tral feature in SpA and the number of scores elaborated in order to standardize it is high, enthesitis remains underdiagnosed in everyday practice.

Clinically, the chronic lower back pain is the most common symptom of SpA. Other features, such as oligoarthritis and dactilitis are usually accompanied by morning stiffness and fatigue. Usually, SpA presents periods of flare and remission or low disease activity and, progressively, evolves towards a reduced mobility. The definition of flare in SpA is still a work in progress, being based on pain, Bath AS Disease Activity Index (BASDAI), C reactive protein (CRP) and varied combinations, such as the composite index AS Disease Activity Score (ASDAS) [3-8].

AxSpA has an estimated incidence of 0.5%, with a prevalence of 30 per 10.000 persons, or up to 1 per 200 persons and even 1.5% (all SpA) in different studies. The progression from nr-ax-SpA to r-ax-SpA is estimated to 5.1% in 5 years and 19% in 10 years. Even with radiographic changes that occur only after several years, and despite not only having a large number of diagnosed patients, but also a wide range of research, published studies and elaboration of good practices, the general goal of early diagnosis of SpA remains mostly under discussed. Consequently, this leads to the "lost tribe" of patients with structural changes and functional deficit when diagnosed [1,9-11]. The presence of baseline structural damage, as well as the male sex, active disease state, higher inflammatory markers (raised CRP and/or ESR) and smoking, include these patients in a high-risk group for progression [12].

In SpA, the enthesis has benefited from a high level of interest in the last two decades, with rising amount of knowledge on the subject and even the terminology evolving from enthesis to entheseal organ and synovio-entheseal complex [13].

The entheses are fibrocartilaginous structures, arising at the insertion sites of tendons, ligaments, joint capsules or nails. The insertional fibrocartilages is generally prone to microdamage, but avascular and lacking immune cells. SpA patients develop a disproportional degree of inflammation after physiological mechanical stress, with a vessel tissue repair responses and vessel ingrowth activation of pro-inflammatory cytokines tumor necrosis factor (TNF) α and interleukin (IL) 17, accompanied by an inflow of innate immune cells [3,13].

TNF, IL-17 and IL-23-mediated immune pathways have a leading role in triggering enthesitis, while the proliferation process is mediated by IL-22. Gut and exogenous bacteria could also trigger and unleash an immune reaction, with autoimmunity aiming for fibrocartilage peptides, such as the versican or the bone morphogenetic protein (BMP), in particular in patients with a genetic predisposition, given by the presence of the HLA-B27 antigen. Also, triggered by TNF-α and IL-1, BMP-7 mostly, accompanied by BMP-2 and BMP-6 are involved in the new bone formation that follows the entheseal inflammation, leading to peripheral and axial bony spurs, enthesophytes and syndesmophytes. Therefore, enthesitis seems to be a diffuse process in SpA, as has been proved by advanced imaging techniques and biopsy results [14-18].

The diagnostic delay in SpA and, especially, in AS, is reported as 8-10 years and under 6 years in more recent publications [19,20]. The determining factor in the more early diagnosis is most probably the use of imaging, in this case, the Magnetic Resonance Imaging (MRI) in the diagnosis of ax-SpA and the use of Assessment of SpondyloArthritis International Society (ASAS) classification criteria [21,22].

Following this example, imaging of the entheses could be the key for a more early diagnosis of not only periphereal, but also ax-SpA. For now, enthesitis remains relatively overlooked and underdiagnosed in the clinical everyday practice, despite being a central feature in SpA and despite the number of scores elaborated in order to standardize it.

Of course, MRI is the gold standard, but still implies high costs, long scanning duration and magnetic limitations, ultrasound being a convenient and comfortable bedside tool for detecting and monitoring enthesitis, with on spot results and fewer limitations, related mostly to the ability of viewing only relatively superficial structures. Musculoskeletal ultrasonography (MSUS) provides high fidelity images of the entheseal structure and detailed information regarding the vascularity, equivalent to the degree of local inflammation and therefore, disease activity; these findings having higher sensibility and specificity for SpA than a physical evaluation alone [23-25].

The primary objective of this study is to evaluate the frequency of clinical versus ultrasound detected enthesitis in Romanian patients with highly active SpA. A secondary objective is to determine the correlation between the presence of MSUS grey scale (GS) and/or power Doppler (PD) entheseal abnormalities and the disease activity, biologic inflammatory markers and to clinical pain, either declared dur-

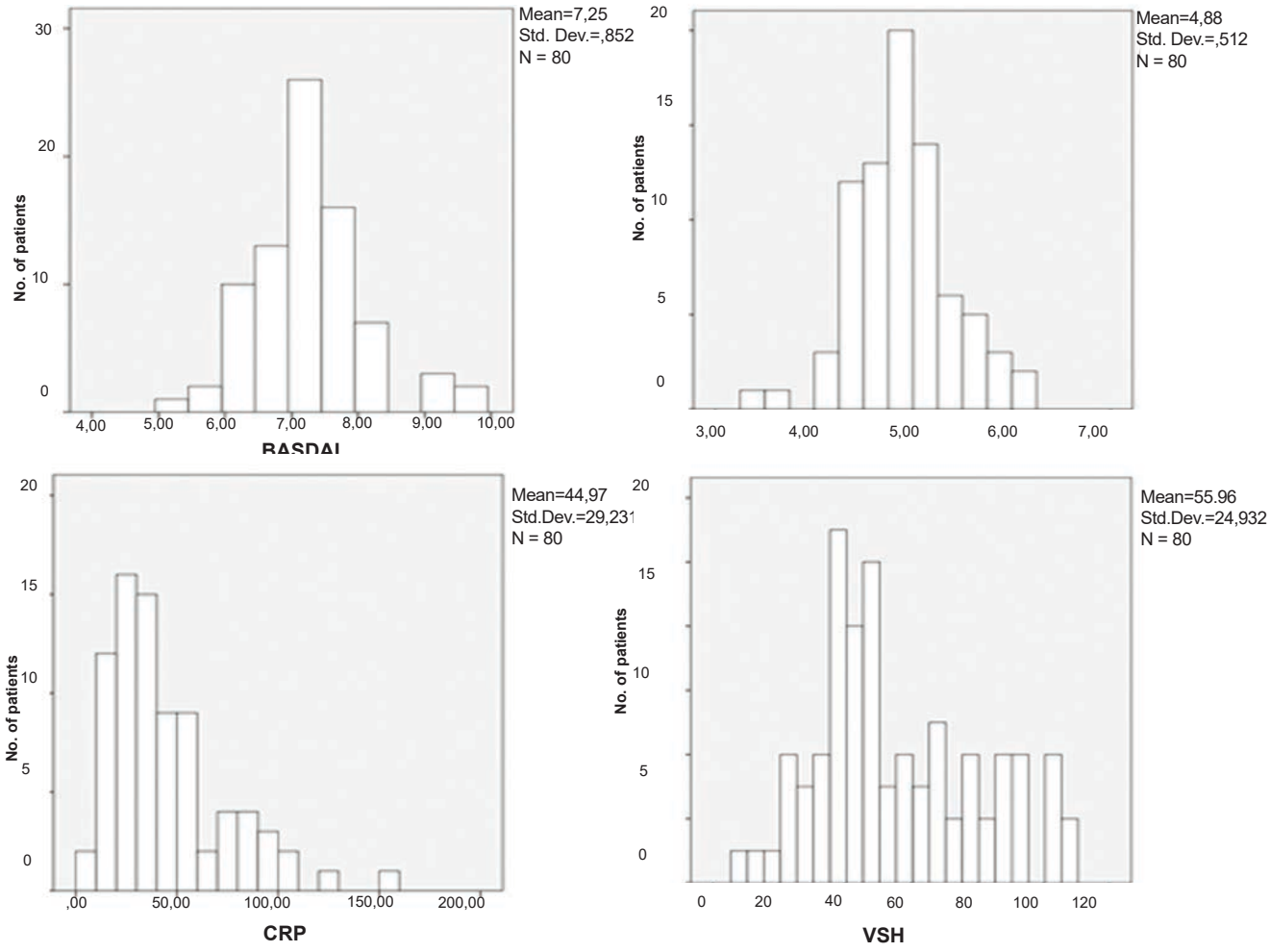

FIGURE 1ABCD. *Number of patients by characteristics*

Statistics

For the distribution of the quantitative variables (i.e., age), the mean and the standard deviation were used, whereas for the distribution of the qualitative variables, the frequency was employed. Moreover, the performance of the ultrasound examination (GS, PD) in comparison to the clinical examination (spontaneous pain, elicited pain) was ascertained with the Cohen's k value, for which the strength of agreement has the following interpretation < 0.2 = poor measurement agreement, 0.21-0.40 = fair measurement agreement, 0.41-0.60 = moderate measurement agreement, 0.61-0.80 = good measurement agreement, > 0.80 = excellent measurement agreement [26].

All tests were considered significant at a p threshold lower than 0.05. Data was collected and analyzed in IBM SPSS version 20.

RESULTS

General and SpA characteristics

General and SpA characteristics are presented in table 1-6 and Figure 1ABCD.

TABLE 1. *General and SpA characteristics (n = 80)*

men (n; %)	51 (63.8%)
age (y; mean (SD))	43.13 (12.35)
smoking (n; %)	16 (20%)
urban dwelling (n; %)	60 (75%)
axial SpA (n; %)	32 (40%)
peripheral SpA (n; %)	30 (37.5%)
axial+peripheral SpA (n; %)	18 (22.5%)
SpA duration (mos; median (SD))	67.28 (85.69)
dactylitis (n; %)	9 (11.3%)
uveitis (n; %)	7 (8.8%)
BASDAI (mean (SD))	7.24 (0.85)
ASDAS (mean (SD))	4.88 (0.51)
CRP (mg/l; mean (SD)	44.97 (29.23)
ESR (mm/h; mean (SD))	55.96 (24.93)
HLA-B27 positive (n; %)	69 (86.3%)
csDMARDs (n; %)	44 (55%)
glucocorticoids (n; %)	22 (27.5%)

ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; CRP – C-reactive protein (normal < 5 mg/l); csDMARDs – conventional synthetic disease-modifying anti-rheumatic drugs; ESR - erythrocyte sedimentation rate (normal < 20 mm/h); mos – months; SD – standard deviation; SpA – spondyloarthritis; y - years

TABLE 2. *Clinical and ultrasound enthesitis prevalence by site (n = 80)*

1. Clinical involvement	**symptomatic (spontaneous)**		**symptomatic (examination)**	
	right	left	right	left
Achilles' tendon	24 (30%)	22 (27.5%)	47 (58.8%)	49 (61.3%)
plantar fascia	9 (11.3%)	10 (12.5%)	14 (17.5%)	13 (16.3%)
quadriceps tendon	25 (31.3%)	27 (33.8%)	38 (47.5%)	36 (45%)
proximal patellar ten-don	4 (5%)	2 (2.5%)	10 (12.5%)	8 (10%)
distal patellar tendon	14 (17.5%)	14 (17.5%)	25 (31.3%)	24 (30%)
triceps tendon	5 (6.3%)	3 (3.8%)	17 (21.3%)	11 (13.8%)
flexor tendons	5 (6.3%)	4 (5%)	8 (10%)	9 (11.3%)
extensor tendons	6 (7.5%)	8 (10%)	13 (16.3%)	12 (15%)
2. Ultrasound involvement	**GS involvement**		**PD involvement**	
	right	left	right	left
Achilles' tendon	62 (77.5%)	60 (75%)	18 (22.5%)	21 (26.3%)
plantar fascia	20 (25%)	18 (22.5%)	8 (10%)	6 (7.5%)
quadriceps tendon	46 (57.5%)	44 (55%)	16 (20%)	16 (20%)
proximal patellar ten-don	18 (22.5%)	15 (18.8%)	8 (10%)	5 (6.3%)
distal patellar tendon	39 (48.8%)	37 (46.3%)	14 (17.5%)	13 (16.3%)
triceps tendon	27 (33.8%)	21 (26.3%)	7 (8.8%)	6 (7.5%)
flexor tendons	16 (20%)	15 (18.8%)	8 (10%)	7 (8.8%)
extensor tendons	22 (27.5%)	22 (27.5%)	15 (18.8%)	15 (18.8%)

GS – grey scale; PD – power Doppler

Enthesitis prevalence

TABLE 3. *Spontaneously symptomatic enthesitis prevalence by SpA type and site (n = 80)*

	Symptomatic (spontaneous)					
	axial SpA		*peripheral SpA*		*axial+peripheral SpA*	
	right	left	right	left	right	left
Achilles' tendon	10 (31.3%)	7 (21.9%)	8 (26.7%)	11 (36.7%)	6 (33.3%)	4 (22.2%)
plantar fascia	3 (9.4%)	3 (9.4%)	3 (10%)	3 (10%)	3 (16.7%)	4 (22.2%)
quadriceps tendon	7 (21.9%)	8 (25%)	11 (36.7%)	11 (36.7%)	7 (38.9%)	8 (44.4%)
proximal patellar ten-don	3 (9.4%)	2 (6.3%)	1 (3.3%)	0	0	0
distal patellar tendon	4 (12.5%)	3 (9.4%)	9 (30%)	9 (30%)	1 (5.6%)	2 (11.1%)
triceps tendon	0	0	3 (10%)	2 (6.7%)	2 (11.1%)	1 (5.6%)
flexor tendons	1 (3.1%)	1 (3.1%)	1 (3.3%)	2 (6.7%)	3 (16.7%)	1 (5.6%)
extensor tendons	3 (9.4%)	3 (9.4%)	1 (3.3%)	2 (10%)	2 (11.1%)	2 (11.1%)

GS – grey scale; PD – power Doppler

TABLE 4. *Symptomatic by examination enthesitis prevalence by SpA type and site (n = 80)*

	Symptomatic (examination)					
	axial SpA		*peripheral SpA*		*axial+peripheral SpA*	
	right	left	right	left	right	left
Achilles' tendon	18 (56.3%)	21 (65.6%)	16 (53.3%)	16 (53.3%)	13 (72.2%)	12 (66.7%)
plantar fascia	3 (9.4%)	4 (12.5%)	8 (26.7%)	5 (16.7%)	3 (16.7%)	4 (22.2%)
quadriceps tendon	12 (37.5%)	10 (31.3%)	18 (60%)	15 (50%)	8 (44.4%)	11 (61.1%)
proximal patellar tendon	7 (21.9%)	5 (15.6%)	2 (6.7%)	3 (10%)	1 (5.6%)	0
distal patellar tendon	8 (25%)	4 (12.5%)	14 (46.7%)	16 (53.3%)	3 (16.7%)	4 (22.2%)
triceps tendon	5 (15.6%)	3 (9.4%)	6 (20%)	4 (13.3%)	6 (33.3%)	4 (22.2%)
flexor tendons	1 (3.1%)	3 (9.4%)	2 (6.7%)	5 (16.7%)	5 (27.8%)	1 (5.6%)
extensor tendons	4 (12.5%)	3 (9.4%)	5 (16.7%)	6 (20%)	4 (22.2%)	3 (16.7%)

TABLE 5. *GS ultrasound enthesitis prevalence by SpA type and site (n = 80)*

	GS involvement					
	axial SpA		*peripheral SpA*		*axial+peripheral SpA*	
	right	left	right	left	right	left
Achilles' tendon	21 (65.6%)	23 (71.9%)	24 (80%)	22 (73.3%)	17 (94.4%)	15 (83.3%)
plantar fascia	7 (21.9%)	4 (12.5%)	10 (33.3%)	9 (30%)	3 (16.7%)	5 (27.8%)
quadriceps tendon	14 (43.8%)	14 (43.8%)	21 (70%)	17 (56.7%)	11 (61.1%)	13 (72.2%)
proximal patellar tendon	9 (28.1%)	7 (21.9%)	6 (20%)	6 (20%)	3 (16.7%)	2 (11.1%)
distal patellar tendon	12 (37.5%)	9 (28.1%)	18 (60%)	20 (66.7%)	9 (50%)	8 (44.4%)
triceps tendon	8 (25%)	6 (18.8%)	10 (33.3)	9 (30%)	9 (50%)	6 (33.3%)
flexor tendons	3 (9.4%)	6 (18.8%)	7 (23.3%)	8 (26.7%)	6 (33.3%)	1 (5.6%)
extensor tendons	8 (25%)	9 (28.1%)	9 (30%)	10 (33.3%)	5 (27.8%)	3 (16.7%)

GS – grey scale

TABLE 6. *PD ultrasound enthesitis prevalence by SpA type and site (n = 80)*

	PD involvement					
	axial SpA		*peripheral SpA*		*axial+peripheral SpA*	
	right	left	right	left	right	left
Achilles' tendon	6 (18.8%)	5 (15.6%)	10 (33.3%)	12 (40%)	2 (11.1%)	4 (22.2%)
plantar fascia	1 (3.1%)	1 (3.1%)	5 (16.7%)	4 (13.3%)	2 (11.1%)	1 (5.6%)
quadriceps tendon	3 (9.4%)	4 (12.5%)	8 (26.7%)	8 (26.7%)	5 (27.8%)	4 (22.2%)
proximal patellar tendon	4 (12.5%)	3 (9.4%)	4 (13.3%)	2 (6.7%)	0	0
distal patellar tendon	2 (6.3%)	4 (12.5%)	9 (30%)	8 (26.7%)	3 (16.7%)	1 (5.6%)
triceps tendon	0	4 (12.5%)	4 (13.3%)	1 (3.3%)	3 (16.7%)	1 (5.6%)
flexor tendons	1 (3.1%)	2 (6.3%)	2 (6.7%)	4 (13.3%)	5 (27.8%)	1 (5.6%)
extensor tendons	4 (12.5%)	5 (15.6%)	6 (20%)	9 (30%)	5 (27.8%)	1 (5.6%)

PD – power Doppler

Correlations with clinical SpA variables

In SpA, the best performance of clinical and ultrasound examination was observed in the evaluation of the flexor tendons of the hand (Table 7), with strong and excellent agreement between the two methods. Conversely, the lowest performance of clinical and ultrasound examination was noticed for Achilles and distal patellar tendons, with low agreement indices

TABLE 7. *Performance and agreement of clinical and US evaluation of enthesitis (n = 80)*

Enthesis	Side	Variables	Measurement agreement	kappa	p
Achilles tendon	R	GS – SP	poor	0.13	0.047
		PD – SP	fair	0.29	0.007
		GS – EP	moderate	0.41	0.001
		PD – EP	fair	0.247	0.003
	L	PD – SP	fair	0.396	0.001
		GS – EP	fair	0.352	0.001
		PD – EP	fair	0.277	0.001
Plantar fascia	R	GS - SP	fair	0.306	0.002
		PD – SP	moderate	0.408	0.001
		GS – EP	moderate	0.481	0.001
		PD – EP	fair	0.375	0.001
	L	GS – SP	moderate	0.404	0.001
		PD – SP	moderate	0.586	0.001
		GS – EP	moderate	0.482	0.001
		PD – EP	moderate	0.589	0.001
Quadriceps tendon	R	GS – SP	moderate	0.408	0.001
		PD – SP	moderate	0.452	0.001
		GS – EP	moderate	0.653	0.001
		PD – EP	fair	0.381	0.001
	L	GS – SP	moderate	0.443	0.001
		PD – SP	moderate	0.472	0.001
		GS – EP	moderate	0.653	0.001
		PD – EP	moderate	0.415	0.001
Proximal patellar tendon	R	PD – SP	moderate	0.643	0.001
		GS – EP	moderate	0.489	0.001
		PD – EP	moderate	0.500	0.001
	L	PD - SP	moderate	0.556	0.001
		GS – EP	moderate	0.550	0.001
		PD – EP	moderate	0.583	0.001

Enthesis	Side	Variables	Measurement agreement	kappa	p
Distal patellar tendon	R	GS – SP	fair	0.212	0.014
		PD – SP	fair	0.394	0.001
		GS – EP	fair	0.394	0.001
		PD – EP	fair	0.306	0.003
	L	GS – SP	fair	0.238	0.008
		PD – SP	moderate	0.510	0.001
		GS – EP	moderate	0.407	0.001
		PD – EP	moderate	0.486	0.001
Flexor tendons of the hand	R	GS – SP	poor	0.162	0.024
		PD – SP	moderate	0.461	0.001
		GS – EP	moderate	0.508	0.001
		PD – EP	moderate	0.524	0.001
	L	GS – SP	poor	0.197	0.003
		PD – SP	moderate	0.415	0.001
		GS – EP	moderate	0.619	0.001
		PD – EP	moderate	0.414	0.001
Extensor tendons of the hand	R	GS – SP	fair	0.352	0.001
		PD – SP	fair	0.307	0.002
		GS – EP	moderate	0.533	0.001
		PD – EP	moderate	0.654	0.001
	L	PD – SP	moderate	0.450	0.001
		PD – EP	moderate	0.600	0.001

EP – elicited pain; GS – grey scale; L – left; PD – power Doppler; R – right; SP – spontaneous pain

TABLE 8. *Prevalence of ultrasound detected enthesitis in asymptomatic entheses per entheseal site*

Asymptomatic entheses (SP = 0 + EP = 0)	GS abnormalities	PD abnormalities
Achilles tendon (64)	35 (54.68%)	4 (6.25%)
Plantar fascia (133)	19 (14.28%)	3 (2.25%)
Quadriceps tendon (86)	22 (25.58%)	2 (2.32%)
Proximal patellar tendon (142)	18 (12.67%)	4 (2.81%)
Distal patellar tendon (111)	37 (33.33%)	7 (6.30%)
Triceps tendon (132)	23 (17.42%)	2 (1.51%)
Flexor tendons of the hand (143)	19 (13.28%)	2 (1.39%)
Extensor tendons of the hand (135)	27 (20%)	11 (8.14%)

EP – elicited pain, GS – gray scale, PD – power Doppler, SP – spontaneous pain

DISCUSSIONS

Enthesitis was detected in higher percentages in patients by ultrasound rather than asking the patient questions about the entheseal pain and by clinical examination, a result that was predictable to some extent, considering the scientific literature [24,25,27].

Ultrasound GS signs of enthesitis were detected in up to 54.68% of the asymptomatic (after both medical history and physical examination) Achilles tendon insertions, while PD signal was detected in lower rates, up to 8.14% in the extensor tendons of the hand insertions.

In all evaluated tendon insertions, ultrasound had a better rate of enthesitis detection than the clinical evaluation alone. The clinical and ultrasound results were better correlated in the flexor tendons of the hands, in regard to the detection of PD, proportional to pain, both spontaneous and elicited. Lower rates of asymptomatic signs of enthesitis were found in points of high mechanical stress and pressure, like the triceps tendon insertion; the olecranon process being prone to mechanical stress and repeated trauma, the Achilles tendon, where it is more likely for an entheseal calcification do cause pain, but interestingly, not the plantar fascia as well [28].

Considering that a highly active disease was one of the inclusion criteria, a comparison with the ultrasound findings in a low disease activity patient is an obvious checkpoint further along this study, but at this point, unavailable.

Also, taking into account the 6 year period measurement and the delay in diagnosing SpA, leading to physical deficits, worse quality of life, with phychological consequences and increased economic burden, a tool for early diagnosis should be considered in every day practice, ultrasonography and MRI being the go-to methods. The choice remains to be wheightened according to the advantages and limitations of each method, while consideringthat an early diagnosis per-se offers better prognosis, adding up to better treatment responses [29,30].

The limitations of the study are mostly with reference to the small number of patients at this point in the study. For better correlations regarding more tendons and the entire lot, more patients are being enrolled in the study. Also, the patients were evaluated dynamically, after undergoing therapy and obtaining variable rates of lower disease activity than at baseline.

Degenerative entheseal abnormalities, mostly GS, could generate false-positive US results, while the clinical examination could also be influenced by the possible overlap with fibromyalgia. According to recent studies, the prevalence of fibromyalgia has been reported in 4-25% of SpA patients, mostly females, compared to 2-8% in the general population. This leads to significantly higher patient-reported outcome rates and ASDAS score in patients with concomitant fibromyalgia [31]. A further research direction on this subject is examining enthesitis patterns in healthy subjects.

This is an ongoing study (prospective research), which will focus on the evaluation the clinical and ultrasound changes after 6 months and 12 months of bDMARD versus non-bDMARD therapy, compared to baseline.

CONCLUSIONS

Enthesitis is a hallmark feature of SpA, preceeding or leading to structural damage in the pathogenetic course of events. The clinical examination itself offers limited information regarding structural abnormalities, local inflammatory status and a weak differentiation between entheseal or referred pain, imaging techniques, such as ultrasound and MRI, having the capacity of completing a well conducted medical history and clinical examination. Between the two, ultrasound is more compatible with the clinical, everyday practice, while MRI could give more accurate information, but limited to a certain segment.

There is a low correlation between entheseal pain and ultrasound GS and/or PD enthesitis, especially in the Achilles and distal patellar tendons.

The significant difference between the clinical findings, either spontaneous or elicited pain, and the ultrasound-detected entheseal involvement, both GS and PD, proves the existence of a gap in diagnosing enthesitis and, therefore, establishing the full extent of SpA in each patient. These findings come in support to the already declared need for an imagistic enthesitis score in the diagnostic process of SpA.

Entheseal ultrasonography could be useful for the screening of patients with chronic low back pain or unclassified arthritis, in order to diagnose SpA early, before the structural damage formation occurs and it may help in establishing the full extent of the disease, but also to design a more personalized therapeutic plan, even more so, considering the need to distinguish between the disease-related patient-reported outcomes and the possible intricate degenerative of psychosomatic pathology.

Acknowledgements

This paper and the research behind it would not have been possible without the exceptional support of the Rheumatology physicians and trainees from the Internal Medicine and Rheumatology Departments of the "Sfânta Maria" Clinical Hospital and "Dr. I. Cantacuzino" Clinical Hospital, in Bucharest, who referred patients that matched the study inclusion criteria.

The authors would also like to show our deepest gratitude to Claudiu C. Popescu, who previously offered a pattern that helped the elaboration of this paper.

Conflict of interest: none declared
Financial support: none declared

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