

Ultrasonographic depiction of knee joint alterations in systemic lupus erythematosus

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ABSTRACT

Objective. *The aim of this study was to assess inflammatory changes within the knee joint of systemic lupus erythematosus (SLE) patients by using ultrasound (US). Rheumatoid arthritis (RA) patients and healthy subjects (HS) were evaluated as controls. US findings were correlated with disease activity parameters.*

Methods. *Twenty-six SLE patients were enrolled in the study, 25 RA patients and 15 HS were selected as controls. US was performed by two different experienced operators, using an Agilent-HP Image point Hx machine equipped with a 10 MHz linear transducer. Power Doppler (PD) was used to determine local synovial perfusion (PFR 700-1100 Hz; gain 60-65dB; low filter). Knee joints were examined bilaterally. US findings, expressed after consensus of the 2 operators, were correlated to clinical and serological parameters of disease activity. Statistical analysis was performed by the EPI-STAT program.*

Results. *In SLE, synovitis was found in 21 knees (40%), joint effusion in 12 (23%), synovial proliferation in 12 (23%), positive PD signal in 5 (10%) and gastrocnemius-semimembranosus bursitis in 5 (10%). No erosions were detected. There was a significant difference respect to RA for synovitis ($p < 0.003$), synovial proliferation ($p < 0.002$) and positive PD signal ($p < 0.01$). No correlation was found between US alterations and SLE disease activity parameters. In the HS group 1 patient showed mild synovial proliferation.*

Conclusion. *This is the first study that investigates knee joint involvement in SLE by ultrasonography. US was able to depict inflammatory alterations in the articular tissues of SLE patients, revealing some common characteristics with RA, except for the presence of erosions. We believe that US might be of help in the global evaluation of SLE patients with inflammatory joint involvement, providing relevant information to the clinician.*

Introduction

Lupus patients often complain about pain and swelling of joints, which may

be caused by inflammation located in different articular tissues, sometimes difficult to discern during clinical examination. Musculoskeletal ultrasound (US) allows a direct comparison between clinical and anatomical findings, providing useful information that might influence the therapeutic approach (1). The US characteristics of joint effusion, synovial proliferation and erosions have been extensively described (2). Furthermore, power Doppler (PD) has become an essential part of US examination in inflammatory rheumatic diseases, given its ability to detect increased haematic perfusion of the synovial membrane, which is considered an estimate of the level of local inflammation (3). The distinction between inflammatory and non-inflammatory synovial tissue may be important for therapeutic purposes (4).

We have previously described the alterations detected by US in the wrists of a group of patients with systemic lupus erythematosus (SLE) (5). Herein, we report the sonographic findings detected in the knees of the same patients, correlating US data to clinical and laboratory parameters of disease activity.

Patients and methods

Twenty-six SLE patients fulfilling the American College of Rheumatology (ACR) criteria for the disease were consecutively enrolled in the study from the in- and out-patient population of the Rheumatology Unit of the "Sapienza" University of Rome, Italy, as previously reported (5, 6). The study was conducted in compliance with the protocol, good clinical practices and the Declaration of Helsinki principles. The patients underwent a medical examination in which the following information was recorded: demographic data, past and recent medical history, disease duration (expressed in years from the first diagnosis), number of painful and swollen joints, current therapy and SLE Disease Activity Index (SLEDAI). On the same occasion, a blood sample was collected from each patient to calculate, in our laboratory, levels of erythrocyte sedimentation rate (ESR) (normal value < 15 mm/h) and C3 (normal value > 70 mg/dl),

Competing interests: none declared.

which were considered as laboratory disease activity parameters. C4 was not measured because of the potential bias due to genetic deficiencies (7). All data were later transferred to a computer database. The control groups consisted of 25 rheumatoid arthritis (RA) patients diagnosed according to the ACR criteria and consecutively recruited from the same in- and out-patient population and in the same period of SLE patients (8), and of 15 healthy subjects (HS) sex- and age-matched with SLE patients.

On the same day of the clinical assessment, patients and controls underwent an US evaluation of both knees. The exam was performed by two independent rheumatologists, experienced in musculoskeletal US (AO, AI), blinded to the subject diagnosis, clinical and laboratory data. Each examination was performed twice and separately by the two operators. Alterations were recorded in both longitudinal and transverse scans according to EULAR guidelines for musculoskeletal US in rheumatology (9). Power Doppler was applied in all the performed scans analysing the synovial tissue. The final results were expressed by consensus of the 2 operators analysing the stored images. An Agilent-HP Image point Hx, with a 10 MHz linear transducer, capacitated with PD (PFR 700-1100 Hz; gain 60-65 dB; low filter) was used.

The following parameters were evaluated by US according to literature data (3, 9-11): synovial proliferation, defined as the presence of hypertrophic and thickened synovial tissue in the

joint; positive power-Doppler, defined as a high colour persistence of the power-Doppler signal in the synovial tissue; joint effusion, defined as an intrarticular anechoic/hypoechoic fluid collection determining capsular distension; synovitis, defined as the presence of synovial proliferation and/or joint effusion with or without positive PD signal; bone erosions, defined as a cortical break or defect with an irregular floor, seen in both longitudinal and transverse scans; gastrocnemius-semimembranosus (GS) bursitis, defined as a fluid distension of the bursa with possible presence of local synovial proliferation. All data were recorded with the "absent-present" criterion.

Statistical analysis

Data analysis was performed using the EPISTAT program. Chi-square and Fisher's exact test were used to compare qualitative differences between the groups, while the student *t*-test was chosen to compare quantitative parameters in large samples of similar variance. The findings were expressed by mean and standard deviation from the mean. Values of $p < 0.05$ were considered to be statistically significant.

Results

Demographic and clinical data of SLE patients and controls are shown in Table I. For the majority of patients, treatment was based on corticosteroids \pm various different Disease Modifying Anti-Rheumatic Drugs (hydroxychloroquine, cyclosporine, methotrexate and

cyclophosphamide). As there was a great variability between patient treatments, we decided not to divide patients according to the different dosages and administered drugs.

Fifty-two knees of patients with SLE, 50 of patients with RA and 30 of HS were examined by US. The results are reported in Table II.

Twenty knees in SLE, 35 knees in RA and 1 knee in HS, showed at least one alteration on US scanning. US was able to detect inflammatory changes due to synovitis in intrarticular structures in 14 patients (37.8%) having a negative physical examination at the investigated joint. HS did not show any of the considered alterations, except for one patient with mild synovial proliferation and no symptoms at the joint. As expected, pathological findings suggestive of joint inflammation were more prevalent in RA than in SLE patients (Fig. 1). Signs of synovitis were detected in 21 knees (40%) of 15 SLE patients (58%), versus 31 knees (62%) of 18 RA patients (72%) ($p < 0.003$). The major alteration depicted in SLE was joint effusion, detected in 12 knees (23%) of 8 patients (31%); for this parameter, there was no statistical difference with RA. Synovial proliferation was present in 12 knees (23%) of 11 SLE patients (42%), while a positive PD signal was present in 5 knees (10%) of 4 SLE patients (15%). Both parameters were more prevalent in RA, with a significant statistical difference. GS bursitis was detected in 5 knees (10%) of 4 SLE patients (15%), showing no statistical difference with

Table I. Demographic and clinical data of SLE and RA patients.

Patients	SLE (26)	RA (25)	HS (15)	<i>p</i> -value*
Age (years), Mean \pm SD, (range)	40 \pm 10, (23-64)	51 \pm 15, (24-72)	40 \pm 12, (20-60)	0.005 RA vs. SLE, and HS
F/M, ratio	23/3, 8:1	22/3, 7:1	13/2, 6.5:1	NS
Disease duration (years), Mean \pm SD, (range)	15 \pm 7, (1-27)	13.4 \pm 13, (0-40)	–	NS
No. of total tender joints per patient Mean \pm SD, (range)	3.2 \pm 5, (0-21)	6.4 \pm 6, (0-17)	0.7 \pm 1.3, (0-4)	0,03 RA vs. SLE 0,001 RA vs. HS
No. of tender knee joints, percentage	15 (28.8%)	20 (40%)	0	NS
No. of swollen knee joints, percentage	1(1.9%)	9 (18%)	0	0,008 RA vs. SLE
ESR (mm/hr) Mean \pm SD, (range)	29 \pm 28, (4-101)	31 \pm 16, (8-66)	11 \pm 5, (2-16)	0,0003 RA vs. HS 0,04 SLE vs. HS
C3 values (mg/dl), Mean \pm SD, (range)	111 \pm 43, (38-173)	–	–	–
SLEDAI score Mean \pm SD	2 \pm 1.0	–	–	–

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HS: healthy subjects; SD: standard deviation; F: female; M: male; ESR: erythrocyte sedimentation rate; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; NS: not significant; *results not shown were not significant.

Table II. Comparison of ultrasonographic findings in SLE and RA.

Joints	US findings	SLE (52 knees)	RA (50 knees)	HS (30 knees)
Knee	Synovial proliferation	12	28*	1
	Positive PD signal	5	17**	0
	Joint effusion	12	16	0
	Erosions	0	9***	0
	GS bursitis	5	8	0

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HS: healthy subjects; PD: power Doppler; * $p < 0.002$, ** $p < 0.01$, *** $p < 0.001$.

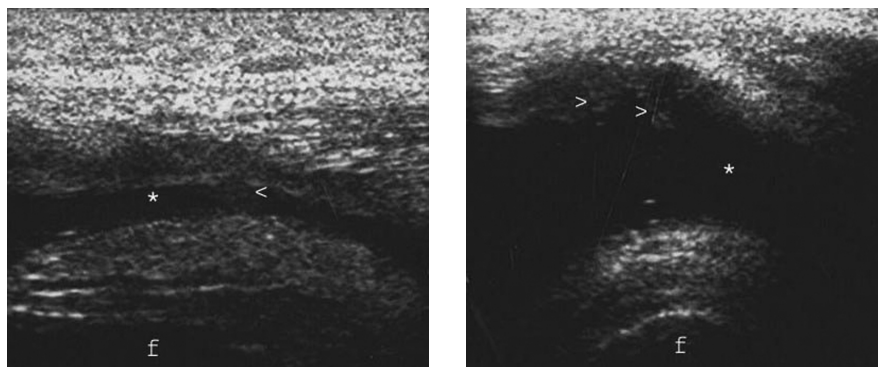


Fig. 1. US examination of the knee; Suprapatellar transverse scan. Left: systemic lupus erythematosus: mild joint effusion and synovial proliferation. Right: rheumatoid arthritis: severe joint effusion with evident signs of synovial proliferation. f: femur; *: joint effusion in the suprapatellar pouch; arrowhead: synovial proliferation.

RA. We did not find any erosions in the SLE group. Finally, US alterations were not significantly associated to disease activity parameters evaluated by ESR, C3, and SLEDAI.

Discussion

Extensive literature exists on the usefulness of US as a diagnostic and monitoring tool in several rheumatologic diseases, such as RA (12, 13), psoriatic arthritis (14, 15), and negative spondyloarthritis (16). Recently, an elegant review by Riente and colleagues provided an update on the available data concerning the application of US in connective tissue diseases (17). PD has added important information regarding inflammation in the synovial tissue, as highlighted by the work of Schmidt and colleagues, which confronted color Doppler findings with histological results in the knees of patients with RA and osteoarthritis (18).

To our knowledge, after our publication, only Wright and colleagues have studied SLE joint involvement, describing hand and wrist alterations by a pictorial assay

(19). A recent case report by Saketkoo and colleagues, has also been published on the less common deformities in SLE caused by Jaccoud’s arthropathy (20). Thus, new studies are needed to further elucidate joint involvement in SLE, considering that joints symptoms are one of the most frequent manifestations at onset, time of diagnosis and follow up, with a prevalence in up to 85% of the patients (21).

In our study, we examined the knees of 26 SLE patients by US and compared the results with those found in RA patients and HS. SLE showed an unexpected high prevalence of inflammatory pathological changes (synovitis in up to 40% of the examined joints), although US joint alterations were more frequent in RA for all the considered parameters, reflecting the greater articular involvement clinically observed in this group of patients. Interestingly, in SLE, joint effusion did not show a statistical difference in frequency with respect to RA, while synovial proliferation and positive PD varied significantly between the two diseases ($p < 0.002$ and $p < 0.01$ respectively). These findings

probably reflect a milder joint inflammatory process in SLE, given by the different pathophysiological pathways involved in the two diseases and confirmed by the clinical experience of a less severe and destructive pattern of joint involvement (22). Concordantly, the absence of erosions in our SLE patients supports the assertion by which the inflammatory process does not probably reach, in most cases, the necessary degree of aggressiveness needed to produce an interruption of the bone surface. A well-known exception is the clinical subset of Rhupus, which is characterized by an overlap between SLE and RA features (23).

We did not detect signs of synovial proliferation in the knees of patients in which there was a normal amount of synovial fluid. For this parameter there might be a bias due to the fact that in the absence of anechoic collection within the joint cavity, it is often more difficult to highlight the presence of synovial thickening. Interestingly, SLE and RA did not differ statistically for the presence of GS bursitis, which is a relatively common pathological finding in patients with painful knee by different causes (24). Since the aim of the study was to define inflammatory changes due to synovitis in intrarticular structures, several pathologic conditions were not recorded, such as the alterations of cartilage and bones due to osteoarthritis or orthopaedic diseases. Nevertheless, it could be important to document the presence of concomitant pathologies in this typology of patients, since they may influence some US findings such as the presence of joint effusion.

Interestingly, US was able to reveal inflammation in 37.8% knees of asymptomatic patients showing a negative physical examination. The concept that physical exam may underestimate knee inflammation has been previously reported (25).

The lack of correlation between systemic disease activity parameters (number of symptomatic joints, ESR, C3, SLEDAI) and US joint findings, stresses once again the importance of a global assessment of the patient, which may include US as an imaging technique

able to show disease activity at a local level. Pain and inflammation in a joint might not be accompanied by other important signs of systemic disease or by major organ involvement, thus SLEDAI might not be the appropriate tool to assess local disease activity, although the small sample size does not allow us to draw firm conclusions on this.

US has many advantages over other imaging techniques such as conventional radiography or MRI: it is safe, it has low costs of management, and provides repeatability and reproducibility, accompanied by a good patients' acceptance (26). The use of a multiplanar scanning technique offers the chance to visualize and confirm alterations in different planes and to explore broad areas of the joint. Assessment of international accepted guidelines and recent definition of ultrasonographic pathology have significantly improved the reliability of US, which is still greatly influenced by the operator experience and capability (27, 28).

New fields of research, such as the use of ultrasound contrast agents to better evaluate the degree of synovial membrane vascularization and three dimensional US, are probably going to empower the potential of this imaging tool in the study of rheumatic diseases (29). Moreover, US can be useful in monitoring the effects of therapy, suggesting a potential future role for this technique in treatment decision changes (30).

In conclusion, this is the first study that analyses knee joint alterations in SLE by US. In our lupus patients, US was able to depict inflammatory changes and to detect the presence of active synovitis by the use of power-Doppler. Even though we did not detect any erosion in our SLE patients, our overall results show common characteristics between the two diseases for many of the detected knee joint alterations, thus differential diagnosis between lupus and RA must not rely on US findings. In the expert hands of the rheumatologist, who knows the clinical patterns and pathogenesis of the disease that produce the different anatomic alterations, US represents a valuable tool, complementary rather than competitive with other imaging techniques. Thus,

we believe that US examination should be included in the global evaluation of SLE patients with articular symptoms, especially in those cases in which physical examination is not conclusive.

References

- FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al.*: Ultrasound imaging for the rheumatologist. *Clin Exp Rheumatol* 2006; 24: 1-5.
- FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al.*: Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25: 5-10.
- WALTHER M, HARMS H, KRENN V, RADKE S, FAEHNDRICH TP, GOHLKE F: Correlation of power Doppler Sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 331-8.
- FILIPPUCCI E, IAGNOCCO A, SALAFFI F, CERIONI A, VALESINI G, GRASSI W: Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. *Ann Rheum Dis* 2006; 65: 1433-7.
- IAGNOCCO A, OSSANDON A, COARI G *et al.*: Wrist joint involvement in systemic lupus erythematosus. An ultrasonographic study. *Clin Exp Rheumatol* 2004; 22: 621-4.
- TAN EM, COHEN AS, FRIES JF *et al.*: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
- YANG Y, CHUNG EK, ZHOU B *et al.*: The intricate role of complement component C4 in human systemic lupus erythematosus. *Curr Dir Autoimmun* 2004; 7: 98-132.
- ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
- BACKHAUS M, BURMESTER GR, GERBER T *et al.*: Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60: 641-9.
- WAKEFIELD RJ, GIBBON WW, CONAGHAN PG *et al.*: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000; 43: 2762-70.
- GRASSI W, FILIPPUCCI E, FARINAA, CERVINI C: Sonographic imaging of tendons. *Arthritis Rheum* 2000; 43: 969-76.
- HOVING JL, BUCHBINDER R, HALL S *et al.*: A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J Rheumatol* 2004; 31: 663-75.
- KARIM Z, WAKEFIELD RJ, QUINN M *et al.*: Validation and reproducibility of ultrasonography in the detection of synovitis in the knee: a comparison with arthroscopy and clinical examination. *Arthritis Rheum* 2004; 50: 387-94.
- WIELL C, SZKUDLAREK M, HASSELQUIST M *et al.*: Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis. *Arthritis Res Ther* 2007; 9: R119.
- FIOCCO U, FERRO F, VEZZÙ M *et al.*: Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. *Ann Rheum Dis* 2005; 64: 899-905.
- RIENTE L, DELLE SEDIE A, FILIPPUCCI E *et al.*: Ultrasound imaging for the rheumatologist IX. Ultrasound imaging in spondyloarthritis. *Clin Exp Rheumatol* 2007; 25: 349-53.
- RIENTE L, DELLE SEDIE A, FILIPPUCCI E *et al.*: Ultrasound imaging for the rheumatologist XIV. Ultrasound imaging in connective tissue diseases. *Clin Exp Rheumatol* 2008; 26: 230-3.
- SCHMIDT WA, VÖLKER L, ZACHER J, SCHLÄFKE M, RUHNKE M, GROMNICA-IHLE E: Colour Doppler ultrasonography to detect pannus in knee joint synovitis. *Clin Exp Rheumatol* 2000; 18: 439-44.
- WRIGHT S, FILIPPUCCI E, GRASSI W, GREY A, BELL A: Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. *Lupus* 2006; 15: 501-6.
- SAKETKOO LA, QUINET R: Revisiting Jacoud arthropathy as an ultrasound diagnosed erosive arthropathy in systemic lupus erythematosus. *J Clin Rheumatol* 2007; 13: 322-7.
- SWAAK AJ, VAN DEN BRINK HG, SMEENK RJ *et al.*: Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. *Rheumatology* 1999; 38: 953-8.
- DUBOIS EL, TUFFANELLI DL: Clinical manifestations of systemic lupus erythematosus. Computer analysis of 520 cases. *JAMA* 1964; 190: 104-11.
- FERNANDEZA A, QUINTANA G, MATTESON EL *et al.*: Lupus arthropathy: historical evolution from deforming arthritis to rhupus. *Clin Rheumatol* 2004; 23: 523-6.
- LABROPOULOS N, SHIFRIN DA, PAXINOS O: New insights into the development of popliteal cysts. *Br J Surg* 2004; 91: 1313-8.
- KANE D, BALINT PV, STURROCK RD: Ultrasonography is superior to clinical examination in the detection and localization of knee joint effusion in rheumatoid arthritis. *J Rheumatol* 2003; 30: 966-71.
- OSTERGAARD M, SZKUDLAREK M: Imaging in rheumatoid arthritis-why MRI and ultrasonography can no longer be ignored. *Scand J Rheumatol* 2003; 32: 63-73.
- SCHMIDT WA, SCHMIDT H, SCHICKE B, GROMNICA-IHLE E: Standard reference values for musculoskeletal ultrasonography. *Ann Rheum Dis* 2004; 63: 988-94.
- WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al.*: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32:2485-7.
- FILIPPUCCI E, MEENAGH G, EPIS O *et al.*: Ultrasound imaging for the rheumatologist. XIII. New trends. Three-dimensional ultrasonography. *Clin Exp Rheumatol* 2008; 26: 1-4.
- IAGNOCCO A, FILIPPUCCI E, PERELLA C *et al.*: Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. *J Rheumatol* 2008; 35: 35-40.