Mémoire de Maîtrise en médecine No 33

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Lausanne, le 15 décembre 2011

Prevalence and clinical significance of small joint synovitis detected by ultrasonography in axial SpA

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Running title: Small joint synovitis in axial SpA

Key words: axial spondylarthritis, ultrasonographic synovitis, small joint synovitis, function, m-SACRAH

Abstract

Objectives: The aim of this study was to estimate the prevalence of subclinical small joint synovitis detected by ultrasonography in patients with axial SpA, and to evaluate their relevance in terms of function or and disease activity.

Methods: Forty axial SpA patients, 40 RA and 20 healthy subjects were evaluated by ultrasonography, using a reproducible semi-quantitative score by B-mode and Doppler, for synovitis, while disease activity and function were assessed using validated instruments (DAS28, BASDAI, BASFI, m-SACRAH and HAQ).

Results: Median B-mode score were respectively 8.2 for axial SpA, 11.5 for RA and 6.0 for healthy subjects, corresponding to a prevalence of clinical significant synovitis of respectively 37.5%, 60% and 11% for a level of significance at > 8 chosen to classify as active > 75% of RA patient with DAS28 >2.6 and < 10% of controls. Addtionally, Doppler was positive in 8% of SpA, 30 % of RA and none of the healthy subjects. Echographic synovitis correlated with disease activity (DAS28) and function (HAQ, mSACRAH) in RA patients, but no correlation were found for SpA patients with disease activity (BASDAI) or function (BASFI, HAQ, mSACRAH). Cases of synovitis using classification by Doppler positivity were insufficient to allow any statistical analysis.

Conclusions: B-mode ultrasonographic evaluation can demonstrate subclinical synovitis in almost 40% of SpA patients, but they do not appear to correlate with disease activity or function on the contrary to what is observed in RA patients, representing potentially different processes

Introduction

The definition of new classification criteria for axial spondyloarthropathies (SpA) [1] has allowed us to diagnose them much earlier than the previous cases of established ankylosing spondylitis (AS), as defined by the modified New York criteria [2]. With those new criteria, there is also the recognition that the disease is much more prevalent than initial believed, affecting probably more than 1% of the population [3,4]. We also observe a change in the recognized features of the disease, with much more female patients [5], and the appreciation that severe ankylosis is not at all mandatory [6].

If oligoarthritis is a classical feature of axial SpA [7,8], affecting about 30% of patients, small joints peripheral arthritis is not a typical feature of SpA, but for psoriatic arthritis[9]. However, with this shift in population, it appears to us that perhaps more patients, especially women, complain of pain from small peripheral joints in the absence of obvious clinical synovitis. Musculoskeletal ultrasound (US) and MRI imaging have convincingly demonstrate the limitation of clinical examination at detecting small joint synovitis in rheumatoid arthritis (RA) [10-13], as well as the importance of those subclinical synovitis in term of disease activity and treatment strategies [13-15].

The present study was undertook to estimate the prevalence of subclinical small joint synovitis detected by echography in patients suffering from axial SpA, without obvious peripheral disease, and to evaluate if the detected synovitis were relevant in terms of function, a fact which could influence the view on disease management and strategies, or in terms of disease activity, as a simple objective mean to quantify disease activity would be useful in this disease.

Patients and methods

Forty consecutive adult patients with axial SpA, as well as 40 consecutive RA patients were recruited from the outpatient clinic of our Department of Rheumatology. All SpA patients had to fulfill the new ASAS classification criteria for axial disease [1]. SpA patients were included regardless of treatment or disease activity, without any exclusion but for the presence or history of documented oligoarthritis. Similarly, RA patients were included regardless of treatment or disease activity, but had to fulfill the ACR 1987 criteria [16] and had to have an ACR functional class of ≤ 2 [17]. Furthermore, 20 healthy subjects without any known rheumatologic diseases were recruited as controls from patient's relatives or within our department.

All patients and healthy subjects underwent clinical and ultrasonographic evaluation in a standardized order the same day. Participants were initially asked to complete the following self-evaluation assessments for disease activity (BASDAI) [18], function (BASFI) [19], hand function (m-SACRAH) [20] and quality of life (HAQ) [21], regardless of the diagnosis. Evaluation was followed by a clinical (28-joint count) and US assessment by two independent investigators (CM and PZ) blinded to patient's evaluations, but not diagnosis.

All US assessments were performed using a Philips HD-11 US machine with a 15mHz linear probe using the Swiss Sonography in Arthritis and Rheumatism (SONAR) score, a reproducible semi-quantitative score for synovitis in RA using OMERACT criteria (PZ, manuscript in preparation). The score includes B-mode and Doppler evaluation of metacarpophalangeal and proximal interphalangeal joints 2 to 5, wrists, elbows and knees (22 joints). Each joint is graded from 0 (normal) to 3 for synovitis using reference image (fig 1) with a maximum score of 66 points. In

addition, each joint is separately evaluated for Doppler abnormalities (positive or negative) (fig 1). Final score was determined by consensus of the two ultrasonographers. In short, patients were asked to adopt the most appropriate position that produced an optimal sonographic scan of the various joints. Gel was applied to the skin to provide an acoustic interface and US examination was carried out first in grey-scale modality, with additional Doppler evaluation.

All procedures were reviewed by the local ethic committee (Commission cantonale d'éthique de la recherche sur l'être humain, Lausanne, Switzerland) and a signed informed consent was obtained before any evaluation.

Statistical analysis

Data analysis was performed using Stata 11.0 (Stata Corporation, College Station, Texas, USA). The significance level was set at 0.05. For categorical variables, between groups comparisons were computed using a Fisher's exact test. Numerical variables were analyzed using ANOVA followed by Tukey HSD tests, or Kruskal-Wallis rank test with Mann-Whitney tests for post-hoc comparisons, where appropriate. To account for multiple comparisons, a Keppel's modified Bonferroni correction [22] was used (α = df $\perp$ 0.05/c, where α, df and c are respectively adjusted p value, degrees of freedom and number of comparisons). Accordingly, the significance thresholds of post-hoc analyzes were set at P<0.033 and P<0.017 when the number of modalities of the independent variable was respectively 3 and 6. Correlations of B-mode score with other scores were analyzed using Spearman's rho. Within RA patients, disease-related scores in Doppler positive and negative patients were compared using a Mann-Whitney test.

Results

Patients demographics

Finally, 40 consecutive adult patients with axial SpA and 40 RA patients were evaluated, as well as 18 healthy subjects. The main clinical and demographic features are shown in table 1. Groups were similar in term of gender and age. Disease activity was low for our RA group, with a median DAS28 within the LDAS range, an observation reflecting a treated population. For axial SpA, disease activity appeared seemingly higher, with a median BASDAI of 6.4. However, sedimentation rate and CRP were low and similar between RA and SpA patients. Finally, if swollen and tender joints counts were low as expected in this population, there was a statistically significant difference between both groups and the controls, as well as between RA and SpA. Similarly, the HAQ and m-SACRAH scores were significantly higher in SpA and RA than in the healthy subjects, but no significantly different between the two diseases.

Echographic synovitis (table 1 and fig 2).

As echographic joint evaluation can demonstrate positive score by B-mode even in normal healthy subjects, we had to set a level of clinical significance for echographic synovitis to calculate a prevalence of echographic synovitis in our population. The level of significance for B-mode was chosen as such as to classify as significant < 10% of controls and > 75% of the active RA (DAS28 > 2.6), while any Doppler positive joint was considered positive.

Mean B-mode score was 11.5 (± 7.7) for RA, 8.2 (± 4.2) for axial SpA and 6.0 (± 2.1) for healthy subjects without known joint diseases, with a calculated score for the level

of significance at > 8. If axial SpA did not differ, as a group from normal subjects in this treated population, 37,5% of SpA patients had significant echographic synovitis as defined by the level of significance, as compared to 60 % of the RA population. In contrast, Doppler was positive in only 8% of axial SpA (3 patients) and 30 % of RA (12 patients), but none of the healthy subjects.

Disease activity, function and correlation with echographic synovitis

If presence of echographic synovitis evaluated by B-mode correlated with disease activity in terms of DAS28 in RA patients, no correlation was found in SpA patients with disease activity as evaluated with the BASDAI (table 2), nor with the third item of the BASDAI evaluating peripheral symptoms. Likewise, swollen and tender joints counts were highly correlated to the B-mode scores in RA patients, while only swollen joints counts showed a trend in axial SpA, not reaching statistical significance. Interestingly, in these mild diseases, CRP and sedimentation rate did not correlate with synovitis as detected by B-mode (table 2).

Likewise, if HAQ and m-SACRAH scores were highly correlated to B-mode score in RA, no significant correlation was found in SpA. BASFI scores did not display either any correlation with ultrasonographic synovitis by B-mode score in axial SpA. However, when RA patients were asked to fill the same self-evaluation assessment, their scores were highly correlated with the B-mode score (table 2).

Discussion

Small joints peripheral arthritis is the hallmark of RA [16], while oligoarthritis is a classical and well recognized peripheral feature of axial SpA [7,8]. It is however fairly uncommon, affecting about 30% of patients at some point of the disease. In recent years, the concept of subclinical synovitis has been well established in RA [10,11], and its importance is underlined by the numerous studies evaluating the role of US in our current treat-to-target strategy [15,23]. If small joint synovitis is not a recognized feature of SpA, there is a current change in our appreciation and view on this disease with less stress put on ankylosis and radiologic changes. With this shift, we see more women with more general complaints, including pain in hands and small peripheral joints, which could potentially be related to undiagnosed subclinical synovitis. To our knowledge, no formal evaluation of subclinical synovitis had been undertaken in this population, and the present study was set up to estimate the prevalence of such subclinical small joint synovitis detected by echography in patients suffering from axial SpA, without obvious peripheral disease, and to evaluate their clinical significance.

The first hurdle in all echographic joint evaluation is the definition of significance. As the literature has clearly demonstrated the clinical significance of echographic synovitis in RA, we set our level of significance using RA patients and healthy subjects to define a prevalence of clinically significant synovitis, while avoiding as much as possible any overestimation. Using this threshold, subclinical synovitis was demonstrated by B-mode US in almost 40% of axial SpA and 60% of RA patients. Thus, small joints synovitis detected by ultrasonography using a similar protocol as for RA appears fairly common in axial SpA and much more prevalent than usually regarded. However, the clinical significance of such observation remains doubtful. If

in RA patients, we observed a clear correlation between US synovitis and disease activity on one hand, and functional scores on the other, an observation confirming a larger study using SONAR score in the swiss RA cohort (SCQM) on more than 500 patients (PZ, manuscript in preparation), we did not find any correlation in axial SpA between B-mode synovitis and either disease activity or functional scores. If US synovitis correlated very well with disease activity (DAS28) or the swollen and tender joint counts in RA, we were unable to demonstrate any correlation in our SpA population with disease activity using the BASDAI. We did not find correlation either with the third item of the BASDAI evaluating specifically peripheral symptoms (BASDAI3: “How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?”). Interestingly, we did find a correlation when RA patients where asked the same question, pointing toward a different meaning of the observed US changes.

Another important question was to know if the observed synovitis did correlated with function or quality of life. US synovitis seems to correlate very well in RA patients to function and quality of life (HAQ), and more specifically to the hand function using the m-SACRAH score, underlining its clinical relevance in this disease, especially in low disease activity state. Nevertheless, we were unable again to demonstrate any correlation between the observed US synovitis and function or quality of life in our axial SpA population, using either the BASFI, the HAQ or the m-SACRAH.

From our observation, it appears that if subclinical synovitis can be demonstrated in almost 40% of axial SpA using a similar protocol than for RA patients, their clinical significance is totally different in both diseases, with little significance in axial SpA; and that these images probably represent different histological and pathophysiological processes.

It is possible that Doppler positivity would be a better mean to define clinical significant synovitis in axial SpA. However, while 30% of RA were positive using this criterion, only 3 of our patients with axial SpA (8%) were positive, preventing any statistical evaluation. Nevertheless, for RA at least, we observed the same correlation between clinical significant synovitis defined by Doppler with disease activity and function than observed with the B-mode evaluation (table 3), and it appears unlikely that both mode of evaluation represent totally different pathological processes.

There are surely limitations to our study. Evaluators were not blinded to diagnosis, as most patients and controls were known to them. Similarly, clinical examinations were performed by the same evaluators. However, the relation between clinical and ultrasonographic synovitis is similar between the three groups, speaking against a true bias. Mean to assess disease activity are also very different. In RA, synovitis is part of the evaluation and finding a correlation appears obvious, while the BASDAI has no direct correlation to small joint disease. However, disease activity was much higher in the axial SpA (median BASDAI 6.4) than in RA (median DAS28 3.0), a difference that would favors the probability to demonstrate a correlation in the group with the highest activity. In spite of that, we were unable to demonstrate any correlation in SpA, on the contrary to the RA despite a very low median disease activity. Furthermore, restricting the evaluation of disease activity only to peripheral symptoms in SpA (BASDAI3) was not more conclusive, while significant again in RA. In addition, if we did not use the ASDAS index to evaluate disease activity [24], it is unlikely that it would yield significant results as it is based mainly on the BASDAI plus the CRP, an additional parameter that did not correlate either with the observed synovitis.

Globally, the function and quality of life data appear more solid as we used generic questionnaire (HAQ and m-SACRAH), less dependent on the population studied. Finally, there is always the question of the size of the studied population, but it seems to us that groups of 40 are reasonable, a fact underlined by the demonstration of very significant correlation in the RA population. If a much larger sample could perhaps yield statistically significant results, it is unlikely they would drastically change the clinical implication of our observation.

In conclusion, if musculoskeletal ultrasound allows to readily demonstrate subclinical synovitis in a substantial number of axial SpA, their clinical significance remains dubious and debatable. In an era where US gains more popularity in the evaluation of SpA, in particular enthesitis [25-27], we should be cautious not to overestimate the clinical significance of all imaging observations.

Key messages

- B-mode ultrasonographic evaluation demonstrates subclinical synovitis in almost 40% of SpA patients
- But ultrasonographic subclinical synovitis do not correlate with disease activity or function in SpA.

Acknowledgements

The authors are grateful to Dr Federico Balagué for his helpful review of the manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. 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. Annals of the Rheumatic Diseases 2009;68:777-83.
2. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the new york criteria. Arthritis Rheum 1984;27:361-8.
3. Akkoc N. Are spondyloarthropathies as common as rheumatoid arthritis worldwide? A review. Current Rheumatology Reports 2008;10:371-8.
4. Braun J, Sieper J. Ankylosing spondylitis. The Lancet 2007;369:1379-90.
5. Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol 2000;12:239-47.
6. Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. Rheumatology (Oxford, England) 2005;44:1483-91.
7. Bodur H, Ataman S, Buğdaycı DS, et al. Description of the registry of patients with ankylosing spondylitis in turkey: Trasd-ip. Rheumatology International 2010
8. Olivieri I, Barozzi L, Padula A, De Matteis M, Pavlica P. Clinical manifestations of seronegative spondylarthropathies. European Journal of Radiology 1998;27 Suppl 1:S3-6.
9. Cantini F, Niccoli L, Nannini C, Kaloudi O, Bertoni M, Cassarà E. Psoriatic arthritis: A systematic review. International journal of rheumatic diseases 2010;13:300-17.

10. Wakefield RJ, Green MJ, Marzo-Ortega H, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Annals of the Rheumatic Diseases 2004;63:382-5.
11. Wakefield RJ, Kong KO, Conaghan PG, Brown AK, O'Connor PJ, Emery P. The role of ultrasonography and magnetic resonance imaging in early rheumatoid arthritis. Clinical and experimental rheumatology 2003;21:S42-9.
12. Cheung PP, Dougados M, Gossec L. Reliability of ultrasonography to detect synovitis in rheumatoid arthritis: A systematic literature review of 35 studies (1,415 patients). Arthritis care and research : the official journal of the Arthritis Health Professions Association 2010;62:323-34.
13. Larché MJ, Seymour M, Lim A, et al. Quantitative power doppler ultrasonography is a sensitive measure of metacarpophalangeal joint synovial vascularity in rheumatoid arthritis and declines significantly following a 2-week course of oral low-dose corticosteroids. The Journal of Rheumatology 2010
14. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EMA, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: The utility of power doppler ultrasound when added to conventional assessment tools. Annals of the Rheumatic Diseases 2010;69:417-9.
15. Saleem B, Brown AK, Keen H, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Annals of the Rheumatic Diseases 2011

16. Arnett FC, Edworthy SM, Bloch DA, et al. The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis and rheumatism 1988;31:315-24.
17. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 1949;140:659-62.
18. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The bath ankylosing spondylitis disease activity index. J Rheumatol 1994;21:2286-91.
19. 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.
20. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the m-sacrah, a modified, shortened version of sacrah (score for the assessment and quantification of chronic rheumatoid affections of the hands). Rheumatology (Oxford, England) 2004;43:1409-13.
21. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
22. Keppel G. Design and analysis : A researcher's handbook, ed 3rd. Englewood Cliffs, N.J., Prentice Hall, 1991.
23. Schueller-Weidekamm C. Quantification of synovial and erosive changes in rheumatoid arthritis with ultrasound--revisited. European Journal of Radiology 2009;71:225-31.
24. Lukas C, Landewé R, Sieper J, et al. Development of an asas-endorsed disease activity score (asdas) in patients with ankylosing spondylitis. Annals of the Rheumatic Diseases 2009;68:18-24.

25. D'Agostino M-A, Aegerter P, Bechara K, et al. How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power doppler ultrasonography. Annals of the Rheumatic Diseases 2011

26. De Miguel E, Muñoz-Fernández S, Castillo C, Cobo-Ibáñez T, Martín-Mola E. Diagnostic accuracy of enthesis ultrasound in the diagnosis of early spondyloarthritis. Annals of the Rheumatic Diseases 2011;70:434-9.

27. Spadaro A, Iagnocco A, Perrotta FM, Modesti M, Scarno A, Valesini G. Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis. Rheumatology (Oxford, England) 2011;50:2080-6.

Figure legends:

Figure 1: reference images for the SONAR grade 1 to 3 (grade 0 = normal) and Doppler positivity (http://sonar.irheuma.com).

Figure 2: Individual B-mode scores for synovitis in SpA, RA and healthy controls using the SONAR protocol. (Grey zone = below level of significance).

Figure 1

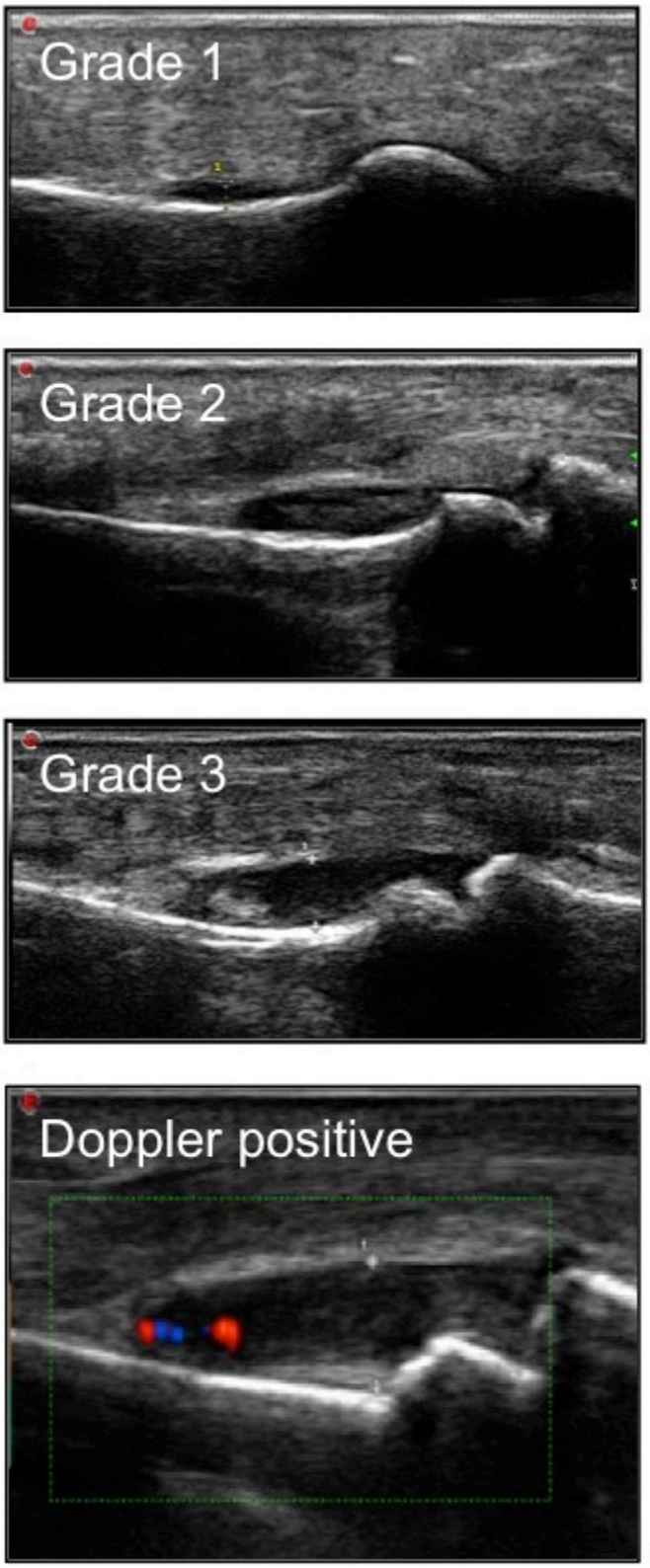

Figure 2

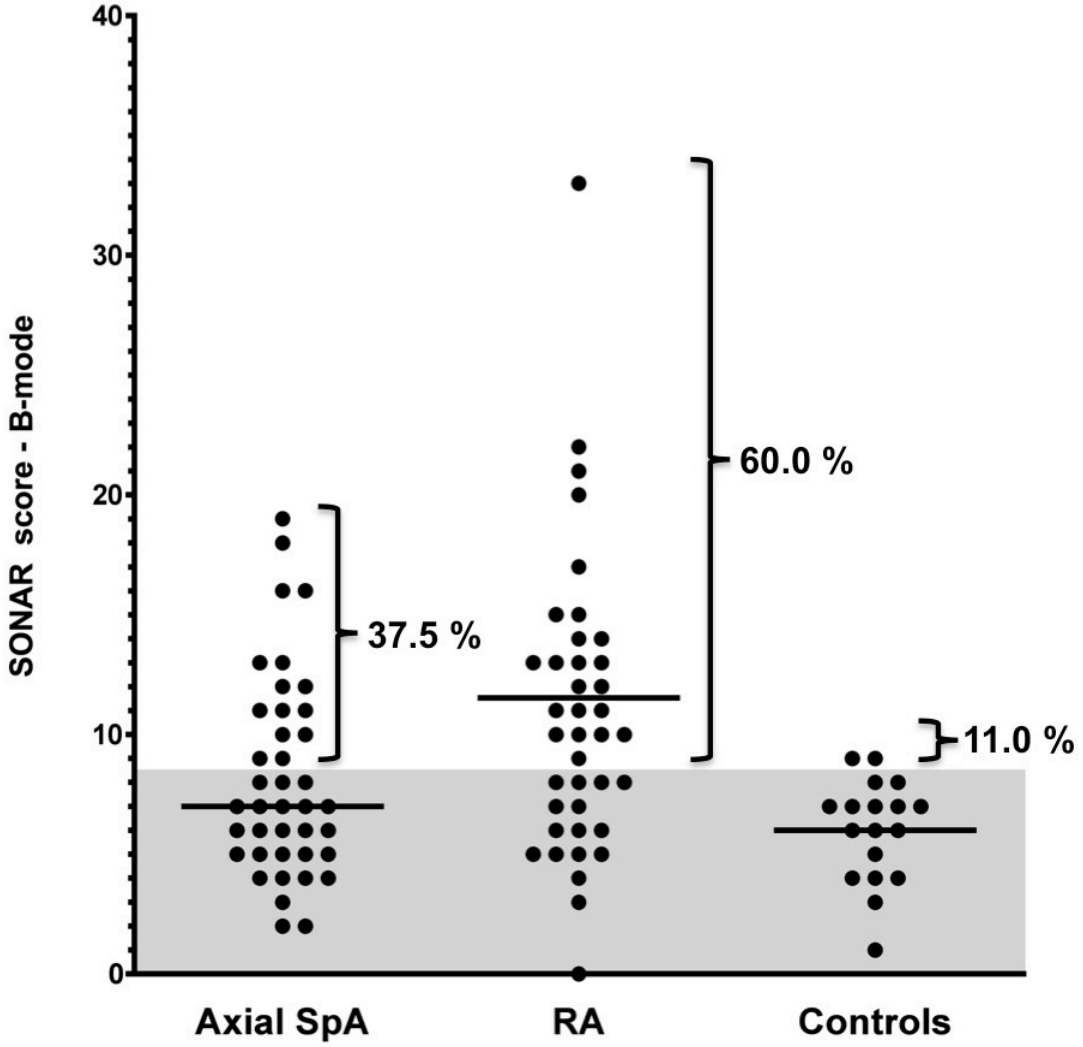
SONAR score - B-mode
40
30
20
10
0
37.5 %
60.0 %
11.0 %
Axial SpA
RA
Controls

Table 1

	SpA n=40	**RA n=40**	**Control n=18**	**P**
Age, *mean (SD)*	48.4 (11.1)	54.2 (11.5)	48.0 (10.3)	0.052 [§]
Gender, *n (%) females*	24 (60%)	30 (75%)	13 (72%)	0.361 [£]
BASDAI, *median (IQR)*	6.4 (6.5)			NR
DAS28, *median (IQR)*		3.0 (1.8)		NR
ESR, *median (IQR)*	10.0 (14.5)	10.0 (14.0)	ND	0.642 [#]
CRP, *median (IQR)*	2.0 (3.0)	2.0 (2.0)	ND	0.946 [#]
Swollen joints, *median (IQR)*	0.0 (0.0) [b, c]	0.5 (3.5) [c]	0.0 (0.0)	**<0.001** [#]
Tender joints, *median (IQR)*	0.5 (3.5) [b, c]	3.0 (5.5) [c]	0.0 (1.0)	**<0.001** [#]
B-mode score, *mean (SD)*	8.2 (4.2)	11.5 (7.7) [c]	6.0 (2.1)	**0.002** [§]
Significant synovitis by B mode, n (%)	15 (37.5%) [b, c]	24 (60%) [c]	2 (11%)	**0.001** [£]
Doppler positif, *n (%)*	3 (8%) [b]	12 (30%) [c]	0 (0%)	**0.003** [£]
HAQ, *median (IQR)*	0.56 (1.4) [c]	0.9 (1.4) [c]	0.0 (0.0)	**0.001** [#]
BASFI, *median (IQR)*	3.7 (7.5)			NR
m-SACRAH, *median (IQR)*	17.1 (30.8) [c]	27.2 (48) [c]	0.0 (0.0)	**<0.001** [#]

SpA = axial spondyloarthritis; RA = rheumatoid arthritis; SD = standard deviation; IQR = interquartile range; ND = not done, NR = not relevant; [§] ANOVA ; [#] Kruskal-Wallis rank test; [£] Fisher's exact test; [b, c] significant difference with RA (b) or control (c).

Legend: Main clinical and demographic features

Table 2

	SpA (n=40)		RA (n=40)	
	ρ	P §	*ρ*	P §
DAS28			0.57	**(<0.001)**
SJC	0.31	0.055	0.54	**(<0.001)**
TJC	0.02	0.917	0.44	**0.004**
CRP	0.00	0.994	0.29	0.077
ESR	-0.36	0.061	-0.03	0.858
BASDAI	-0.12	(0.449)		
BASDAI3	0.01	(0.952)	0.34	**(0.040)**
HAQ	-0.09	(0.574)	0.37	**(0.021)**
BASFI	-0.18	(0.280)		
m-SACRAH	-0.05	(0.754)	0.52	**(0.001)**

SpA = axial spondyloarthritis; RA = rheumatoid arthritis;

§ Spearman's rho analysis

Legend: Correlation between disease and functional scores and clinically significant synovitis detected by B mode US.

Table 3

	Doppler + (n=12)	Doppler - (n=28)	P §
DAS28	3.6 (1.7)	2.7 (1.4)	0.053
SJC	3.0 (3.0)	0.0 (1.5)	**0.002**
TJC	5.0 (3.5)	2.0 (5.5)	0.143
CRP	4.0 (5.0)	2.0 (1.0)	**0.038**
ESR	22.0 (25.0)	10.0 (9.0)	**0.032**
HAQ	1.2 (1.6)	0.8 (1.4)	0.141
m-SACRAH	50.0 (37.3)	18.3 (38.4)	**0.027**

Values expressed as median (interquartile range). § Mann-Whitney test

Legend: Disease-related scores in Doppler + and Doppler - RA patients