Ultrasound imaging for the rheumatologist XXII. Achilles tendon involvement in spondyloarthritis. A multi-centre study using high frequency volumetric probe

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ABSTRACT

Three-dimensional (3D) US is a new sonographic modality which represents a promising tool in the assessment of joint and periarticular tissues abnormalities in rheumatic diseases. The available literature has recently underlined its advantages mainly related to the virtual operator independence due to image acquisition of infinite 3D data sets obtained by transducer automated sweeping. Shortening of the US examination time represents another notable advantage over conventional two-dimensional (2D) US. The aim of the present study was to investigate the validity of 3D US in assessing Achilles tendon enthesitis by comparing it with 2D US. US examinations were performed by using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) equipment with a high-frequency (8-15 MHz) volumetric probe. One hundred and eighty-six Achilles tendon enthesis of 93 SpA patients were examined. The analysis of each basic US finding demonstrated from good to excellent agreement rates between 3D and 2D US, both in dichotomous assessment of sonographic lesions and in the use of semi-quantitative grading. Excellent agreement between the two modalities was demonstrated in the assessment of both inflammatory changes and structural lesions. Our study for the first time demonstrated that 3D US is a valid imaging modality for the assessment of Achilles tendon enthesitis.

Introduction

Involvement of enthesis is a typical trait of spondyloarthritis (SpA) and may appear in different moments during the course of the disease, often representing the first and early manifestation of it. Enthesitis is characterised by the presence of inflammatory lesions at the bony insertion of ligaments, tendons and joint capsules which can lead to destructive changes and contemporaneous new bone formation (1). Enthesis are ubiquitously present in the musculoskeletal system and all of them may be involved in SpA, Achilles tendon enthesis representing, however, the most characteristic and, frequently, the first site of involvement. In some occasions it may present as an isolated expression of SpA, in other cases it can be asymptomatic and underestimated by clinical examination, thus being detected only by imaging tools (1). Among them, musculoskeletal ultrasound (US) has widely spread in last years and interesting studies have been conducted on its use and application for evaluating enthesis involvement in SpA (1-5). Much has been written in the last decade, and some focus on validity and reliability of US in the assessment of enthesitis in spondyloarthropathies both by using grey-scale and power Doppler US has been developed. US provides accurate depiction of tendon and bony cortex abnormalities at all stages of the disease process and has a wide range of advantages over other imaging tools mainly represented by dynamic capabilities, lack of radiation burden, good reliability, reproducibility and relatively low-cost (6). More recently, three-dimensional (3D) US is emerging as a new US modality with a number of possible advantages over conventional sonography, mainly represented by the fact that it requires not particular skill to be performed, can be mastered in very short time and is not operator-dependent in

the acquisition process, shifting in the balance between image acquisition and interpretation (7).

Since this new imaging modality has never been used in the evaluation of enthesitis in SpA, the aim of the present study was to investigate the validity of 3D US in assessing Achilles tendon enthesitis by comparing it with conventional two-dimensional (2D) US.

Patients and methods

Patients

Ninety-three patients with SpA, fulfilling the European Spondyloarthropathy Study Group (ESSG) criteria (8) were included in the present multi-centre study which has been conducted in 4 Italian rheumatology units: the rheumatology department of the Sapienza University of Rome, the rheumatology department of the Università Politecnica delle Marche, the rheumatology department of the University of Pavia and the rheumatology department of the University of Pisa. Patients' women/men ratio was 1.2 (51/42), mean age was 56 years (range 14-81), mean disease duration was 7.9 years (range 1-16). Consecutive patients were included in the study, independently from clinical involvement of Achilles tendon enthesis.

This study was conducted in compliance with good clinical practices and according to local regulations.

US examination

A consensus meeting was convened at the beginning of the study, previously to patient enrolment, for the aim of clarifying the study methodology and obtaining agreement on scanning protocol and image interpretation.

In each rheumatology unit, US examinations were independently performed by a rheumatologist sonographer, experienced in musculoskeletal US, by using a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) equipped with a broadband high-frequency (8-15 MHz) volumetric probe. Both grey-scale and power Doppler setting had been previously standardized and the same setting was used in all cases. Focus was positioned at the level of the region of interest; grey-scale frequency was 15 MHz; power Doppler pulse repetition frequency was 900 Hz; Doppler frequency was 9.1 MHz; low wall filters were used. Colour gain was adjusted just below the level that caused the appearance of noise artefacts (9). Colour box was positioned at the level of the Achilles tendon enthesis, enlarging the box to upper part of the image. The same grey-scale and power Doppler settings were used for both the 2D and 3D examinations.

Patients were asked to lie prone keeping both feet hanging out the examination table, in neutral position. In all cases, bilateral examination of Achilles tendon enthesis was carried out after having previously applied gel to the skin to provide an acoustic interface; during the examination, attention was paid on not applying probe pressure on the anatomical structures under examination. The same protocol was used for both the 2D and 3D examinations.

– 2D US examination

All Achilles tendons and enthesis were scanned in both longitudinal and transverse scans. During the same scanning session, US was firstly performed in B-mode modality to detect morphological changes and immediately afterwards by using power Doppler technique to detect abnormal vascularization (1). According to recently published Outcome Measures in Rheumatology Clinical Trials (OMERACT) preliminary definitions of enthesopathy, the following changes were registered (10): tendon hypoechogenicity at the level of bony attachment; tendon thickening at the level of bony attachment; intra-tendinous calcifications; enthesophytes; bony erosions; bony cortex irregularities; presence of Doppler signal at the level of bony attachment; presence of intra-tendinous Doppler signal. Furthermore, bursal involvement was registered, as follows: enlargement of deep calcaneal bursa; enlargement of superficial calcaneal bursa. Finally, both partial and full-thickness tendon lesions were registered. Findings had to be confirmed by 2 perpendicular planes. All lesions were scored on both a dichotomous scale (present/absent) and a 4 points semi-quantitative scale (0=absent; 1=mild; 2=moderate; 3=severe).

– 3D US examination

Immediately after the execution of 2D US exams, the acquisition of 3D data sets was obtained placing the volumetric transducer over the area of interest. The acquisition time of a single 3D data set ranged from 3 to 6 seconds according to the value of the volume angle.

All the 3D data sets were collected and the stored cubes were blindly assessed by the same operators after a period of time which varied from 4 to 6 weeks. The software displays automatically the 3 main perpendicular planes (longitudinal, transverse and coronal), indicating the exact point of their intersection (6). This was particularly useful to confirm the presence of both tendon and bony cortex changes at the level of enthesis. Power Doppler signal was evaluated using the 3D image reconstruction and the tomographic US imaging.

Statistical analysis

Agreement between 2D and 3D evaluation was calculated by using kappa-statistics (unweighted kappa for dichotomous evaluation and linear weighted kappa for semi-quantitative scoring). A kappa-value of 0–0.20 was considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent (12). The MedCalc (Belgium, version 10.1.2.0) software for Windows XP was used.

Results

One hundred and eighty-six Achilles tendon enthesis were examined by using both 2D and 3D US modalities. Results are shown in Tables I and II where the kappa values, estimating the agreement between the 2D US and the 3D US findings, are reported. All changes were assessed both for presence/absence and ordinal scale, according to semi-quantitative grading.

The analysis of each basic US finding demonstrated from good to excellent agreement rates between 3D and 2D US, both in dichotomous assessment of sonographic lesions and in the use of semi-quantitative grading (Table I): comparison of results obtained from the two modalities showed unweighted kappa values for the presence/absence evaluations ranging from 0.733 to

Table I. Agreement between 3D and 2D US assessment of Achilles tendon enthesis.

US Finding	2D-3D US Presence/Absence Unweighted kappa values ± standard error (95% CI)	2D-3D US Semi-quantitative assessment Weighted kappa values ± standard error
Tendon hypoechogenicity	0.918 ±0.030 (0.859–0.978)	0.921 ± 0.057
Tendon thickening	0.902 ±0.036 (0.831–0.973)	0.894 ± 0.058
Intra-tendinous calcifications	0.898 ±0.035 (0.828–0.967)	0.927 ± 0.063
Enthesophytes	0.924 ±0.033 (0.858–0.990)	0.910 ± 0.052
Calcaneal bone erosions	0.866 ±0.054 (0.761–0.972)	0.860 ± 0.060
Calcaneal bone irregularities	0.842 ±0.044 (0.756–0.929)	
Entheseal power Doppler signal	0.883 ±0.082 (0.722–1.044)	0.935 ± 0.060
Intra-tendinous power Doppler signal	0.950 ±0.035 (0.882–1.019)	0.969 ± 0.060
Enlargement of deep calcaneal bursa	0.942 ±0.029 (0.886–0.998)	0.942 ± 0.062
Enlargement of superficial calcaneal bursa	0.733 ±0.107 (0.523–0.943)	0.762 ± 0.062
Tendon lesion	0.797 ±0.202 (0.401–1.193)	0.856 ± 0.063

Table II. Levels of agreement between 2D and 3D US in the detection of lesions related to inflammation and structural damage.

	2D-3D US Presence/Absence Unweighted kappa values ± standard error (95% CI)	2D-3D US Semi-quantitative assessment Weighted kappa values ± standard error
Group I lesions (indicative of Achilles tendon enthesis inflammation)	0.847 ± 0.032 (0.784–0.911)	0.920 ± 0.046
Group II lesions (indicative of Achilles tendon enthesis structural damage)	0.843 ± 0.034 (0.777–0.910)	0.894 ± 0.047

0.950 and weighted kappa values for semi-quantitative assessments ranging from 0.762 to 0.969.

Further analysis was then conducted, dividing the US findings in 2 groups, depending on their correlations either with inflammation or structural damage: group I included changes indicative of Achilles tendon enthesis inflammation (*i.e.* tendon hypoechogenicity; tendon thickening; presence of Doppler signal at the level of bony attachment; presence of intra-tendinous Doppler signal; enlargement of deep calcaneal bursa; enlargement of superficial calcaneal bursa); group II comprised findings indicative of Achilles tendon enthesis tissue damage (*i.e.* intra-tendinous calcifications; partial and full-thickness tendon lesions; enthesophytes; bony erosions; bony cortex irregularities) (3). Excellent agreement between 2D and 3D US in the detection of group I sonographic findings was demonstrated obtaining unweighted kappa values = 0.847 for dichotomous evaluation and weighted kappa values = 0.920 for semi-quantitative grading (Table II).

Excellent agreement was also found by the analysis of results from the two modalities in the assessment of group II US changes with unweighted kappa values = 0.843 for presence/absence evaluation and weighted kappa values = 0.894 for semi-quantitative assessment (Table II).

Discussion

Enthesitis is a characteristic feature of SpA and is considered as the primary lesion in this group of pathologies (13, 14). Particularly, inflammatory involvement of Achilles tendon enthesis is considered the hallmark of the disease and currently clinical evidence of heel enthesitis is included in the ESSG criteria (8). However, clinical examination has a low sensitivity in the detection and differentiation of joint and periarticular tissues changes, hence peripheral enthesitis is frequently mixed up with other disorders and its presence may be underestimated in SpA (1). Thus, imaging tools may play a relevant role in the assessment of enthesitis. Plain radiography has been considered the gold standard for evaluating joint damage in SpA but it has evident limitations in imaging soft tissues abnormalities. MRI has a series of advantages which include its non-invasiveness, multiplanar capability and excellent soft tissue contrast. However, it is expensive, time consuming and not widely available for routine use. Sonographic assessment of enthesitis is more sensitive than physical examination and validity of US has been recently tested in more than one study focused either on the evaluation of Achilles tendon enthesis or on a comprehensive assessment of enthesitis in SpA (1-3, 5). US is widely available, safe, relatively inexpensive, and can give much information on peripheral enthesis abnormalities. OMERACT definition of enthesopathy has been recently published and US-detectable changes indicative of enthesis involvement have been described (10). Sonography is, however, weighted down by a long learning curve that still represents a barrier to a widespread use of this tool in the clinical practise and to wide development of multi-centre research studies. Furthermore, it is still considered a highly operator-depend-

ent technique. Main variability in the sonographic assessment of enthesis lesions is related to acquisition of US images, due to inadequate inclination or positioning of the transducer which produce interface and/or thickness artefacts, hence causing possible errors and misinterpretations, even when US is performed by experienced operators. The complex anatomy of enthesis accounts for the emergence of additional difficulties in the detection of local abnormalities in SpA patients.

However, in recent times, technological advances have enabled sonographic exploration of musculoskeletal system by using high-frequency volumetric probes (7, 11, 15-17). These kinds of transducers provide the possibility of acquiring an infinite number of 2D US images within a 3D data set which are generated automatically, during electronic probe sweeping (18-22). This new technology proposes to rectify the operator dependency of US in the acquisition process and sensibly shortens examination time (7).

However, before promoting the use of any method, it is essential to demonstrate its validity and reproducibility. Recent studies have shown that 3D US is a valid modality for evaluating joint tissue changes in inflammatory arthritis and osteoarthritis (18-22). Concordance between independent operators in the acquisition of 3D US imagery has been recently tested in the hand joints of healthy individuals (15). Interesting results have been obtained in this preliminary study which showed that previous US experience or skills are not necessary for obtaining US images indistinguishable from those of the experts. For the first time that exercise verified the operator independent nature of the 3D volumetric probe in acquiring US images of the metacarpophalangeal joints in healthy subjects (15).

More recently, another interesting study designed to compare 3D centralised reading and 2D US findings indicative of joint involvement in patients with rheumatoid arthritis (11). The results indicated that good-to-excellent agreement rates can be obtained for both joint inflammation and structural damage, demonstrating the operator independency of 3D US in the image acquisition process (11).

To the best of our knowledge, this is the first study designed to compare 2D and 3D US in the assessment of Achilles tendon enthesitis in SpA patients. The validity of 3D US in the analysis of single basic findings was investigated by comparing it with conventional 2D US, both by using grey-scale and power Doppler sonography. Moreover, basic changes related to inflammation and structural damage were assembled in two groups and separately analysed (3). Four to six weeks after acquisition, the same expert operators separately evaluated 3D US stored cubes of all enthesis, thus guaranteeing the blindness in image reading.

A high number of Achilles tendon enthesis were examined in the present study and the analysis of each basic US finding both related to inflammation and structural damage demonstrated from good to excellent agreement rates between the two modalities. Similar results were found both in dichotomous assessment of sonographic lesions and in the use of semi-quantitative grading, confirming the validity of the 3D assessment. Even when investigating the overall enthesis involvement by separate analysis (groups I and II) of results, excellent agreement between the two modalities was demonstrated, thus confirming the validity of this new US tool in the assessment of both inflammatory changes and structural lesions.

The availability of valid and reproducible imaging modalities to detect and quantify enthesis inflammation and damage is necessary for improving assessment of peripheral lesions in SpA patients and evaluate disease progression. Our study for the first time demonstrated that 3D US is a valid imaging modality for the assessment of Achilles tendon enthesitis. However, more studies are warranted focussing on the evaluation of other peripheral enthesis and to response to local and systemic treatment in researches aimed to assess also responsiveness to change of this new US tool.

Link

For ultrasound images, go to www.clinexprheumatol.org/ultrasound

References

1. D'AGOSTINO MA, SAID-NAHAL R, HACQUARD-BOUDER C *et al*.: Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003; 48: 523-33.
2. 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.
3. FILIPPUCCI E, AYDIN SZ, KARADAG O *et al*.: Reliability of high-resolution ultrasonography in the assessment of Achilles tendon enthesopathy in seronegative spondyloarthropathies. *Ann Rheum Dis* 2009; [Epub ahead of print].
4. BALINT PV, KANE D, WILSON H *et al*.: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 905-10.
5. DE MIGUEL E, COBO T, MUÑOZ-FERNÁNDEZ S *et al*.: Validity of enthesis ultrasound assessment in spondylarthropathy. *Ann Rheum Dis* 2009; 68: 169-74.
6. MEENAGH G, FILIPPUCCI E, DELLE SEDIE A *et al*.: Ultrasound imaging for the rheumatologist XIX. Imaging modalities in rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 3-6.
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.
8. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al*. and the EUROPEAN SPONDYLARTHROPATHY STUDY GROUP: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
9. IAGNOCCO A, EPIS O, DELLE SEDIE A *et al*.: Ultrasound imaging for the rheumatologist XVII. Role of colour Doppler and power Doppler. *Clin Exp Rheumatol* 2008; 26: 759-62.
10. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
11. FILIPPUCCI E, MEENAGH G, DELLE SEDIE A *et al*.: Ultrasound imaging for the rheumatologist. XX. Sonographic assessment of hand and wrist joint involvement in rheumatoid arthritis: comparison between two- and three-dimensional ultrasonography. *Clin Exp Rheumatol* 2009; 27: 197-200.
12. LANDIS JR, KOCH GG: The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159-74.
13. MCGONAGLE D, KHAN MA, MARZO-ORTEGA H *et al*.: Enthesitis in spondyloarthropathy. *Curr Opin Rheumatol* 1999; 11: 244-25.
14. MCGONAGLE D, MARZO-ORTEGA H, O'CONNOR P *et al*.: Histological assessment of the early enthesitis lesion in spondyloarthropathy. *Ann Rheum Dis* 2002; 61; 534-7.
15. FILIPPUCCI E, MEENAGH G, DE AGUSTIN JJ *et al*. Level of agreement between rheumatologists on US image acquisition using a 3D volumetric probe. *Clin Exp Rheumatol* 2007; 25: 116.

16. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al*.: Ultrasound imaging for the rheumatologist. *Clin Exp Rheumatol* 2006; 24: 1-5.
17. DOWNEY DB, FENSTER A, WILLIAMS JC: Clinical utility of three-dimensional US. *Radiographics* 2000; 20: 559-71.
18. MEENAGH G, FILIPPUCCI E, ABBATTISTA T *et al*.: Three-dimensional power Doppler sonography in short-term therapy monitoring of rheumatoid synovitis. *Rheumatology* 2007; 46: 1736.
19. STRUNK J, LANGE U: Three-dimensional power Doppler sonographic visualization of synovial angiogenesis in rheumatoid arthritis. *J Rheumatol* 2004; 31: 1004-6.
20. STRUNK J, STRUBE K, MÜLLER-LADNER U *et al*.: Three dimensional power Doppler ultrasonography confirms early reduction of synovial perfusion after intra-articular steroid injection. *Ann Rheum Dis* 2006; 65: 411-2.
21. STRUNK J, STRUBE K, RUMBAUR C *et al*.: Inter-observer agreement in two- and three-dimensional power Doppler sonographic assessment of synovial vascularity during anti-inflammatory treatment in patients with rheumatoid arthritis. *Ultraschall Med* 2007; 28: 409-15.
22. JU JH, KANG KY, KIM IJ *et al*.: Three-dimensional ultrasonographic application for analyzing synovial hypertrophy of the knee in patients with osteoarthritis. *J Ultrasound Med* 2008; 27: 729-36.