Effect of Enthesitis on 1505 Brazilian Patients with Spondyloarthritis

Sueli Carneiro, Adriana Bortoluzzo, Celio Gonçalves, José Antonio Braga da Silva, Antonio C. Ximenes, Manoel Bértolo, Sandra Lúcia Ribeiro, Mauro Keiserman, Thelma Skare, Rita Menin, Valderilio Azevedo, Walber Vieira, Elisa Albuquerque, Washington Bianchi, Rubens Bonfiglioli, Cristiano Campanholo, Hellen Mary de Carvalho, Izaias da Costa, Ángela Duarte, Charles Kohem, Nocy Leite, Sonia A.L. Lima, Eduardo S. Meirelles, Ivânio A. Pereira, Marcelo M. Pinheiro, Elizandra Polito, Gustavo G. Resende, Francisco Airton C. Rocha, Mittermayer B. Santiago, Maria de Fátima L.C. Sauma, Valéria Valim, and Percival D. Sampaio-Barros

ABSTRACT. ***Objective.*** To analyze the clinical effect of enthesitis in a large Brazilian cohort of patients with spondyloarthritis (SpA).

Methods. A common protocol of investigation was prospectively applied to 1505 patients with SpA in 29 centers in Brazil. Clinical and demographic variables and disease indexes were investigated. The Maastricht Ankylosing Spondylitis Enthesitis Score was used to investigate the enthesitis component. Ankylosing spondylitis was the most frequent disease in the group (65.4%). Others were psoriatic arthritis (18.4%), undifferentiated SpA (6.7%), reactive arthritis (3.3%), and enteropathic arthritis (3.2%).

Results. At least 1 affected enthesis was observed in 54% of the patients with SpA, with a mean of 2.12 ± 2.98 entheses affected. According to the clinical presentation, enthesitis was significantly more frequent in patients with axial + peripheral joint involvement compared to isolated axial or peripheral involvement ($p < 0.001$). There was a statistical association between the presence of enthesites and axial symptoms (buttock pain, cervical pain, and hip pain), and peripheral symptoms (lower limb arthritis, number of painful and swollen joints; $p < 0.05$). Patients with enthesitis also presented higher mean scores of Bath Ankylosing Spondylitis Functional Index (BASFI; $p < 0.001$), Bath Ankylosing Spondylitis Disease Activity Index ($p < 0.001$), and Ankylosing Spondylitis Quality of Life (ASQoL; $p < 0.001$). Multivariate logistic regression showed that BASFI ($p < 0.0001$; OR 74.839), ASQoL ($p = 0.0001$; OR 14.645), and Achilles tendonitis ($p = 0.0059$; OR 7.593) were associated with work incapacity.

Conclusion. The clinical presence of enthesitis in this large cohort of patients with SpA was frequent and was associated with a significant increase in disease activity and decline in functional capacity and quality of life. (J Rheumatol First Release July 15 2013; doi:10.3899/jrheum.121145)

Key Indexing Terms:
SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS ENTHESITIS MAASTRICHT ANKYLOSING SPONDYLITIS ENTHESITIS SCORE

From the Brazilian Registry of Spondyloarthritis: Universidade Federal do Rio de Janeiro, Universidade Estadual do Rio de Janeiro, Santa Casa do Rio de Janeiro, and Faculdade de Medicina Souza Marques, Rio de Janeiro; Insper Institute of Education and Research, and Division of Rheumatology and Instituto de Ortopedia e Traumatologia, Universidade de São Paulo, and Santa Casa de São Paulo, and Hospital do Servidor Público Estadual, São Paulo; Universidade de Brasília, and Hospital de Base, Brasília; Hospital Geral de Goiânia, Goiânia; Universidade de Campinas, and Pontifícia Universidade Católica, Campinas; Universidade Federal do Amazonas, Manaus; Pontifícia Universidade Católica, Porto Alegre; Hospital Evangélico de Curitiba, and Universidade Federal do Paraná, Curitiba; Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto; Hospital Geral de Fortaleza, and Universidade Federal do Ceará, Fortaleza; Universidade Federal do Mato Grosso do Sul, Campo Grande; Universidade Federal de Pernambuco, Recife; Universidade Federal do Rio Grande do Sul, Porto Alegre; Universidade Federal de Santa Catarina, Florianópolis; Santa Casa de Belo Horizonte, and Universidade Federal de Minas Gerais, Belo Horizonte; Escola de Medicina e Saúde Pública, Salvador; Universidade Federal do Pará, Belém; and Universidade Federal do Espírito Santo, Vitória, Brazil.

The electronic version of the Brazilian Registry of Spondyloarthritis is supported by an unrestricted grant from Wyeth/Pfizer Brazil. Dr. Sampaio-Barros is a recipient of a research grant from Federico Foundation.

S. Carneiro, MD, PhD, Universidade Federal do Rio de Janeiro and Universidade Estadual do Rio de Janeiro; A. Bortoluzzo, PhD, Insper Institute of Education and Research; C. Gonçalves, MD, PhD; P.D. Sampaio-Barros, MD, PhD, Division of Rheumatology, Universidade de São Paulo; J.A. Braga da Silva, MD, Universidade de Brasília; A.C. Ximenes, MD, PhD, Hospital Geral de Goiânia;

M. Bértolo, MD, PhD, Universidade de Campinas; S. Ribeiro, MD, PhD, Universidade Federal do Amazonas; M. Keiserman, MD, MSc, Pontifícia Universidade Católica, Porto Alegre; T. Skare, MD, Hospital Evangélico de Curitiba; R. Menin, MD, Faculdade de Medicina de São José do Rio Preto; V. Azevedo, MD, MSc, Universidade Federal do Paraná; W. Vieira, MD, PhD, Hospital Geral de Fortaleza; E. Albuquerque, MD, PhD, Universidade Estadual do Rio de Janeiro; W. Bianchi, MD, PhD, Santa Casa do Rio de Janeiro; R. Bonfiglioli, MD, PhD, Pontifícia Universidade Católica; C. Campanholo, MD, Santa Casa de São Paulo; H.M. de Carvalho, MD, PhD, Hospital de Base; I. da Costa, MD, PhD, Universidade Federal do Mato Grosso do Sul; A. Duarte, MD, PhD, Universidade Federal de Pernambuco; C. Kohem, MD, MSc, Universidade Federal do Rio Grande do Sul; N. Leite, MD, PhD, Faculdade de Medicina Souza Marques; S.M.L. Lima, MD, Hospital do Servidor Público Estadual; E.S. Meirelles, MD, PhD, Instituto de Ortopedia e Traumatologia, Universidade de São Paulo; I.A. Pereira, MD, PhD, Universidade Federal de Santa Catarina; M.M. Pinheiro, MD, PhD, Universidade Federal de São Paulo; E. Polito, MD, Santa Casa de Belo Horizonte; G.G. Resende, MD, Universidade Federal de Minas Gerais; F.A.C. Rocha, MD, PhD, Universidade Federal do Ceará; M.B. Santiago, MD, PhD, Escola de Medicina e Saúde Pública; M.F.L.C. Sauma, MD, MSc, Universidade Federal do Pará; V. Valim, MD, PhD, Universidade Federal do Espírito Santo.

Address correspondence to Dr. P.D. Sampaio-Barros, Disciplina de Reumatologia, Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo, 455–3 Andar, Cerqueira César, São Paulo, SP, Brazil CEP 01246-903. E-mail: pdsampaiobarros@uol.com.br

Accepted for publication June 11, 2013.

The spondyloarthritides (SpA) represent a heterogeneous group of chronic inflammatory diseases with a common clinical and genetic background, affecting around 1% of the population. Ankylosing spondylitis (AS) is the core disease in the group, which includes psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated SpA (USpA)[1]. Because all diseases in the SpA group can present enthesitis involvement, enthesitis was included as an important variable in the classification criteria of axial SpA[2] and peripheral SpA[3].

Since the differentiation of SpA from rheumatoid arthritis (RA) by Moll and Wright, SpA has been characterized by spinal inflammation, peripheral joint oligoarthritis, distinctive radiographic changes, and enthesitis, associated with HLA-B27[4]. Entheses are adapted to resist shear and compression forces and thus minimize joint damage associated with the high levels of mechanical loading that they bear[5]. Although the traditional concept of enthesitis relates to focal inflammatory changes at the insertion of tendons, ligaments, fascia, or capsule into bones, several entheses comprise more than simply the insertion site. This concept of functional entheses represents a unifying basis for SpA[6].

In patients with PsA, the most frequently affected sites of enthesitis are Achilles tendon, plantar fascia, costochondral joints, and elbows. Patients with clinical complaints frequently show abnormalities on ultrasound (US) scans[7]. Patients with cutaneous psoriasis and no joint symptoms can also present subclinical entheseal inflammation[8]. Even in normal joints, normal insertions are associated with microdamage and inflammatory changes, suggesting that local tissue-specific (autoinflammatory) factors may dictate disease expression[9].

Musculoskeletal complaints are the most common extraintestinal manifestations of IBD, presenting as articular (arthritis) or periarticular (enthesitis, myositis, or soft-tissue rheumatism) inflammation; although its clinical course can be independent, most frequently enthesitis correlates with the intestinal activity[10]. In ReA, enthesitis can be more frequent than arthritis[11]. Positron emission tomography/computed tomography can be useful for the early diagnosis of enthesitis in early stages of ReA, even before the possible confirmation of the infectious site[12]. US is useful for the detection of affected entheses in young patients with poststreptococcal ReA[13].

Because enthesitis is a primary clinical feature in SpA, various instruments were proposed to investigate it. In 1987, Mander, *et al* proposed an index (the Mander Enthesis Index; MEI) analyzing 66 entheses by local pressure, with intensity of pain graded on a 0–3 scale[14]. This instrument is not practical for daily use because it involves many sites and is time-consuming. In 2003, a group of experts from the Assessment of SpondyloArthritis International Society proposed an alternative to the MEI with much better feasibility, the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); it analyzes 13 anatomical sites[15]. In 2009, the Spondyloarthritis Research Consortium of Canada (SPARCC) conducted clinical validation of an enthesitis instrument, for which the selection of entheses sites was based primarily on published sonographic and magnetic resonance imaging (MRI) studies, the SPARCC index[16].

The main objective of our study was to analyze the importance of the enthesitis involvement in the different disease patterns in a large cohort of 1505 patients with SpA.

MATERIALS AND METHODS

This was a prospective, observational, multicenter cohort of consecutive patients with SpA recruited from 29 referral centers participating in the Brazilian Registry of Spondyloarthritis (RBE – Registro Brasileiro de Espondiloartrites). All patients, from each of the 5 major geographic areas in Brazil, were classified according to the European Spondylarthropathy Study Group criteria[17]. The data were collected from June 2006 to December 2009. The RBE is part of the RESPONDIA group, consisting of 9 Latin American countries (Argentina, Brazil, Costa Rica, Chile, Ecuador, México, Perú, Uruguay, and Venezuela) and Spain and Portugal.

In our study, a protocol of investigation was applied to 1505 patients with SpA. The diagnosis of AS was considered if the patients fulfilled the New York modified criteria[18], and for PsA if they fulfilled the Moll and Wright criteria[19]; ReA was considered when asymmetric inflammatory oligoarthritis of lower limbs was present, associated with enthesopathy and/or inflammatory low back pain following enteric or urogenital infections[20], and enteropathic arthritis when the patient presented inflammatory axial and/or peripheral joint involvement associated with confirmed IBD (Crohn's disease or ulcerative colitis).

All patients were interviewed and clinically examined by the study center coordinator. Our protocol of investigation considered as axial the predominant involvement of spinal joints that could also affect girdle (hips

and shoulders) and/or anterior chest wall joints; peripheral as the predominant involvement of large and/or small joints of upper and/or lower limbs; enthesitic when predominantly entheses were affected; and "mixed" when there was not a predominance of axial or peripheral involvement.

Demographic and clinical data were collected including time of disease duration, tender and swollen joint count, and visual analog scale (VAS) for pain according to the patient. A VAS for patient and physician global perception of disease activity (patient global and physician global assessment, respectively) was also collected. Peripheral articular involvement was assessed by the 66 tender/swollen joint count.

Patients were asked whether they have a family member (2 generations) with known diagnosis of AS, PsA, ReA, arthritis related to IBD, or USpA. Family members were not assessed.

To analyze physical activity, we asked the patients about the daily mean time that they spent on physical exercises. We considered "total job incapacity" when the patient was completely and definitely unable to do his/her job, and "partial job incapacity" when the patient was able to do his/her activities only during some periods in the year, with some periods of incapacity.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were also registered.

The index for evaluating enthesis used in this study was the MASES, which evaluated pain at 13 anatomical sites (11 axial and 2 peripheral)[15]. The enthesitic sites studied were bilateral first and seventh costochondral joints, anterior-superior and posterior spina iliaca, iliac crests, insertion of the Achilles tendon into the posterior surface of the calcaneus, and the fifth lumbar spinous process. Before the start of data collection, the coordinators of all the participating centers attended 2 training meetings, where the MASES was demonstrated.

Disease activity and functional status were evaluated according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[21] and the Bath Ankylosing Spondylitis Functional Index (BASFI)[22], respectively. Quality-of-life data were recorded through Ankylosing Spondylitis Quality of Life (ASQoL) questionnaires[23]. All questionnaires used were previously translated, cross-translated, validated, and culturally adapted to the Portuguese language[24]. Radiological evaluation was performed by the Bath Ankylosing Spondylitis Radiology Index (BASRI), including BASRI-spine (lumbar and cervical spine and sacroiliac joints) and BASRI-total (BASRI-spine and BASRI-hips)[25].

Statistical analysis. After the descriptive analysis of each enthesis and their distribution according to clinical presentation (axial, peripheral, axial + peripheral) and specific disease into the SpA group, the patients were divided into a group "with enthesitis" and another "without enthesitis." Categorical variables were compared by chi-square and Fisher's exact test, and continuous variables were compared by ANOVA test. A value of $p < 0.05$ was considered significant, and $0.05 > p > 0.10$ was considered a statistical trend. To analyze the correlation among enthesitis and work capacity, 2 multivariate logistic regressions were performed: the first analyzed the 7 enthesitic sites and work incapacity, and the second analyzed all the demographic and clinical variables involving work incapacity.

RESULTS

Among the 1505 patients with SpA, AS was the most frequent disease (65.4%). The others were PsA (18.4%), USpA (6.7%), ReA (3.3%), and enteropathic arthritis (3.2%). At least 1 affected enthesis was observed in 54% of the patients.

The mean number of entheses affected was 2.12 ± 2.98. The frequency of involvement of each enthesis in the MASES index is shown in Table 1; posterior spina iliaca and Achilles tendon were the most frequently affected entheses. When the degree of interdependency of the 7 different enthesitic sites was analyzed, it was shown that the presence of any of the 7 enthesitic sites was significantly associated with the other sites, with the only exception the fifth lumbar spinous process. Among the 54% of patients with enthesitis, 24.6% had 1 affected enthesis and 29.4% had ≥ 2 enthesites (10.6% two entheses, 7.8% three, 5.7% four, 3.1% five, 2% six, and 0.2% seven). When just 1 enthesis was painful at the physical examination, the most frequently involved entheses were the fifth lumbar spinal process (39.5% of 287 patients) and the Achilles tendon (23.6% of 293 patients). These were less often affected as a single painful enthesis: posterior spina iliaca (14.0%), first costochondral (7%), anterior-superior spina iliaca (6.5%), seventh costochondral (5.5%), and iliac crest (3.9%).

Enthesitis was significantly more frequent in patients with axial + peripheral joint involvement (2.44 ± 3.08) compared with isolated axial (1.42 ± 2.43) or peripheral (1.28 ± 2.15) involvement ($p < 0.001$). Eighty-three patients (6.2%) were considered predominantly enthesitic, with Achilles tendonitis predominating in cases of USpA and ReA. Patients with USpA had enthesitis in 70.4% of cases, followed by PsA (53.8%), AS (53.3%), ReA (49%), and arthritis associated to IBD (47.9%). The frequencies of the affected entheses of the MASES in the different diseases of the SpA group are shown in Table 2. Non-AS diseases more

Table 1. Enthesitic sites, according to the Maastricht Ankylosing Spondylitis Enthesitis Score, in 1505 patients.

Site	n	%
First costochondral	287	19.1
Seventh costochondral	215	14.3
Iliac crest	267	17.7
Anterior-superior spina iliaca	282	18.7
Posterior spina iliaca	343	22.8
Spinal process — L5	287	19.1
Achilles tendon	293	19.5

Table 2. Enthesitic sites of the Maastricht Ankylosing Spondylitis Enthesitis Score in 1505 patients, according to specific disease in the SpA group. Except for p values, all data are percentages.

Site	AS	PsA	USpA	ReA	IBD	p
First costochondral	19.9	18.8	19.4	16.3	14.6	NS
Seventh costochondral	15.9	10.3	15.3	14.3	12.5	NS
Iliac crest	17.5	17.0	27.3	10.2	16.7	NS
Anterior-superior spina iliaca	20.0	15.1	19.4	8.2	16.7	NS
Posterior spina iliaca	19.0	19.9	18.4	20.4	20.8	NS
Spinal process — L5	23.3	19.6	29.6	18.4	31.2	NS
Achilles tendon	18.1	17.7	37.8	26.5	16.7	< 0.001

SpA: spondyloarthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; USpA: undifferentiated spondyloarthritis; ReA: reactive arthritis; IBD: arthritis associated with inflammatory bowel disease; NS: not significant.

frequently presented the involvement of Achilles enthesitis ($p < 0.001$).

Regarding the demographic data, the presence of enthesitis was associated with being female ($p = 0.014$) and with fewer daily hours of exercise ($p = 0.002$). Although the patients' ages were similar, patients with enthesitis presented shorter disease duration ($p = 0.001$; Table 3).

Analysis of the clinical data showed that patients with enthesitis had significantly higher frequency of axial pain [buttock pain ($p < 0.001$), cervical pain ($p < 0.001$), and hip pain ($p < 0.001$)] than the group without enthesitis. Patients with enthesitis also had significantly higher frequency of peripheral symptoms [lower limb arthritis ($p = 0.010$), number of painful ($p < 0.001$) and swollen ($p = 0.05$) joints], as well as higher patient (5.53 ± 2.69 vs 4.07 ± 2.88; $p <$ 0,001) and physician (4.64 ± 2.56 vs 2.95 ± 2.45; $p <$ 0,001) global assessments, compared with the group without enthesitis. Specific variables, such as dactylitis, psoriasis, nail involvement, uveitis, urethritis, and IBD were not statistically correlated (Table 4).

Laboratory data also showed statistical associations between enthesitis and higher ESR (27.25 ± 23.63 vs 22.20 ± 20.55; $p < 0.001$) and CRP (11.72 ± 24.77 vs 8.12 ± 16.02; $p = 0.004$; Table 4). Patients with enthesitis had higher mean scores for BASDAI (4.95 ± 2.22 vs 3.32 ± 2.26; $p < 0.001$), BASFI (5.17 ± 2.64 vs 3.82 ± 2.76; $p < 0.001$), and ASQoL (9.08 ± 5.29 vs 6.19 ± 5.08; $p < 0.001$; Table 4). Values for BASRI were similar among the groups.

As enthesitis was also associated with partial or total work incapacity ($p < 0.001$), a logistic regression was performed. First, we performed a multivariate logistic regression analyzing the 7 enthesitic sites: iliac crest ($p = 0.0064$; OR 7.437, 95% CI 1.159–2.461), posterior spina iliaca ($p < 0.0001$; OR 17.031, 95% CI 1.460–2.894), and Achilles tendon ($p = 0.0023$; OR 9.303, 95% CI 1.202–2.333) were associated with work incapacity.

Table 3. Comparison of demographic variables in patients with enthesitis versus without enthesitis in 1505 patients with spondyloarthritis. Except for p values, all data are percentages unless otherwise indicated.

Variable	Enthesitis, n = 813	No Enthesitis, n = 692	p
Age, yrs, mean (SD)	41 (12)	45 (13)	0.310
Disease duration, yrs, mean (SD)	13.1	14.9	0.001
Male	69.7	75.4	0.014
Female	30.3	20.4	
Family history	15.3	18.1	0.141
HLA-B27+	67.5	71.0	0.306
Physical activity, h/week, mean (SD)	1.5 (3)	1.87 (2)	0.021
Job — total incapacity	25.6	22.1	< 0.001
Job — partial incapacity	35.8	29.1	< 0.001
Work outdoors	38.4	45.6	< 0.001
Work at home	11.1	9.3	0.020

Table 4. Comparison of clinical, laboratory, and disease indices data in patients with enthesitis versus without enthesitis, among 1505 patients with spondyloarthritis.

Variables	Enthesitis, n = 813	No Enthesitis, n = 692	p
Lumbar pain, %	69.2	65.3	0.105
Buttock alternating pain, %	37.8	27.3	< 0.001
Cervical pain, %	36.8	24.1	< 0.001
Hip pain, %	28.8	21.0	< 0.001
Lower limb arthritis, %	51.9	45.2	0.010
Upper limb arthritis, %	23.7	20.5	0.135
No. painful joints, mean ± SD	5.45 ± 8.93	1.87 ± 4.90	< 0.001
No. swollen joints, mean ± SD	1.91 ± 4.83	1.19 ± 4.65	0.005
Dactylitis, %	8.7	9.2	0.727
Uveitis, %	17.7	20.5	0.166
Psoriasis, %	18.8	17.1	0.374
Nail involvement, %	10.5	10.3	0.902
Urethritis, %	5.0	3.6	0.177
Inflammatory bowel disease, %	4.8	4.5	0.771
Phys. global assessment, mean ± SD	4.64 ± 2.56	2.95 ± 2.45	< 0.001
Pt. global assessment, mean ± SD	5.53 ± 2.69	4.07 ± 2.88	< 0.001
BASDAI, mean ± SD	4.95 ± 2.22	3.32 ± 2.26	< 0.001
BASFI, mean ± SD	5.17 ± 3.82	3.82 ± 2.76	< 0.001
ASQoL, mean ± SD	9.08 ± 5.40	6.19 ± 5.08	< 0.001
BASRI, mean ± SD	7.05 ± 4.38	7.03 ± 4.67	0.953
BASRI, hip, mean ± SD	1.71 ± 1.33	1.14 ± 1.43	0.361
ESR, mean ± SD	27.25 ± 23.63	22.20 ± 20.55	< 0.001
CRP, mean ± SD	11.72 ± 24.77	8.12 ± 16.02	0.004

ASQoL: Ankylosing Spondylitis Quality of Life score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Another multivariate analysis, including all the demographic and clinical variables, showed that BASFI ($p < 0.0001$; OR 74.839, 95% CI 1.156–2.359), ASQoL ($p = 0.0001$; OR 14.645, 95% CI 1.034–1.111), and Achilles tendonitis ($p = 0.0059$; OR 7.593, 95% CI 1.156–2.359) were associated with work incapacity.

DISCUSSION

Our study analyzed the clinical importance and the correlations of enthesitis in 1505 patients with SpA in Brazil. Enthesitis was confirmed to be a common manifestation of SpA, affecting all the different diseases in the SpA spectrum. In this large SpA cohort, enthesitis was a frequent manifestation (54% of patients) and was strongly associated with a more severe clinical picture (axial and/or peripheral) and more significant pain and functional incapacity. We also found a direct correlation with inflammatory activity represented by higher levels of ESR and CRP.

The choice of the MASES for assessing the entheses was based on its feasibility in daily practice. After 2 training sessions, rheumatologists were able to start searching for the

enthesitic component in patients with SpA; it is important to remember that the fourth question of the BASDAI is related to the enthesitic component[20]. It was also noteworthy that all the axial entheses were described as painful by SpA patients with statistically similar frequencies. The only peripheral enthesis in MASES, the Achilles tendon insertion, was mentioned preferentially by patients with USpA and ReA.

A major finding was the correlation between enthesitis and work incapacity. Iliac crest, posterior spina iliaca, and Achilles tendon were the entheses statistically associated with work incapacity in a logistic regression including the 7 enthesitic sites. When a multivariate logistic regression analysis was performed with all the demographic and clinical variables, BASFI, ASQoL, and Achilles tendon were associated with work incapacity. Because Achilles tendon is evaluated in MASES and SPARCC, these data are important; they characterize enthesitis as a major prognostic factor to be considered in the management of patients with AS and SpA. It is also important that 23.6% of the patients with Achilles enthesitis had just 1 affected enthesis. Because these results were obtained in a cross-sectional study, the longitudinal second phase of RBE (2013-2014), which will analyze these patients after 5 to 7 years of followup, will be vital to confirm these prognostic findings.

Some previous studies have analyzed the relationship between enthesitis and clinical measures in SpA. One study analyzed disease activity in 100 patients with SpA, through laboratory data, VAS for spinal and peripheral pain, and using MEI and MASES (both subdivided into P for patient, and D for physician), as well as BASDAI, BASFI, and BASRI[26]. In multiple linear regression analysis, BASFI, VAS, and female sex (41.3%) were the best predictors of MEI-D, whereas BASFI, VAS, female sex, and ESR (32.5%) were the best predictors of MASES-D. The study observed statistical correlations between MEI and MASES and BASDAI and BASFI, but did not find correlation with laboratory data[26]. Another study analyzed enthesitis in a group of 180 patients with SpA using MEI and Medical Outcomes Study Short Form-36 (SF-36) and found a prevalence of 84.9%, showing a striking correlation between MEI, morning stiffness, disease duration, joint pain, and 6 subgroups of SF-36; the higher correlation was found among MEI and the number of painful joints[27]. A study analyzing the relationship among enthesitis and clinical, laboratory, and QOL measurements in 76 patients with AS, using MASES, MEI, BASDAI, BASFI, and SF-36, found that severity of enthesitis correlated significantly with BASDAI and BASFI, but not with disease duration or laboratory variables[28]. Another study investigated QOL in 962 patients with the diagnosis of AS according to the modified New York criteria; BASDAI, BASFI, fatigue (question 1 of BASDAI), and pain were the most significant variables associated with QOL. Metrologic and radiographic variables were not significant[29]. Enthesitis was more frequent in women in our series, as observed in a previous study[30]. In that English study, 516 patients (344 women, 172 men) were analyzed. SpA progressed differently in women, who had more neck, knee, and hip pain at presentation and neck pain, back pain (lower and upper), fatigue, and enthesitis during the course of the disease than the men[30]. In our present study, those patients who presented at least 1 affected enthesis in MASES showed a significant statistical association with axial and peripheral symptoms, as well as with higher mean scores of BASDAI, BASFI, and ASQoL, confirming that enthesitis must be considered a factor for worse prognosis in SpA.

We did not use US or MRI to evaluate the affected entheses. Although power Doppler US can confirm the diagnosis of enthesitis[31,32,33,34,35,36], the importance of subclinical enthesitis in patients with SpA is not yet completely understood. MRI can be superior to US for the study of entheses because it can show more clearly the initial phases of the bone marrow edema[37,38], and it is the best method to analyze sacroiliitis[37].

Our study has some potential biases that need to be discussed. The first is the large number of centers involved (29); there are difficulties in the standardization of the evaluation of the enthesitic component in such large groups. We tried to standardize this investigation in 2 previous meetings with the study coordinators. The second is that enthesitis was characterized only clinically, without an imaging method to confirm the diagnosis. Standardized use of US or MRI to analyze the 13 entheses of MASES in 1505 patients in 29 study centers would be difficult and expensive. The third is that because the patients with higher prevalence of enthesitis were women with higher mean ASQoL scores, it was important to assess fibromyalgia (FM) as a differential diagnosis. Some studies have analyzed the presence of FM associated with AS[39,40], a clinical situation that can possibly confound the results related to enthesitis. Another study in Brazil, evaluating 71 patients with AS (54.5% women, 45.5% men), observed that FM was more prevalent among women (3.8:1) and may have influenced the higher BASDAI, BASFI, and ASQoL scores in the patients with associated FM[41]. FM, as well as specific questionnaires for anxiety and depression, was not assessed in our study, but all the participants were instructed to avoid the misclassification of a tender point as an enthesitis.

The enthesitic component has become so important in the context of SpA that specific studies about response to treatment were done for the entheses with the biologic agents used for treatment of SpA[42,43,44], and enthesitis is considered separately in the algorithm for the treatment of PsA[45].

Enthesitis is a common manifestation in the SpA group, and needs to be systematically investigated in the

management of these patients, because it represents a significant increase in disease activity and a decline in functional capacity and QOL. Achilles tendonitis, an easy enthesis to examine, must be considered a prognostic factor in cohorts where patients with SpA frequently present axial and peripheral involvement, as in the Brazilian cohort.

REFERENCES

1. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: A guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl II:ii1-44.
2. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Brandt J, Braun J, 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;68:770-6.
3. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis. Ann Rheum Dis 2011;70:25-31.
4. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. Medicine 1974;53:343-64.
5. McGonagle D, Benjamin M, Marzo-Ortega H, Emery P. Advances in the understanding of entheseal inflammation. Curr Rheumatol Rep 2002;4:500-6.
6. Benjamin M, McGonagle D. The enthesis organ concept and its relevance to the spondyloarthropathies. Adv Exp Med Biol 2009;649:57-70.
7. Li CA, Kim HO, Lee SY, Lee SI. Assessment of Achilles enthesitis in the spondyloarthropathies by colour Doppler energy ultrasound in the context of the "enthesis organ". Scand J Rheumatol 2010;39:141-7.
8. Gisondi P, Tinazzi I, El-Dalati G, Gallo M, Biasi D, Barbara LM, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: A hospital-based case-control study. Ann Rheum Dis 2008;67:26-30.
9. McGonagle D. Enthesitis: An autoinflammatory lesion linking nail and joint involvement in psoriatic disease. J Eur Acad Dermatol Venereol 2009;Suppl 1:9-13.
10. Bourikas LA, Papadakis KA. Musculoskeletal manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2009;15:1915-24.
11. Townes JM, Deodhar AA, Laine ES, Smith K, Krug HE, Barkhuizen A, et al. Reactive arthritis following cultured-confirmed infections in Minnesota and Oregon: A population-based study. Ann Rheum Dis 2008;67:1689-96.
12. Taniguchi Y, Kumon Y, Nakayama S, Arii K, Ohnishi T, Ogawa Y, et al. F-18 FDG PET/CT provides the earliest findings of enthesitis in reactive arthritis. Clin Nucl Med 2011;36:121-3.
13. Sarakbi HA, Hammoudeh M, Kanjar I, Al-Emadi S, Mahdy S, Siam A. Poststreptococcal reactive arthritis and the association with tendonitis, tenosynovitis, and enthesitis. Clin Rheumatol 2010; 16:3-6.
14. Mander M, Simpson JM, McLellan A, Walker D, Goodacre JA, Dick WC. Studies with an enthesis index: A method of clinical assessment in ankylosing spondylitis. Ann Rheum Dis 1987;46:197-202.
15. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen R, Landewé R, van der Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127-32.
16. Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis 2009;68:948-53.
17. Dougados M, van der Linden S, Juhlin R, Huitfeldt, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. Arthritis Rheum 1991;34:1218-27.
18. 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.
19. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
20. Kingsley G, Sieper J. Third International Workshop on Reactive Arthritis, 23-26 September 1995, Berlin, Germany. Ann Rheum Dis 1996;55:564-84.
21. 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.
22. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Malorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: The development of the Bath Ankylosing Functional Index. J Rheumatol 1994;21:2281-5.
23. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: A quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.
24. Cusmanich KG. Validação para a língua portuguesa dos instrumentos de avaliação de índice funcional e índice de atividade de doença em pacientes com espondilite anquilosante [Validation into Portuguese of assessment tools functional index and index of disease activity in patients with ankylosing spondylitis]. Master's degree dissertation. Faculdade de Medicina da Universidade de São Paulo, 2006.
25. Wanders AJ, Landewe RB, Spoorenberg A, Dougados M, van der Linden S, Mielants H, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. Arthritis Rheum 2004; 50:2622-32.
26. Sivas F, Baskan BM, Ínal EE, Aktekin LA, Barça N, Ozoran, et al. The relationship between enthesitis indices and disease activity parameters in patients with ankylosing spondylitis. Clin Rheumatol 2009;28:259-64.
27. Turan Y, Duruöz MT, Cerrahoglu L. Relationship between enthesitis, clinical parameters and quality of life in spondyloarthritis. Joint Bone Spine 2009;76:642-7.
28. Laatiris A, Amine B, Yacoub YI, Hajjaj-Hassouni N. Enthesitis and its relationships with disease parameters in Moroccan patients with ankylosing spondylitis. Rheumatol Int 2012;32:723-7.
29. Bodur H, Ataman S, Rezvani A, Buğdaycı DS, Cevik R, Birtane M, et al. Quality of life and related variables in patients with ankylosing spondylitis. Qual Life Res 2011;20:543-9.
30. Roussou E, Sultana S. Spondyloarthritis in women: Differences in disease onset, clinical presentation, and Bath Ankylosing Spondylitis Disease Activity and Functional indices (BASDAI and BASFI) between men and women with spondyloarthritides. Clin Rheumatol 2011;30:121-7.
31. Spadaro A, Iagnocco A, Perrota FM, Modesti M, Scarno A, Valesini G. Clinical and ultrasonography assessment of peripheral enthesitis in ankylosing spondylitis. Rheumatology 2011;50:2080-6.
32. D'Agostino MA, Aegerter P, Bechara K, Salliot C, Judet O, Chimenti MS, et al. How to diagnose spondyloarthritis early: Accuracy of peripheral enthesitis detection by power Doppler ultrasonography. Ann Rheum Dis 2011;70:1433-40.

33. Hamdi W, Chelli-Bouazis M, Ahmed MS, Ghannouchi MM, Kaffel D, Ladeb MF, et al. Correlations among clinical, radiographic, and sonographic scores for enthesitis in ankylosing spondylitis. Joint Bone Spine 2011;78:270-4.
34. Coates LC, Heliwell PS. Disease measurement — enthesitis, skin, nails, spine and dactylitis. Best Pract Res Clin Rheumatol 2010;24:659-70.
35. De Miguel E, Muñoz-Fernández S, Castillo C, Cobo-Ibánez T, Martin-Mola E. Diagnostic accuracy of enthesis ultrasound in the diagnosis of early spondyloarthritis. Ann Rheum Dis 2011; 70:434-9.
36. Naredo E, Möller I, de Miguel E, Batlle-Gualda E, Acebes C, Brito E, et al; Ultrasound School of the Spanish Society of Rheumatology and Spanish ECO-APs Group. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: A prospective case-control study. Rheumatology 2011;50:1838-48.
37. Eshed I, Bollow M, McGonagle D, Tan AL, Althoff CE, Asbach P, et al. MRI of enthesitis of the appendicular skeleton in spondyloarthritis. Ann Rheum Dis 2007;66:1553-9.
38. Emad Y, Ragab Y, Bassyouni I, Moawayh O, Fawzy M, Saad A, et al. Enthesitis and related changes in the knees in seronegative spondyloarthropathies and skin psoriasis: Magnetic resonance imaging case-control study. J Rheumatol 2010;37:1709-17.
39. Barlow JH, Macey SJ, Struthers GR. Gender, depression, and ankylosing spondylitis. Arthritis Care Res 1993;6:45-51.
40. Aloush A, Ablin J, Reitblat T, Caspi D, Elkayan O. Fibromyalgia in women with ankylosing spondylitis. Rheumatol Int 2007;27:865–8.
41. Azevedo VF, Paiva Edos S, Felippe LR, Moreira RA. Occurrence of fibromyalgia in patients with ankylosing spondylitis. Rev Bras Reumatol 2010;50:646-50.
42. Naredo E, Batlle-Gualda E, García-Vivar ML, García-Aparicio AM, Fernández-Sueiro JL, Fernández-Prada M, et al; Ultrasound Group of the Spanish Society of Rheumatology. Power Doppler ultrasonography assessment of entheses in spondyloarthropathies: Response to therapy of entheseal abnormalities. J Rheumatol 2010;37:2110-7.
43. Dougados M, Combe B, Braun J, Landewé R, Sibilla J, Cantagrel A, 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.
44. Song IH, Hermann K, Haibel H, Althoff CE, Listing J, Burmester G, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): A 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590-6.
45. Gossec L, Smolen J, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012;71:4-12.