The Role of Structured Musculoskeletal Ultrasound in the Early Diagnosis of Rheumatoid Arthritis and Psoriatic Arthritis Patients: Correlation with Clinical Disease Activity Scores

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Abstract

Background: Currently, musculoskeletal ultrasound (MSUS) holds significance in predicting the progression of psoriatic (PsA) and rheumatoid arthritis (RA) in individuals at risk. The lack of diagnostic biomarkers for PsA may lead to delayed diagnosis and the development of clinical and radiological damage.

Objectives: To assess the role of MSUS in early diagnosis of RA and PsA: correlation with clinical disease activity scores.

Patients and methods: Twenty patients with RA fulfilling the criteria of EULAR/ACR 2010, twenty patients with PsA fulfilling the criteria of CASPAR classification and twenty age and sex matched healthy persons as control. Musculoskeletal examination, complete blood count, liver function, renal function, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-nuclear antibody, anti-citrullinated protein antibody, clinical, simplified activity scores, DAS-28ESR, DAS-28CRP, USDAS28 scores, and plain x-ray both hands.

Results: In RA patients, 12 (20.0%); 11 (55.0%) PsA patients were positive for bone erosions; 4 (20.0%) patients with RA; 8 (40.0%) patients with PsA had synovitis; 13 (65.0%) RA patients, 15 (75.0%) PsA patients were clinically active; 6 (30.0%) patients with RA; 9 (45.0%) patients with PsA demonstrated significant disease activity using PDUS ($p=0.002$). There was a significant correlation between DAS-28ESR ($p=0.001$), DAS28-CRP($P=0.001$), USDAS-28ESR ($p<0.001$), USDAS-28CRP ($p<0.001$) and disease activity scores. MSUS shows flexor tendon tenosynovitis in RA and characteristic findings of enthesitis in PsA patients.

Conclusion: MSUS in rheumatoid arthritis can detect early inflammation. In PsA, it complements clinical examination, adding sensitivity and specificity in identifying inflammatory and structural lesions, thus improving qualitative assessment.

Keywords: Ultrasonography; Rheumatoid arthritis; Psoriatic arthritis.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic connective tissue disease characterized by symmetrical involvement of multiple joints and extra-articular symptoms **(Hum et al., 2023; Gouze et al., 2024).** Accurate assessment of disease activity is of paramount importance for effective treatment with judicious use of medication that might otherwise impair functional capacity and lead to radiographic progression **(Nell et al., 2004; Finckh et al., 2006; Kyburz et al., 2011; Pascu et al., 2023).**

Disease activity was measured using composite scores; in these scores, clinical assessments are subjective, with a very high number of tender joints, small changes in ESR disproportionately affect scores at the lower end of the reference range, and variability in these scores has been documented. Joint count is an indirect assessment of joint inflammation and can hardly be considered an objective measure **(Gardiner et al., 2005).** The 2016 EULAR guideline for early arthritis recommends that arthritis in the joint be confirmed by (US) **(Combe et al., 2017).** Conventional radiographic parameters initially remained the mainstay of RA patient evaluation because they showed late signs of disease activity, such as cartilage or bone destruction. US and magnetic resonance imaging (MRI) are now preferred in RA and PsA to assess earlier symptoms **(Wakefield et al., 2000; Sommer et al., 2005 ; Botar et al., 2010).**

In individuals at risk," positive autoantibodies with symptoms but no synovitis" US showed promising predictive value for the development of clinical arthritis **(Smolen et al., 2016).** Grayscale ultrasonography (GSUS) is more sensitive than clinical examination for the detection of synovitis and conventional radiography for the detection of bone erosions **(Wakefield et al., 2004; Baillet et al., 2011; Smerilli et al., 2023).** Additionally, ultrasound correlates better with histology and MRI in RA compared to clinical examination **(Hoving et al., 2004; Matteo et al., 2024).** Ultrasound scoring systems are essential to distinguish between active and inactive disease. The Ultrasound Disease Activity Score (USDAS) is the first attempt to create an index that does not rely on a clinical score of swollen and tender joints **(Damjanov et al., 2012).** According to the 2010 ACR/ EULAR criteria; individuals who are seronegative must show more clinical signs before a diagnosis of RA compared to those who are seropositive and may need a delayed diagnosis **(Verschueren et al., 2015; Nordberg et al., 2017).**

Early polyarticular PsA is often the predominant differential diagnosis of seronegative early RA. Its diagnosis can be challenging when dealing with mild or unusual skin or nail symptoms **(Raychaudhuri., 2023).** This imaging approach can successfully identify pathology and basic symptoms such as pain, stiffness and limited range of motion, US can be used to identify structural and inflammatory lesions, monitor disease progression, and detect early erosions, enthesitis, and subclinical synovitis **(Ostergaard et al., 2019).** The finding of enthesitis of the extensor tendon attachment in the distal interphalangeal (DIP) joint, is a typical sign of PsA, therefore US can distinguish RA from PsA **(Tan et al., 2007).**

Our study aims to assess the role of musculoskeletal ultrasound in early diagnosis of patients with RA and PsA: correlation with clinical disease activity scores.

Patients and methods

Sample size calculation

To determine a sufficient sample size, one can apply the following formula:

$$n = \frac{z^2 p (1-P)}{d^2}$$

where;

n is the sample study.

z is standard normal variant (at 5% type1 error (p>0.05))= 1.96.

p is expected proportion in population based on previous studies or pilot studies= 3%

d is absolute error or precision= 0.05.

Type of the study: Prospective observational study.

Setting: The study was conducted on 60 patients aged above 16 years old divided into 3 groups, RA group (N=20), PsA group (N=20), and control group (N=20), recruited from the Rheumatology, PsA Clinics of Alexandria Main University Hospital, and from Internal Medicine department.

Ethical consideration: An informed written consent from all patients was obtained according to the declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Alexandria University (EC serial number: 0306836) (IRB NO: 00012098-FWA NO: 00018699).

Inclusion criteria: Twenty patients with RA met the EULAR/ACR 2010 classification criteria for RA **(Aletaha et al., 2010).** Twenty patients with PsA fulfilled the CASPAR classification criteria **(Taylor et al., 2006).**Twenty "age and sex" matched healthy persons as control.

Exclusion criteria: Current autoimmune disease, cancer, active hepatitis B,C infection, systemic vasculitis, uncontrolled diabetes mellitus, history of malignancy, and active local or systemic infection.

Methods

Clinical evaluation: Complete physical examination with an emphasis on the musculoskeletal system. In addition, each patient was thoroughly questioned about age of onset, symptoms, disease course and duration, recent and previous medications, comorbidities, extra-articular manifestations, and family history for autoimmune diseases.

Laboratory examination: CBC **(Brain 2010),** liver function **(Johnston et al., 1999),** renal function **(Tippins et al., 2009),** ESR 1st hour **(Gabay et al., 1999),** CRP **(Lant et al., 2000),** RF **(Hermann et al., 1996),** ANA **(Satoh et al., 2007),** Anti-CCP Abs **(Montes et al., 2016),** and functional QoL assessment using HAQ score **(Thorsen et al., 2016**) to all patients and healthy controls.

Measures for disease activity: Activity scores; CDAI **(VanGestel et al., 1998),** SDAI **(Smolen et al ., 2003),** DAS28-ESR **(Van der Heijde et al ., 1990),** " DAS28-CRP " **(Hensor et al., 2010),** swollen joint count (SJC), tender joint count (TJC), patient global assessment (PGA), and CRP score with remission (≤ 2.6), low disease activity (>2.6 ≤ 3.2), moderate disease activity (>3.2 ≤ 5.1), and high disease activity (>5.1). Plain x-ray of both hands in patients with RA and PsA.

Ultrasound examination: The sonographer was blinded to clinical data, disease symptoms, and involvement of the distal interphalangeal joint. The device used for ultrasound examination was Esa ote MyLabX5 (Fishers, IN, USA)**.**The

study used a high frequency linear probe operating at a frequency range of 6-19 MHz, accompanied by a low-pass filter. PDUS settings have been adjusted to optimize low flow detection. USDAS28-ESR**,** USDAS28-CRP **(kotz et al., 2006)** in which SJC and TJC scores were replaced. Specific musculoskeletal manifestations of PsA including distal interphalangeal joints, extensor tendon attachment, synovitis, and enthesitis were investigated.

Statistical analysis

Data were entered into a computer system and subsequently analyzed using the IBM SPSS version 20.0 software package (Armonk,NY: IBM Corp).Normality was tested using Kolmogorov-Smirnov test. Quantitative data were analysed using range minimum, maximum, mean, and standard deviation, median, and interquartile range (IQR). Qualitative data were evaluated using Chi-square test. To compare between groups, an independent t test was used. Pooled results were evaluated for statistical significance at the 5% significance level. Values <0.05 were considered statistically significant.

Results

Distribution of the two studied groups according to demographics, and routine laboratory examination; in the RA group 8 (40.0%) males and 12 (60.0%) females; in the PsA group 5 (25.0%) males and 15 (75.0%) females; while in the control group 15 (75.0%) females and 5 (25.0%) males, (**Table.1).**

Table 1. Demographics and routine laboratory examination in the studied groups

Parameter	**RA (n=20)**		**PsA (n=20)**		**Controls (n=20)**		**T**	**P-value**
Sex.	**No**	**%**	**No**	**%**	**No**	**%**		
Male .	8	40.0	5	25.0	5	25.0	X^2 =0.053	0.818
Female .	12	60.0	15	75.0	15	75.0		
Age (years).								
min-max.	33.0 - 55.0		17.0 - 46.0		19.0 - 50		t =0.186	0.853
Mean ± SD.	38.14 ± 2.3		34.03 ±10.33		32.2 ± 7.61			
Disease Duration (months)								
Min-Max.	5.0 - 21.0		5.0 - 24.0				MW=0.583	0.560
Median (IQR)	12.5(5.0-21.0)		11.0(5.0-24.0)					
Hb (g/dl)								
Min-Max.	8.90 - 13.90		8.50 - 12.80				t =1.700	0.097
Mean ± SD.	11.61 ± 0.93		11.05 ± 1.14					
WBC total *10 ^{3}/µL								
Min-Max.	5.70 - 12.0		4.0 - 16.0				t =0.840	0.406
Mean ± SD.	8.71 ± 2.57		9.46 ± 3.09					
Platelets *10 ^{3}/ µL								
min-max.	160.0 - 340.0		134.0 - 380.0				t =0.112	0.911
mean ± SD.	251.45 ±72.15		248.90 ±71.61					

Blood Urea (mg/dl)					
min-max.	25.0 - 56.0	20.0 - 49.0		t =0.263	0.794
mean ± SD.	29.55 ± 10.18	30.45 ± 11.82			
Creatinine (mg/dl)					
min-max.	0.55 - 1.50	0.46 - 1.52		t =0.514	0.610
mean ± SD.	1.04 ± 0.22	1.0 ± 0.23			

χ2: chi-square test; t: student t-test; MW: mann-whitney test; SD: standard deviation IQR:interquartile range

Distribution of the studied groups according to DAS-28 score, HAQ score, BMI, SDAI, and CDAI, the mean SDAI was 7.88 ± 3.13 in RA group; 10.14 ± 2.73 in the PsA group; while SDAI was 6.17 ± 2.93 in the control group; mean CDAI in RA group was 6.80 ± 3.47; while in the PsA group it was 9.4 ± 2.9 and 3.18 ±1.32 in the control group, **(Table.2).**

Table 2.DAS-28 Score, HAQ Score, BMI, SDAI, and CDAI in the studied groups

Parameter	**RA (n=20)**		**PsA (n=20)**		**Controls (n=20)**		**T**	**P-value**
DAS28 Score								
Min- Max Mean ± SD	2.10 - 5.50 3-51 ± 0.85		2.60- 5.50 3.31 ± 0.78		2.40 -3.50 2.49 ± 0.74		t = 0.563	t = 0.563
HAQ Score								
Min - Max. Mean ± SD	0.30 – 2.40 1.37 ± 0.54		0.55 – 2.40 1.34 ± 0.50		0.20 - 2.10 1.29 ± 0.50		t = 0.302	0.765
BMI (kg/m2)								
normal	5	25.0 %	3	15.0 %	2	10.0%	X^2 =1.236	^{FE}p =0.648
overweight	6	30.0 %	7	35.0 %	9	45.0%		
obese class I	8	40.0 %	5	25.0 %	6	30.0%		
class II	1	5.0%	5	25.0 %	3	15.0%		
class III	0	0.00	0	0.00	0	0.00		
SDAI								
mean ± SD.	7.68 ± 3.13		10.41 ± 3.72		6.17 ± 2.93		t = 0.346	0.149
CDAI								
mean ± SD.	6.80 ± 3.47		9.4 ± 2.93		3.18 ± 1.32		t = 0.254	0.109

χ2: chi-square test; t: student t-test; FE fisher exact test; SD: standard deviation; DAS-28: disease activity score of 28 joints ; HAQ: health assessment questionnaire; SDAI: simplified disease activity index; CDAI: clinical disease activity index.

Comparison between the studied groups according to the level of ESR, CRP, RF and Anti-CCP Abs; In RA group, the anti-CCP Abs ranged from

18.60 -337.0 (IU/ml) with a mean of 110.67 ± 90.28; in the PsA group ranged from 2.0 -9.0 with a mean of 4.08 ±1.75 (IU/ml); while in the control group; Anti-CCP Abs ranged from 2.00 -10.0 with a mean **of** 4.48 ± 2.24 (IU/ml), **(Table.3).**

Table 3. The level of ESR, CRP, RF, and Anti-CCP Abs in the studied groups.

Parameter	RA (n=20)	PsA (n=20)	Controls (n=20)	T	P-value
ESR 1st hr (mm/hr).					
Min-Max.	2.0-35.0	4.0 - 31.0	3.0- 45.0		
Mean ± SD.	17.12 ± 9.48	15.55 ± 8.65	19.60 ±10.32	0.879	0.385
CRP (mg/dl)					
Min-Max.	2.0 - 25.0	2.0 - 22.0	2.0 - 26.0		
median (IQR)	8.0	5.0	8.50	MW=0.800	0.423
RF (IU/ml)					
Min-Max.	5.0 - 24.0	7.0 - 28.0	6.0 - 20.0		
Mean ± SD .	10.34 ± 2.65	9.35 ± 2.05	10.50 ± 4.25	0.128	0.899
Anti-CCP (IU/ml)					
min-max.	18.60 - 337.0	2.0 - 9.0	2.0 - 10.0		
mean ± SD .	110.67 ± 90.28	4.08 ± 1.75	4.48 ± 2.24	0.356	0.001

χ2:chi-square test; t :student t-test; MW: mann-whitney test ; SD: standard deviation; RF :rheumatoid factor ; Anti-CCP: citrullinated protein antibody.

Comparison between the studied groups according to radiographic findings, US, and PDUS, 4 (20.0%) RA patients had synovitis, 16 (80.0%) had hyperaemia, 8 (40.0%) PsA patients had synovitis, 12 (60.0%) had hyperaemia by US and were statistically significant (p<0.001); In RA group 13 (65.0%) were clinically active, 6 (30.0%) were active by PDUS and statistically significant (p=0.002); and 4 (20.0%) were active by PDUS; in PsA group 15 (75.0%) were clinically active, 9 (45.0%) were active by PDUS; and 3 (15.0%) were PDUS active. In the RA group, the mean value of USDAS28-ESR was 4.81 ± 1.02, while the mean USDAS28-CRP was 4.34 ± 0.99; in the PsA group, the mean value of USDAS-28ESR was 3.59 ± 0.12, while the mean value of USDAS-28CRP was 3.63 ± 0.45; in the control group, the mean USDAS-28 ESR was 3.66 ± 0.09 (p<0.001), the mean USDAS-28 CRP was 3.00 ± 0.84 (p<0.001) and was statistically significant, **(Table.4).**

Table 4.X-ray, US, and PDUS in the studied groups

Parameters	RA (n=20)		PsA (n=20)		Controls (n=20)		T	P-value
X-ray (erosion)	**No**	**%**	**No**	**%**	**No**	**%**		
Positive	12	60.0	11	55.0	0	0.00	$X^2 = 2.807$	0.174
Negative	8	40.0	9	45.0	0	0.00		

MSUS								
Positive synovitis	4	20.0	8	40.0	0	0.00	$X^2 = 3.892$	< 0.001
Positive hyperaemia	16	80.0	12	60.0	0	0.00		
Disease Activity								
Clinically active	13	65.0	15	75.0	0	0.00	$X^2 = 1.758$	0.002
PDUS active	6	30.0	9	45.0	0	0.00		
Clinically inactive	7	35.0	5	25.0	0	0.00	$X^2 = 0.382$	0.064
PDUS active	4	20.0	3	15.0	0	0.00		
	Mean ± SD.		**Mean ± SD.**		**Mean ± SD.**		t = 9.410	0.001
DAS28-ESR	4.02 ± 1.1		3.95 ± 0.72		2.71 ± 0.68			
DAS28-CRP	3.56 ± 1.1		3.45 ± 0.51		2.29 ± 0.75		t = 0.960	0.001
US DAS28-ESR	4.81 ± 1.02		3.59 ± 0.12		3.66 ± 0.09		$X^2 = 3.772$	< 0.001
US DAS28-CRP	4.34 ± 0.99		3.63 ± 0.45		3.00 ± 0.84		$X^2 = 2.903$	< 0.001

χ2 chi-square test; t student t-test; SD standard deviation; PDUS power doppler US.

US of the flexor tendon of the finger shows thickening of the fluid and synovial fluid within the tendon sheath. A strong doppler signal is also observed within the tendon sheath, **(Fig.1).** US view through the flexor tendon of the finger shows thickening of the fluid and synovial fluid within the tendon sheath, **(Fig.2).**

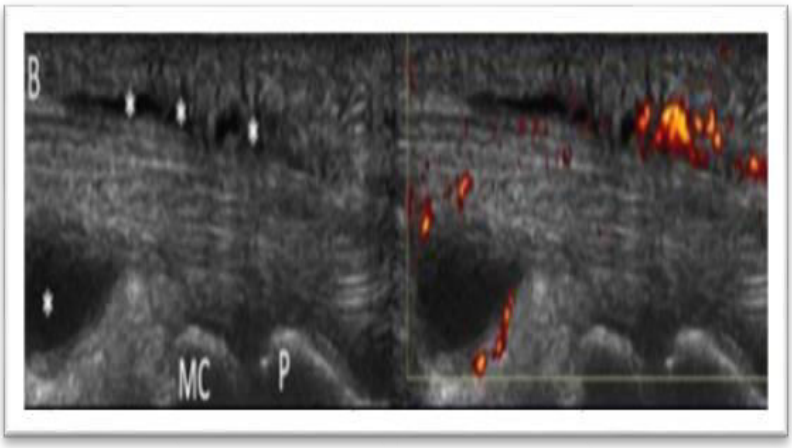

Fig1.Characteristic ultrasound findings of early psoriatic arthritis ; longitudinal view through the flexor tendon of the digit shows thickening of the fluid and synovium fluid inside the tendon sheath. A strong Doppler signal is also observed within the tendon sheath.

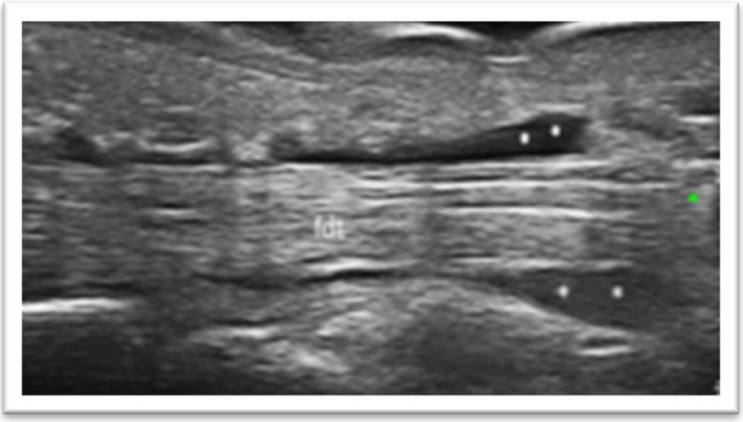

Fig2. Flexor tendon tenosynovitis in early rheumatoid arthritis. Longitudinal scan of the flexor tendons of the finger shows the presence of synovial hypertrophy and synovial effusion in the sheath of the synovial tendon.

US scan of the flexor tendons of the finger shows the presence of synovial hypertrophy and synovial effusion in the sheath of the synovial tendon,(**Fig3a).**Infrapatellar ultrasound of the knee shows signs of infrapatellar enthesitis, including attachment thickening, hypoechoic appearance, loss of fibrous structure, and cortical irregularity seen on the power Doppler signal in the attachment,(**Fig3b).**Grayscale image of the right elbow shows the bursal muscle attachment site, showing thickening of the attachment, hypoechoic appearance, loss of fibrous structure, cortical irregularity, and enthesitis, (**Fig3c).**Grayscale scan of the left patellar fascia shows a thickness of 5.9 mm, hypoechoicity, loss of normal fibrillar pattern,and enthesitis,(**Fig3d).**

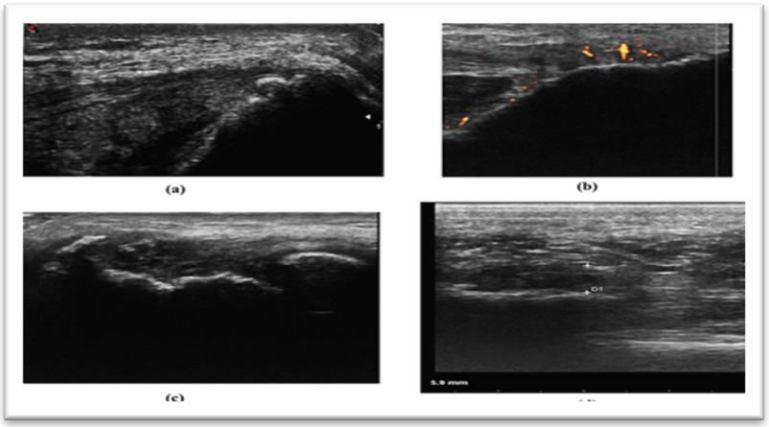

Fig3.Characteristic sonographic findings of psoriatic enthesitis. (**a**).longitudinal suprapatellar ultrasound of the knee (grayscale)reveals a loss of fibrous structure at the superior pole of the patella, characterized by a hypoechoic appearance and signs of enthesitis at the quadriceps tendon insertion.(**b**).longitudinal infrapatellar ultrasound of the knee shows evidence of infrapatellar enthesitis, including thickening, hypoechoic appearance,loss of fibrous structure, and cortical irregularity observed on the power

doppler signal.(**c**).longitudinal grayscale image of the right elbow displays the bursal muscle attachment site, thickening of the attachment, hypoechoic appearance, loss of fibrous structure, cortical irregularity, and enthesitis. (**d**).longitudinal grayscale scan of the left patellar fascia showing a thickness of 5.9 mm, hypoechoicity, loss of the normal fibrillar pattern and enthesitis.

Discussion

In this study the aim was to assess the role of musculoskeletal ultrasound in early diagnosis of RA, PsA: correlation with clinical disease activity scores; 20 patients with RA fulfilling the criteria of EULAR/ACR 2010, 20 patients with PsA fulfilling the CASPAR classification criteria, 20 healthy "age and sex" matched as controls were included in the study.

Our results showed that 4 (20.0%) RA patients had synovitis, 16 (80.0%) had hyperaemia, 8 (40.0%) PsA patients had synovitis, 12 (60.0%) had hyperaemia by US and were statistically significant ($p<0.001$); In RA group 13 (65.0%) were clinically active, 6 (30.0%) were active by PDUS and statistically significant ($p=0.002$); and 4 (20.0%) were active by PDUS; in PsA group 15 (75.0%) were clinically active, 9 (45.0%) were active by PDUS; and 3 (15.0%) were PDUS active. In the RA group, the mean value of USDAS28-ESR was 4.81 ± 1.02, while the mean USDAS28-CRP was 4.34 ± 0.99; in the PsA group, the mean value of USDAS-28ESR was 3.59 ± 0.12, while the mean value of USDAS-28CRP was 3.63 ± 0.45; in the control group, the mean USDAS-28 ESR was 3.66 ± 0.09 ($p<0.001$), the mean USDAS-28 CRP was 3.00 ± 0.84 ($p<0.001$) and was statistically significant.

Although RA and PsA share some similar symptoms, their underlying causes and treatment responses are distinct, with substantially different clinical outcomes. Utilizing advanced laboratory and imaging techniques can be beneficial in differentiating RA and PsA.Once an accurate diagnosis has been made, appropriate therapy should be used to provide maximal improvements based on patient and disease characteristics.

Because of the unique presentation of enthesitis of the proximal interphalangeal joint and the finger extensor tendons, para-tendinitis may help differentiate early PsA from RA Clinical evaluation of PsA is limited in detail by pathologic assessment. US findings can be semi-quantitatively evaluated on grayscale (GS) and power doppler (PD). Synovitis is often present in RA and PsA with a predilection for tendon and entheseal lesions **(Tan et al ., 2016).** The presence of flexor tenosynovitis and insertional enthesopathy of the flexor tendons is common in psoriatic arthritis. **(Mankia et al., 2016)** compared US findings in patients with psoriatic arthritis and RA; findings of synovitis and tenosynovitis were observed in both psoriatic arthritis and RA, and extra-synovial changes were specific to psoriatic arthritis (enthesitis, capsularis, juxta-articular periosteal reaction, deep enthesopathy, and distal flexor tendon attachment), phalanx thickening and subcutaneous soft tissue thickening of the nails or entire digit. **(Gutierrez et al., 2011)** compared images hand flexor tendons in PsA patients and RA patients in the US, identifying the following symptoms specific to PsA; soft tissue swelling in the periarticular area with signs of PD (30%); PsA flexor tendon enthesopathy, including new bone formation at the

insertion site, compared to none in RA (65% in PsA vs.15% in PsA), and tenosynovitis (38% in PsA vs.13% in RA).**Tang et al. (2018)** found extrasynovial changes in 84% of PsA fingers compared to none in RA, and extensor tendinitis was found in 65.8% of metacarpophalangeal joints in PsA compared to RA. **(Zabotti et al., 2018)** demonstrated that patients with early PsA had more symptoms and frequent extrasynovial and synovio-entheseal complex involvement on US compared to early RA. **(Ruta et al., 2017)** found that joint inflammation was present in 15 of 240 fingers (6.3%) in 8 patients with PsA (26.7%) and in 1 of 240 fingers (0.4%) of 1 patient with RA(3.3%), inflammation may be characteristic in PsA compared to RA patients . Presence of RA-related synovitis and bony features of PsA compared to RA, erosions are an important part of these criteria **(Horton et al., 2017).** Both these ACR/EULAR criteria and the EULAR guidelines for the management of early RA recognize the potential value of additional imaging; other than X-ray such as US to confirm the presence of inflammation. **(Marchesoni et al., 2012).**

In the context of a treat-to-target (T2T) strategy, early identification of patients with undifferentiated arthritis who will eventually develop RA is critical to guide early treatment.

Limitations of the study: MSUS was not compared with other imaging modalities such as MRI.Despite this, scanning in the US still has huge advantages when it comes to screening. Another limitations with MSUS is that "abnormalities" detected in healthy persons and the presence of disease comorbidities, leading to questioning the clinical significance of the use of US in detecting subclinical disease.

Conclusion

Musculoskeletal US in RA can reveal early inflammation. In PsA, it complements clinical examination, adds sensitivity and specificity to the affected area and improves qualitative assessment. There are discrepancies between clinical and ultrasound evaluation that require further study.

Conflicts of Interest: No conflicts of interest.

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