TITLE

"Peritenon extensor tendon inflammation in Psoriatic Arthritis is an enthesitis-related lesion "

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ABSTRACT

Objective

To analyse the association between enthesitis, synovitis and peritenon extensor tendon inflammation (PTI) in Psoriatic Arthritis (PsA).

Methods

PsA patients with swelling of metacarpophalangeal joints were included. Grey scale (GS) and power Doppler (PD) were used for synovitis and PTI ultrasound identification. Madrid Sonographic Enthesis Index (MASEI) was used for enthesitis assessment. PD activity was evaluated using PD item of MASEI and PD OMERACT definition.

Results

Synovitis had no association with enthesitis. PTI was associated with PD MASEI and PD OMERACT. Only PD OMERACT showed a positive correlation with PTI.

Conclusions

In PsA, PTI is associated to enthesitis, on contrary to synovitis.

INTRODUCTION

Enthesitis is a cornerstone of Psoriatic Arthritis (PsA) physiopathology. Synovitis is another landmark of PsA, considered secondary to enthesitis by some authors(1). Metacarpophalangeal joint (MCPj) swelling is a frequent finding in PsA, assumed to be caused by synovitis. However, peritenon extensor tendon inflammation (PTI) has emerged as another cause of MCPj swelling, demonstrating to be a specific feature of PsA with value in the differential diagnosis with other inflammatory diseases(2,3). Some authors consider PTI as an enthesitis-like lesion(3–6) due to the relation between the extensor tendon and the retinaculum pulley structure at MCPj(7), creating a functional enthesis with great similarities to the "*enthesis organ*" concept(5).

Ultrasound (US) is a sensitive, specific and reliable tool to evaluate structural and inflammatory changes both in enthesis(8) and synovium(9), and we have previously shown high reliability on evaluation of PTI(10). In order to improve the pathophysiological understanding of PsA, US could be used to explore the role of PTI.

As far as we know, the connection between PTI and enthesitis in PsA has not been studied. Our objective was to explore the association between both PTI and synovitis in MCPj with enthesitis in PsA patients, using the enthesis US score MASEI (Madrid Sonographic Enthesis Index)(11) as well as power Doppler (PD) MASEI and PD OMERACT (Outcome Measures in Rheumatology) definitions.

MATERIAL AND METHODS

Study population

This is an post-hoc study of a previous publication from our group(10) where consecutive non selected PsA patients fulfilling CASPAR criteria(12) with clinical swelling of at least one of the 2nd to 5th MCPj were included. In addition to the MCPj assessment, we performed an enthesis US exam using MASEI. Clinical examination was performed by a rheumatologist before US assessment. Patients <18 years and those with other explanations than PsA for MCPj swelling were excluded. Demographic, clinical and laboratory data were collected. The study

was approved by the local ethics committee (Hospital Clínico Valladolid, PI 15-275). Informed consent was obtained from all patients according to the Declaration of Helsinki.

Ultrasound settings

All US examinations were performed by an expert rheumatologist blinded to clinical data. A MyLab 70 XVG machine (Esaote S.p.A., Genoa, Italy) with a 13 MHz linear transducer was used. PD settings were: pulse repetition frequency 750 Hz, wall filter 3, persistence 4 and Doppler frequency 7.1 MHz. Colour gain was set just below the level of noise. 3-5 seconds videos were recorded both for MCPj and enthesis for posterior reliability assessments.

Metacarpophalangeal joint ultrasound assessment

As previously reported(10), the dorsal aspect of 2nd to 5th MCPj of both hands were examined by US with the patient seated in front of the sonographer, with hands lying in prone position on a table. Both longitudinal and transverse scans were performed moving the transducer from proximal to distal and from radial to ulnar sides of MCPj dorsal surface. Plenty of gel was used to avoid compression. PTI was defined as a hypoechoic image surrounding the extensor digitorum tendon with or without PD signal(2,3,13), and synovitis based on the OMERACT definition(14). At least 16 videos per patient were obtained, and in each joint presence or absence of PTI and synovitis in grey scale (GS) and PD modes was scored. As previously described, reliability assessment was performed among five readers, and consensus of at least three was defined as the true result(10).

Enthesis ultrasound assessment

The six enthesis included in MASEI index (bilateral triceps, quadriceps, proximal and distal patellar and Achilles tendons and proximal insertion of plantar aponeurosis) and the elementary lesions included (structure, thickening, erosion, enthesophytes, PD and bursa) were evaluated in longitudinal and transverse views obtaining at least 24 videos per patient. In addition to the MASEI PD item (defined as PD signal in cortical bone profile, intratendon or bursa on the enthesis insertion area), OMERACT definition for PD in enthesis (PD

signal at enthesis ≤ 2 mm to the cortical bone profile insertion)(15) was also evaluated as present or absent. Reliability assessment was performed among three readers, and consensus of at least two was defined as the true result.

Statistical analysis

Quantitative variables are given as mean (SD). Intraclass correlation coefficient (ICC) with 95% confident intervals was calculated for the reliability analysis of MASEI based on a mean-rating (k=3), absolute-agreement, two-way mixed effect model. In order to take into account the observed low prevalence of the PD subtypes, a prevalence and bias adjusted kappa (PABAK) was used for evaluating its reliability. PTI and synovitis reliability was calculated by Cohen`s Kappa test. Student's T-test for independent samples was used to compare continuous variables and $X^2$ for qualitative variables. Correlations were calculated with Spearman`s Rho test. SPSS statistical package version 20 (SPSS Inc, Chicago, IL) for statistical analysis and STATA version 12 (Stata, College Station, Texas, USA) for PABAK analysis were used.

RESULTS

Patient characteristics

Twenty-seven PsA patients were included. Clinical characteristics are summarized in Table 1.

Metacarpophalangeal joint ultrasound assessment

As previously described(10), a total of 216 MCPj were evaluated clinically and by US. PTI PD was found in 18 patients (66,7%) and 38 joints (17,6%) and PTI GS in 19 patients (70,3%) and 41 joints (18,9%). Synovitis PD was found in 18 patients (66,7%) and 41 joints (18,9%) and synovitis GS in 23 patients (85,1%) and 63 joints (29,16%). Both PTI and synovitis US achieved good reliability(10).

Enthesis ultrasound assessment

A total of 324 enthesis were scanned by US. Mean (SD) MASEI score was 30,62 (13,89). PD MASEI was found in 59/324(18,2%) enthesis and PD OMERACT in 33/324(10,2%). The inter-reader reliability achieved for MASEI was excellent

with ICC 0,918 (0,846-0,960). The inter-reader reliability of the PD subtypes was also excellent with PABAK 0,860 (0,756-0,960) for PD MASEI and 0,864 (0,759-0,962) for PD OMERACT.

Association and correlation between PTI, synovitis, MASEI and PD subtypes

Results are shown in Tables 2 and 3. PD and GS synovitis were not associated with MASEI, any of its items or with PD OMERACT. However, both PD and GS PTI demonstrated significant association with PD MASEI and PD OMERACT. PTI GS also showed significant association with erosions. PD OMERACT showed a positive correlation with PTI PD and GS. PTI, both PD and GS, showed a significant association with synovitis PD (p 0.009 and p 0.037, respectively). GS synovitis had no association with PD or GS PTI (p 0.055 and p 0.334, respectively).

DISCUSSION

According to the synovio-entheseal model(16), enthesitis is the initial site of inflammation in PsA, positioning synovitis as a secondary lesion. In a previous study we demonstrated that MCPj swelling in PsA has two etiopathological lesions: synovitis and PTI(10). In the present study we tried to clarify a non-previously evaluated topic: if PTI is an enthesitis-related lesion. We found that synovitis at MCPj was not associated with enthesitis. However, PTI showed a significant association with active enthesitis (PD MASEI, PD OMERACT) and erosions. The reason of evaluating PD subtypes is because we still do not have absolute agreement about which zone to restrict US enthesis lesions meaning inflammation(15), but there is full agreement about PD as the main indicator of active enthesitis.

The extensor tendon at MCPj level with its stabilizing wrapping-around band system and the local sesamoid fibrocartilage is considered a functional enthesis by some authors(3–6). Our findings are in agreement with this hypothesis and with the concept of an entheseal organ(5), representing pathologic changes that extend from the enthesis to the adjacent soft tissues. Moreover, although our

study does not explore causality, our finding of relation between PTI and synovitis and between PTI and enthesitis, but not between enthesitis and synovitis, could be in agreement with the theory that the origin and epicenter of inflammation in spondyloarthritis is in the enthesis, considering synovitis as a secondary feature to enthesitis(1,17).

As far as we know, there is no evidence of association between MASEI and PTI. This is also the result of our study. A possible explanation is because of the different chronic and active lesions that make up this index, while PTI is an inflammatory lesion. On contrary, when analyzing the association and correlation of PTI with PD, being the last the most characteristic US lesion of active enthesitis(18,19) we found statistical association between them. Our results support the hypothesis of PTI being an enthesitis related lesion, mainly with its inflammatory changes.

Our study has some limitations. Sample size is low. Clinical enthesis data were not available. The reliability exercise was based on videos, not real scanning. However, a high-level machine was used, and the produced videos gave a close real time examination. In addition, the reliability exercise included only sonographers with the highest level of competence (EULAR competency assessment level 2) and long experience in evaluation and investigation in US enthesis lesions.

In conclusion, the present study finds PTI to be associated with active enthesitis as opposed to MCPj synovitis, which may support a functional association between PTI and enthesitis, and reinforces the role of PTI in PsA as an enthesis-related lesion. This possible association should be explored further in larger studies, as well at the implication of PTI on PsA treatment.

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Table 1. Clinical features of the patients. CRP C reactive protein. ESR erythrocyte sedimentation rate. SD standard deviation. CRP, ESR and their respective DAS28 calculations were only available in 18 patients.

Patients	27
Men (%)	17 (63)
Women (%)	10 (37)
Age (years ± SD)	56 ± 11
Disease duration (months ± SD)	109 ± 101
Type of psoriasis	
First degree relative (%)	1 (3,7)
Skin psoriasis (%)	10 (37,1)
Nail psoriasis (%)	1 (3,7)
Skin and nail psoriasis (%)	15 (55,5)
Type of Psoriatic Arthritis	
Peripheral (%)	21 (78)
Axial and peripheral (%)	6 (22)
CRP mg/l (mean ± SD)	8,3 ± 8,2
ESR mm/h (mean ± SD)	21,9 ± 19,3
DAS28 CRP (mean ± SD)	3,6 ± 0,9
DAS28 ESR (mean ± SD)	3,9 ± 1,2

Table 2. Association between PTI, synovitis, MASEI and PD subtype.

Results expressed as mean ± standard deviation. p value < 0.05 is considered statistically significative and marked with a star.

	PTI power doppler			Synovitis power doppler			PTI grey scale			Synovitis grey scale		
	Present	**Absent**	**p**	**Present**	**Absent**	**p**	**Present**	**Absent**	**p**	**Present**	**Absent**	**p**
MASEI	32.44±15.62	27±9.33	0.270	32±16.16	27.89±7.72	0.380	33.15±15.49	24.6±6.43	0.054	30.78±14.54	29.75±11.02	0.876
Structure MASEI	7.27±2.90	7.33±2.95	0.964	7.33±3	7.22±2.72	0.924	7.52±3.02	6.75±2.54	0.505	7.26±2.84	7.5±3.41	0.902
Thickness MASEI	5.5±3.34	5.66±3.42	0.906	5.88±3.12	4.88±3.75	0.503	5.84±3.57	4.87±2.64	0.447	5.34±3.25	6.75±3.86	0.533
Erosion MASEI	2.83±5.19	0.66±2	0.133	2.66±5.23	1±2.12	0.253	3±5.09	0±0	**0.019***	2.08±4.73	2.25±2.87	0.928
Calcification MASEI	6.44±2.57	7.33±3.12	0.473	6.77±2.81	6.66±2.73	0.923	6.68±2.70	6.87±2.99	0.879	6.69±2.8	7±2.7	0.846
Bursa MASEI	0.22±0.54	0.55±0.52	0.145	0.22±0.54	0.55±0.52	0.145	0.21±0.53	0.62±0.51	0.082	0.34±0.57	0.25±0.5	0.740
PD MASEI	8±6	3.67±3.28	**0.023***	6.83±6.15	6±4.5	0.694	7.73±5.94	3.75±3.49	**0.041***	6.91±5.89	4.5±3	0.249
PD OMERACT	1.61±1.33	0.56±1.01	**0.033***	1.39±1.46	1±1	0.426	1.57±1.30	0.5±1.06	**0.040***	1.26±1.35	1.25±1.25	0.988

Table 3. Correlation between PTI, synovitis and MASEI items. Rho is Rho Spearman value. p value < 0.05 is considered statistically significative and marked with a star.

	PTI power doppler		Synovitis power doppler		PTI grey scale		Synovitis grey scale	
	Rho	**p**	**Rho**	**p**	**Rho**	**p**	**Rho**	**p**
MASEI	+0.227	0.255	+0.115	0.567	+0.280	0.157	+0.137	0.497
Structure MASEI	+0.044	0.826	+0.052	0.798	+0.138	0.493	-0.032	0.873
Thickness MASEI	+0.095	0.637	+0.247	0.213	+0.179	0.371	+0.202	0.311
Erosion MASEI	+0.147	0.465	+0.094	0.640	+0.220	0.271	-0.045	0.823
Calcification MASEI	-0.079	0.694	+0.204	0.307	-0.006	0.978	+0.176	0.381
Bursa MASEI	-0.467	**0.014***	-0.405	**0.036***	-0.540	**0.040***	-0.042	0.835
PD MASEI	+0.357	0.067	-0.083	0.681	+0.329	0.094	-0.041	0.841
PD OMERACT	+0.441	**0.021***	+0.045	0.825	+0.423	**0.028***	-0.032	0.874