

## ORIGINAL ARTICLE

# Chronic but not inflammatory changes at the Achilles' tendon differentiate patients with peripheral spondyloarthritis from other diagnoses – Results from a prospective clinical trial

Xenofon Baraliakos,<sup>1</sup> Uta Kiltz,<sup>1</sup> Heiner Appel,<sup>2</sup> Friedrich Dybowski,<sup>3</sup> Manfred Igelmann,<sup>4</sup> Ludwig Kalthoff,<sup>3,4</sup> Claudia Klink,<sup>5</sup> Dietmar Krause,<sup>5</sup> Ertan Saracbasi,<sup>6</sup> Elmar Schmitz-Bortz,<sup>7</sup> Feras Rahmeh,<sup>8</sup> Juergen Braun<sup>1</sup>

**To cite:** Baraliakos X, Kiltz U, Appel H, *et al.* Chronic but not inflammatory changes at the Achilles' tendon differentiate patients with peripheral spondyloarthritis from other diagnoses – Results from a prospective clinical trial. *RMD Open* 2017;**3**:e000541. doi:10.1136/rmdopen-2017-000541

Part of this work was presented at the ACR meeting 2013.

Received 16 July 2017  
Revised 23 November 2017  
Accepted 24 November 2017



CrossMark

For numbered affiliations see end of article.

#### Correspondence to

Dr Xenofon Baraliakos, Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum; xenofon.baraliakos@elisabethgruppe.de

#### ABSTRACT

**Background** Imaging has an essential role in the new spondyloarthritis (SpA) classification criteria for axial but not for peripheral manifestations. We evaluated the impact of imaging findings for identification and treatment decisions in patients with peripheral spondyloarthritis (pSpA) and controls (non-SpA).

**Methods** Patients with pSpA (Assessment of SpA international Society criteria, n=30) and non-SpA (n=30), aged <45 years, with painful heels or knees, were recruited. Conventional radiography, grey-scale ultrasound including power Doppler (US/PDUS) and MRI of symptomatic areas were performed to assess inflammatory and structural changes. Mann-Whitney U test was used for group comparisons.

**Results** In total, 105 painful entheses (71 heels, 34 knees) in 60 patients were examined. Differences between diagnoses were found for symptom duration (pSpA: 17.2±27.5 vs non-SpA: 4.4±4.3 months), human leucocyte antigen B27 prevalence (67% vs 13%) and gender distribution (53.3% vs 20% male, respectively), all P<0.05. Logistic regression analysis for baseline differences showed that chronic changes (erosions and calcification) in the heel were more frequent in pSpA versus non-SpA by US/PDUS (62.5% vs 28.6% patients and 59.5% vs 26.5% entheses, P<0.05). Inflammatory changes in heel or knee by US/PDUS and MRI could not differentiate between non-SpA and pSpA.

**Conclusions** Differentiation between pSpA and non-SpA was only possible based on structural but not inflammatory changes in the heels and knees of symptomatic patients. US/PDUS was superior to MRI for this purpose. These findings imply that pSpA is associated with erosive changes at enthesitic sites, while inflammation and susceptibility are of minor influence for the development of erosions and calcification to pSpA.

#### INTRODUCTION

The term spondyloarthritis (SpA) covers non-radiographic axial SpA (nr-axSpA),

#### Key messages

##### What is already known about this subject?

- ▶ The concept of peripheral spondyloarthritis (pSpA) relies mainly on peripheral symptoms, but imaging characteristics are not well studied.

##### What does this study add?

- ▶ This is the first study to prospectively compare imaging findings in pSpA and controls.
- ▶ Identification of patients with pSpA in daily practice may not only rely on active but frequently also on chronic changes.

##### How might this impact on clinical practice?

- ▶ Chronic changes are more relevant for the differentiation between spondyloarthritis (SpA) and non-SpA than active changes such as enthesitis.

ankylosing spondylitis (AS) and peripheral spondyloarthritis (pSpA). The SpAs are characterised by inflammatory and structural changes in the axial skeleton and in peripheral joints and entheses. Enthesopathy of the lower limbs and especially of the heels is a typical feature of SpA, which is predominant in pSpA,<sup>1,2</sup> while nr-axSpA and AS mainly affect the axial skeleton.<sup>3</sup> Clinical assessment of peripheral symptoms, including peripheral enthesitis, is included in the core set of the Assessment of SpA international Society (ASAS)<sup>4</sup> for evaluation of SpA disease controlling and treatment. The term enthesitis is commonly used for referring to inflammatory enthesal involvement and is included in the overall term of enthesopathies,

**Table 1** Detailed demographics and clinical characteristics of the patients in both groups that were examined in this study

Parameter	pSpA (n=30)	non-SpA (n=30)	P value
Male gender (%)	53.3	20.0	0.008
Age (years, mean±SD)	37.5±5.9	36.9±7.7	0.694
CRP (mg/dL) mean±SD	0.54±0.9	0.58±0.9	0.473
ESR (mm/1 hour, mean±SD)	15.2±18.4	14.9±11.5	0.486
HLA-B27 positive (%)	66.7%	13.3%	0.001
Symptom duration (months)	17.2±27.5	4.4±4.3	0.005
PatGA (0–10, mean±SD)	5.6±1.6	6.5±2.5	0.066
PhysGA (0–10, mean±SD)	5.2±1.4	6.1±2.2	0.099
BASDAI (0–10, mean±SD)	5.3±2.9	–	–
ASDAS (mean±SD)	2.1±β.7	–	–
BASFI (0–10, mean±SD)	4.7±2.3	–	–
ASQoL (mean±SD)	9.9±5.2	–	–
NSAIDs intake (% patients)	66.7	56.7	0.430
NSAID index (mean±SD)	37.0±42.2	22.4±30.6	0.161
Steroids intake (% patients)	23.3	26.7	0.767
DMARDs intake (% patients)	16.7	33.3	0.139
Biologics intake (% patients)	20.0	13.3	0.492

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; non-SpA, other diagnoses than spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; PatGA, patients' global assessment; PhysGA, physicians' global assessment; pSpA, peripheral spondyloarthritis.

together with the occurrence of tendon or ligament pathology detected as loss of normal echostructure and/or thickening, as described in a consensus definition of the Outcome Measures in Rheumatology Clinical Trials Ultrasound Group.<sup>5</sup> In daily practice, patient's complaints and clinical investigation are the features that most physicians will rely on for decision-making with respect to individual treatment of patients with enthesopathy. Due to the increasing availability and knowledge about the use of imaging procedures in the last decade, imaging techniques such as ultrasound (US)<sup>6–8</sup> including power Doppler (PD) US<sup>9</sup> and MRI<sup>10–11</sup> are playing and increasing role in the assessment of axial and peripheral symptoms in patients with SpA.<sup>9–12</sup> Scoring systems for the evaluation and quantification of enthesitic lesions especially in the lower limbs have been introduced.<sup>6–7,13</sup>

However, and despite these efforts, imaging has an essential role in the new SpA classification criteria for axial<sup>3</sup> but not for peripheral<sup>14</sup> manifestations. This is largely due to limited knowledge about the value of imaging to detect peripheral arthritis and enthesitis in SpA and also about its ability to differentiate SpA from other rheumatic or non-rheumatic conditions (non-SpA).<sup>15</sup>

The aim of this study was to evaluate the value of imaging procedures commonly used in daily practice for the differential diagnosis of patients with peripheral involvement of the lower limbs in pSpA versus non-SpA, with a primary hypothesis that the two conditions can be differentiated. In addition, the influence of imaging on treatment decision in those patients was evaluated.

## METHODS

All patients gave informed consent for participation in the study (study number: 3988–11). All patients gave written consent to participate in the study and for publication of their data as results of the study.

### Patient selection and examination procedures

Patients were recruited either by their treating rheumatologists working in a private setting or by the outpatient clinic of our tertiary rheumatology hospital (Rheumazentrum Ruhrgebiet). According to the study protocol, patients were asked to participate in the study if they either visited their rheumatologist because of a painful heel or knee or if there was a finding of heel or knee pain after taking a history or at the physical examination (the sites of interest are described in [table 2A](#), where also the imaging examinations were performed in a standardised manner). In addition, the physician had to confirm based on the clinical examination that the pain was located in the entheses of the same sites. However, the physicians were told to not proactively provoke tenderness at these sites in order not to include patients in the study without an appropriate reason. 'Enthesitic' pain was defined as pain precisely localised at the area of the tendon insertion at the bone, which was also present or worsened by local pressure at exactly the same area. Any signs of tendinopathy differing from this definition were not taken into account. In addition, patients with swelling in the respective painful joints were also not recruited, in order to avoid painful sites due to swelling and misinterpretation of the clinical and imaging results.

All patients had to be ≤45 years of age at the time point of the investigation to be included in the study. Furthermore, the recruiting rheumatologist had to set the diagnosis of pSpA or non-SpA. In addition, the study protocol required that all patients with the diagnosis of pSpA had also to fulfil the classification to pSpA as described in ASAS.<sup>14</sup> Even though some patients recognised with pSpA also had axial involvement, they were all classified as pSpA because their predominant symptoms were peripheral (heel or knee). Non-SpA patients could have any other rheumatological diagnosis. Exclusion criteria

were a contraindication for conventional radiographs and MRI examinations, the primary diagnosis of psoriatic arthritis (PsA) and any previous surgery in the heel or knee that was currently painful for enthesitis.

After fulfilling the informed consent, all patients were sent to the Rheumazentrum Ruhrgebiet where they were examined clinically by another experienced rheumatologist ('examiner') for assessment of pain in the sites that were previously reported to be painful. This examination was performed within 2 working days after the examination of the recruiting rheumatologist. The 'examiner' was blinded for the patient's diagnosis throughout the study. In case of more than one painful heel or knee per patient, all painful heels or knees of the same patient were assessed by the examiner. Non-painful areas were not examined by the 'examiner' and not included in the study. At the time of presentation to the 'examiner', also patient's pain level and physician's judgement of impairment due to enthesitic pain on a 0–10 Numeric Rating Scale in the symptomatic sites were recorded.

For patients with pSpA, disease activity (Bath AS Disease Activity Index<sup>16</sup>) and function (Bath AS Functional index<sup>17</sup>), AS Disease Activity Score<sup>18</sup> and the AS Quality of Life Questionnaire<sup>19</sup> were assessed but were not shown to the 'examiner' and were entered in the electronic data analysis sheet at the end of the study. In addition, the non-steroidal anti-inflammatory drug (NSAID) intake of all patients was calculated according to recently proposed ASAS index<sup>20</sup> and documented in the same manner as for the patient's reported outcomes described above.

After clinical examination of the enthesitic pain (performed without knowledge of the patient's diagnosis), the 'examiner' set a decision on the possible further treatment (eg, analgesics only, local corticosteroid injection, non-steroidal antirheumatic drugs, disease-modifying antirheumatic drugs (DMARDs)) of each patient based on his clinical findings and diagnostic assumption only and recorded this decision. Thereafter, on the same day, a conventional radiograph and US/PD of all painful sites was performed by the 'examiner'. MRI examinations of the same sites were also performed either on the same day or during the following day (without change of medication prior to performance of MRI) and were evaluated also by the 'examiner'. Documentation of the US/PD and MRI findings was performed by a standardised scoring sheet that included all possible imaging findings for inflammatory and chronic lesions (see the Evaluation of imaging section and also the description of the lesions in table 2). After performance and evaluation of all imaging procedures, the 'examiner' took the imaging results into consideration and re-evaluated his initial treatment decision. Changes in this decision were documented for more intensive versus equal versus less intensive treatment. The examiner also noted the imaging findings that lead to the decision of adjustment of treatment.

### Imaging protocols

Conventional radiographs were performed using the sagittal view for the heel and both the sagittal and the anteroposterior view for the knee.

US/PD examinations were performed with the patients lying prone and their feet hanging relaxed over the edge of the examination table.

MRI examinations were performed in T1-sequences before and after injection of contrast agent (gadolinium), with a slice thickness of 3–4 mm and sagittal, coronal and axial slice orientation, according to the standard protocol of our hospital.

### Evaluation of imaging

All images were evaluated by the examiner, who is an experienced reader for interpretation of conventional radiographs and MRIs.

Conventional radiographs were evaluated for any pathological findings at the clinically painful sites.

Assessment of enthesitic pain by US/PD and MRI included the following sites, based on the features collected as proposed in different US scoring systems for enthesitis in SpA<sup>6 7 13</sup> and using the definitions of<sup>5</sup> (used similarly for both US/PD and MRI):

#### Inflammatory changes

Intratendinous or peritendinous inflammatory signal.

Bone marrow oedema at the painful sites (MRI examinations only).

#### Chronic changes

Thickness of the painful tendon at the area of clinical enthesitic symptoms. For patients with heel pain, the thickness of the Achilles' tendon and plantar fascia was measured, while for patients with knee pain, the thickness of the quadriceps tendon at the upper and the lower patellar pole and at the tibial tuberosity was measured.

Normal versus pathological finding of fibrous structure including rupture of the painful tendon.

Bone erosion (defined as cortical disruption and loss of continuity) or calcification/enthesophyte formation at the site of examination.

In cases where not only sole chronic or only sole inflammatory findings but a combination of different chronic or different inflammatory findings was found (eg, combination of erosions and calcification and/or osteophytes in the calcaneus), this was considered as one chronic finding. Similarly, the combination of intratendinous and/or peritendinous inflammatory involvement and bone marrow oedema (on MRI) was considered as one inflammatory finding. In case of coexisting inflammatory and chronic changes, both changes were recorded separately for chronic and for inflammatory changes.

### Statistical analysis

Comparisons of imaging findings were performed on patient basis but also based on single enthesitic sites. Continuous data are presented in a descriptive manner, and binary data (*presence of a lesion yes/no*) are presented

as proportion of patients or sites being positive or negative. Comparisons of the baseline characteristics between both diagnoses were made by Mann-Whitney U test. Since from all baseline characteristics the duration of enthesitic symptoms, gender distribution and human leucocyte antigen (HLA) B27 status were found to be different between groups, comparison of the imaging findings was performed by univariate logistic regression analysis adjusted for these parameters. All analyses were performed using SPSS V.21.0.

## RESULTS

### Patient characteristics

A total of 60 patients were included, 30 with the diagnosis of pSpA and 30 with other diagnoses (non-SpA), and a total of 105 entheses, 71 heels and 34 knees were reported to be clinically painful and were evaluated.

In the SpA group, 16 patients also reported axial symptoms, and in the non-SpA group, 9 patients were diagnosed with rheumatoid arthritis, 8 with achillobodynia, 4 with osteoarthritis of the hands, 2 with sarcoidosis (Löfgren's syndrome) and 1 each with adult Still's disease, systemic lupus, undifferentiated arthritis of the ankle, undifferentiated connective tissue disease and a degenerative heel spur.

The groups were similar for most demographic assessments but not for mean symptom duration of enthesitic pain (pSpA: 17.2±27.5 vs non-SpA: 4.4±4.3 months,  $P=0.005$ ), HLA-B27-positive status (pSpA: 66.7% vs non-SpA: 13.3%,  $P=0.001$ ) and gender distribution (pSpA: 53.3% male patients vs non-SpA: 20% male patients,  $P=0.008$ ). At the time of examination, <66% of patients were taking NSAIDs, <35% DMARDs and <20% biologics in both groups. The detailed demographics and clinical characteristics of the patients in both groups are shown in [table 1](#).

### Clinical evaluation

Of the 30 patients with pSpA, 17 (56.7%) reported heel symptoms only, 6 (20%) reported knee symptoms only and 7 (23.3%) reported symptoms in at least one heel and at least one knee. In comparison, of the 30 patients with non-SpA, 14 (46.7%) reported heel symptoms only, 8 (26.7%) reported knee symptoms only and another 8 (26.7%) reported symptoms in at least one heel and at least one knee.

Of the 105 entheses, 37 heels and 13 knees were assessed in patients with pSpA and 34 heels and 21 knees were assessed in patients with non-SpA.

No single findings in the clinical assessment were able to differentiate between pSpA and non-SpA, but there was a numerical trend towards lower scores in patients' global assessment in patients with pSpA (5.6±1.6) versus non-SpA (6.5±2.5), which was similar also in the physicians' global assessment ([table 1](#)).

After the clinical evaluation, a modification of the current treatment for enthesitic pain was proposed in

14/30 (46.7%) patients with pSpA and in 17/30 (56.7%) non-SpA patients ( $P=0.53$ ).

### Imaging findings

In the analysis on a basis *per lesion*, significant differences between patients with pSpA and those with no SpA were found for bone erosions at the insertion of the Achilles' tendon as assessed by US, with 59.5% lesions found in patients with pSpA versus 26.5% lesions found in non-SpA patients ( $P=0.008$ ). After adjusting for symptom duration, this difference remained significant ( $P=0.041$ ). In contrast, other comparisons including erosions of the Achilles' tendon as assessed by MRI or inflammatory changes in and around tendons as assessed by both imaging techniques did not show any difference between pSpA and non-SpA. Findings on conventional radiographs could not differentiate between diagnoses at any of the painful sites. Detailed data of all lesions as detected by the different imaging techniques are shown in [table 2A,B](#). An overview about the prevalence of chronic and inflammatory lesions on both US/PD and MRI is shown in [figures 1-3](#).

In the analysis on the prevalence of lesions on a *per patient* basis, similar results were found, with 62.5% patients with pSpA versus 28.6% non-SpA showing bone erosions at the insertion of the Achilles' tendon ( $P=0.036$ ) as assessed by US/PD, while all the other analyses revealed no statistically significant differences between the two groups.

### Impact of imaging on the patient's treatment

After evaluation of US/PD and MRI, a change of medication based on the imaging findings (while the examining physician was still blinded for diagnosis) was decided in an additional 4/30 patients (additional 13.3%) in the SpA group, as compared with the decision based on clinical examination only. In all of these cases, the treatment modification was made towards a more intense anti-inflammatory treatment. In contrast, in the non-SpA group, the initial clinical decision for intensification of treatment by the clinical investigation was confirmed in only 8/17 patients (47%) after imaging, while in the remaining 9/17 patients, the clinical decision was not supported by the imaging result. As noted by the examiner, treatment modification was based on the general impression of the image, without a specific lesion having more or less impact on treatment decisions. Findings on conventional radiographs did not contribute to any change of medication in either group.

## DISCUSSION

This study is the first to examine and compare clinical findings of patients with peripheral SpA and controls who both had heel and/or knee pain with the results of established imaging techniques such as conventional radiographs, US/PD and MRI. In addition, the influence of imaging on clinical decision-making for treatment was analysed in a daily practice setting.

**Table 2A** Detailed data on the prevalence of lesions as assessed by PDUS or MRI

Imaging	Site	Heel	pSpA (n=37)	Non-SpA (n=34)	P value	
PDUS	Plantar fascia	Tendon rupture (total or partial)	0	0	-	
		Accompanying bone erosion	2 (5.4%)	1 (2.9%)	0.609	
	Achilles' tendon	Calcification/enthesophyte	5 (13.5%)	1 (2.9%)	0.112	
		Inflammatory signal (intratendinous)	1 (2.7%)	2 (5.9%)	0.509	
		Tendon rupture (total or partial)	1 (2.7%)	2 (5.9%)	0.509	
		Accompanying bone erosion	22 (59.5%)	9 (26.5%)	0.008	
		Calcification/enthesophyte	5 (13.5%)	3 (8.8%)	0.535	
		Inflammatory signal (intratendinous)	12 (32.4%)	10 (29.4%)	0.785	
	MRI	Plantar fascia	Tendon rupture (total or partial)	1 (2.7%)	2 (5.9%)	0.509
			Accompanying bone erosion	5 (13.5%)	2 (5.9%)	0.285
Achilles' tendon		Calcification/enthesophyte	3 (8.1%)	1 (2.9%)	0.349	
		Inflammatory signal (peritendinous)	9 (24.3%)	11 (32.4%)	0.456	
		Inflammatory signal (intratendinous)	3 (8.1%)	4 (11.8%)	0.608	
		Inflammatory signal (bone marrow oedema)	3 (8.1%)	2 (5.9%)	0.716	
		Tendon rupture (total or partial)	0	0	-	
		Accompanying bone erosion	12 (32.4%)	10 (29.4%)	0.785	
			Calcification/enthesophyte	0	0	-
			Inflammatory signal (peritendinous)	16 (43.2%)	18 (52.9%)	0.417
	Inflammatory signal (intratendinous)		7 (18.9%)	5 (14.7%)	0.638	
	Inflammatory signal (bone marrow oedema)		7 (18.9%)	6 (17.6%)	0.891	

Continued

Table 2A Continued

Imaging	Site	Knee	pSpA (n=13)	Non-SpA (n=21)	P value
PDUS	Tibial tuberosity	Tendon rupture (total or partial)	0	1 (4.8%)	0.431
		Accompanying bone erosion	1 (7.7%)	5 (23.8%)	0.238
		Calcification/enthesophyte	0	0	-
		Intratendinous inflammatory signal	4 (30.8%)	4 (19%)	0.440
		Tendon rupture (total or partial)	0	0	-
		Accompanying bone erosion	0	0	-
		Calcification/enthesophyte	0	0	-
		Intratendinous inflammatory signal	5 (38.5%)	7 (33.3%)	0.765
		Tendon rupture (total or partial)	0	0	-
	Accompanying bone erosion	1 (7.7%)	0	0.204	
	Calcification/enthesophyte	0	0	-	
	Intratendinous inflammatory signal	3 (23.1%)	10 (47.6%)	0.159	
	MRI	Tibial tuberosity	Tendon rupture (total or partial)	0	0
Accompanying bone erosion			0	0	-
Calcification/enthesophyte			0	1 (4.8%)	0.431
Inflammatory signal (peritendinous)			6 (46.2%)	5 (23.8%)	0.182
Inflammatory signal (intratendinous)			1 (7.7%)	2 (9.5%)	0.857
Inflammatory signal (bone marrow oedema)			0	1 (4.8%)	0.431
Tendon rupture (total or partial)			0	0	-
Accompanying bone erosion			0	0	-
Calcification/enthesophyte			0	0	-
Distal patellar tendon		Inflammatory signal (peritendinous)	0	3 (14.3%)	0.160
		Inflammatory signal (intratendinous)	0	0	-
		Inflammatory signal (bone marrow oedema)	0	0	-
		Tendon rupture (total or partial)	0	0	-
Proximal patellar tendon	Accompanying bone erosion	1 (7.7%)	2 (9.5%)	0.857	
	Calcification/enthesophyte	0	0	-	
	Inflammatory signal (peritendinous)	1 (7.7%)	0	0.204	
	Inflammatory signal (intratendinous)	0	0	-	
Inflammatory signal (bone marrow oedema)	0	0	-		

PDUS, power Doppler ultrasound; pSpA, peripheral spondyloarthritis; SpA, spondyloarthritis.

**Table 2B** Detailed data on the measurements by PDUS and MRI of the tendons in the knee and heel

Examination site: tendon thickness	Imaging modality	pSpA	Non-SpA	P value	
		Mean±SD			
Knee	Proximal patellar tendon	PDUS	0.36±0.10	0.39±0.12	0.845
		MRI	0.39±0.07	0.39±0.06	0.929
	Distal patellar tendon	PDUS	0.37±0.08	0.36±0.11	0.522
		MRI	0.35±0.07	0.32±0.05	0.220
Tibial tuberosity	PDUS	0.35±0.08	0.37±0.10	0.558	
	MRI	0.34±0.08	0.34±0.05	0.922	
Heel	Achilles' tendon	PDUS	0.43±0.09	0.43±0.08	0.940
		MRI	0.43±0.09	0.40±0.06	0.077
	Plantar fascia	PDUS	0.26±0.05	0.27±0.05	0.917
		MRI	0.22±0.05	0.22±0.06	0.742

All values are measurements in millimetre±SD.

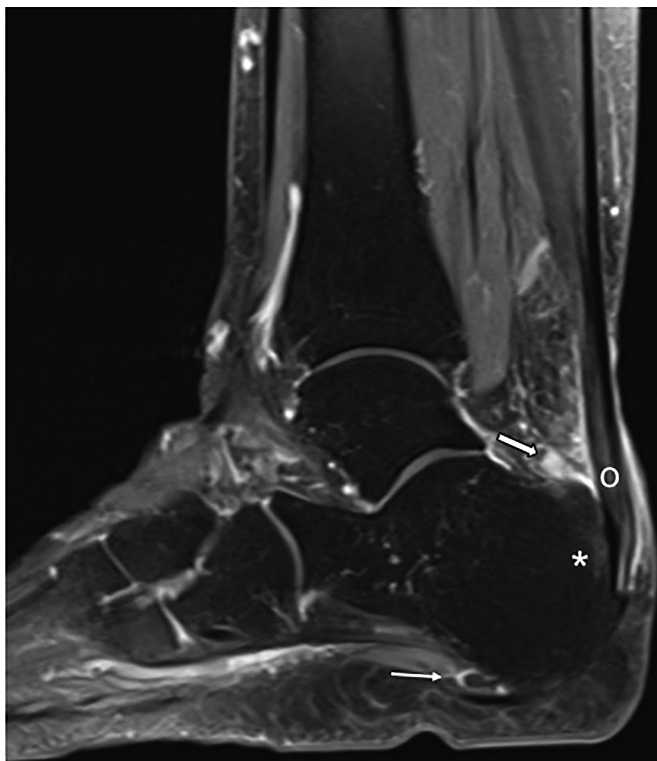
PDUS, power Doppler ultrasound; pSpA, peripheral spondyloarthritis; SpA, spondyloarthritis.

The most interesting finding of this study is that it was rather the erosive changes at the heel entheses and not the active inflammatory changes that were more frequent in patients with pSpA. This is in contrast to the landmark paper of McGonagle *et al.*<sup>21</sup> who reported enthesitis to be the main differentiating factor in patients with symptomatic knee arthritis with rheumatoid arthritis versus SpA (mostly PsA). Since the patients participating in the

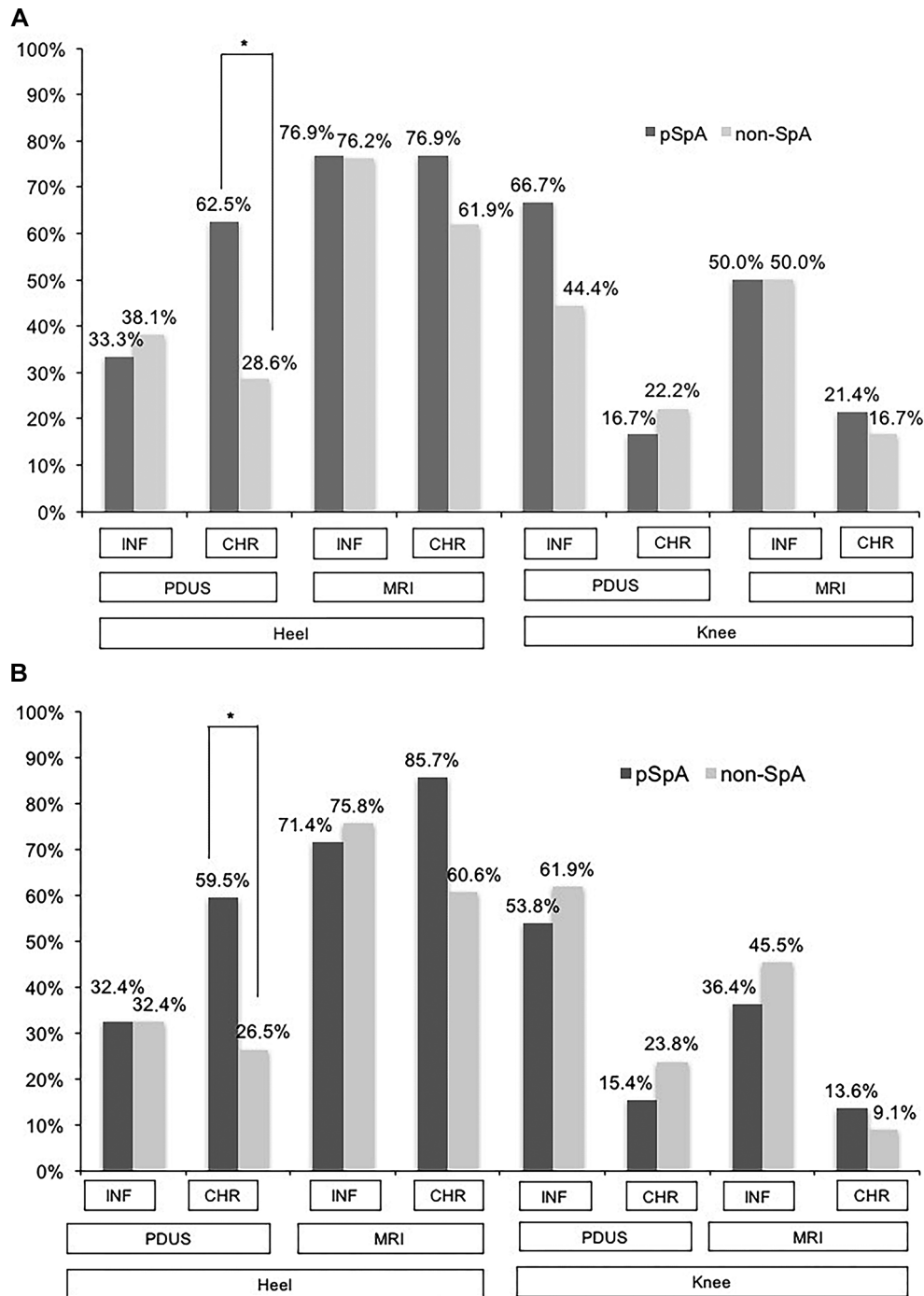
present study were included only with apparent clinical symptoms, we think that it fits to the imaging finding that there was a significant difference in the mean age between the groups and this, although the patients were all included based on their current age <45 years. However, formal proof of that will have to include a reinvestigation of the patients after some time to confirm the higher prevalence of chronic, postinflammatory changes in patients with pSpA compared with other diseases with similar symptoms and pathology. Our observation and the associated hypothesis may imply that, in patients with pSpA with an enthesal affection of the lower limbs, structural changes at these sites occur more frequently and probably earlier than in other diseases, which would also explain the longer symptom duration. However, we think that, if confirmed in other studies, our findings may become clinically even more important, since they indicate that, in patients, the item 'enthesitis', which is important in the ASAS classification criteria, may have to be reversed to 'enthesopathy confirmed by imaging'.

The high prevalence of HLA-B27 found in patients with pSpA was expected. From our data, however, it appears that the occurrence of HLA-B27 may not so much be associated with susceptibility but rather with chronicity of enthesal pathology. This would be in line with older data in reactive arthritis<sup>22</sup> and recent data of limited spinal inflammation in non-SpA patients, which are unlikely to develop into syndesmophytes as has been shown to occur in axSpA.<sup>23</sup> However, as already mentioned, these data should be confirmed in other studies and centres.

Interestingly and not really expected, we obtained the same rate of inflammatory changes in patients with non-SpA as compared with pSpA in both the heel and the knee examinations. One reason to explain this result might be that definition used for imaging abnormalities was obtained based on the publication that has been used in our hospital<sup>5</sup> but is slightly different from the most recent definitions published by Terslev *et al.*<sup>24</sup> A less



**Figure 1** Example of pathological MRI (T1-weighted sequence after gadolinium) of the ankle from a patient with peripheral spondyloarthritis (female, 46 years). 'O', tendinitis; \*, bone marrow oedema; fat arrow, sub-Achillean bursitis; thin arrow, oedema in the tendon of the plantar aponeurosis, in this case due to a plantar spur.

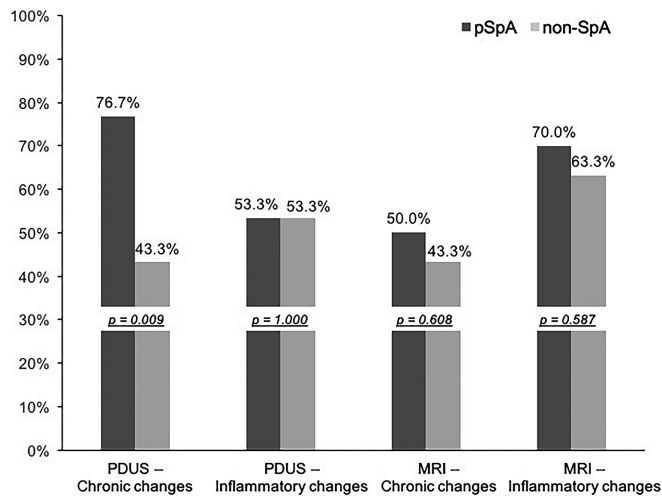


**Figure 2** (A) Detailed comparison of the prevalence of *single pathological lesions* in both heel and knee in patients with SpA and non-SpA patients, as assessed by PD and MRI for both inflammatory and chronic changes. \* $P=0.008$ . (B) Detailed comparison of the prevalence of pathological lesions on a *per patient basis* in both heel and knee in patients with SpA and non-SpA, as assessed by PD and MRI for both inflammatory and chronic changes. \* $P=0.036$ . CHR, chronic structural lesion; INF, inflammatory lesion; PD, power Doppler; PDUS, power Doppler ultrasound; pSpA, peripheral spondyloarthritis; SpA, spondyloarthritis.

stringent definition of (inflammatory) abnormalities in our dataset might explain the relatively high prevalence of inflammatory abnormalities in controls, as compared with pSpA. Comparable data have been previously published in examinations of the heel only in patients with predominantly axial SpA or non-inflammatory back pain independent of the presence of peripheral symptoms<sup>15</sup> and

also in an earlier study that investigated patients with SpA-associated clinical symptoms and mechanically induced enthesopathy of the plantar fascia.<sup>25</sup> Limitations of MRI to depict inflammation in the axial skeleton of patients with AS have been recently reported in two studies, in which histological examinations had been performed for direct comparisons.<sup>26 27</sup> Whether the same would apply





**Figure 3** Prevalence of any pathological finding for inflammation (intratendinous or peritendinous inflammatory signal, bone marrow oedema at the painful sites) or chronic (thickness of painful tendon, pathological finding of fibrous structure including rupture of the painful tendon, bone erosion or calcification/enthesophyte formation at the site of examination) changes in the lower limbs (heel and knee) between patients with SpA and no SpA. The numbers given are proportions of sites being positive for inflammatory or chronic changes in PD and MRI in both heel and knee. Overall, only the difference between pSpA and non-SpA for chronic changes as assessed by PD was statistically significant. This finding was mainly based on the difference for bone erosions at the insertion of the Achilles' tendon. PD, power Doppler; PDUS, power Doppler ultrasound; pSpA, peripheral spondyloarthritis; SpA, spondyloarthritis.

in patients with peripheral involvement in pSpA for comparison with other non-SpA conditions that are not known to be primarily associated with involvement of the entheses of the lower limb is unknown.

As mentioned above, we did not identify any significant differences in the prevalence of other US/PD and MRI findings and no major differences between these techniques. This is different from what has been reported in other studies, where both focal thickening and very early calcification foci in the tendon of the heel or knee area could be more frequently detected by grey-scale US than by MRI.<sup>28,29</sup> With respect to conventional radiographs, it may have been expected that erosive changes in heels and knees should have been more frequently detected. However, probably also due to the young age of the patients, this was not the case here.

Another interesting finding of our study is the different impact of the clinical examination and the imaging results on the physician's treatment decisions in patients presenting with enthesal pain of the lower limbs. Based on clinical examination, there was only a slight difference in the proportion of patients with pSpA (47%) versus non-SpA (57%) in whom the blinded physician failed the decision of treatment modification. However, after inclusion of imaging, this decision changed the result only in patients with pSpA (additional 13%), while in the non-SpA group,

the clinical decision of treatment modification could not be confirmed based on imaging. Interestingly, none of the lesions (neither inflammatory nor structural) assessed was found to be primarily responsible for these decisions, but it was rather the overall impression of the MRI and US/PD examination that drove this decision, while conventional radiographs were not considered to be helpful. In contrast to the inability in differentiation between diagnoses, these findings confirm an important role of US/PD and MRI for decision-making in daily clinical rheumatology practice in patients with SpA in general and with pSpA in particular. Furthermore, and since imaging in pSpA leads to an increase in the proportion of patients needing more intensive treatment, our findings confirm the knowledge that clinical examination underestimates (the frequently silent) enthesitic involvement, as compared with findings obtained by imaging.<sup>6,30-32</sup>

This study has some limitations. First of all, we did not assess the asymptomatic sites of the patients included but concentrated only on the sites where patients claimed to be painful prior to examination and which were the reasons for them to visit a rheumatologist. Definitely, an analysis of the clinically not painful sites of the same patients would have been interesting for examination of so-called 'silent' lesions. However, due to the limited resources especially for MRI examinations for all tendons in all patients, this analysis was not possible in the present study, and therefore, this information was not collected. The fact that all examinations were performed by one physician could also be considered as a limitation. Nevertheless, the examining physician is an experienced person in the use and interpretation of imaging with the different techniques used here. In addition, this physician was blinded for the diagnosis of the patients during the entire period of the examinations, in order not to influence the interpretation of the images and treatment decision before and after imaging. In fact, we believe that this approach is rather an advantage, since this person could perform US/PD and evaluate imaging results also from radiographs and MRI based on the clinical complaints and his own findings after clinical examinations before the final treatment decision. This procedure excludes faults in interpretation, if secondary physicians who were not involved in clinical examination would have evaluated the images.

In conclusion, in symptomatic patients with peripheral knee or heel involvement, the prevalence of inflammatory lesions, including enthesitis, was similar in patients classified as peripheral SpA based on the ASAS classification criteria and in those with other diagnoses. Imaging modalities such as MRI and US/PD could not differentiate between diagnoses; however, erosive changes were more frequently prevalent in patients with pSpA. Together with the higher prevalence of HLA-B27 in patients with pSpA, it seems that it is rather the chronicity than the susceptibility of the symptoms that is associated with SpA. Furthermore, imaging (US/PD and MRI) of symptomatic sites was associated with an increase in anti-inflammatory treatment in patients with pSpA but not in those with non-SpA.

Overall, these findings add to the up to now only limited knowledge about the role of imaging in patients with pSpA according to the ASAS classification criteria.

#### Author affiliations

- <sup>1</sup>Rheumazentrum Ruhrgebiet, Herne, Germany  
<sup>2</sup>Practice for Internal Medicine and Nephrology, Herne, Germany  
<sup>3</sup>Rheumatology Practice Ruhr, Herne, Germany  
<sup>4</sup>Rheumatology Practice Bochum, Bochum, Germany  
<sup>5</sup>Rheumatology Practice Gladbeck, Gladbeck, Germany  
<sup>6</sup>Rheumatology Practice Oberhausen, Oberhausen, Germany  
<sup>7</sup>Rheumatology Practice Hattingen, Hattingen, Germany  
<sup>8</sup>Orthopaedic Practice Neuwied, Neuwied, Germany

**Acknowledgements** We thank all participating patients for their willingness to participate in this study.

**Contributors** XB: idea, study organisation, patient examination, statistical analysis, writing of manuscript. JB: idea, study organisation, writing of manuscript. UK, HA, FD, MI, LK, CK, DK, ES, ES-B and FR: recruitment of patients, comments on manuscript. FR: study organisation.

**Funding** This study was supported by an unrestricted research grant from Pfizer Germany after an independent external project review process. The grant was used for performance of the imaging techniques, laboratory examinations and data documentation.

**Disclaimer** Pfizer had no influence on study design, protocol, patient selection, treatment, interpretation of results or writing of the manuscript.

**Competing interests** None declared.

**Ethics approval** Ethical Committee of the Ruhr-University of Bochum, Germany.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

## REFERENCES

- Dougados M, van der Linden S, Juhlin R, *et al.* The European spondylarthropathy study group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34:1218–27.
- Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57:85–9.
- Rudwaleit M, van der Heijde D, Landewé R, *et al.* The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
- van der Heijde D, Calin A, Dougados M, *et al.* Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS working group. assessments in ankylosing spondylitis. *J Rheumatol* 1999;26:951–4.
- Wakefield RJ, Balint PV, Szkudlarek M, *et al.* Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005;32:2485–7.
- Balint PV, Kane D, Wilson H, *et al.* Ultrasonography of enthesal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002;61:905–10.
- de Miguel E, Cobo T, Muñoz-Fernández S, *et al.* Validity of enthesal ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009;68:169–74.
- D'Agostino MA. Role of ultrasound in the diagnostic work-up of spondyloarthritis. *Curr Opin Rheumatol* 2012;24:375–9.
- 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.
- Eshed I, Bollow M, McGonagle DG, *et al.* MRI of enthesitis of the appendicular skeleton in spondyloarthritis. *Ann Rheum Dis* 2007;66:1553–9.
- Dougados M, Combe B, Braun J, *et al.* A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: the HEEL trial. *Ann Rheum Dis* 2010;69:1430–5.
- D'Agostino MA, Aegerter P, Bechara K, *et al.* How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power Doppler ultrasonography. *Ann Rheum Dis* 2011;70:1433–40.
- Alcalde M, Acebes JC, Cruz M, *et al.* A sonographic enthesitic index of lower limbs is a valuable tool in the assessment of ankylosing spondylitis. *Ann Rheum Dis* 2007;66:1015–9.
- Rudwaleit M, van der Heijde D, Landewé R, *et al.* The assessment of spondyloarthritis international society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25–31.
- Feydy A, Lavie-Brion MC, Gossec L, *et al.* Comparative study of MRI and power Doppler ultrasonography of the heel in patients with spondyloarthritis with and without heel pain and in controls. *Ann Rheum Dis* 2012;71:498–503.
- Garrett S, Jenkinson T, Kennedy LG, *et al.* A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. *J Rheumatol* 1994;21:2286–91.
- Calin A, Garrett S, Whitelock H, *et al.* A new approach to defining functional ability in ankylosing spondylitis: the development of the bath ankylosing spondylitis functional index. *J Rheumatol* 1994;21:2281–5.
- Machado P, Landewé R, Lie E, *et al.* Ankylosing spondylitis disease activity score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis* 2011;70:47–53.
- Doward LC, Spoorenberg A, Cook SA, *et al.* Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis* 2003;62:20–6.
- Dougados M, Simon P, Braun J, *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis* 2011;70:249–51.
- McGonagle D, Gibbon W, O'Connor P, *et al.* Characteristic magnetic resonance imaging enthesal changes of knee synovitis in spondylarthropathy. *Arthritis Rheum* 1998;41:694–700.
- Leirisalo M, Skylv G, Kousa M, *et al.* Followup study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum* 1982;25:249–59.
- van den Berg R, de Hooge M, van Gaalen F, *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology* 2013;52:1492–9.
- Terslev L, Naredo E, Iagnocco A, *et al.* Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. *Arthritis Care Res* 2014;66:741–8.
- McGonagle D, Marzo-Ortega H, O'Connor P, *et al.* The role of biomechanical factors and HLA-B27 in magnetic resonance imaging-determined bone changes in plantar fascia enthesopathy. *Arthritis Rheum* 2002;46:489–93.
- Appel H, Kuhne M, Spiekermann S, *et al.* Immunohistologic analysis of zygapophyseal joints in patients with ankylosing spondylitis. *Arthritis Rheum* 2006;54:2845–51.
- Gong Y, Zheng N, Chen SB, *et al.* Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. *Arthritis Rheum* 2012;64:1399–406.
- Kamel M, Eid H, Mansour R. Ultrasound detection of knee patellar enthesitis: a comparison with magnetic resonance imaging. *Ann Rheum Dis* 2004;63:213–4.
- Kamel M, Eid H, Mansour R. Ultrasound detection of heel enthesitis: a comparison with magnetic resonance imaging. *J Rheumatol* 2003;30:774–8.
- Mandl P, Niedermayer DS, Balint PV. Ultrasound for enthesitis: handle with care!. *Ann Rheum Dis* 2012;71:477–9.
- Maffulli N, Kenward MG, Testa V, *et al.* Clinical diagnosis of achilles tendinopathy with tendinosis. *Clin J Sport Med* 2003;13:11–15.
- Weckbach S, Schewe S, Michaely HJ, *et al.* Whole-body MR imaging in psoriatic arthritis: additional value for therapeutic decision making. *Eur J Radiol* 2011;77:149–55.