One year clinical and ultrasonographic follow up of the Pilot Study for the Referral of Patients with Early Spondyloarthritis (ESPIDEP)

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A B S T R A C T

Objectives: To characterize a cohort of early spondyloarthritis (SpA) patients, to demonstrate the usefulness of enthesis ultrasonography for the diagnosis and follow up, and to develop a statistical model to predict persistent activity.

Patients and methods: A 1 year prospective study with clinical, radiological and ultrasonographic evaluations was performed in patients with SpA from the Pilot Study for the Referral of Patients with Early SpA (ESPIDEP). Enthesis ultrasonography was explored by the MADrid Sonographic Enthesis Index (MASEI), and its diagnostic utility was determined to be a cutoff score of ≥18 points. The clinical, radiological and MASEI scores were studied. Finally, a statistical model from factors predicting persistent activity was developed.

Results: A 1 year follow-up of 32 patients was carried out. The baseline MASEI reached a sensitivity and specificity of 78.12% and 84.37% respectively, positive and negative predictive value was 83.3% and 79.41% respectively, and positive and negative likelihood ratios were 5 and 0.26, respectively. The improvement of BASMI and the MASEI scores were significant (P=.001 and P=.007, respectively). From the beginning, women had more peripheral affection, and men had higher axial radiological progression and higher CRP (P<.05). The statistical model that best predicted persistent activity was constituted by nocturnal back pain, BASDAI and CRP.

Conclusions: Enthesis ultrasonography can be useful when beginning the evaluation and follow-up of early SpA. Disease patterns are different according to sex. The ability to predict persistent activity in early stages supports the use of more intensive treatments.

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R E S U M E N

Objetivos: Caracterizar a una cohorte de pacientes con espondiloartritis (SpA) precoz, demostrar la utilidad de la ecografía de entesitis en el diagnóstico y seguimiento, y desarrollar un modelo para predecir actividad persistente.

Pacientes y métodos: Estudio prospectivo a 1 año de los pacientes con SpA del EStudio Piloto de Derivación de pacientes con Espondiloartritis Precoz (ESPIDEP). Se llevó a cabo una evaluación clínica, radiológica y ecográfica. La ecográfica de entesitis se realizó con el MADrid Sonographic Enthesis Index (MASEI), y su utilidad diagnóstica se determinó con el punto de corte ≥18. Se examinó la evolución clínica, radiológica y del MASEI. Finalmente se desarrolló un modelo a partir de los factores que predicen actividad persistente.

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Resultados: Se realizó el seguimiento durante 1 año a 32 pacientes. El MASEI basal alcanzó una sensibilidad y especificidad de 78,12% y 83,37%, un valor predictivo positivo y negativo del 83,3% y el 79,41%, y una razón de verosimilitud positiva y negativa de 5 y 0,26, respectivamente. La mejora del BASMI y el MASEI fue significativa (p = 0,001 y p = 0,007, respectivamente). Las mujeres tuvieron más afectación periférica desde el inicio y los hombres mayor progresión radiológica axial y PCR más elevada (p < 0,05). El modelo que mejor predijo actividad persistente estaba formado por dolor axial nocturno, BASDAI y PCR.

Conclusiones: La ecografía de entesis puede ser útil en la evaluación inicial y el seguimiento de las SpA precoces. El patrón de enfermedad difiere según el sexo. Predecir actividad persistente en estadios precoces apoya la utilización de tratamientos más intensivos.

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Introduction

At present there are different lines of research aimed at improving early diagnosis of patients with spondyloarthritis (SpA) and knowing the peculiarities that they may have regarding the established forms of disease. In some countries, including ours, clinical and radiological characteristics of patients with early SpA have been described. However, these are cross-sectional studies of prospective general cohorts (both early and late disease). There are few studies related to specialized units using referral criteria. In this sense, the pilot study of Referral of patients with Early Spondyloarthritis (ESPIDEP) is the first experience in Spain and introduces referral from primary care to specialized units using the following criteria: patients under 45 years of age with inflammatory back pain and/or asymmetric lower limb arthritis lasting from 3 to 24 months. It demonstrates for the first time in clinical practice the usefulness of criteria agreed upon with primary care. At the same time, it describes the initial clinical characteristics of patients who met the criteria for referral and have SpA.

Enthesitis is a clinical-anatomical lesion that can appear in all forms and stages of development of SpA. Ultrasound allows a more sensitive and specific evaluation than clinical examination. Recently we have demonstrated the validity of enthesis ultrasound in the correct classification between SpA and healthy subjects using the MAdrid Enthesis Sonographic Index (Masei). This index assesses elementary lesions of 6 bilateral entheses using B-mode ultrasound and power Doppler.

In all chronic and debilitating inflammatory diseases such as SpA, recognizing patients that will have a more severe progression from the early stages of the disease we can help make good treatment decisions.

The objectives of this study are to define the clinical and radiographic findings of an early SpA cohort “ESPIDEP” after a year of progression, and demonstrate the usefulness of enthesis ultrasound in its diagnosis and monitoring. The article proposes a model to predict persistent activity early.

Patients and methods

This was designed as a prospective longitudinal 1 year study of a cohort of patients with early SpA from the ESPIDEP trial. These patients had been correctly referred from primary care to area 5 of Madrid to the SpA unit of the Hospital Universitario La Paz (HULPE). The diagnosis was made with the criteria of the European Group for the Study of Spondyloarthopathies. Throughout follow up we again applied these criteria if a patient had a change in diagnosis. The ethics committee of the HULPE approved this study.

We carried out a protocol that included:

1) Variables related to referral to the early SpA unit: a) duration and number of symptoms, b) the number of referral criteria for the ESPIDEP study c) presence of: inflammatory back pain, asymmetric arthritis, alternating buttock pain, radiological sacroiliitis and a family history of SpA, d) history of psoriasis, inflammatory bowel disease, Achilles tendinitis, plantar fasciitis, diarrhea / urethritis, uveitis and e) HLA B27 positivity.

2) Clinical and laboratory variables at baseline, at 3, 6 and 12 months: tender joint count (TJC), swollen joint count (SJC), global evaluation of disease by the patient (GEDP), axial pain at night (PAIN) on a visual analogue scale 0-100 mm, morning stiffness (MS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), degree of chest expansion in centimeters, number of painful entheses as defined by the Maastricht Ankylosing Spondylitis enthesitis Score (AMESH), C-reactive protein (CRP) and ESR.

3) Evaluation of enthesis ultrasound at baseline, 6 and 12 months to determine the Masei9 index ultrasonographic. We used an Acuson Antares Medical ultrasound systems with a linear 5-13 MHz probe.

4) Radiological variables at baseline and 12 months, radiographs of cervical, thoracic and lumbar anteroposterior and lateral spine and anteroposterior pelvis. One of the study rheumatologists read and scored the radiographs using the total Bath Ankylosing Spondylitis Radiological index (BASRI).

Both the rheumatologist who performed the ultrasound and the one that read the radiographs were blinded to clinical or diagnostic data.

The treatment was started according to the recommendations of the Spanish Society of Rheumatology (SER) and SER consensus document on the use of tumor necrosis factor antagonists (TNF). Statistical analysis included:

1) Assessment of the validity of the Masei in the correct classification of SpA, using ≥ 18 as a cutoff value and 32 healthy subjects as controls matched for age and sex. We determined the sensitivity, specificity, positive (PPV) and negative predictive values (NPV), positive likelihood (PLR) and negative ratios (NLR) at baseline.

2) Temporal study of evolution per visits by a clinical, laboratory and ultrasound index determining the possible differences by repeated ANOVA measures with the Greenhouse-Geisser test and Bonferroni post-test when needed.

3) Determination of the degree of radiological progression at one year by the difference between total BASRI at one year and baseline using the nonparametric Wilcoxon test for paired data.

4) Bivariate evaluation of the differences in the clinical, laboratory and radiology variables such as gender, HLA B27 and presenting the baseline Masei ≥18. Mann-Whitney’s U was used for quantitative variables and chi square or Fisher exact test for qualitative variables.

5) Analysis of persistent activity:
Table 1
Distribution of the 32 patients according to diagnosis, sex and HLA B27

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>Male (%)</th>
<th>HLA B27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated SpA</td>
<td>23 (71.87)</td>
<td>12 (52.17)</td>
<td>11 (47.82)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>4 (12.5)</td>
<td>1 (25)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>2 (6.25)</td>
<td>2 (100)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>2 (6.25)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SpA associated with ulcerative colitis</td>
<td>1 (3.12)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (100)</td>
<td>16 (100)</td>
<td>16 (100)</td>
</tr>
</tbody>
</table>

Table 2
Clinical, laboratory and echographic variables for each visit

<table>
<thead>
<tr>
<th>Description of the clinical, laboratory and ultrasound</th>
</tr>
</thead>
</table>
| Of the 35 patients diagnosed with SpA in the ESPIDEP study, two were lost to follow up and the initial diagnosis was not confirmed in another and therefore were not included. Of the 32 patients enrolled, 50% were HLA B27 positive and 50% male; all maintained the same initial diagnosis at the end of follow up (Table 1). To analyze the validity of the index Masei we included 32 healthy controls (15.62%) had a Masei ≥18, with a mean value of 26.17±13.68 and 13.34±7.97 in patients and controls respectively (P<0.01). The Masei, used as a criterion to correctly classify SpA and healthy controls, had a sensitivity of 78.12%, a specificity of 84.37%, PPV of 83.3%, a NPV of 79.41%, a PLR and a NLR of 5 and 0.26, respectively.

Description of the clinical, laboratory and Masei at each visit are shown in Table 2. The variables improve from the onset except the value of MS, BASFI, BASMI, which worsen at 3 months and subsequently improvement in the rest of the visits with respect to baseline. The SJC fluctuates, but at the final visit improves over the baseline. Evolution towards improvement of BASMI and the Masei index throughout visits is significant (P<0.01 and P<0.007, respectively).

Regarding the treatments used: 15 patients (46.9%) required ≥2 NSAIDs, 13 patients required DMARD (40.6%), 7 patients a biological (21.9%) and 5 patients local infiltration (15.6%). DMARDs used were: sulfasalazine in 10 patients, methotrexate in 2 patients and in 3, both. Etanercept and infliximab were used in 4 and 3 patients, respectively.

We performed the analysis of the variables at the initial visit to determine gender differences HLA B27 status and having a baseline Masei ≥18, including:

- The biggest SJC in women (0.50±0.63 vs 0.06±0.63, P<0.01).
- A Masei higher in men (33.07±15.05 vs 22±11.87, P<0.03).
- The higher value of the GEDP (53.5±24.33 vs 28.57±18.64, P<0.02) and BASFI (3.2±2.44 vs 0.98±0.93, P<0.01) in patients with a baseline Masei ≥18.

Subsequently, repeated analysis was applied to the area under the curve (AUC) of each variable during the year or in the case of TJC and SJC to the annual sum. We obtained significance (P<0.05) ([Table 3] and [Table 4]) in:

- The higher SJC among women.
- The higher CRP in men and patients with a baseline Masei ≥18.
- The Masei index tended to be significantly increased among men (P<0.07).

Evaluation of the radiologic features

Regarding the total BASRI index, the baseline score was 1.58±1.38 and 3.88±1.72 at one year. No differences in the value of total baseline BASRI by gender, HLA B27 or basal Masei ≥18 (P>0.05) was seen. The level of total BASRI radiological progression was significant compared to baseline: 2.29±2.01 (95% CI 1.44 to 3.14, P<0.00).

By analyzing differences in the degree of radiological progression per year, we confirmed that it is significantly higher in men than women and in patients with a baseline Masei ≥18 ([Table 3] and [Table 4]).
Analysis of persistent activity

The 7 patients treated with anti-TNF-α during the year met the criteria for persistent activity.

1) Factors predicting persistent activity at one year:

To perform the analysis we used baseline variables found in Table 5. Univariate analysis showed that baseline pain (P=.05), MS at baseline (P=.03), baseline BASDAI (P=.02) and the number of enthesitis at baseline (P=.007) are associated significantly to persistent annual activity. Multivariate analysis showed that of the previous variables, baseline PAIN is the only one that predicts continued activity independently, with an AUC ROC of 0.737±0.112, 95% CI 0.518–0.956 (P=.05) (Figure 1).

2) Model predictor of persistent activity:

The model is formed by the variable resulting from the multivariate analysis, baseline PAIN, to which the BASDAI index and baseline CRP were added. This is the combination which most increased the ROC AUC value obtained by the baseline pain variable and more accurately predicted persistent activity per year (baseline AUC ROC of baseline PAIN + baseline BASDAI + baseline CRP=0.810±0.081, 95% CI 0.651–0.966; P=.01) (Figure 2).

It was confirmed that in all the combinations made, the value of AUC was higher when CRP was used as compared to when the ESR was used as an acute phase reactant (data not shown).

Discussion

This study identifies clinical features typical of the early forms of disease. This is the first time an ultrasound index is used to assess both the initial enthesitis in the short-term in an early disease cohort. In addition, we propose a model to predict persistent activity with the intent of selecting early patients with more severe disease.

The MASEI ultrasound Enthesis index allows us to classify ultrasound in SpA after introduction of treatment, sensitivity to change in spite of a small sample size and short follow-up time. Recent work also suggests sensitivity to change of enthesis ultrasound in SpA after introduction of treatment, although this feature has not been evaluated in early forms as in our study.

Table 3
Clinical, echographic and radiologic variables in which gender played a role in its behavior during the year

<table>
<thead>
<tr>
<th>SJC, mean (SD)</th>
<th>CRP, mean (SD)</th>
<th>MASEI, mean (SD)</th>
<th>Radiologic progression, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Yes 0.33 (115) 40.92 (25.99) 55.82 (24.82) 3.09 (1.81)</td>
<td>No 1.00 (1.27) 14.73 (4.54) 41.71 (15.90) 1.62 (1.98)</td>
<td>P=.02 P=.01 P=.07 P=.04</td>
<td></td>
</tr>
</tbody>
</table>

CRP indicates C reactive protein; MASEI, Madrid Sonographic Enthesis Index; TJC, tender joint count.

Table 4
Clinical, echographic and radiologic variables in which the baseline MASEI ≥ 18 influences its behavior during the year

<table>
<thead>
<tr>
<th>Baseline MASEI ≥18</th>
<th>CRP, mean (SD)</th>
<th>MASEI, mean (SD)</th>
<th>Radiologic progression, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes 28.38 (22.21) 54.22 (21.57) 2.787 (2.07)</td>
<td>No 12.15 (0.13) 29.7 (7.5) 0.83 (0.75)</td>
<td>P=.03 P=.002 P=.03</td>
<td></td>
</tr>
</tbody>
</table>

CRP indicates C reactive protein; MASEI, Madrid Sonographic Enthesis Index.

Table 5
Baseline variables for the analysis of persistent activity

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>33.47 (8.23); range (15-45)</td>
</tr>
<tr>
<td>Duration of symptoms, months, mean (SD)</td>
<td>11.39 (6.73); range (3-24)</td>
</tr>
<tr>
<td>No. of SpA symptoms, mean (SD)</td>
<td>3.03 (1.37); range (1-7)</td>
</tr>
<tr>
<td>Referral criteria, n (%)</td>
<td></td>
</tr>
<tr>
<td>Only inflammatory back pain</td>
<td>20 (62.5%)</td>
</tr>
<tr>
<td>Only asymmetric arthritis</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Both criteria</td>
<td>6 (18.8%)</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Psoriasis, n (%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>ID, n (%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Achilles tendinitis, n (%)</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>Plantar fascitis, n (%)</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Diarrhea/urticaria, n (%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Uveitis, n (%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Alternating buttock pain, n (%)</td>
<td>8 (24.3%)</td>
</tr>
<tr>
<td>Inflammatory back pain, n (%)</td>
<td>26 (81.3%)</td>
</tr>
<tr>
<td>Sacroilitsis, n (%)</td>
<td>19 (59.4%)</td>
</tr>
<tr>
<td>Baseline asymmetric arthritis, n (%)</td>
<td>12 (37.5%)</td>
</tr>
<tr>
<td>HLA B27, n (%)</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>SJC, mean (SD)</td>
<td>0.25 (0.53)</td>
</tr>
<tr>
<td>Baseline BASDAI</td>
<td>0.83 (2.35)</td>
</tr>
<tr>
<td>GEGR, mean (SD)</td>
<td>50.58 (23.24)</td>
</tr>
<tr>
<td>PAIN, mean (SD)</td>
<td>40.58 (35.28)</td>
</tr>
<tr>
<td>MS, mean (SD)</td>
<td>26.46 (32.61)</td>
</tr>
<tr>
<td>BASDAI, mean (SD)</td>
<td>4.49 (1.81)</td>
</tr>
<tr>
<td>BASFI, mean (SD)</td>
<td>2.63 (2.22)</td>
</tr>
<tr>
<td>TE, mean (SD)</td>
<td>5.17 (1.88)</td>
</tr>
<tr>
<td>BASMI, mean (SD)</td>
<td>1.50 (1.03)</td>
</tr>
<tr>
<td>No. enthesitis, mean (SD)</td>
<td>1.27 (2.86)</td>
</tr>
<tr>
<td>ESR, mean (SD)</td>
<td>20.84 (24.45)</td>
</tr>
<tr>
<td>CRP, mean (SD)</td>
<td>12.74 (19.88)</td>
</tr>
<tr>
<td>MASEI, mean (SD)</td>
<td>26.17 (13.68)</td>
</tr>
</tbody>
</table>

BASDAI indicates Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; ESR, Erythrocyte Sedimentation Rate GEDP, Global Evaluation of Disease by the patient; MASEI, Madrid Sonographic Enthesis Index; MS, Morning Stiffness; PAIN, nocturnal axial pain; SJC, Swollen Joint Count; TE, degree of thoracic expansion; TJC, tender joint count.
modified Stoke Ankylosing Spondylitis Spine Score

19

Activity Index (BASDAI) and C-reactive protein (CRP) as shown in Figure. 

(PAIN) is formed by combining variables with Bath Ankylosing Spondylitis Disease curve (AUC) receiver operating characteristic (ROC) of the variable night axial pain Figure 2.

multivariate analysis was significantly associated to persistent activity, presenting an area under the curve (AUC) as indicated in the study points in the same direction. Patients with ≥18 baseline Masei had more severe disease as assessed by CRP and radiological progression, and we also found that it is men who have more early enthesopathy as defined by the Masei index (33.07±15.05 (males) vs 22±11.87 (females), \( P=0.03 \)).

HLA B27 does not influence any clinical or radiological variable, or persistent activity of the disease. Similar data have been shown in recent studies. Finally we determined that baseline nocturnal axial pain predicts persistent activity at one year independently (AUC ROC was 0.737±0.112, 95% CI 0.518 to 0.956 (\( P=0.05 \)). The need to use a biological as recommended by the SER17 was selected as a criterion of persistent activity. We consider this more accurate than radiologic damage because the latter would be minimal or undetectable in some patients in early forms. A model was developed from the AUC of nocturnal baseline axial pain to which BASDAI and CRP were added, improving baseline AUC (AUC 0.810±0.081, 95% CI 0.651 to 0.966, \( P=0.01 \)) as well as our capacity to predict persistent activity at ≤1 year of follow-up. During the process of obtaining the model we confirmed that CRP always led to further improvement of the AUC over ESR. Several studies have attempted to identify predictors of persistent activity as defined by radiological damage, function or activity of the disease, but usually not in early cohorts. We have not found studies in early SpA that use a common outcome measure in daily practice such as the indication for biological and that seek to detect persistent activity in such a short-term.

The possible implication of our model is that patients with high baseline night axial pain are more likely to need biological therapy before one year, especially if they also have a high CRP and high baseline BASDAI associated.

However, there are limitations in our study such as the small number of patients and short follow-up time. Although some new results are suggested, these must be confirmed in larger cohorts with longer follow up.

In conclusion, enthesus ultrasound can help in the diagnosis and monitoring of patients with early SpA. As in the established forms, women have a primarily peripheral pattern of disease and men have a predominantly axial one. Using a predictive model of persistent activity in early stages of the disease can help us select patients for disease-modifying treatments that minimize structural damage and improve the quality of life.

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**Conflict of interest**

The authors declare no conflict of interest.
References


