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# Chronic Pain and Assessment of Pain Sensitivity in Patients With Axial Spondyloarthritis: Results From the SPARTAKUS Cohort

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***ABSTRACT.*** ***Objective***. To study differences in pain reports between patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA), and to assess how pain sensitivity measures associate with disease and health outcomes.

***Methods.*** Consecutive patients with axial SpA (axSpA) were enrolled in the population-based SPARTAKUS cohort (2015–2017) and classified as AS (n = 120) or nr-axSpA (n = 55). Pain was assessed with questionnaires (intensity/duration/distribution) and computerized cuff pressure algometry to measure pain sensitivity (pain threshold/pain tolerance/temporal summation of pain). Linear regression models were used to compare pain measures between patients with AS and nr-axSpA, and to assess associations between pain sensitivity measures and disease and health outcomes.

***Results***. Of 175 patients with axSpA, 43% reported chronic widespread pain, with no significant differences in any questionnaire-derived or algometry-assessed pain measures between patients with AS and nr-axSpA. Lower pain tolerance was associated with longer symptom duration, worse Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP), Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Metrology Index (BASMI), more pain regions, unacceptable pain, worse Maastricht AS Enthesitis Score (MASES), fatigue, anxiety, and health-related quality of life. Further, lower pain threshold was associated with worse ASDAS-CRP and MASES, whereas higher temporal summation was associated with longer symptom duration, unacceptable pain, and worse BASMI.

***Conclusion***. Chronic pain is common in axSpA, with no observed differences in any pain measures between patients with AS and nr-axSpA. Further, higher pain sensitivity is associated with having worse disease and health outcomes. The results indicate that patients with AS and nr-axSpA, in line with most clinical characteristics, have a similar pain burden, and they highlight large unmet needs regarding individualized pain management, regardless of axSpA subgroup.

*Key Indexing Terms*: ankylosing spondylitis, chronic pain, health, pain thresholds, spondyloarthritis

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Patients with spondyloarthritis (SpA) can present with mainly axial symptoms (inflammatory back pain, stiffness), peripheral manifestations (arthritis), or both. Regardless of presentation, enthesitis is common and extraarticular features occur.[1] According to the modified New York (mNY) classification criteria,[2] ankylosing spondylitis (AS) requires definite structural changes in the sacroiliac (SI) joints for fulfillment.[2] However, such changes may take years to develop and not all patients may do so.[3,4] In order to also include patients at early disease stages or with a different phenotype, the more recent classification criteria for axial SpA (axSpA) by the Assessment of SpondyloArthritis international Society (ASAS) cover both patients with and without structural radiographic changes in the SI joints: radiographic axSpA and nonradiographic axSpA (nr-axSpA).[5] AS and nr-axSpA have so far been found to be similar regarding most clinical characteristics and rates of treatment response, although patients with nr-axSpA are more often women and generally have lower C-reactive protein (CRP) values.[6,7]

As in most rheumatic diseases, pain is an important and common symptom of axSpA, and may include periods of both fluctuating and more persistent pain.[8,9] It may also develop into chronic pain, a more complex biopsychosocial phenomenon[10] comprising chronic widespread pain (CWP) and chronic regional pain. Currently, the development of hyperalgesia, allodynia, and other changes in pain sensitivity are not fully understood. In rheumatoid arthritis (RA), reports have suggested that pain sensitivity can be attributed to long-standing painful stimulation such as inflammation,[11] which may eventually lead to a sensitization of the nociceptive system,[12,13] and to noninflammatory pain mechanisms such as augmented central pain processing.[14] More recently, the awareness and concern regarding treatment and classification difficulties in patients with axSpA and concomitant CWP have increased. Such concerns stem from reports of inadequate treatment response to disease-modifying antirheumatic drugs (DMARDs) in patients with SpA and concomitant fibromyalgia (FM),[15] the more severe end of the CWP continuum,[16] and that the coexistence of FM may negatively affect patient-reported items in instruments used to evaluate the disease.[17] Another concern is that non-axSpA–related pain conditions might meet the ASAS classification criteria for nr-axSpA, especially in HLA-B27–positive individuals.[18] Despite its potentially large effect, there have been few reports of CWP in axSpA. The prevalence of concomitant FM in AS has been reported to range between 4% and 15%,[19,20] and for nr-axSpA, a previous study found a prevalence of 24%.[21] When not limiting CWP to FM, our group found concomitant CWP in almost half of patients with a clinical diagnosis of AS (45%) or undifferentiated SpA (49%).[22] More pain regions and higher pain intensity were important risk factors for both development and persistence of CWP.[23] With a better understanding of different pain aspects in axSpA subgroups, awareness of improved pain assessments and, accordingly, better pain diagnosis and pain management may increase.

Assessments of pain perception are challenging and require different methodologies. Frequently used instruments to quantify pain are the visual analog scale (VAS) for assessment of pain intensity and pain mannequins[24] for assessment of pain distribution. Another validated technique to quantify pain is to measure pain sensitivity by pressure algometry.[25,26] Computerized cuff pressure algometry (CPA) is a development of the handheld tool and measures the degree of muscle and deep-tissue pain sensitivity in terms of pain threshold, pain tolerance, and facilitated temporal summation of pain.[27] Temporal summation of pain is a natural neurophysiological phenomenon and defined as increased pain intensity in response to a sequence of pain stimulation of the same magnitude.[28]

Owing to the need for better understanding of pain in axSpA and considering the high CWP prevalence previously observed,[22] a more comprehensive assessment of different pain aspects, including pain sensitivity, in a well-defined axSpA cohort would be of value. In particular, a comparison between patients with AS and nr-axSpA could shed further light on the similarities and differences between the subgroups and is also of interest in view of the abovementioned concern regarding nr-axSpA classification difficulties in patients with non-SpA-related pain conditions. Thus, the aims of this study were to compare pain distribution, pain intensity, and pain sensitivity between patients with AS and nr-axSpA, and to assess how pain sensitivity measures are associated with disease and health outcome measures in axSpA.

## METHODS

*Study population and assessments*. The SPARTAKUS study is a clinical study with a population-based, cross-sectional design, based at the Department of Rheumatology, Skåne University Hospital, Sweden.[29,30] All patients with a clinical diagnosis corresponding to axSpA according to the International Classification of Diseases, 10th revision, who resided within a defined geographical area and had ≥ 1 outpatient visit during 2011–2014 were eligible. Since the study focused on axSpA, patients with undifferentiated SpA diagnoses (M46.8 and M46.9) had to report back pain for ≥ 3 months with onset before the age of 45. In the present work, patients consecutively enrolled during the first 2 years of the study (November 2015–November 2017) and were classified as having AS (mNY criteria; n = 120) or nr-axSpA (ASAS axSpA criteria; n = 55) were included. For further details on the classification algorithm, see the Supplementary Material (available with the online version of this article).

All patients attended a structured study visit, including a thorough medical history; questionnaires (pain [VAS and mannequin], disease activity, physical and mental function, health-related quality of life [HRQOL]); clinical examinations by a rheumatologist, physiotherapist, and research nurse; sampling of blood (e.g., HLA-B27 analysis, CRP); and a pain sensitivity examination by computerized CPA. Current medication regarding conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), and corticosteroids was recorded. The study was approved by the Regional Ethical Review Board, Lund University, Sweden (Dnr. 2015/436). Oral and written consent was obtained from all patients in compliance with the Declaration of Helsinki.

The CPA pain sensitivity examinations followed a predefined protocol and were performed by the same research nurse. Altogether, 140 patients with axSpA completed the pain sensitivity examinations. Measures for pain threshold and pain tolerance could be obtained from 139 patients and measures for Temporal Summation Index (TSI) could be obtained from 138 patients. For the remaining 35 patients (AS: n = 26 [22%]; nr-axSpA: n = 9 [16%]), CPA examinations were not performed in patients who were unable to withdraw painkillers 48 hours before the assessment (n = 14), patients undergoing anticoagulant therapy (n = 8), and those who opposed

going through the examination (n = 4). For 9 patients, data on pain sensitivity could not be obtained due to technical problems (n = 9).

*Definitions of pain measures*. Pain intensity was assessed with a VAS, ranging from 0 to 100 mm (representing no pain to worst imaginable pain), and it was also dichotomized into VAS pain > 40 mm (unacceptable pain) or VAS pain ≤ 40 mm according to the patient acceptable symptom state.[31,32] Chronic pain was defined as persistent or recurrent pain for more than 3 months during the previous 12 months, and pain distribution was assessed with a mannequin with 18 predefined body regions and explanatory names for each region.[24] If the chronic pain definition was fulfilled and pain was indicated (1) in the right and left side of the body, (2) above and below the waist, and (3) in the axial regions of the mannequin, the patients were categorized as having CWP.[33] Patients who fulfilled the criteria for chronic pain, but not those for CWP, were categorized as having chronic regional pain, whereas patients who answered "no" to the question defining chronic pain were categorized as having no chronic pain.

*Definitions of pain sensitivity measures.* Pain threshold, pain tolerance, and temporal summation were assessed by CPA by means of a DoloCuff.[27] The DoloCuff consists of a tourniquet cuff with 2 chambers and a computer-controlled air compressor. Attached to the system is a handheld electronic 10-cm VAS, which enabled the patients to report pain continuously during the examinations. All patients were examined in a supine position, with the cuff tightly fitted to the widest part of the calf muscle on the dominant side. Nonsteroidal antiinflammatory drugs (NSAIDs) and analgesics were paused 48 hours before the assessments. Each CPA assessment included an initial "short" sequence to introduce the patient to the assessment. This was followed after 3 minutes by the "auto" sequence (which included 3 "short" measures), which continued automatically with 3 minutes of rest between each pressure stimulation. Pain threshold and pain tolerance were determined during the "short" sequences and a mean value of 3 readings was calculated for each measure. Pain threshold was defined as the pressure (kPa) of the cuff when the sensation of strong pressure first became painful (indicated by the VAS exceeding 0 on the vertical 10-cm scale), and pain tolerance was defined as the pressure (kPa) of the cuff when the pressure was stopped due to reaching worst tolerable pain. The degree of temporal summation of pain was assessed during a "long" sequence (10 min) when the cuff was inflated to a constant pressure, based on each patient's individual pain threshold and pain tolerance,[26] and maintained during the whole assessment. Patients were kept unaware of the constant pressure, and were asked to continuously report increasing, decreasing, or unchanged pain intensity. If the pain intensity increased to become intolerable, the patients were instructed to tell the nurse to stop the examination. To describe the degree of temporal summation of pain, a measure previously shown to be associated with central sensitization,[34,35] an index (TSI) was calculated (Supplementary Material, available with the online version of this article).[36]

*Additional measures*. Symptom duration (time from self-reported onset of symptoms to date of visit) was collected from the patient's medical journal. Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index[37] and the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP).[38] To assess enthesitis, the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[39] was used (modified to also include bilateral plantar fascia: 0–15 sites). The entheseal sites were evaluated as being tender (1) or not tender (0). Physical function was assessed with the Bath Ankylosing Spondylitis Functional Index (BASFI),[40] spinal mobility with the Bath Ankylosing Spondylitis Metrology Index (BASMI),[41] and fatigue and patient global assessment of health with VAS ranging from 0 (best) to 100 (worst). Further assessments included psychological status by the Hospital Anxiety and Depression Scale (HADS)[42] for anxiety and depression, with subscales ranging from 0 (no symptoms) to 21 (severe symptoms), and HRQOL by the generic European Quality of Life 5 Dimensions (EQ-5D) instrument,[43] rendering utility values anchored at 0 (death) and 1 (full health). Age, sex, symptom duration, ASDAS-CRP, BASFI, BASMI, pain regions, unacceptable pain, MASES, fatigue, EQ-5D, HADS-anxiety, and HADS-depression were analyzed to find possible associations with the CPA-assessed pain sensitivity measures.

*Statistical analysis*. Demographics, as well as disease, health, and treatment characteristics were compared between patients with AS and nr-axSpA using *t* test or chi-square test, as appropriate. Analyses of between-group differences (AS vs nr-axSpA) regarding pain variables were performed univariate (*t* test or chi-square test), and for continuous variables also adjusted for age and sex by ANCOVA. Further, factors associated with the pain sensitivity measures (pain threshold, pain tolerance, and TSI) were assessed by age- and sex-adjusted ANCOVA for all patients with axSpA (AS and nr-axSpA) combined. Correlation analyses between possible associated factors showed that some independent variables were highly correlated. Therefore, we used a basic model with age- and sex-adjustment and separate analyses for each of the independent variables. Symptom duration and BASMI were only adjusted for sex due to high correlation to age ($r > 0.8$, $r = 0.64$). Assumptions for the models were checked with residual analyses, and linearity graphically explored by scatterplots. Any $P$ value of $< 0.05$ was considered statistically significant. All analyses were performed with SPSS v25 for Windows (IBM Corp.).

## RESULTS

The patients with axSpA (n = 175; 46% female) had a mean symptom duration of 27 (SD 14) years. A higher proportion of the patients with AS (n = 120) were older, were male, had longer symptom duration, had worse spinal mobility, and were smokers, as compared to patients with nr-axSpA (n = 55), who in turn had higher self-reported enthesitis scores (Table 1). No differences in ongoing pharmacological treatments (csDMARDs, bDMARDs, or corticosteroids) were found between the axSpA subgroups.

*Aspects of pain*. A clear majority of the patients with axSpA had chronic pain, with 43% reporting CWP and 33% reporting chronic regional pain, with a mean number of pain regions of 4.8 (SD 4.3). The mean pain intensity level was 35 (SD 27) mm, and as many as 40% of all patients with axSpA reported unacceptable pain levels (VAS > 40 mm). The mean pain threshold was 30.1 (SD 15.0) kPa, mean pain tolerance was 62.5 (SD 26.5) kPa, and mean TSI was 0.66 (SD 0.55).

No significant differences in number of pain regions, proportion of different pain groups, pain intensity, frequency of unacceptable pain, or the pain sensitivity measures (pain thresholds, pain tolerance, or TSI) were found between patients with AS and nr-axSpA, either when analyzed separately or when adjusted for age and sex (all $P \geq 0.05$; Table 2 and Figure 1).

*Variables associated with pain sensitivity measures in all patients with axSpA.* Lower pain threshold (when the sensation of strong pressure first became painful) was associated with worse disease activity (ASDAS-CRP) and having higher enthesitis scores when adjusted for age and sex (Table 3), but not with any of the other factors.

Having lower pain tolerance (when the pressure was stopped due to worst tolerable pain caused by the pressure stimulation) was associated with higher ASDAS-CRP and worse physical function, more pain regions, unacceptable pain, higher enthesitis score, worse fatigue, worse health-related quality of life, and worse anxiety (all adjusted for age and sex). In addition, lower pain tolerance was associated with longer symptom duration and worse spinal mobility, adjusted for sex (Table 3).

*Table 1.* Clinical characteristics of patients with axSpA in the SPARTAKUS cohort.

| | AS n = 120 | nr-axSpA n = 55 |
|---|---|---|
| Age, yrs | 55 (13) | 46 (12)** |
| Sex, female, n (%) | 43 (36) | 37 (67)** |
| Duration of symptoms, yrs | 30 (14) | 19 (12)** |
| HLA-B27–positive, n (%) | 99 (85) | 45 (83) |
| Sacroiliitis on plain radiograph, n (%) | 120 (100) | 0 (0)** |
| SIJ MRI available, n (%) | 55 (46) | 39 (71)** |
| SIJ BME on MRI, n (%) | 25 (45) | 20 (51) |
| CRP, mg/L | 4.3 (6.2) | 2.5 (2.7)* |
| ASDAS-CRP | 2.0 (1.0) | 1.9 (0.9) |
| BASDAI | 3.2 (2.3) | 3.4 (2.2) |
| BASFI | 2.5 (2.5) | 2.2 (2.2) |
| BASMI | 3.6 (1.8) | 2.4 (1.1)** |
| Chest expansion, cm | 4.6 (1.9) | 5.1 (1.9) |
| Vital capacity, L | 3.6 (1.1) | 3.8 (1.0) |
| MASES, 0-15 | 4.2 (3.7) | 5.7 (4.1)* |
| VAS fatigue, 0–100 | 37 (27) | 41 (29) |
| VAS global, 0–100 | 33 (26) | 39 (25) |
| EQ-5D utility[a] | 0.71 (0.26) | 0.69 (0.24) |
| HADS, 0–21 | | |
| Anxiety | 5.4 (3.7) | 6.2 (3.9) |
| Depression | 4.3 (2.9) | 4.6 (4.0) |
| Smoking, n (%) | | |
| Ever | 56 (48) | 13 (24)* |
| Never | 62 (53) | 42 (76) |
| BMI, n (%) | | |
| < 18.5 | 1 (1) | 1 (2) |
| 18.5–24.9 | 42 (35) | 23 (42) |
| 25–29.9 | 44 (37) | 18 (33) |
| > 30 | 33 (27) | 13 (23) |
| Treatment, n (%) | | |
| csDMARDs | 22 (18) | 14 (26) |
| bDMARDs | 51 (43) | 23 (42) |
| Corticosteroids | 13 (11) | 2 (4) |

Presented as mean (SD) unless otherwise indicated. * $P < 0.05$. ** $P < 0.001$ for comparison with the AS group. [a] Utilities calculated by the British time trade-off–based preference set. Missing data: HLA-B27, 7 (3%); CRP, 13 (7%); ASDAS-CRP, 26 (12%); BASDAI, 6 (3%); BASFI, 8 (5%); BASMI, 1 (0.6%), chest expansion, 1 (0.6%); vital capacity, 2 (1%); VAS fatigue/global, 3 (2%); EQ-5D, 6 (3%); HADS-anxiety/depression 14 (8%); smoking, 2 (1%); corticosteroids, 1 (0.6%). AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD: biologic disease-modifying antirheumatic drugs; BME: bone marrow edema; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; EQ-5D: EuroQol-5 Dimensions; HADS: Hospital Anxiety and Depression Scale; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; nr-axSpA: nonradiographic axial spondyloarthritis; SIJ: sacroiliac joint.

A higher TSI (increased pain intensity in response to a sequence of pain stimulation of the same magnitude) was associated with unacceptable pain (adjusted for age and sex), longer symptom duration, and worse spinal mobility (adjusted for sex; Table 3), but not with ASDAS-CRP or any other factor.

*Table 2.* Comparison of pain variables in patients with AS and patients with nr-axSpA.

| | AS, n = 120 | nr-axSpA, n = 55 | *P* |
|---|---|---|---|
| Pain group | | | 0.07 |
| NCP | 33 (28) | 7 (13) | |
| CRP | 35 (30) | 22 (40) | |
| CWP | 49 (42) | 26 (47) | |
| Pain regions, 0–18 | 4.4 (4.3) | 5.4 (4.2) | 0.15 |
| Pain intensity, mm, 0–100 | 34 (28) | 37 (25) | 0.39 |
| Pain > 40 mm | 45 (39) | 25 (46) | 0.38 |
| Pain threshold, kPa | 30.4 (15.2) | 29.7 (15.0) | 0.82 |
| Pain tolerance, kPa | 62.3 (24.9) | 62.7 (30.0) | 0.94 |
| TSI | 0.69 (0.58) | 0.59 (0.50) | 0.31 |

Presented as mean (SD) unless otherwise indicated. Group comparisons by *t* test and chi-square test as appropriate. Missing data: pain group, 3 (1%); pain regions, 7 (3%); pain intensity, 3 (1%); pain threshold/pain tolerance, 36 (21%); TSI 37 (21%). AS: ankylosing spondylitis; CRP: chronic regional pain; CWP: chronic widespread pain; MRI: magnetic resonance imaging; NCP: no chronic pain; nr-axSpA: non-radiographic axial spondyloarthritis; SI: sacroiliac; TSI: Temporal Summation Index.

## DISCUSSION

The main findings of this cross-sectional study of well-characterized patients with axSpA were that there were no differences between patients with AS and those with nr-axSpA regarding questionnaire-derived pain measures or pain sensitivity assessed by computerized CPA. The majority of patients with axSpA reported having chronic pain and almost half (43%) reported having CWP, proportions similar to those previously shown by our group in the SpAScania cohort.[22] The current findings provide further evidence that patients with AS and nr-axSpA, when it comes to different pain aspects, are similar and have a comparable burden of disease, and that chronic pain remains an important treatment target. The results are also in line with a study in which patients with nr-axSpA reported similar levels of global pain and back pain as patients with AS.[44] In the present study, lower pain tolerance was significantly associated with worse outcomes in almost all of the disease and health outcome measures assessed, whereas pain threshold and TSI were associated with a few outcomes each. This may reflect that patients with worse physical and mental health could have less tolerance and/or coping ability regarding pain in the higher pain intensity range, as compared to the lower range where pain thresholds are determined. This is also in accordance with a review[45] in which lower pain tolerance was moderately correlated with higher pain intensity and disability in patients with chronic low back pain, while there was only a weak correlation between lower pain threshold and higher pain intensity. Further, our finding that TSI was associated with unacceptable pain is in line with 2 studies in which temporal summation of pain was associated with greater pain severity in patients with low back pain[46] and in patients with osteoarthritis (OA).[35] In both of these studies, the authors suggested that local and central sensitization could contribute to pain, based on heightened pain sensitivity. In light of the above, and considering that a large

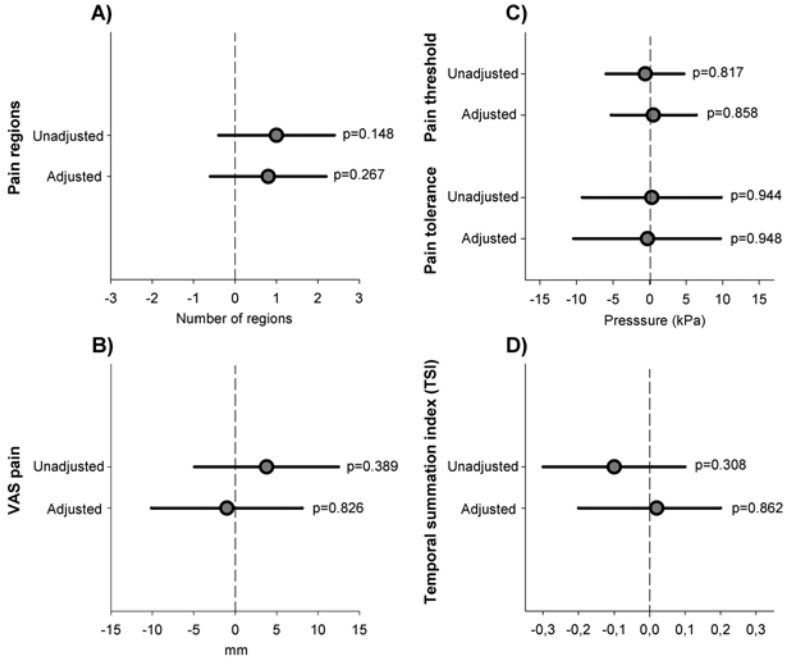


*Figure 1*. Pain outcomes in the patients with nr-axSpA (n = 55) as related to the AS group (n = 120) in the SPARTAKUS cohort. Patient-reported pain outcomes are shown in panels A and B, and algometry-assessed pain sensitivity in panels C and D. The data displayed represent point estimate differences (dots) with 95% CI (whiskers) and *P* values from unadjusted analyses (*t* test) and after adjustment for age and sex (ANCOVA). Missing data: pain regions: 7 (3%); VAS pain: 3 (1%); pain threshold/pain tolerance: 36 (21%); TSI: 37 (21%). AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; nr-axSpA: nonradiographic axial spondyloarthritis; TSI: Temporal Summation Index; VAS: visual analog scale.

proportion of the patients in our cohort reported having chronic pain, one could hypothesize that the higher TSI and the associations found might indicate that a sensitized pain system contributes to chronic pain in patients with axSpA. This also highlights the need for a better understanding of the mechanisms behind increased pain sensitivity in patients with axSpA.

Higher ASDAS-CRP was associated with both lower pain threshold and lower pain tolerance, indicating that there is a connection between pain sensitivity and measures of disease activity. Since ASDAS-CRP comprises both patient-reported symptoms and an acute-phase reactant, a possible explanation might be that ASDAS-CRP may overestimate disease activity due to pain-related symptoms not connected with inflammation. The latter was also argued in a recent study in RA,[47] where high pain sensitivity was found to be associated with elevated Clinical Disease Activity Index scores, and the authors suggested that pain sensitization might contribute to the amplified patient-reported disease activity. Our findings that worse spinal mobility was associated with lower pain tolerance and higher TSI are similar to those reported in a recent study in AS, where more stiffness (measured by duration of morning stiffness) was associated with greater pain and decreased function.[48] This could indicate that stiffness may be involved in the clinical experience of pain and highlight a need for continuous evaluation and coaching to enhance physical function in patients with axSpA.

The DoloCuff device has been used to assess pain sensitivity in patients with other rheumatic diseases such as RA, OA, and FM,[49,50] and in those studies numerically lower pain thresholds and pain tolerance levels were reported, as compared to the present study. The same method has also been used in young healthy adults,[26] and in comparison to those, the patients in our study reported numerically lower pain tolerance and higher TSI levels, in line with our hypothesis of heightened pain sensitization in patients with axSpA. Comparisons are difficult, however, since the above studies almost exclusively included female or younger patients, and the study designs differed from that of the present study.

The strengths of the current study include the cross-sectional and population-based design with thorough patient classification regarding AS and nr-axSpA. To the best of our knowledge, this was also the first study to assess pain sensitivity with CPA in axSpA, enabling a comprehensive comparison of pain aspects between patients with AS and nr-axSpA. Moreover, CPA is a more examiner-independent method than manual pressure algometry and it controls the compression rate more precisely. The placement of the cuff on the lower leg made it possible to examine a large tissue volume of mainly muscle tissue, which has been suggested to minimize within-muscle threshold variability as compared to manual pressure algometry.[27] Compared to studies with CPA/DoloCuff in other rheumatic disorders, our patient cohort was also considerably larger. In addition, we utilized commonly used and validated patient-reported

*Table 3.* Associations between pain sensitivity and demographic and disease/health outcome measures in patients with axSpA (AS/nr-axSpA combined).

| | n | β-est (95% CI) | *P* |
|---|---|---|---|
| Pain threshold | | | |
| Age, yrs[a] | 139 | −0.2 (−0.4 to 0.0) | 0.10 |
| Sex[a] | | | |
| Male | | 0 | |
| Female | 139 | −8.2 (−13.1 to −3.2) | 0.001 |
| Symptom duration, yrs[b] | 139 | −0.1 (−0.4 to 0.0) | 0.14 |
| ASDAS-CRP | 123 | −3.4 (−6.2 to −0.5) | 0.02 |
| BASFI | 133 | −0.6 (−1.9 to 0.7) | 0.37 |
| BASMI[b] | 138 | −0.2 (−1.8 to 1.3) | 0.75 |
| Pain regions, 0–18 | 134 | −0.5 (−1.1 to 0.1) | 0.13 |
| VAS pain | | | |
| ≤ 40 mm | | 0 | |
| > 40 mm | 137 | −2.6 (−7.8 to 2.6) | 0.33 |
| MASES, 0–15 | 139 | −0.8 (−1.5 to −0.2) | 0.02 |
| Fatigue, 0–100 | 137 | −0.0 (−0.1 to 0.1) | 0.38 |
| EQ-5D | 134 | 9.7 (−1.7 to 21.1) | 0.10 |
| HADS, 0–21 | | | |
| Anxiety | 128 | −0.1 (−0.9 to 0.6) | 0.69 |
| Depression | 128 | −0.6 (−1.4 to 0.2) | 0.12 |
| Pain tolerance | | | |
| Age, yrs[a] | 139 | −0.5 (−0.9 to −0.2) | 0.002 |
| Sex[a] | | | |
| Male | | 0 | |
| Female | 139 | −14.6 (−23.1 to −6.2) | 0.001 |
| Symptom duration, yrs[b] | 139 | −0.4 (−0.7 to −0.1) | 0.001 |
| ASDAS-CRP | 123 | −9.9 (−14.5 to −5.3) | ≤ 0.001 |
| BASFI | 133 | −2.6 (−4.8 to −0.4) | 0.02 |
| BASMI[b] | 138 | −4.7 (−7.3 to −2.0) | 0.001 |
| Pain regions, 0–18 | 134 | −1.1 (−2.2 to −0.1) | 0.04 |
| VAS pain | | | |
| ≤ 40 mm | | 0 | |
| > 40 mm | 137 | −15.9 (−24.5 to −7.3) | ≤ 0.001 |
| MASES, 0–15 | 139 | −1.5 (−2.7 to −0.4) | 0.01 |
| Fatigue, 0–100 | 137 | −0.2 (−0.4 to −0.1) | 0.004 |
| EQ-5D | 134 | 28.7 (9.6–47.8) | 0.004 |
| HADS, 0–21 | | | |
| Anxiety | 128 | −1.5 (−2.7 to −0.3) | 0.02 |
| Depression | 128 | −1.2 (−2.6 to 0.2) | 0.09 |
| TSI | | | |
| Age, yrs[a] | 138 | 0.01 (0.00–0.02) | 0.007 |
| Sex[a] | | | |
| Male | | 0 | |
| Female | 138 | −0.04 (−0.22 to 0.15) | 0.71 |
| Symptom duration, yrs[b] | 138 | 0.01 (0.00–0.01) | 0.03 |
| ASDAS-CRP | 121 | 0.04 (−0.08 to 0.15) | 0.54 |
| BASFI | 131 | 0.03 (−0.02 to 0.08) | 0.21 |
| BASMI[b] | 137 | 0.10 (0.04–0.16) | 0.001 |
| Pain regions, 0–18 | 133 | 0.00 (−0.02 to 0.03) | 0.75 |
| VAS pain | | | |
| ≤ 40 mm | | 0 | |
| > 40 mm | 135 | 0.20 (0.00–0.39) | 0.048 |
| MASES, 0–15 | 138 | 0.02 (−0.01 to 0.05) | 0.13 |
| Fatigue, 0–100 | 135 | 0.00 (−0.00 to 0.00) | 0.87 |
| EQ-5D | 132 | −0.26 (−0.69 to 0.17) | 0.24 |
| HADS, 0–21 | | | |
| Anxiety | 127 | −0.00 (−0.03 to 0.02) | 0.88 |
| Depression | 127 | −0.01 (−0.04 to 0.02) | 0.49 |

[a] Sex is age-adjusted and age is sex-adjusted. [b] Adjusted for sex only, due to high correlation to age (symptom duration $r > 0.8$, and BASMI $r = 0.64$). All other variables are age- and sex-adjusted. AS: ankylosing spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein; axSpA: axial spondyloarthritis; β-est: β estimate. BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; EQ-5D: EuroQol-5 Dimensions; HADS: Hospital Anxiety and Depression Scale; MASES: Maastricht Ankylosing Spondylitis Enthesits Score; nr-axSpA: nonradiographic axial spondyloarthritis; TSI: Temporal Summation Index; VAS: visual analog scale.

instruments to evaluate other dimensions of pain such as intensity, duration, and distribution.

This study also had limitations. First, patients who were unable to withdraw NSAIDs and opioids 48 hours before the CPA examination (n = 14) were excluded, so some patients with more severe pain conditions may not have been represented. The 48-hour limit was chosen to diminish the direct effect on pain by pharmacological treatment, even though some drugs have longer half-lives, but we did not find it ethically justifiable to pause effective medication for a longer period. Another limitation was the lack of instruments to capture quality of pain, which might have added yet another viewpoint regarding the nature and effect of chronic pain in axSpA. Finally, results from this cross-sectional study, aimed at the enrollment of all prevalent patients from a defined geographical area, might not be fully generalizable with axSpA incipient cohorts with shorter duration of symptoms, and the design with only 1 evaluation timepoint meant that we were unable to draw any conclusions regarding causality.

In our cross-sectional study of well-characterized patients with axSpA, chronic pain was common, affecting three-quarters of the patients with almost half reporting chronic widespread pain. No significant differences in any of the questionnaire-derived or algometry-assessed pain measures were found between patients with AS and those with nr-axSpA, suggesting that the disease subgroups have a similar pain presentation. Moreover, several axSpA disease and health outcomes were associated with the pain sensitivity measures, indicating that heightened pain sensitivity adds to the experience of pain in patients with axSpA. Overall, the results suggest that pain algometry can complement pain assessments, and they highlight the fact that there are unmet needs regarding individualized pain management, including pharmacological and nonpharmacological interventions, regardless of the axSpA subgroup.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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