Imaging of joints in systemic lupus erythematosus

C. Tani, L. Carli, C. Stagnaro, E. Elefante,
V. Signorini, F. Balestri, A. Delle Sedie, M. Mosca

Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

Chiara Tani, MD, PhD
Linda Carli, MD
Chiara Stagnaro, MD
Elena Elefante, MD
Viola Signorini, MD
Francesca Balestri, MD
Andrea Delle Sedie, MD
Marta Mosca, MD, PhD

Please address correspondence to:
Dr Chiara Tani,
Divisione di Reumatologia,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: chiara.tani@for.unipi.it

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ABSTRACT

Musculoskeletal symptoms are among the most common manifestations in patients with systemic lupus erythematosus (SLE), being reported in up to 95% of patients; joint and tendon involvement can range from arthralgia to severe deforming arthropathy; while myositis a rare manifestation, comorbid fibromyalgia is reported in up to 40% of SLE patients. All these manifestations have a significant impact on the patients' quality of life, possibly leading to disability and functional impairment in daily living activities.

In recent years, thanks to the availability of new imaging techniques for the assessment of tendon and joint pathologies, the approach to the definition and characterisation of these manifestations in SLE is constantly evolving.

In this review we will therefore illustrate the state of the art of imaging techniques in the assessment of joint involvement in SLE, focusing on ultrasounds (US) and magnetic resonance (MRI), discussing their advantages, drawbacks and possible future developments.

The main findings that emerge from the recent literature is that imaging studies may allow a more accurate definition of disease subtypes revealing an unexpected higher prevalence of joint and tendon involvement with respect to what known by clinical evaluation and standard radiography. Indeed, US and MRI also made possible the identification of joints and tendons pathologies in patients with no or very mild clinical symptoms. On the other hand, the interpretation of some findings remains uncertain, as well as the validity and feasibility of this analysis in clinical practice.

Thus, further studies should clarify the clinical meaning of subclinical abnormalities detected in US and MRI scans and their impact on the long-term outcomes.

Introduction

Musculoskeletal symptoms are reported in up to 90% of patients with SLE, and are the presenting symptom in about 80% of cases (1, 2). Inflammatory arthralgia and non-erosive non-deforming arthritis are the most common complaints described in up to 90% and 85% of patients, respectively. Deforming arthropathy – known as Jaccoud arthropathy – and RA-like erosive arthritis (so called Rhupus) are less frequent, reported in up to 35% and 10% of patients, respectively (3-5).

Myositis also is seen, although inflammatory muscle damage is rare (<5%). More often SLE patients refer non-inflammatory myalgias or a frank fibromyalgia, a frequent comorbid condition that complexity presents in the differential diagnosis of the muscular and joint pain in these patients (6, 7).

Despite traditional consideration as generally mild and non-life-threatening condition, musculoskeletal involvement is a frequent cause of disability and poor quality of life in SLE patients. Indeed, joint involvement is one of the main causes of chronic pain, deformities and reported loss of function in daily activities in SLE, especially in case of concomitant fibromyalgia (8, 9).

Functional disability in activities of daily living is reported frequently by patients with SLE, and it is estimated that almost two-third of SLE patients experience periodic or permanent inability to perform some activities at home or work; reduced muscle strength and activity-induced pain are the most commonly reported contributors of reduced physical function in these patients (8-11).

Joint deformities indicate irreversible organ damage, and are the main cause of disability and loss of function; they result from failure of management to control inflammation in joints leading to this undesirable outcome. In a

Table I. Literature summary of US studies on joint involvement in SLE.

Author, year	Number of patients	Pt characteristics	Joints	Synovitis/joint effusion	Tenosynovitis	Erosions
Wright, 2006	17	arthritis	Hands, wrists	Hands 71% Wrists 94%	65%	47%
Iagnocco, 2004	26	Consecutive	Hands, wrists	42.3%	44%	3.8%
Delle sedie, 2009	50	present or past arthritis	Hands, wrists	80%	28%	12%
Gabba, 2012	108	consecutive	Hands, wrists	42.2%	61.1%	25.9%
Torrente-Segarra, 2013	58	consecutive	Hands, wrist	25%	Extensor 39% Flexors 7%	na
Iagnocco, 2014	62	Consecutive	Hands, wrists, foot	87.1%	na	na
Mosca, 2015	102	consecutive	Hands, wrists	42%	38.2%	31.4%
Buosi, 2014	62	Artrhtis/arthralgias	Hands, wrists	Wrist 47% MCP 84% PIP 58%	na	Wrist 18% MCP13% PIP 4%
Ogura, 2017	15	Treatment naive	Hand, wrists	80%	93%	na
Lins, 2018		Jaccoud arthropathy	Hands, wrists	47.5%	22.5%	5%
Salliot, 2018	151	consecutive	Hands, wrists	40.3%	na	na

MCP: metacarpophalangeal; PIP: proximal interphalangeal. Rhupus patients are excluded.

treat-to-target perspective, a modern approach to joint manifestations in SLE should be targeted to a better control of the inflammatory process, to the prevention of disease flares and, therefore, to the prevention of joint damage and deformities (12), as seen for joint involvement in rheumatoid arthritis (13).

Improvement of long-term outcomes of joint involvement in SLE appears to require early and accurate diagnosis, a tailored therapeutic strategy targeted to complete control of inflammatory activity, tight monitoring, toward remission and prevention of progression of tendon and bone damage. In recent years, new information concerning joint involvement in SLE has emerged from new imaging techniques such as ultrasound (US) and magnetic resonance (MRI) (5, 14).

First, new imaging techniques demonstrate a surprisingly higher prevalence of joint involvement in SLE compared to traditional concepts based on clinical examination and standard radiography (14-16). These findings suggest an emerging need for accurate assessment of joint involvement in SLE for diagnostic, therapeutic and prognostic purposes. Indeed, the available clinical disease activity instruments including the most frequently used BILAG and SLEDAI are based on the clinical detection of joint swelling, so they may fail to capture disease activity in a significant proportion of patients who have milder or intermittent symptoms. On the other hand, the clinical and prognostic implications of subclinical joints and tendons abnormalities as detected by imaging are not fully elucidated.

What does ultrasound tell us about joint involvement in SLE?

Ultrasonography (US) with power Doppler (PD) is a valuable imaging technique to evaluate joint and tendon abnormalities, particularly to assess the inflammatory process in the synovia and tendons as well as bone damage (17). US is highly sensitive to detect even minimal alterations of asymptomatic joints; therefore, it has been widely used to diagnose early disease and to evaluate disease activity and damage in many rheumatic diseases, including rheumatoid arthritis, spondyloarthropathies and connective tissue diseases (18-21). Moreover, ultrasound has been increasingly used in the assessment of extra-articular manifestations of these diseases (22-26).

Ultrasonographic abnormalities of hand and wrist joints have been commonly reported in patients with SLE and they are summarised in Table I (14, 27-36).

Despite significant heterogeneity among the studies in clinical setting and methods, the main finding is that US studies indicated a high prevalence of joint and tendon inflammatory pathologies on hands and wrists even in patients with mild or even without clinical signs at physical examination. Similarly, in 2016, Moraes-Lozano *et al*. found a high prevalence of feet pathology (especially metatarsal-phalangeal joints) in consecutive patients with SLE by biomechanical and US assessment which were not captured by standardised assessment of the disease activity. (37)

It remains an open question whether subclinical arthritis or mild non-continuous symptoms should be treated with aggressive therapy, since no definitive prospective data are available to justify this strategy. Indeed, discordance between the clinical and the US assessment of arthritis is a well-known aspect frequently raised also in the RA literature but has not been extensively studied in SLE (21, 38-41).

Nonetheless, even mild and episodic joint symptoms have an impact of the patient's perception of disease and health-related quality of life (42). In 50 consecutive SLE patients, we have shown that hand or wrist arthritis was clinically detectable in 10 (20%) patients, while, at least one joint or tendon abnormality was observed in 18

Table II. Literature summary of MRI studies on joint involvement in SLE.

Author	n. of patients	Examined joint	Patient characteristics	Erosions (%)
Daniel Sà Ribeiro, 2010	20	Hands	Patients with JA	50%
Boutry, 2005	14	Wrist and MCP joints	Early onset arthritis	61%
Ostendorf, 2003	14	Hands	Patients with joint involvement and deformities	57%
Ball, 2014	34	Hands, wrists	Artrhtis/arthralgias	Wrist 93% MCP 61%
Mosca, 2015	102	Hand, wrists	Consecutive SLE patients Healthy subjects	47.7% hands 98.9% wrists 19.6% hands 97.8% wrists

patients (36%). The patients' reported general health, pain and perception of disease activity were poor in patients with US abnormalities than in patients with no US abnormalities (42).

Yoon *et al*. showed subclinical synovitis by US in 58.3% out of 48 consecutive SLE patients who had no musculoskeletal symptoms; the wrist and the second-third metacarpophalangeal joints were the most affected sites. Among patients with subclinical synovitis, new musculoskeletal symptoms were observed over 6 months after US examination in 11 patients (39.3%) (40).

These data, if confirmed in larger prospective cohorts, highlight the limited sensitivity of the clinical assessments based on the joint count both in clinical practice and in clinical trials, and support US for a more sensitive evaluation of disease severity and prognosis, though this not necessarily implies changes in therapies.

Another important finding that emerged from these reports is the high prevalence of tendon pathology in SLE. Hand and wrist flexor and extensor tendon involvement is reported in up to 65% of patients with SLE. Ultrasound presents an advantage over the standard clinical assessment of joint involvement, which usually does not distinguish synovitis from tenosynovitis.

US also allowed a better characterisation of Jaccoud's arthropathy; Ceccarelli *et al*. recently showed the presence of erosive bone damage in 58.8% of JA patients, frequently localised at the first and second MCP; similarly, Piga *et al*. found a prevalence of erosions detected by US and CT of 50.0% and 80.0%, respectively (43, 44). Thus, in the light of these observations, the definition of non-erosive arthritis for JA could be carefully revisited.

Similarly to RA, power Doppler signal (PD) appears to have the most important clinical prognostic significance in SLE. Piga *et al*. found that baseline PD-synovitis score independently predicted musculoskeletal flares within 2 years of and US examination in 80 SLE patients with non-deforming non-erosive arthropathy over a period of 5 years (45).

What does MRI tell us about joint involvement in SLE?

In recent years, several studies have demonstrated that MRI is more sensitive for detection of inflammatory and destructive joint changes in rheumatic diseases than conventional clinical and radiographic methods (46). Similar accuracy has been reported using low-field dedicated extremity MRI systems versus a conventional high-field MRI system, significantly increasing accessibility and patient discomfort, while reducing costs (47).

MRI also provides in-depth information concerning the severity of synovitis, oedema, and erosion, at diagnosis and during follow-up, thereby enabling early identification of treatment responders. The RAMRIS (OMERACT rheumatoid arthritis MRI scoring system) is a practicable scoring system for morphological and semiquantitative evaluation of MRI findings in RA and it is widely used in clinical trials (48).

Gadolinium (Gd)-enhanced MRI provides highly sensitive assessment for synovitis; indeed, inflamed tissues with synovitis show increased signal intensity (enhancement) on T1-weighted post-Gd injection images. However, Gd injection prolongs examination time, increases invasiveness, and is not free of possible adverse events, especially in patients with systemic involvement such as SLE patients. Ostergaard *et al*. demonstrated that omitting IV contrast injection does not have significant impact on scores for erosions and edema but decreases the reliability of synovitis scores. This disadvantage, as stated by the authors, may be outweighed in some cases by the possibility to assess more joints with greater feasibility (49).

In recent years, MRI (especially unenhanced) has been applied to studies on joint involvement in SLE.

The prevalence of bone erosions as emerged from MRI studies in SLE is summarised in Table II (14, 50-53).

The main common finding is a surprisingly higher prevalence of bone erosions than observed traditionally with standard radiography. Hand erosions, described in more than half of SLE patients with joint involvement, appear more specific than wrist erosions, that are almost ubiquitous.

Indeed, when having a single erosion was used as a positive test, in the controlled study by Mosca *et al*., many healthy subjects showed at least one erosion at wrist while erosive changes in the hand were present in less than 20%. This phenomenon is well described in RA studies, in which MRI is a highly sensitive tool for identifying and tracking progression of erosions, although a single erosion provides low specificity for RA (54).

These observations suggest that the number and severity of erosions (erosive burden) and their anatomical distribution are more reliable measures of the joint damage in SLE. In a comparative study of 50 SLE patients with joint involvement, 22 RA patients and 48 healthy subjects, the prevalence of bone marrow oedema and erosions was similar in SLE and RA but erosion and oedema scores were higher in the latter condition suggesting a more severe joint damage; on the other side no BME and fewer erosions were ob-

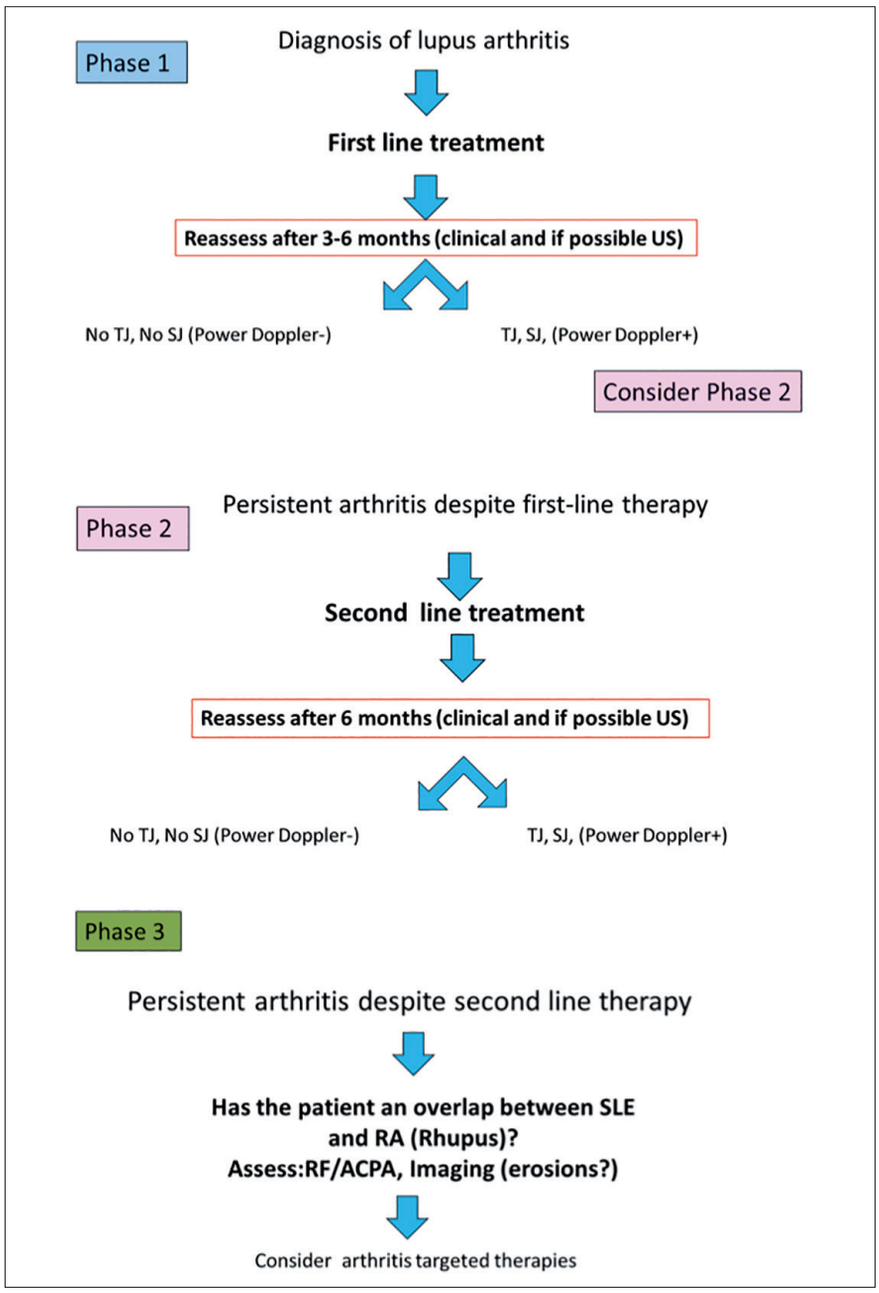

Fig. 1. Proposed management algorithm in lupus arthritis.

served in healthy subjects. Wrist erosions were common in all groups, suggesting that at least one erosion at this level frequently has a nonspecific meaning; however, by considering the cumulative erosive burden, higher scores in SLE and RA patients were found than in healthy subjects, both in the hand and in the wrist, suggesting a difference in erosions severity. As expected, the erosive burden as quantified by MRI was significantly higher in Rhupus patients with respect to non-Rhupus SLE patients (55).

In RA, BME is considered the most specific finding with the higher accuracy for joint damage progression (56). In SLE studies, BME is reported in a low percentage of patients (7.5% and 35.5% at the hand and wrist, respectively) (14) and its prognostic meaning remains to be defined in prospective studies.

In conclusion, MRI is a promising technique for assessment of joint involvement in SLE, although more information concerning interpretation of the findings appears required before this technique could be widely used in clinical research and routine clinical care.

How could new imaging techniques integrate the clinical assessment of joint involvement in SLE?

The management of severe arthritis in SLE is a clinical challenge since the clinician's therapeutic choice should be balanced against possible associated organ involvement, comorbidities and concomitant medications that can limit the use of certain drugs. The frequent coexistence of fibromyalgia substantially raises the diagnostic and therapeutic challenge as well as the patient's burden of the disease.

Moreover, the absence of clinical trials specifically designed for joint involvement leaves a non-standardised clinical approach to this organ involvement.

In our opinion, the integration of the "classical" clinical and serological evaluations with the results of a systematic instrumental assessment of the joint involvement could represent a possible solution to optimise the management of these manifestations. By borrowing some concepts from RA, we hereby propose a treat-to-target strategy for joint involvement in SLE; the approach that we are suggesting comprises a tight control of joint manifestations through clinical, serological and US assessments that are feasible in routine clinical care (Fig. 1). The effectiveness of the application of this approach must be studied in future prospective studies.

Conclusions

In conclusion, new imaging techniques have significantly increased our knowledge and recognition of musculoskeletal involvement in SLE; they may allow a more accurate definition of disease subtypes with different prognoses and different therapeutic approaches and monitoring strategies. US and MRI also made possible the identification of joints and tendons pathologies in patients with no or very mild clinical symptoms.

On the other hand, although there is an increasing literature on the use of new imaging techniques in SLE, the interpretation of some findings remains uncertain, as well as the validity and fea-

sibility of this analysis in clinical practice. Moreover, associations between imaging findings and other outcome measures in use in SLE (such as disease activity indices) were not consistent across the literature, suggesting that there could be a substantial discrepancy between what we see on imaging and clinical outcomes (57).

Thus, prospective studies should clarify the clinical meaning of subclinical abnormalities detected in US and MRI scans and their impact on the long-term outcomes.

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