculated as the total number of erosions per patient (as all the joints have been scored in a binary manner; 1 - present, 0 - absent). Only joints without osteophytes on US were taken into consideration when calculating the total PD score (to minimise the risk of mis-interpreting active synovitis associated with osteophytes as manifestation of inflammatory arthritis associated with SLE or SS).

Assessment of active inflammation or chronic inflammatory changes affecting the extensor and flexor tendons overlying the above-mentioned joints was performed using the scoring system previously described (Naredo, et al. 2013). In this study, we analysed only on the proportion of patients with signs of active and chronic tenosynovitis.

The duration of US examination, including scoring of US parameters was approximately 20-25 min/patient. Figures 1-3 provide examples of US abnormalities found in patients with SLE and SS.

**Hand radiography**

All patients underwent a posterior-anterior radiography of their hands.

**Treatment optimisation**

All patients with active synovitis (defined as presence of PD signal) found at the US examination of their hands had their treatment optimised. This optimisation included...
systemic therapy (escalation of DMARD therapy – conventional or biologic, addition or increase in the oral/intramuscular steroids) or local therapy (US-guided intra-articular injections).

Statistical analysis
Analysis was conducted using IBM SPSS Statistics (IBM 2013. Armonk, New York, USA). Outcome measures with normal distribution such as age, CRP, ESR, SJC, TJC, total PD score, were expressed as mean ± standard deviation (SD). Certain results were expressed as a percentage of the total of that group. Median and interquartile range (IQR) were used to characterize variables with skewed distribution (such as disease activity scores and US scores), while Mann Whitney U test was used to compare them between the two patient groups. In this study, we assessed correlations between disease duration, clinical joint examination (SJC, TJC) and disease activity scores with US outcome measures using Spearman’s correlation test for continuous variables and logistic regression for the binary outcome measures. For all statistical tests, p<0.05 was considered significant.

RESULTS
Clinical and laboratory findings
Eighteen SLE patients and twenty-three SS patients who attended the US outpatient clinic between 2014-2017 were included in this study, which represented only 41/503 (8.15%) from all the patients referred to the rheumatologist-led US clinic for the suspicion of inflammatory arthritis or assessment of their disease control in the case of a previous diagnosis of an inflammatory arthritis. All patients apart from one SLE patient were female. The age of patients ranged from 24 to 68 years old. There was no statistically significant difference regarding age or disease duration between the two patient groups (Table 1).
The clinical parameters recorded at the time of US examination did not show any statistically significant difference between SLE and SS patients. The clinical examination revealed a small number of swollen finger joints (3.29 +/- 4.29 vs. 2.24 +/- 6.11, p=0.58). This was concordant with the clinical assessment of the referring clinicians who interpreted finger joint swelling as potentially related to Raynaud’s phenomenon, inflamed finger skin lesions or possible OA; therefore referring these patients to have a confirmatory US scan.

In terms of serological differences, ANA seropositivity was more frequently encountered in the SLE group compared to SS (p=0.006). Although all SLE patients were ANA positive at the time of diagnosis and at many other assessments during their disease course, only 77.8% SLE patients were positive at the time of the US scan, findings that suggested well-controlled disease and concordant with patients’ numerical BILAG scores, which were low (4.4+/−5.02). Similarly, the ESSDAI score of the SS group was also low (2.31 +/- 1.58). In this study sample, more patients with SLE were treated with oral steroids at the time of US examination compared to patients with SS (p=0.02). There were no significant differences in disease duration, clinical examination, patient reported outcome (global VAS) and treatments between the two patient groups, with the exception of treatment with steroids, which was more frequently used in patients with SLE (Table 1).

**US Findings**

Despite having equivocal clinical examination for the presence of active synovitis in their hands and wrists, we found active subclinical synovitis on US in 27.8% of SLE patients and 21.7% of SS patients (p=0.653). Patients with SLE had a higher overall median GS score compared to SS (p=0.012). A large proportion of patients (61.1% and 60.9% for SLE and SS respectively) had osteophytes in at least one hand joint (p=0.984). Unexpectedly, 55.6% of SLE patients (10/18) included in the study also had erosions, despite no previous diagnosis of
arthritis associated with SLE, while a lower proportion (34.8%, 8/23) had erosions in the SS patient group, without reaching statistical significance (p=0.184). Erosions were found in four of the SLE patients at the wrist level alone, while the other six patients had erosions in various joints, including wrists, metacarpophalangeal and interphalangeal joints (median erosion score/patient was 2, IQR-3.5). In contrast, the majority of the erosions were found at the wrist level in SS patients (7/8 patients, 87.5%). The number of erosions per patient in the SS group was lower than in the SLE group (median erosion score/patient was 0, IQR-1).

The majority of SLE patients (55.6%) had at least one joint with moderate SH (grade 2), while patients with SS had predominantly mild SH (grade 1), which was detected in 40.7%. Active tenosynovitis was found in at least one tendon in 27.8% patients with SLE and 8.69% patients with SS (p=0.653). Eight patients with SLE (44.4%) and five patients with SS (21.7%) had active inflammation in either their joints and/or tendons.

A higher proportion of patients in both groups had osteophytes in at least one joint (61.1% SLE patients vs. 60.9% SS patients, p=0.98).

Hand radiography

All patients had hand radiography organised by their clinicians for the suspicion of associated inflammatory arthropathy (in the last 12 months), and none had erosions on radiography. Osteophytes were found on X-rays in 33.3% (6/18) SLE patients and 30.4% (7/23) SS patients.

Correlations between US outcome measures and clinical outcomes and treatment at the time of the scan
We explored the association between different treatments (conventional and biologic DMARDs or steroids) and various US outcome measures, such as PD score, GS score, GS and PD scores for tenosynovitis (Table 2).

GS score correlated with the disease duration in the SS patient group ($r=0.61$, $p=0.0038$).

From all treatments, only the use of conventional DMARDs (hydroxychloroquine and methotrexate) correlated with the osteophyte score and only in the SS patient group as assessed by a logistic regression analysis model ($p=0.0079$). As expected, there was a moderate positive correlation between the erosion score and duration of disease in the SLE group ($r=0.48$, $p=0.049$), but no correlation with any of the treatments used. In the SS group, treatment with biologics (rituximab) correlated significantly with the erosion score in a logistic regression model ($p=0.002$), despite the limitation posed by the very low number of patients treated with rituximab in this group.

In addition, the association between disease duration and musculoskeletal domain of disease activity scores (BILAG and ESSDAI), damage indexes (SLICC and SSDDI), and US outcome measures were also explored (Table 3). We highlight the lack of relationship between various US outcome measures (total GS, PD, and erosions scores) with the disease severity scores (BILAG or ESSDAI) in both disease groups. The only statistically significant correlations identified were between SJC and both osteophyte and GS scores; and between TJC and both PD and erosion scores in the SLE group, while SJC correlated significantly with both GS and PD scores in the SS group (Table 3). In the SS group we also identified positive correlations between GVAS and both GS and osteophyte scores.

The disease damage scores (SLICC or SSDDI) showed a strong correlation with the GS score in both patient groups. In addition, SLICC also correlated significantly with the PD score in SLE patients and the SSDDI score correlated with the erosion score in SS patients.
Discussion


The results of this study highlighted that the presence of both active synovitis and erosions in SLE and SS patients was not reflected by the parameters commonly used in clinical practice (TJC, SJC, serological markers or disease activity scores). This observation was similar to other US studies in SLE (Iagnocco, et al. 2014, Ruano, et al. 2017), while discordant to another one, which found good correlation between US detected synovitis and BILAG score (Gabba, et al. 2012).

The present report identified a slightly lower proportion of patients active synovitis/tenosynovitis at the time of the scan than studies which included patients with Rhupus, Jaccoud’s arthropathy or CCP positive joint pain associated with SLE (Iagnocco, et al. 2014), but more than found in asymptomatic SLE patients (Ruano, et al. 2017). This suggests that patient heterogeneity in clinical presentation is likely to influence significantly the US findings in SLE.

Although the proportion of SLE patients with erosions was higher in this study compared to other studies (Ball, et al. 2014, Mosca, et al. 2015, Piga, et al. 2016), this can be explained by the concomitant detection of erosions and osteophytes in our study. As none of the previous studies reported on the presence of osteophytes a direct comparison cannot be made. We can
conclude that in our study, SLE patients had erosions due to an inflammatory arthropathy (in a similar proportion to the previous reported figures), while a small proportion also had concomitant erosive OA changes.

The utility of US in assessing the joint abnormalities associated with symptomatic SS was explored using various US protocols (Amezcua-Guerra, et al. 2013, Iagnocco, et al. 2002, Iagnocco, et al. 2010); however, none of the previous studies reported data on the prevalence of US-detected osteophytes in SS patients.

Inflammatory arthritis associated with SS is less well characterised and considered to be non-erosive and a rare clinical occurrence. In our pSS patient group, approximately one in three patients had at least one joint with erosions, while previous studies found erosions in 3.12% and 18% respectively (Amezcua-Guerra, et al. 2013, Iagnocco, et al. 2010). The higher prevalence of erosions in our SS patient group might be explained by additional subclinical erosive OA identified in our pSS patient group, while the other studies did not comment on the presence of erosive OA features. In addition, the above mentioned studies investigated different patient groups (Italian versus Mexican population) and used different US examination protocols (wrist assessment for erosions in the study by Iagnocco et al. 2010, and assessment of hands, wrists, ankles, elbows and knees in the study by Amezcua-Guerra et al. 2013). In addition, both studies included a relatively small number of pSS patients (32 and 17 patients respectively).

The significant proportion of SLE and SS patients found with osteophytes in at least one joint in our study (approximately 2/3) is not surprising, considering the patients’ mean age. A recent study found hand OA in 45.5% SS patients compared to 14.7% SLE patients on hand radiography (Aksoy, et al. 2016), which is recognised as being less sensitive than US (Hussain, et al. 2018). Unfortunately, none of the previous US studies in SLE or SS reported data about the presence of osteophytes to enable a comparison.
Obvious limitations of this study are the low sample size and the use of only one ultrasonographer; therefore, the results cannot be generalised or used to guide treatment or make patient management recommendations.

Conclusion:
This study explored for the first time in parallel clinical, serological and US outcome measures in two groups of patients (SLE and SS) who have overlapping clinical and serological features, and found that the two groups of patients are not very dissimilar. The main finding (undoubtedly associated clinical implications) was the lack of correlation between US parameters and disease activity or damage scores in both diseases, raising clinician awareness of an unmet need for better characterisation of subclinical synovitis and joint damage that could be responsible for symptoms in patients with SLE and SS. This disparity between the US detected active synovitis and disease activity scores suggests that patients with SLE and SS might have active arthritis even if their disease is not active in other organs and systems in the same time, or could be explained by the small sample size.

Although the increased sensitivity of US examination compared to clinical examination or validated outcome measure was established in various clinical studies in RA (Ciurtin, et al. 2016, Ten Cate, et al. 2013), future research is needed to identify the clinical relevance of the US findings for the management of patients with SLE and SS.

References

Ball EM, Gibson DS, Bell AL, Rooney MR. Plasma IL-6 levels correlate with clinical and ultrasound measures of arthritis in patients with systemic lupus erythematosus. Lupus 2014; 23:46-56.


Ten Cate DF, Luime JJ, Swen N, Gerards AH, De Jager MH, Basoski NM, Hazes JM, Haagsma CJ, Jacobs JW. Role of ultrasonography in diagnosing early rheumatoid


Figure legends:

Figure 1 – Chronic tenosynovitis of the flexor tendon of the index finger: tendon irregularity – white arrow; synovial hypertrophy – open arrow; and fluid within the tendon sheath – white star) in a patient with systemic lupus erythematosus (SLE).

Figure 2 – Established erosions (white arrow) affecting a proximal interphalangeal joint in a patient with Sjögren’s syndrome (SS).

Figure 3 – Various degrees of active synovitis affecting proximal interphalangeal joints in a patient with systemic lupus erythematosus (SLE).

A – synovial hypertrophy grade 3 (synovial thickening significantly bulging over the line linking tops of the periarticular bones with extension), PD grade 1 (single vessels)
B – synovial hypertrophy grade 2 (synovial thickening bulging over the line linking tops of the periarticular bones with extension one side of the joint), PD grade 3 (confluent vessels, >50% of joint area)

C – synovial hypertrophy grade 2 (synovial thickening minimally bulging over the line linking tops of the periarticular bones, but with extension one side of the joint), PD grade 2 (confluent vessels, <50% of joint area)
Table 1: Patients’ demographics, clinical and serological parameters, and US outcome measures


<table>
<thead>
<tr>
<th></th>
<th>SLE (n=18)</th>
<th>SS (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years, mean +/- SD)</strong></td>
<td>45.7 +/- 12</td>
<td>51.4 +/- 14</td>
<td>p=0.18</td>
</tr>
<tr>
<td><strong>Gender (% females)</strong></td>
<td>94.4</td>
<td>100</td>
<td>p=0.25</td>
</tr>
<tr>
<td><strong>Disease duration (months, mean +/- SD)</strong></td>
<td>168.5 +/- 177.1</td>
<td>106.9 +/- 118.1</td>
<td>p=0.21</td>
</tr>
<tr>
<td><strong>% patients on steroids</strong></td>
<td>66.7</td>
<td>13.0</td>
<td>p=0.0004</td>
</tr>
<tr>
<td><strong>Dose of oral prednisolone (mg/day; mean +/- SD)</strong></td>
<td>6.88 +/- 3.40</td>
<td>10 +/- 0</td>
<td>p=0.27</td>
</tr>
<tr>
<td><strong>% patients on cDMARDs</strong></td>
<td>88.9</td>
<td>52.2</td>
<td>p=0.01</td>
</tr>
<tr>
<td><strong>% patients on Methotrexate</strong></td>
<td>5.6</td>
<td>4.3</td>
<td>p=0.85</td>
</tr>
<tr>
<td><strong>% patients on Hydroxychloroquine</strong></td>
<td>77.8</td>
<td>43.5</td>
<td>p=0.02</td>
</tr>
<tr>
<td><strong>% patients ever treated with Rituximab</strong></td>
<td>11.1</td>
<td>8.7</td>
<td>p=0.79</td>
</tr>
<tr>
<td><strong>% patients treated with Rituximab in the last 6 months</strong></td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>% patients ever treated with Belimumab</strong></td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>%ANA positive</strong></td>
<td>100</td>
<td>52.17</td>
<td>p=0.009</td>
</tr>
<tr>
<td><strong>%dsDNA positive</strong></td>
<td>27.8</td>
<td>4.3</td>
<td>p=0.23</td>
</tr>
<tr>
<td><strong>% ENA positive</strong></td>
<td>55.6</td>
<td>56.5</td>
<td>p = 0.95</td>
</tr>
<tr>
<td><strong>% RF positive</strong></td>
<td>22.2</td>
<td>34.7</td>
<td>p = 0.37</td>
</tr>
<tr>
<td><strong>% CCP autoantibody positive</strong></td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>CRP (mg/L, mean +/- SD)</strong></td>
<td>4.98 +/- 4.17</td>
<td>4.69 +/- 6.04</td>
<td>p=0.87</td>
</tr>
<tr>
<td><strong>ESR (mm/h, mean +/- SD)</strong></td>
<td>31.41 +/- 26.11</td>
<td>23.35 +/- 19.78</td>
<td>p=0.27</td>
</tr>
<tr>
<td><strong>SJC (mean +/- SD)</strong></td>
<td>3.29 +/- 4.29</td>
<td>2.24 +/- 6.11</td>
<td>p=0.58</td>
</tr>
<tr>
<td><strong>TJC (mean +/- SD)</strong></td>
<td>6.17 +/- 7.54</td>
<td>6.17 +/- 7.54</td>
<td>p=0.74</td>
</tr>
<tr>
<td>Domain</td>
<td>BILAG</td>
<td>ESSDAI</td>
<td>p-value</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Musculoskeletal domain</strong></td>
<td>0 (4)</td>
<td>0 (2)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Damage scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total GS score/patient</strong></td>
<td>8 (15.5)</td>
<td>2 (5)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Total PD score/patient</strong></td>
<td>0 (1.5)</td>
<td>0 (0)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Total erosion score/patient</strong></td>
<td>2 (3.5)</td>
<td>0 (1)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Total osteophyte score/patient</strong></td>
<td>1 (5)</td>
<td>2 (4)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Total GS tendonitis score/patient</strong></td>
<td>0 (2)</td>
<td>0 (1.5)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>% patients with PD signal</strong></td>
<td>27.8</td>
<td>21.7</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>% patients with osteophytes</strong></td>
<td>61.1</td>
<td>60.9</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>% patients with erosions</strong></td>
<td>55.6</td>
<td>34.8</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>% patients with erosions and osteophytes in the same joint</strong></td>
<td>16.6</td>
<td>26.08</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>% patients with joints with SH grade 1</strong></td>
<td>38.9</td>
<td>47.8</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>% patients with joints with SH grade 2:</strong></td>
<td>55.6</td>
<td>30.4</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>% patients with joints with SH grade 3:</strong></td>
<td>22.2</td>
<td>8.7</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>% patients with active tendonitis</strong></td>
<td>27.8</td>
<td>8.7</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>% patients with subclinical synovitis and active tendonitis</strong></td>
<td>44.4</td>
<td>21.7</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Table 2: Regression analysis and correlations between US parameters and disease duration, as well as treatments in the two patient groups.


<table>
<thead>
<tr>
<th></th>
<th>SLE (n=18)</th>
<th>SS (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation between disease duration and GS score/patient</td>
<td>R=0.399, p=0.101</td>
<td>R=0.61, <strong>p=0.0038</strong></td>
</tr>
<tr>
<td>Logistic regression analysis of association of various treatments with GS score</td>
<td>DMARDs: p=0.612, Biologics: N/A, Steroids: p=0.093</td>
<td>DMARDs: p=0.580, Biologics: N/A, Steroids: p=0.385</td>
</tr>
<tr>
<td>Correlation between disease duration and PD score/patient</td>
<td>R=0.39799, p=0.114</td>
<td>R=0.02791, p=0.907</td>
</tr>
<tr>
<td>Logistic regression analysis of association of various treatments with PD score</td>
<td>DMARDs: p=0.0994, Biologics: p=0.554, Steroids: p=0.952</td>
<td>DMARDs: p=0.400, Biologics: p=0.311, Steroids: N/A</td>
</tr>
<tr>
<td>Correlation between duration with osteophytes</td>
<td>R=0.27902, p=0.262</td>
<td>R=0.38018, p=0.098</td>
</tr>
<tr>
<td>Logistic regression analysis of association of various treatments with osteophyte score</td>
<td>DMARDs: p=0.514, Biologics: p=0.514, Steroids: p=0.474</td>
<td>DMARDs: <strong>p=0.0079</strong>, Biologics: p=0.1701, Steroids: N/A</td>
</tr>
<tr>
<td>Correlation between disease duration and erosion score</td>
<td><strong>R=0.48</strong>, <strong>p=0.049</strong></td>
<td>R=0.39159, p=0.088</td>
</tr>
<tr>
<td>Logistic regression analysis of association of various treatments with erosion score</td>
<td>DMARDs: p=0.3462, Biologics: p=0.346, Steroids: p=0.066</td>
<td>DMARDs: p=0.1401, Biologics: <strong>p=0.002</strong>, Steroids: p=0.955</td>
</tr>
</tbody>
</table>
Table 3: Correlation between US outcome measures and clinical and disease activity parameters.


<table>
<thead>
<tr>
<th>Spearman’s correlations</th>
<th>SLE (n=18)</th>
<th>SS (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS score and musculoskeletal domains of BILAG and ESSDAI</td>
<td>R = 0.410, p = 0.091</td>
<td>R = 0.084, p = 0.702</td>
</tr>
<tr>
<td>GS score and SLICC or SSDDI</td>
<td>R = 0.533, p = 0.023</td>
<td>R = 0.542, p = 0.008</td>
</tr>
<tr>
<td>PD score and musculoskeletal domains of BILAG and ESSDAI</td>
<td>R = 0.362, p = 0.140</td>
<td>R = 0.328, p = 0.126</td>
</tr>
<tr>
<td>PD score and SLICC or SSDDI</td>
<td>R = 0.478, p = 0.045</td>
<td>R = 0.351, p = 0.101</td>
</tr>
<tr>
<td>Erosion score with musculoskeletal domains of BILAG and ESSDAI</td>
<td>R = 0.205, p = 0.597</td>
<td>R = 0.223, p = 0.407</td>
</tr>
<tr>
<td>Erosion score and SLICC or SSDDI</td>
<td>R = 0.115, p = 0.659</td>
<td>R = 0.439, p = 0.036</td>
</tr>
<tr>
<td>Osteophyte score with musculoskeletal domains of BILAG and ESSDAI</td>
<td>R = -0.0259, p = 0.943</td>
<td>R = -0.280, p = 0.293</td>
</tr>
<tr>
<td>Osteophyte score and SLICC or SSDDI</td>
<td>R = 0.214, p = 0.394</td>
<td>R = 0.237, p = 0.275</td>
</tr>
<tr>
<td>SJC and GS score</td>
<td>R = 0.717, p = 0.00392</td>
<td>R = 0.580, p = 0.00589</td>
</tr>
<tr>
<td>SJC and PD score</td>
<td>R = 0.493, p = 0.0732</td>
<td>R = 0.730, p = 0.0004</td>
</tr>
<tr>
<td>SJC and erosion score</td>
<td>R = 0.651, p = 0.0160</td>
<td>R = 0.234, p = 0.308</td>
</tr>
<tr>
<td>SJC and osteophyte score</td>
<td>R = 0.0272, p = 0.926</td>
<td>R = 0.240, p = 0.294</td>
</tr>
<tr>
<td>TJC and GS score</td>
<td>R = 0.303, p = 0.293</td>
<td>R = 0.0586, p = 0.806</td>
</tr>
<tr>
<td>TJC and PD score</td>
<td>R = 0.604, p = 0.0221</td>
<td>R = 0.281, p = 0.291</td>
</tr>
<tr>
<td>TJC and erosion score</td>
<td>R = 0.556, p = 0.0483</td>
<td>R = -0.258, p = 0.273</td>
</tr>
<tr>
<td>TJC and osteophyte score</td>
<td>R = 0.162, p = 0.580</td>
<td>R = 0.1884, p = 0.426</td>
</tr>
<tr>
<td>GVAS and GS score</td>
<td>R = 0.307, p = 0.388</td>
<td>R = 0.495, p = 0.0432</td>
</tr>
<tr>
<td>GVAS and PD score</td>
<td>R = 0.145, p = 0.689</td>
<td>R = -0.0353, p = 0.893</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>p</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td>GVAS and erosion score</td>
<td>0.332</td>
<td>0.383</td>
</tr>
<tr>
<td>GVAS and osteophyte score</td>
<td>0</td>
<td>1</td>
</tr>
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