The relationship between physical examination and ultrasonography for large entheses is best for the Achilles tendon and patellar tendon origin

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Running head: Accuracy of entheseal ultrasound

Abstract

Background: To investigate the relationship between physical examination (PE) and sonographic features of enthesitis, based on anatomical sites.

Methods: The analysis was done using merged raw data of 3 studies on 2298 entheses.

Results: Patients with clinical Achilles enthesitis had more abnormalities on ultrasound (hypoechogenicity ($p<0.001$), thickening ($p=0.01$), Doppler ($p=0.002$) and erosions ($p=0.02$). The patellar tendon origin also correlated with PE but distal patellar tendon insertion and plantar aponeurosis were uncoupled from the ultrasound.

Conclusion: The relationship between clinical and sonographic findings for large entheses is dependent on the anatomical site and is best for the Achilles tendon and patellar tendon origin.

Introduction:

Enthesitis is a characteristic sign and hallmark of spondyloarthritis (SpA) and is clinically defined as pain or tenderness at the attachment site of a tendon/ligament to the bone with, or without, swelling. However, physical examination (PE) is neither sensitive nor specific for the evaluation of enthesitis (1). Ultrasonography (US) has been increasingly used for the assessment of enthesitis as it has the advantage of visualizing both soft tissue and bony changes (2,3). Comparison between US with PE has mostly been reported in relationship to the summation of total US scores with overall PE scores from multiple entheseal sites, rather than elementary lesions of enthesitis on US and per site (4-6). US is usually considered to be more sensitive than PE to detect enthesitis. However, it is also true whereby patients with clinical entheseal tenderness sometimes have no US feature of enthesitis (7,8). Unlike synovitis, it is not feasible to evaluate and validate sonographic or clinical enthesitis against the "gold standard" of tissue biopsy, so the relevance of clinical and imaging findings for enthesitis is difficult to disentangle.

Our hypothesis is that PE may be overrating enthesitis at certain sites whereas the link between US and PE can be better in others. There is limited information on the relationship between clinical and imaging findings from individual US lesions on multiple entheseal sites.

Materials and methods

The raw data of three previous studies were used for this analysis (8-10). All 3 studies were approved by 3 different ethic boards (Marmara University Ethics Board, No: 09.2014.0143, Leeds (East) REC 09/H1306/105; The University Health Network REB# is 08-0126-AE). The Marmara University Ethics Board was contacted and was declared that additional approval was not required for additional analysis by combining the raw data. The first study by Aydin et al comparing the entheseal differences in PsA, psoriasis and healthy controls (8), had one sonographer (SZA) and PE was performed by one investigator (ZRA) on the same day, blinded to each other's assessment. A Logiq-E9 (General Electric, Wauwatosa, Wisconsin, USA) was used to scan 12 entheses: quadriceps insertion, patellar tendon origin and insertion, Achilles tendon and plantar aponeurosis insertions and lateral epicondyle for the common extensor tendon origin, bilaterally. The elementary lesions defined by the Outcome Measures in Rheumatology (OMERACT) group have been used: hypoechogenicity, thickening, entheseal PD signals, erosions, enthesophytes and calcifications (11). All findings were graded between 0-3, quantitatively for thickening and erosions and semi-quantitatively for the other lesions to determine lesion severity on US (8).

For the second study by Arslan et al, comparing the differences between PsA and ankylosing spondylitis (AS) (9) the sonographer was the same (SZA) using the same methodology as the aforementioned study, except the US machine being an MyLab70-XVG (Esaote, Genoa, Italy), with a 6-18 Mhz linear transducer. One clinician performed the PE of the entheses on the same day as the US (FA), blinded to each other's assessment. For these 2 studies, only psoriasis or PsA data were extracted.

The third study by Polachek et al examined the association between sonographic enthesitis and the severity of radiographic features of damage in the peripheral and axial joints in patients with PsA (10). The US scans were done by one sonographer (LE) using a MyLab70-XVG (Esaote, Genoa, Italy) equipped with a 6–18 MHz linear transducer. Clinical assessment of the entheses was performed at the same day by the rheumatologist evaluating the patient. MAdrid Sonographic Enthesitis Index (MASEI) scoring system was used in this study (12). Therefore, in addition, the triceps tendon insertion was also scanned, however this site was not analyzed as not being included in the previous studies. The same elementary lesions were investigated. There were some differences for the scoring of the severity of the lesions: Doppler signals and erosions were scored as 0 or 3 whereas hypoechogenicity and thickening were scored as 0 or 1.

Statistical analysis

All analysis was done per entheseal site. As there were some differences between the scoring methods, two types of analysis were performed, using the appropriate data:

1) The presence and absence of each sonographic elementary lesion was compared with findings on PE at the same entheseal site, by using all 3 data sources as this was captured by all.

2) The weighted analysis including the scoring of the findings were only performed by using the first 2 databases as scoring were done between 0-3 for all lesions.

The frequency of each elementary lesion on US was explored and presented as frequencies (percentages). The dependence between PE and US scores was assessed using chi-square or Fisher's exact tests, as appropriate. SPSS V-21 was used for analysis (SPSS Inc., Chicago, IL, USA).

Results:

A total of 2298 enthesis from 377 patients (341 with psoriatic arthritis, 36 with psoriasis) were compared using US and PE.

The presence of elementary lesions:

Patients with clinical Achilles enthesitis had more frequent abnormalities on US (hypoechogenicity: p<0.001, thickening: p=0.01, Doppler positivity: p=0.002 and erosions: p=0.02) (Table). Similarly, hypoechogenicity (p=0.001) and enthesophytes/calcifications (p=0.028) at the patellar tendon origin were more common in patients with clinical enthesitis and there was a tendency for more erosions but it did not reach statistical significance (p=0.065). The clinical quadriceps enthesitis was related to hypoechogenicity on US (p=0.001) and patients with clinical enthesitis on the lateral elbow had more frequent Doppler signals (p=0.007). The rest of the entheseal sites were uncoupled from the US features, especially distal patellar tendon insertion and plantar aponeurosis (Table).

We have repeated the analysis by removing the psoriasis patients. Only focusing on PsA patients, the results were very similar with the whole group, with the exception of patellar tendon origin for calcifications (data not given).

The severity of elementary lesions on US:

Quadriceps tendon insertion: Clinical enthesitis was linked to severity of hypoechogenicity (p=0.026) and calcifications (p=0.020) on US (Supplementary Table, Figure).

Patellar tendon origin: Patients with clinical enthesitis had more severe hypoechogenicity (p<0.001), thickening (p<0.001), enthesophytes (p<0.001) and calcifications (p=0.003) on US.

Achilles enthesitis: Clinical enthesitis was associated with the severity of hypoechogenicity (p=0.008) and power Doppler (p=0.048) on US.

Common extensor tendon origin: The severity of hypoechogenicity (p=0.018) and power Doppler (p=0.017) was associated with clinical enthesitis (Supplementary Table, Figure).

Discussion:

The findings from this study confirm that the link between PE and US for enthesitis is dependent on the anatomical site. Patellar tendon origin and Achilles entheses are the 2 sites where PE is significantly linked to US findings, supporting the construct validity of US to visualize enthesitis.

The discrepancies between PE and US across different entheseal sites can be due to the difficulties to identify the enthesis accurately by PE and different pain thresholds at different entheseal sites. For sites where PE is not linked to US such as the plantar aponeurosis or the patellar tendon insertion, US may improve the assessment by eliminating the false positives and negatives of PE. However, there may also be technical difficulties to detect some of the entheseal changes by US, such as the very low prevalence of Doppler signals in the plantar aponeurosis or US not being capable of detecting osteitis. Our group has previously reported the relationship between each elementary lesion with PE findings directly at the entheseal insertions using US on 21 patients with SpA, for the enthesis around the knee

only (13). That study suggested that clinical enthesitis was associated with more hypoechogenicity and thickening on US. To the best of our knowledge, this is the first study on a large number of entheses and at multiple sites to explore the agreement between various sonographic features and PE to understand the clinical significance of individual lesions on US.

The enthesis is a very important structure in SpA, not only since it is frequently involved but also due to its significant impact on patients' pain, global assessment and quality of life. The recognition of enthesitis is important both at diagnosis and at follow up to decide the most appropriate treatment. However, the enthesis is probably the most difficult musculoskeletal structure to assess as the same sites are commonly affected by mechanical tendinopathies/enthesopathies and due to the proximity of fibromyalgia tender points (14). It is important to accurately assess the cause of pain at the entheseal insertions not to over or under-treat the patients.

The major strengths of this study are the large number of entheses and the representation of 2 experienced sonographers' in 3 different settings. As the same scoring method was not applied, it was not possible to include all patients to link the severity of the US features with PE but using the same definitions of elementary lesions, the presence/absence data were comparable. There were multiple clinical assessors for the 3rd study which may be considered as a limitation, however this perfectly reflects real-life experience and the assessors have been trained by the same individual.

In summary, the relationship between US and PE for enthesitis assessment depends on the entheseal site. US may be used to prove the presence of entheseal inflammation when their diagnostic uncertainty or when disease activity is not clear and/or therapies are considered. In the absence of a gold standard histological method, we believe that these findings provide a platform for the assessment of clinically relevant enthesitis. Future research should aim to confirm these findings and further validate the currently existing clinical scoring systems for enthesitis in SpA.

References

1. McGonagle D, Khan MA, Marzo-Ortega H, O'Connor P, Gibbon W, Emery P. Enthesitis in spondyloarthropathy. Curr Opin Rheumatol 1999;11:244-50.

2. Kaeley GS, Eder L, Aydin SZ, Gutierrez M, Bakewell C. Enthesitis: A hallmark of psoriatic arthritis. Semin Arthritis Rheum 2018;48:35-43.

3. Gandjbakhch F, Terslev L, Joshua F, Wakefield RJ, Naredo E, D'Agostino MA. Ultrasound in the evaluation of enthesitis: status and perspectives. Arthritis Res Ther 2011;13:188.

4. Husic R, Gretler J, Felber A, Graninger WB, Duftner C, HermannJ, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis 2014;73:1529-36.

5. Bandinelli F, Prignano F, Bonciani D, Bartoli F, Collaku L, Candelieri A, et al. Ultrasound detects occult entheseal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity. Clin Exp Rheumatol 2013;31:219-24.

6. Borman P, Koparal S, Babaoglu S, Bodur H. Ultrasound detection of entheseal insertions in the foot of patients with spondyloarthropathy. Clin Rheumatol 2006;25:373-7.

7. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. Ann Rheum Dis 2002;61:905–10.

8. Aydin SZ, Castillo-Gallego C, Ash ZR, Marzo-Ortega H, Emery P, Wakefield RJ, et al. Ultrasonographic assessment of nail in psoriatic disease shows a link between onychopathy and distal interphalangeal joint extensor tendon enthesopathy. Dermatology 2012;225:231-5.

9. Alhussain FA, Gunal EK, Kurum E, Bakirci Ureyen S, Ozturk AB, McGonagle D, et al. Greater magnitude of entheseal micro-damage and repair in Psoriatic Arthritis compared to Ankylosing Spondylitis on Ultrasound. Rheumatology (Oxford) 2019;58:299-303.

10. Polachek A, Cook R, Chandran V, Gladman DD, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis. Arthritis Res Ther 2017;19:189.

11. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken) 2014;66:741-8.

12. de Miguel E, Cobo T, Munoz-Fernandez S, Naredo E, Uson J, Acebes JC, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis 2009;68:169-74.

13. Aydin SZ, Tan AL, Hodsgon R, Grainger A, Emery P, Wakefield RJ, et al. Comparison of ultrasonography and magnetic resonance imaging for the assessment of clinically defined knee enthesitis in spondyloarthritis. Clin Exp Rheumatol 2013; 31:933-6.

14. Roussou E, Ciurtin C. Clinical overlap between fibromyalgia tender points and enthesitis sites in patients with spondyloarthritis who present with inflammatory back pain. Clin Exp Rheumatol 2012;30:24-30.

	Enthesitis on physical exam																	
	Quadriceps			Patellar proximal			Patellar distal			Achilles			Plantar			Lat epicondyle		
	PE (+)	PE (-)	p	PE (+)	PE (-)	p	PE (+)	PE (-)	p	PE (+)	PE (-)	p	PE (+)	PE (-)	p	PE (+)	PE (-)	p
Hypoechogenicity n/total (%)	16/23 (69.6)	144/402 (35.8)	**0.001**	13/30 (43.3)	72/386 (18.7)	**0.001**	6/30 (20)	91/389 (23.4)	0.671	22/54 (40.7)	64/379 (16.9)	**<0.001**	8/47 (17)	55/382 (14.4)	0.632	9/24 (37.5)	47/151 (31.1)	0.534
Thickening n/total (%)	10/23 (43.5)	106/402 (26.4)	0.073	18/30 (60)	176/386 (45.6)	0.128	22/30 (73.3)	247/389 (63.5)	0.279	14/54 (25.9)	49/379 (12.9)	**0.001**	10/47 (21.3)	67/375 (17.9)	0.568	6/23 (26.1)	29/151 (19.2)	0.443
Power Doppler n/total (%)	0/23 (0)	21/400 (5.2)	0.260	2/30 (6.7)	11/384 (2.9)	0.250	2/30 (6.7)	21/387 (5.4)	0.774	9/54 (16.7)	20/378 (5.3)	**0.002**	0/47 (0)	0/375 (0)	-	5/24 (20.8)	8/151 (5.3)	**0.007**
Enthesophytes n/total (%)	17/21 (81)	196/305 (64.3)	0.120	13/30 (43.3)	85/296 (28.7)	0.096	6/30 (20)	63/296 (21.3)	0.870	17/19 (89.5)	124/144 (86.1)	0.687	19/45 (42.2)	125/28 (44.5)	0.777	3/16 (18.8)	48/138 (34.8)	0.197
Calcifications n/total (%)	2/21 (9.5)	9/305 (3)	0.107	2/30 (6.7)	4/29 (1.4)	**0.039**	0/30 (0)	22/296 (7.4)	0.122	0/43 (0)	3/283 (1,1)	0.498	0/4 (0)	2/281 (0.7)	0.570	0/16 (0)	11/140 (7.9)	0.245
Erosion n/total (%)	1/24 (4.2)	14/398 (3.5)	0.868	4/30 (13.3)	20/386 (5.2)	0.065	0/30 (0)	5/389 (1.3)	0.532	8/54 (14.8)	23/379 (6.1)	**0.020**	0/47 (0)	15/375 (4)	0.163	2/24 (8.3)	11/151 (7.3)	0.856
Enthesophytes or	17/23	258/400	0.357	14/30	94/340	**0.028**	6/30	104/389	0.419	46/54	302/379	0.341	21/47	179/375	0.693	9/24	58/151	0.932

Calcifications n/total (%)	(73.9)	(64.5)		(46.7)	(27.6)		(20)	(26.7)		(85.2)	(79.7)		(44.7)	(44.7)		(37.5)	(38.4)	

Table : The frequency of each sonographic finding categorized according to the having enthesitis on physical exam (+) vs not (-) at different sites, based on the raw data obtained from all 3 studies (9-11). In this table, US findings have been analysed as present or absent only, without any grading. The numbers are given as the numbers of positives/total number with available data (%). PE: physical examination; Lat: lateral. The dependence between PE and US scores was assessed using chi-square or fisher's exact tests. The latter was employed when the assumptions of the chi-square test was not met.

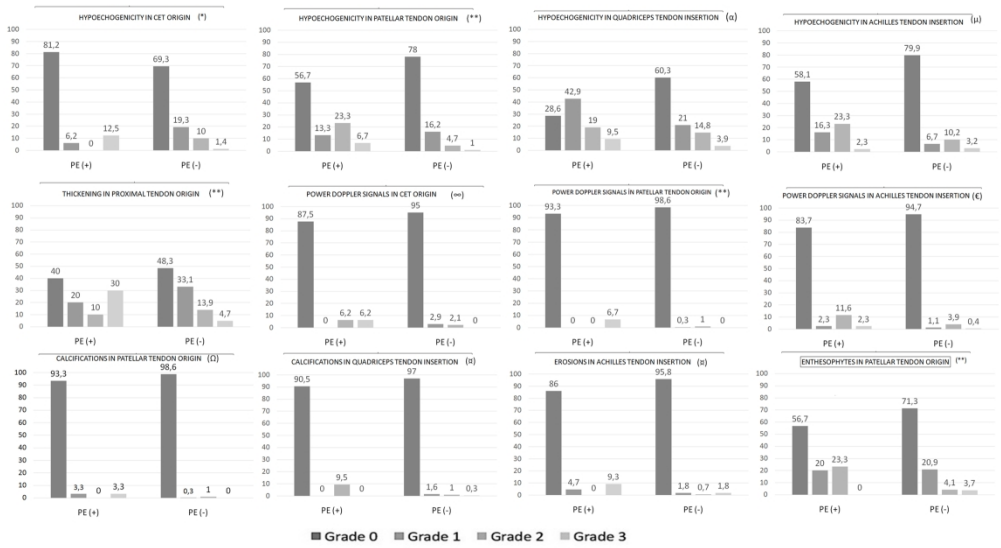

Figure legend: The severity of each sonographic finding categorized according to the having enthesitis on physical exam (+) vs not (-) at different sites, based on the raw data obtained from 2 studies (9-10). The numbers are given as the %. PE: physical examination; CET: common extensor tendon. Only statistically significant data were given for figure 1. hypoechogenicity in CET origin (*); p=0,018, hypoechogenicity in patellar tendon origin, thickening in patellar tendon origin, power Doppler signals in patellar tendon origin, enthesophytes in patellar tendon origin (**); p=<0,001, hypoechogenicity in quadriceps tendon insertion (α); p=0,026, hypoechogenicity in Achilles tendon insertion (μ); p=0,008, power Doppler signals in CET origin (∞); p=0,017, power Doppler signals in Achilles tendon insertion (€); p= 0,048, calcification in patellar tendon origin (Ω); p=0,003, calcification in quadriceps tendon insertion, erosion in Achilles tendon insertion (¤); p = 0,020.

96x52mm (600 x 600 DPI)