Comprehensive evaluation of finger flexor tendon entheseal soft tissue and bone changes by ultrasound can differentiate psoriatic arthritis and rheumatoid arthritis

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Abstract

Objective

To determine whether a detailed sonographic evaluation of the hand flexor tendon compartment could help differentiate between psoriatic arthritis (PsA) and rheumatoid arthritis (RA).

Methods

Thirty-seven patients with PsA, 47 with RA and 10 healthy controls (HC) had flexor tendon (FT) compartment imaging of the dominant hand 2nd to 4th tendons using grey scale (GS) and power Doppler (PD) ultrasound (US) with evaluation for tenosynovitis, peri-tendinous lesions, soft tissue oedema and bony changes at FT insertions. 24/37 PsA and 19/47 RA cases had morning stiffness and 19/37 PsA and 10/47 RA had swollen and/or tender fingers.

Results

Tenosynovitis was more common in PsA (25/37) despite higher DAS28 scores in RA (25/37 versus 10/45; p<0.001). Peri-tendinous dermal soft tissue oedema with associated PD signal was evident in one third of PsA patients but in no RA patients (p=0.003). Flexor tendon enthesopathy including new bone formation at the insertional site was significantly more common in PsA (p=0.001). Considering a total inflammatory score per patient summing up the three modifications of the flexor tendon (tenosynovitis, peri-tendinous oedema and insertional enthesophytes) the difference between PsA and RA remained statistically significant (p<0.001)

Conclusion

Our study adds to the growing body of literature that high resolution US of the hand FT compartment may help differentiate between RA and PsA, which needs assessment in the diagnostic setting.

Key words
rheumatoid arthritis, psoriatic arthritis, tenosynovitis, oedema, flexor, ultrasound

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Introduction

There is a great interest in using imaging to facilitate in differentiation between rheumatoid arthritis (RA), especially seronegative RA, and psoriatic arthritis (PsA). Synovial joint and tenosynovial inflammation are seen in both conditions. Both magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MKUS) including that of the knees and metacarpo-phalangeal (MCP) joints have shown a greater degree of enthesitis and extra-synovial involvement in PsA (1-4).

The most characteristic finger joints lesion in PsA is dactylitis where florid flexor tenosynovitis on imaging was reported (5), but flexor tenosynovitis was also reported in RA.

A pivotal MKUS study using grey scale (GS) showed significant differences in the flexor tendon compartment in chronic PsA compared to RA with entheseal new bone formation and "pseudotenosynovitis" or peri-tendinous oedema being the more specific lesions of PsA (6). However, this study evaluated only 25 fingers per group, had limited utilisation of PD techniques, did not have a healthy control group and the micro-anatomical basis for these soft tissues lesions was poorly defined (6).

In recent years there has been an appreciation of "mini-enthesitis" in the small entheses of the hands in PsA. For example, Zabotti *et al*. have shown that MSKUS detectable peritendon extensor digitorum tendon inflammation and central slip enthesitis at the proximal interpalangeal joints (PIP) is specific of early PsA and is helpful for differentiation from early RA (7). A recent MRI study suggests that entheseal abnormalities at the accessory pulley entheseal network of entheses may be a fundamental lesion in PsA dactylitis (8). Gutierrez *et al*. described flexor tenosynovitis, synovitis and soft tissue oedema as typical MKUS features of PsA dactylitis fingers (9).

The aim of the present study was to undertake a comprehensive US evaluation of flexor tendon findings in PsA and RA with an emphasis on entheseal and associated peri-tendinous lesions as differentiators between both conditions. We revisited the use of MSKUS in a larger group of patients than any other previous studies including healthy controls and scanned multiple joints to ascertain whether the pattern of entheseal related tenosynovitis in PsA could be useful in the differentiation from RA.

Material and methods

Patients

The study was approved by the local Ethics Committee and was conducted in conformity with the Declaration of Helsinki and with the guidelines for good clinical practice. A written informed consent was obtained from all participants. Thirty-seven consecutive cases of PsA and forty-seven cases of RA were enrolled by two Italian Rheumatology Centres (Negrar-Verona and Reggio Emilia, Italy)

All participants satisfied either the 2010 ACR/EULAR criteria for RA or the CASPAR criteria for PsA (10,11) A group of 10 healthy control (HC) patients were also evaluated. Clinical assessment was carried out before US examination by one expert rheumatologist for each centre (AM, DC), who recorded tenderness and swelling of the finger joints, the presence of tenosynovitis or dactylitis.

All selected cases had a history of hand involvement and had low to moderate disease activity at the time of US examination (Table I). The patient groups were matched for diseases duration, age and BMI. The majority of them were under therapy with conventional DMARDs and none were treated with biological drugs.

Ultrasound protocol

The 2nd to 4th digit of the dominant hand were scanned on the palmar side by two rheumatologists (IT, PM), both experts in MSKUS examination, blinded to the clinical and laboratory data. Intraobserver and inter-observer reliabilities for flexor tenosynovitis, peritendinous oedema and flexor tendon enthesophytes were tested before patients enrolment using static images of 20 patients (10 PsA and 10 RA patients).

All ultrasound scans were performed using a MyLab Twice US machine (Esaote, Genova, Italy) equipped with a 6–18 MHz linear transducer. The US

grey-scale (GS) imaging parameters were optimised for maximal image resolution and power Doppler (PD) settings were standardised with a pulse repetition frequency of 750 Hz, 3 for wall filter, 4 for persistence and colour gain between 45-55%. The pathological US findings were graded in GS and PD with 0 when absent and 1 if present.

The following changes were recorded: tenosynovitis, pseudotenosynovitis (peri-tendinous oedema) and enthesophytes of the flexor tendon insertion at the distal phalanx. According with OMERACT definition, tenosynovitis was defined in grey scale as abnormal anechoic and/or hypoechoic tendon sheath widening which could be related to the presence of fluid collection and/or tenosynovial hypertrophy (12). The presence of power Doppler (PD) was defined as the presence of vascular signal within the tendon sheath (12). Peritendinous oedema was defined as a diffuse hypo/isoechoic thickening of the peritendinous soft tissues around flexor tendon with vascular signal at PD examination (pseudotenosynovitis) (6).

Enthesophytes of the flexor tendon insertion were defined using OMERACT definition (*i.e.* calcification or hyperechoic foci seen in two perpendicular planes, detected at the tendon insertion into the bone) (13). Ten HCs were also scanned in order to verify the prevalence of the same elementary lesions.

Statistical analysis

The reliability was tested on 20 static images for each elementary lesion (enthesophytes, tenosynovitis and peritendinous oedema) collected from 10 consecutive patients with PsA and 10 with RA from the arthritis clinic of Sacro Cuore Hospital (Negrar, Verona) and then assessed by Cohen's κ. Interobserver reliability was studied by calculating the mean κ on all pairs (*i.e.* Light's κ) (14). Kappa coefficients were interpreted according to Landis and Koch (15).

Descriptive statistics, reported as mean ± standard deviation, were used to summarise the data

Continuous variables were compared using *t*-test or non-parametric tests when appropriate. Non continuous variables were compared using Chi-square test p-value <0.05 was considered as significant. Statistical analysis was performed using SPSS v. 22.

Table I. Clinical characteristics of the patients and HCs.

	PsA (37)	RA (45)	HCs (10)
Sex distribuition (M/F)	15/22	13/32	4/6
Age in years (mean ± SD)	59.2± 9.7	60± 11.7	56 ±17.3
Duration of symptoms, years (mean ± SD)	4.8± 3.3	5.6± 4.1	
DAS28 CRP (mean ± SD)	2.9± 0.6	3.2± 0.9	
Swollen fingers of dominant hand at time of scan (n, %)			
II finger	2 (5)	0	
III finger	4 (11)	0	
IV finger	3 (8)	0	
Painful fingers of dominant hand at time of scan (n, %)			
II finger	7 (19)	5 (11)	
III finger	8 (22)	4 (9)	
IV finger	4 (11)	2 (4)	
Rheumatoid factor + (n, %)	0 (0)	38 (84)	ND
ACPA + (n, %)	0 (0)	34 (76)	ND
Morning sfitness ≥30 min (n, %)	24 (65)	19 (42)	0
Diabetes (n, %)	1 (3)	2 (4)	0
Dislipidaemia (n, %)	9 (24)	6 (13)	0
BMI (mean ± SD)	26.1± 3.6	24.4± 3.5	23.0 ±3.8
Employment (n, %)			
Manual	18 (49)	18 (40)	4 (40)
Intellectual	16 (43)	20 (44)	5 (50)
Unemployed	3 (8)	7 (16)	1 (10)
Nail involvement (n, %)	17 (46)	0	0
Dactylitis clinical evident at time of scan (n, %)	5 (14)	0	0
Therapy (n, %)			
Only NSAID	8 (22)	0	
MTX	16 (43)	30 (67)	
SSZ	2 (5)	0	
CsA	2 (5)	2 (4)	
LEF	4 (11)	6 (13)	
Combo therapy (≥2 DMARDs)	5 (14)	7 (16)	

PsA: psoriatic arthritis; RA: rheumatoid arthritis; HCs: healthy controls; DAS28: Disease Activity Score 28; CRP: C-reactive protein; ACPA: anti-cytrullinated peptide antibodies; SD: standard deviation; BMI: body mass index; NSAID: non-steroidal anti-inflammatory drugs; MTX: methotrexate; SSZ: sulfasalazine; CsA: cyclosporine A; LEF: leflunomide; DMARDs: disease-modifying anti-rheumatic drugs; ND: not done.

Results

Intra-observer reliability between the 2 sonographers (IT, PM) was substantial good to identify enthesophytes and tenosynovitis evaluated in static images (κ values were 0.68 and 0.72, respectively). Intra-observer and inter-observer reliability was fair for peritendinous oedema identification on static images (κ value 0.39). After the reliability test a total of 82 consecutive patients from two Italian Rheumatology Centres were included in the study in a period of 3 months: 37 with PsA and 45 with RA. Both RA patients and PsA patients were predominantly female (respectively 71% and 59%). The majority of RA patients were seropositive (82% positive for rheumatoid factor; 76% for anti-citrullinated peptide antibodies). The RA patients had a longer disease duration (mean 5.6 years ± 4.1) than the PsA patients (mean 4.8 years ±3.3)

DAS28 CRP was slightly higher in RA patients (3.2±0.9 *vs*. 2.9±0.6 in PsA patients; p=ns) but PsA patients presented more often swollen fingers and painful fingers at clinical evaluation of the flexor tendon than RA patients (Table I). No RA cases had active dactylitis whereas 5 PsA patients had dactylitis at least in one of the fingers examined during the study. Overall, 64% of PsA and 34% of RA patients complained of hand morning stiffness for 30 minutes or more at the time of clinical evaluation. All RA patients were taking DMARDs therapy (67% were taking methotrexate mono-

Table II. Frequency of US findings in RA and PsA patients of II-IV digits of the dominant hand.

	PsA (n=37)	RA (n=45)	*p*-value
Presence of flexor tenosynovitis per pt (GS) (n, %)	14 (38)	6 (13)	0.008
Total flexor tenosynovitis (GS) (median, range)	0 (0-3)	0 (0-2)	0.045
Flexor tenosynovitis (GS) per digit (n, %)			
II digit	10 (27)	3 (7)	0.010
III digit	8 (22)	4 (9)	0.092
IV digit	7 (19)	2 (4)	0.033
Presence of flexor tenosynovitis per pt (PD) (n, %)	8 (22)	2 (4)	0.016
Total flexor tenosynovitis (PD) (median, range)	0 (0-3)	0 (0-1)	0.054
Flexor tenosynovitis (PD) per digit (n, %)			
II digit	5 (14)	2 (4)	ns
III digit	3 (8)	0	0.048
IV digit	5 (14)	0	0.010
Presence of peritendinous oedema per pt (GS+PD) (n, %)	11 (30)	0	<0.001
Total peritendinous oedema (median, range)	0 (0-3)	0 (0-0)	0.001
Peritendinous oedema per digit (GS+PD) (n, %)			
II digit	8 (22)	0	0.001
III digit	8 (22)	0	0.001
IV digit	6 (16)	0	0.005
Presence of FT enthesophytes per pt (n, %)	24 (65)	4 (9)	<0.001
Total FT enthesophytes (median, range)	2 (0-3)	0 (0-3)	0.001
FT enthesophytes per digit (GS) (n, %)			
II digit	20 (54)	2 (4)	<0.001
III digit	12 (32)	2 (4)	0.003
IV digit	18 (49)	4 (9)	<0.001
Presence of finger inflammation per pt*(n, %)	25 (68)	10 (22)	<0.001
Total inflammatory score* (median, range)	2 (0-8)	0 (0-3)	<0.001

PsA: psoriatic arthritis; RA: rheumatoid arthritis; GS: grey-scale; PD: power-Doppler; FT: flexor tendon; DIP: distal interphalangeal joints; *summing up.

therapy and 15% were taking combo therapy); whereas 78% of PsA patients were taking DMARDs (43% methotrexate monotherapy and 13% were taking combo therapy). The 10 HCs were matched for age (56±17) and BMI (23.0±3.8) and were predominantly female (60%) (see Table I).

Ultrasound findings

A total of 246 digits of the enrolled patients and 30 digits in HCs were scanned. None of the HCs enrolled had tenosynovitis.

As shown in Table II, the PsA patients had a significantly higher prevalence of flexor tenosynovitis than RA evaluated both with grey scale and PD examination. Flexor tenosynovitis was observed in 6 out 45 of RA patients and 14 out 37 patients of PsA patients (p=0.008). In the group of RA patients only two of six patients with flexor tenosynovitis presented increase of PD signal; whereas 8 of 14 patients affected by PsA (p=0.016). Figure 1 shows flexor tenosynovitis in a RA patient and PsA patient and PD signal distribution.

None of HCs and RA patients enrolled presented peritendinous oedema. Exclusively PsA patients had peritendinous oedema or "pseudotenosynovitis" (11 out of 37). We found an increase of fluid and PD of soft tissue not only around the flexor tendon but also under the derma in PsA patients as it is shown in Figure 2. Two HCs enrolled had flexor tendon insertion enthesophytes.

The presence of flexor tendon insertion enthesophytes was more frequent in PsA patients than RA (p<0.001). Figure 3 shows two examples of longitudinal and transversal view of flexor enthesophytes in PsA patients. Interestingly there were differences in lesions across digits in PsA with FT enthesophytes being commoner in the second digit and tenosynovitis itself being commoner in the longest 3rd digit (Table II).

Twenty-five out of 37 patients with PsA had at least one finger with US presence of inflammatory changes (flexor tendon tenosynovitis, flexor tendon oedema and/or flexor insertional ethesophytes) as compared to ten over 45 of the RA group (p<0.001). We finally summed up the flexor alterations (tenosynovitis, peri-tendinous oedema and flexor insertional enthesophytes) for 3 fingers of each patient as a total flexor inflammatory score. Considering the median of the total flexor inflammatory score per patient (range 0–9) the difference between PsA and RA was again statistically significant (median 2, range 0–8, for PsA and 0, range 0–3 for RA, p<0.001).

A total of 43 patients (65% PsA patients and 43% RA) complained morning stiffness for more than 30 minutes at the moment of US examination; we found a significant correlation with this symptom and tenosynovitis for RA and PsA combined (p=0.016) and a correlation close to significance with peritendinous oedema in PsA (p=0.076).

Discussion

The purpose of this study was to compare the pattern of flexor tendon disease between PsA and RA with a focus on global enthesis related abnormalities between both conditions. This study suggests that PsA cases have a much higher burden of abnormalities in the mini-entheses of the hand flexor tendons including insertional enthesophtyes and also peritendinous oedema. These findings corroborate a study over a decade ago by Fournie *et al*. (7) and support the growing body of evidence of the involvement of the synovio-entheseal complex and the-mini entheses of the hand in the pathogenesis of PsA related tenosynovitis. An ultrasound strategy for the diagnostic evaluation of early inflammatory arthritis with hand involvement based on RA synovial linked disease and PsA related synovio-entheseal complex diseases is needed to evaluate whether these findings can be applied for diagnostic purposes especially in seronegative arthritis.

A previous study defined the soft tissue changes in the flexor tendon compartment as inflammation of the "fibrous skeleton" of the digit suggesting a role of the extra-synovial structures and digital enthesitis in the development of psoriatic arthritis (7). We replicated these findings in a multi-centre study using more modern high-resolution US. We also formally showed that

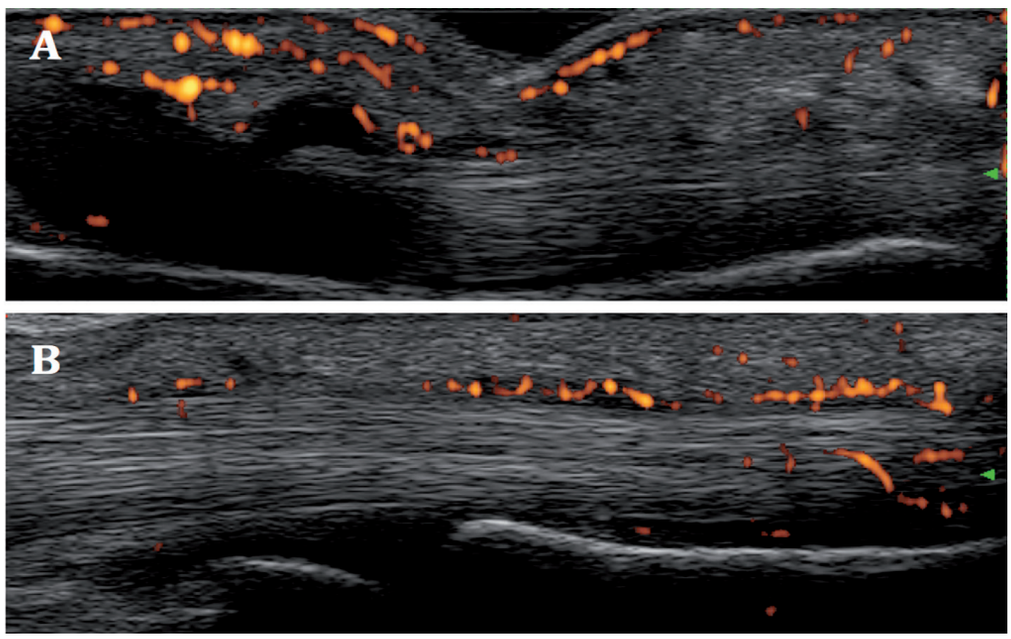

Fig. 1. Longitudinal view of flexor tenosynovitis in a PsA patient (**A**) and an RA patient (**B**).
Power Doppler signal is located more in subdermal tissue and around the flexor in PsA, whereas in RA is located inside the flexor sheet.

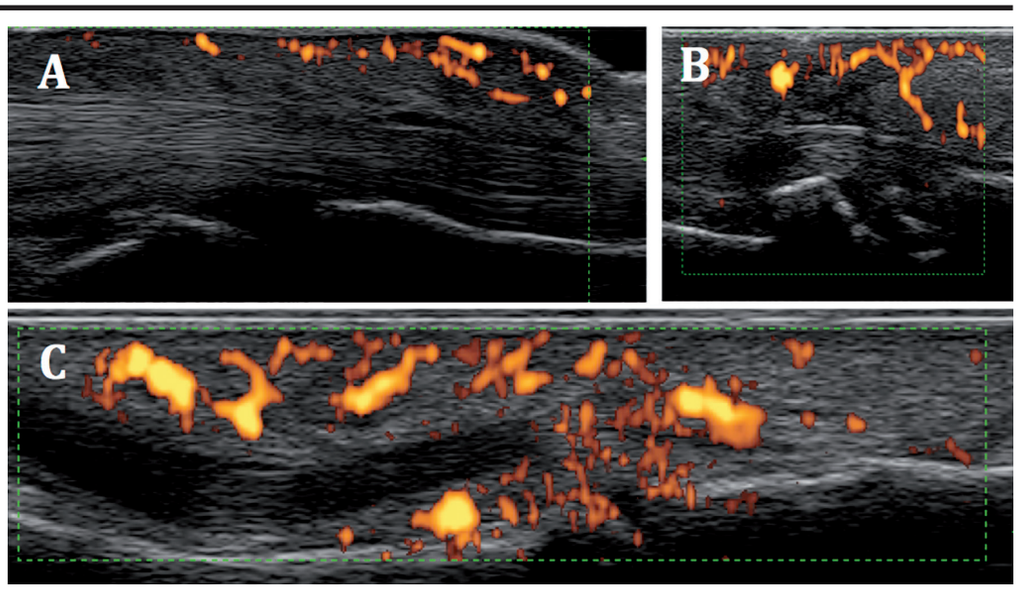

Fig. 2. Examples of oedema around the flexor tendon in PsA patients.

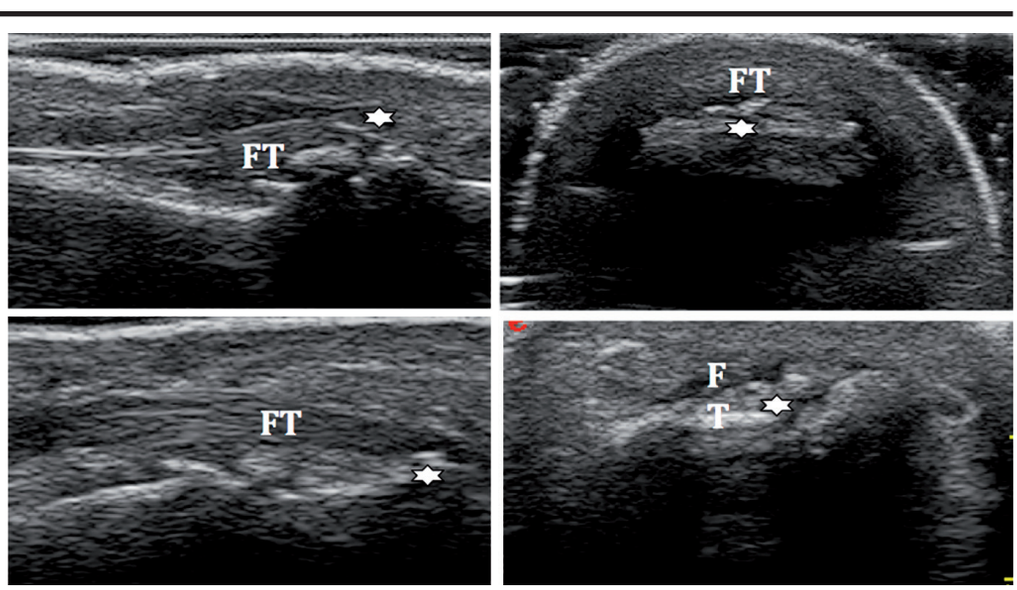

Fig. 3. Flexor enthesophytes in PsA patients in longitudinal and transverse planes.

these PsA related peritendinous lesions were associated with high PD signal. We also looked at both symptomatic and non-symptomatic joints. We noted a greater degree of FT enthesophytes compared to the preliminary study. Based on recent high resolution MRI studies of dactylitis, Tan *at al*. showed that these soft tissue lesions may be related to the A1-A5 accessory pulleys- a type of hand joint-"mini-entheses" (8). A recent review highlighted the role of MSKUS in studying mechanical and functional hand enthesitis in psoriatic disease (16). With the improving resolution and capabilities of MKUS these findings may be relevant to understand the involvement of flexor tendon in PsA especially in sites with high mechanical stress.

Our study highlights the role of the flexor compartment involvement in determining hand stiffness, in particular, the fact that patients complained that this symptom frequently presented flexor tenosynovitis or peritendinous oedema. This study had some limitations including an assessment of a limited number of digits per hand due to time constraints. Another bias in differentiation of RA and PsA could be that we examined three digits of the dominant hand, which are potentially more subject to repeated microtrauma and accounted for the changes evident in PsA. However, given the evidence for the pathogenetic role of trauma and microtrauma as an initiator of PsA these features may be an intrinsic part of the disease. Intra-observer agreement was fair for peritendinous oedema – a lesion where there is no agreed definition. Furthermore, enthesophytes have been well defined for lower limbs but there is no agreement on using the same definition in small joints.

In conclusion, we demonstrate the specificity of peritendinous oedema and enthesophytes for PsA and that peritendinous oedema is linked to clinical joint involvement. Taken in conjunction with the previous US data from the hand extensor compartment and the previous US and MRI data from the flexor compartment, our finding point towards a potentially important role for differentiation between RA and PsA based on tendon synovio-entheseal complex disease. This needs to be evaluated in early disease.

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