Central sensitization has major impact on quality of life in patients with axial spondyloarthritis

Kieskamp, Stan C.; Paap, Davy; Carbo, Marlies J.G.; Wink, Freke; Bos, Reinhard; Bootsma, Hendrika; Arends, Suzanne; Spoorenberg, Anneke

Published in:
SEMINARS IN ARTHRITIS AND RHEUMATISM

DOI:
10.1016/j.semarthrit.2021.11.006

Publication date:
2022

Seminars in Arthritis and Rheumatism 52 (2022) 151933

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Central sensitization has major impact on quality of life in patients with axial spondyloarthritis

Stan C. Kieskamp, MD[a,*], Davy Paap, PT/PhD[a,b], Marlies J.G. Carbo, MD[a], Freke Wink, MD[c], Reinhard Bos, MD/PhD[c], Hendrika Bootsma, MD/PhD[a], Suzanne Arends, PhD[a,c], Anneke Spoorenberg, MD/PhD[a,c]

[a] Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, Universitair Medisch Centrum Groningen, Afdeling Reumatologie en Klinische Immunologie, HPC AA20, HPC CB40, Postbus 30.001, 9700 RB, Groningen, the Netherlands
[b] Department of Rehabilitation Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, Universitair Medisch Centrum Groningen, Centrum voor Revalidatie, HPC CB40, Postbus 30.001, 9700 RB, Groningen, the Netherlands
[c] Department of Rheumatology, Medical Center Leeuwarden, Leeuwarden, The Netherlands, Medisch Centrum Leeuwarden, Afdeling Reumatologie, Postbus 888, 8901 BR Leeuwarden, the Netherlands

ARTICLE INFO

Keywords:
Axial Spondyloarthritis
Quality of Life
Central Sensitization
Pain

ABSTRACT

Introduction: Persistent pain has large potential impact on quality of life (QoL). During the course of the disease, many patients with axial spondyloarthritis (axSpA) report persistent pain. Central sensitization (CS) may explain part of this chronic pain. However, the role of CS in relation to QoL has been sparsely studied in axSpA. Therefore, our aim was to explore the relationship between CS and QoL in patients with axSpA.
Methods: Consecutive outpatients from the Groningen Leeuwarden axSpA (GLAS) cohort completed the Central Sensitization Inventory (CSI; range 0–100) and the AS Quality of Life (ASQoL; range 0–18). Multivariable linear regression analysis was used to explore the relationship between CSI and ASQoL scores correcting for potential confounders.
Results: Of the 178 included axSpA patients, mean CSI score was 38.0 ± 14.1 and 45% scored ≥40, which indicates a high probability of CS. Mean ASQoL score was 6.0 ± 5.3 and mean $ASDAS_{CRP}$ 2.1 ± 1.0. A CSI score ≥40 was significantly associated with higher ASQoL score (mean 9.7 vs. 3.3), higher $ASDAS_{CRP}$ (mean 2.6 vs. 1.7), female gender (60% vs. 29%) and more often entheseal involvement (61% vs. 26%). In univariable analysis, CSI score explained a large proportion of the variation in ASQoL (B = 0.06, 95%CI: 0.05–0.07; R^2=0.46). This association remained significant after correction for $ASDAS_{CRP}$, gender, entheseal involvement, comorbidities, symptom duration, smoking status, BMI class and educational level (B = 0.04, 95%CI: 0.03–0.05).
Conclusion: CS is strongly related to patient-reported QoL in patients with axSpA independently from other patient- and disease-related aspects.

Introduction

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease, especially characterized by inflammation of the axial skeleton resulting in back pain and stiffness. This inflammatory process may lead to progressive bone formation and bone resorption. The main treatment goals are to control inflammation, improve symptoms, and to prevent progressive structural damage in order to preserve daily functioning and social participation, and thereby maintaining optimal health-related quality of life (QoL) [1]. During the course of the disease, many patients report persistent symptoms like pain, fatigue, stiffness and sleep disturbance influencing daily life activities, even in spite of potent anti-inflammatory treatment according to the current standard of care [2–4].

Abbreviations: axSpA, axial spondyloarthritis; QoL, quality of life; CS, central sensitization; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; CSI, Central Sensitization Inventory; $ASDAS_{CRP}$, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; GLAS, Groningen Leeuwarden Axial Spondyloarthritis cohort; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; HLA-B27, Human Leukocyte Antigen B27; BASFI, Bath Ankylosing Spondylitis Functional Index; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire; PASS, patient-acceptable symptom state; RDCI, Rheumatic Disease Comorbidity Index; CVD, cardiovascular disease; mSCQ, modified Self-administered Comorbidity Questionnaire

* Corresponding author at: Universitair Medisch Centrum Groningen, Afdeling Reumatologie & Klinische Immunologie / HPC AA21, P.O. box 30.001, t.a.v. Stan Kieskamp, 9700 RB, Groningen, the Netherlands.
E-mail address: s.c.kieskamp@umcg.nl (S.C. Kieskamp).

https://doi.org/10.1016/j.semarthrit.2021.11.006

Central sensitization (CS) has been recently suggested as a possible contributing cause of these persistent symptoms, and thus may affect QoL [5].

CS is a process in which nociceptive neurons in the central nervous system become increasingly responsive to peripheral sensory input. Clinically, CS most prominently manifests as allodynia and (secondary) hyperalgesia [6]. There are two factors that are broadly recognized in the development of CS. First, persistent peripheral nociceptive C-fiber input due to actual or threatened damage [7–9], such as inflammation in axSpA [10]. Second, top-down modulation originating from the central nervous system, which encompasses malfunction of descending pain-inhibitory pathways or enhanced pain facilitation by psychosocial factors such as depression, anxiety, stress and pain-related cognitions [11–13].

There is growing evidence for the presence of central sensitization in a wide range of musculoskeletal diseases [14]. A previous study found that patients with rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) are at risk of developing chronic widespread pain [15]. Another study in several rheumatic diseases reported that patients with RA or SpA may develop CS more often, indicated by the Central Sensitization Inventory (CSI) questionnaire [16]. The CSI, while not intended to be used in isolation for the diagnosis of CS, can be used as a screening instrument in patients with chronic pain. Recently, we found in our longstanding cohort of patients with axSpA that a higher CSI score was associated with higher disease activity assessed with both Ankylosing Spondylitis Disease Activity Score ($ASDAS_{CRP}$) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Interestingly, the CSI score explained 38% of the variance of BASDAI and 23% of the variance of $ASDAS_{CRP}$ scores [17]. A longitudinal analysis of bivariate trajectories showed that QoL and disease activity are tightly linked in patients with axSpA [18].

Therefore, the aim of this study was to also explore the relationship between possible CS indicated by the CSI and QoL in patients with axSpA and whether this relation is affected by patient- and disease-related aspects including disease activity.

Methods

For this prospective observational cross-sectional study, consecutive outpatients from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort were included. This is an ongoing prospective long-term observational cohort study of patients with axSpA from the University Medical Center Groningen and the Medical Center Leeuwarden, which are tertiary and secondary referral centers, respectively. Patients in this cohort have been included since 2004, are being treated according to the international Assessment of SpondyloArthritis international Society (ASAS) guidelines and have follow-up visits according to a standardized protocol. All participating patients are at least 18 years old and met the modified New York criteria for ankylosing spondylitis (AS) and/or the ASAS classification criteria for axSpA. The patients included in this study concern the same population as our previous analyses [17].

The following variables were obtained from the GLAS regular outpatient visits: age, gender, diagnosis (AS or non-radiographic axSpA), symptom duration, HLA-B27 status, smoking status, educational level, body mass index (BMI) (absolute and divided into three subclasses: normal weight <25 kg/m^2, overweight 25–30 kg/m^2, obese ≥ 30 kg/m^2), history of extra-skeletal manifestations (IBD, uveitis or psoriasis), current peripheral arthritis (≥ 1 swollen joint), entheseal involvement (Maastricht Ankylosing Spondylitis Enthesitis Score ≥ 1), $ASDAS_{CRP}$ [19], BASDAI, CRP, Bath AS Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL; range 0–18 [20],) patient-acceptable symptom state (PASS; yes/no [21]), NSAID use, biological DMARD (bMDARD) use and co-morbidities.

Comorbidities were registered in the GLAS cohort database and the Rheumatic Disease Comorbidity Index (RDCI) was calculated [22]. The RDCI combines 11 comorbidities into a single index ranging from 0 to 9, where a higher score indicates more comorbidities. Comorbidities incorporated in the index were: lung disease, heart attack, stroke, hypertension, other cardiovascular disease, diabetes, cancer, gastric ulcer, fracture, and depression. The RDCI was originally developed in patients with RA, and it has been shown to be predictive for both the outcomes death and functional disability.

Additionally, the patients were asked to fill out the CSI questionnaire [23,24]. The CSI is composed of two parts concerning the presence of symptoms associated with CS (part 1) and previous diagnoses possibly associated with CS and central sensitivity syndrome (part 2). The first part of the CSI was analyzed in this study. This part consists of 25 items on a 5-point Likert scale, with a total sum score ranging from 0 to 100. Based on a previous study in patients with chronic widespread pain, a score of ≥ 40 was defined to be associated with a high likelihood of CS [25]. In case of ≤ 4 missing answers, these items were substituted by the average score of the remaining items and if >4 items were missing, the total CSI score was coded as missing.

Statistical analysis

Population characteristics are shown as numbers of patients (%), mean ± standard deviation or median (IQR) for categorical, continuous normally distributed and continuous non-normally distributed variables, respectively. We divided our study population into subgroups using CSI cutoff score of ≥ 40, indicating a high likelihood of CS [25], ASQoL cut-off score of >8, indicating impaired QoL [26], and $ASDAS_{CRP}$ cut-off score ≥ 2.1, indicating high/very high disease activity [27]. We explored the association between CSI and ASQoL in subgroups of patients with inactive/low and high/very disease activity according to the $ASDAS_{CRP}$. Furthermore, univariable and multivariable logistic regression analysis was performed to investigate whether ASQoL score >8 was associated with CSI score ≥ 40, also correcting for the disease activity assessments separately ($ASDAS_{CRP}$, BASDAI, CRP).

Patient characteristics, disease activity and disease outcome were compared between groups with CSI score of <40 and ≥ 40 using Chi-square test, Independent Samples T-test, or Mann-Whitney U test for categorical, continuous normally distributed, and continuous non-normally distributed data, respectively. Univariable and multivariable linear regression analysis was performed to investigate whether CSI score was an independent predictor for ASQoL after correction for potential confounding variables based on our univariable analysis and literature. Regression assumptions including linearity of relationship, normal distribution of residuals, homoscedasticity, and absence of multicollinearity were tested.

All statistical analyses were performed using IBM SPSS Statistics 23.0.0. P-values of <0.05 were considered statistically significant.

Results

For this study we recruited 182 patients, of which 178 and 149 patients completed the CSI and ASQoL questionnaires, respectively. Mean age of all 178 included patients was 47.4 ± 14.1 years, 78 (44%) were female, median symptom duration was 21 (IQR 10–31) years, mean $ASDAS_{CRP}$ was 2.1 ± 1.0 and 88 (52%) were using bDMARDS. Patient characteristics were not significantly different for patients with or without missing CSI or ASQoL (data not shown). All patient characteristics are shown in Table 1.

Mean ASQoL was 6.0 ± 5.3 and 45 (30%) patients had an ASQoL score >8, which indicates impaired QoL. At group level, mean CSI score was 38.0 ± 14.1 and 80 (45%) patients had a CSI score ≥ 40, which is associated with a high likelihood of CS.

These patients with high CSI score (≥ 40) were significantly more often female (60% vs. 29%), had more often a history of depression (18% vs. 6%), more often entheseal involvement (61% vs. 26%), higher $ASDAS_{CRP}$ (mean 2.6 vs. 1.7), higher BASDAI (mean 5.2 vs. 2.8), higher

Table 1
Patient characteristics, disease activity and clinical outcome variables for all patients, stratified for CSI score.

Characteristics	All patients$n$ = 178	Patients with CSI<40 n = 98 (55%)	Patients with CSI≥40 n = 80 (45%)
Age in (years)	47.4 ± 14.1	48.7 ± 15.0	45.8 ± 12.7
Female	78 (44)	27 (29)	44 (60)***
Diagnosis AS	114 (66)	48 (62)	66 (69)
Symptom duration (years)	21.4 ± 13.6	21.5 ± 13.5	21.2 ± 13.8
HLA-B27+	133 (79)	70 (79)	54 (79)
Current smoker	45 (27)	28 (32)	15 (23)
Completed higher education[1]	81 (71)	48 (70)	34 (76)
BMI (kg/m^2)	26.7 ± 5.0	26.2 ± 4.4	27.5 ± 5.8
History of IBD	26 (15)	12 (12)	14 (18)
History of uveitis	46 (26)	22 (22)	24 (30)
History of psoriasis	24 (14)	17 (17)	7 (9)
RDCI (0–9)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.8)
History of CVD (incl. hypertension)	44 (24)	24 (25)	18 (23)
History of depression	20 (11)	6 (6)	14 (18)*
≥1 comorbidity	83 (45)	42 (43)	38 (47)
SJC ≥1	10 (6)	5 (5)	5 (7)
MASES ≥1	64 (40)	23 (26)	38 (61)***
ASDAS$_{CRP}$	2.1 ± 1.0	1.7 ± 0.9	2.6 ± 1.0***
BASDAI (0–10)	3.9 ± 2.2	2.8 ± 1.9	5.2 ± 1.9***
CRP (mg/ml)	2.9 (1.1 – 6.8)	2.6 (1.1–6.0)	3.6 (1.4 – 7.0)
CRP ≥5 mg/ml	59 (34)	31 (32)	28 (36)
BASFI (0–10)	3.4 ± 2.4	2.4 ± 2.1	4.7 ± 2.2***
ASQoL (0–18)	6.0 ± 5.3	3.3 ± 3.6	9.7 ± 4.9***
PASS: yes	114 (78)	72 (87)	39 (65)**
CSI score (0–100)	38.0 ± 14.1	28.0 (23 – 34)	50.0 (43.0 –56.0)$^{N/A}$
NSAID use	78 (51)	41 (51)	31 (50)
Biological DMARD use	88 (52)	49 (52)	39 (51)

Values are n (%), mean ± SD or median (IQR).
[1] Higher education defined as International Standard Classification of Education (ISCED) level >4. *P<0.05; **P<0.01; ***P<0.001. AxSpA: axial spondyloarthritis; CSI: Central Sensitization Inventory; HLA-B27: Human Leukocyte Antigen B27; RDCI: Rheumatic Disease Comorbidity Index; CVD: cardiovascular disease; SJC: swollen joint count; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; NSAID: nonsteroidal anti-inflammatory drug; ASDAS$_{CRP}$: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; BASFI: Bath Ankylosing Spondylitis Functional Index; PASS: Patient Acceptable Symptom State; N/A: not applicable.

ASQoL (mean 9.7 vs. 3.3), and had less frequently reported to have an acceptable symptom state (PASS; 65% vs. 87%) compared to the patients with low CSI score (Table 1).

ASQoL in relation to CSI and disease activity

Patients with ASQoL score >8 had significantly higher CSI scores than patients with a score ≤ 8 (mean 50.1 vs. 31.7; p<0.001). In univariable logistic regression, ASQoL score >8 was significantly associated with CSI score ≥40 (OR: 14.6, 95%CI: 6.0–35.5). This association remained significant after correcting for disease activity determined by ASDAS$_{CRP}$ (OR: 15.5, 95%CI: 5.0–48.3), BASDAI (OR: 5.6, 95%CI: 2.0–15.8) or CRP (OR: 17.5, 95%CI: 6.9–44.8).

Additionally, patients with low ASDAS$_{CRP}$ (<2.1) and also low CSI score (<40) reported good QoL with a median ASQoL score of 1.1 (IQR 0.0–4.0). Patients with low ASDAS$_{CRP}$ combined with high CSI score (≥40) and opposite, patients with high ASDAS$_{CRP}$ (≥2.1) combined with low CSI score, reported somewhat worse QoL with a median ASQoL score of 5.6 (IQR 2.6–7.9) and 4.1 (IQR 2.0–7.6) respectively. The ASQoL scores between these two groups were not significantly different (p = 0.312). Finally, patients with high ASDAS$_{CRP}$ and also high CSI score reported the worst QoL with a median ASQoL score of 12.0 (IQR 8.4–14.5). ASQoL score stratified for high or low CSI score was significantly different, regardless of the disease activity state (p<0.001) (Fig. 1).

CSI an independent predictor of disease related QoL

In univariable linear regression, CSI score was strongly associated with ASQoL score (square root transformed ASQoL; B = 0.06, 95%CI: 0.05–0.07; R^2=0.46). After adjusting for the potential confounders gender, comorbidity score, entheseal involvement, ASDAS$_{CRP}$, smoking status, BMI, and educational level, this association between CSI and ASQoL remained statistically significant (B = 0.04, 95%CI 0.02–0.05) while associations with ASDAS$_{CRP}$ and female gender were also statistically significant (Table 2). Educational level was missing in 32 patients. Comparable results for the association between CSI and ASQoL were found in the multivariable model without education level (B = 0.04, 95%CI: 0.03–0.05) (Supplementary Table S1). The association between CSI and ASQoL was found for both the secondary (B = 0.069, R^2=0.558) and tertiary (B = 0.058, R^2=0.433) referral center.

Discussion

As far as we know, this is the first study investigating the independent association of CS with disease-related QoL in patients with axSpA. Almost half of the patients with axSpA in our study reported CSI score ≥40, which is associated with a high probability of CS. These patients experienced significantly lower QoL than patients with a low probability of CS (mean ASQoL 9.7 vs. 3.3). We also showed that a CSI score indicative of CS is associated with lower disease related QoL, independently from confounding factors including disease activity and gender, which were also independently associated with QoL.

In our multivariable model, CS seems strongly associated with disease related QoL in axSpA, with an explained variance of 46%. In accordance with our results, several other studies have also found indirect associations between CS and QoL in axSpA. Macfarlane et al. [2] found a high correlation between the two components (Symptom Severity Scale and Widespread Pain Index) of the 2010 American College of

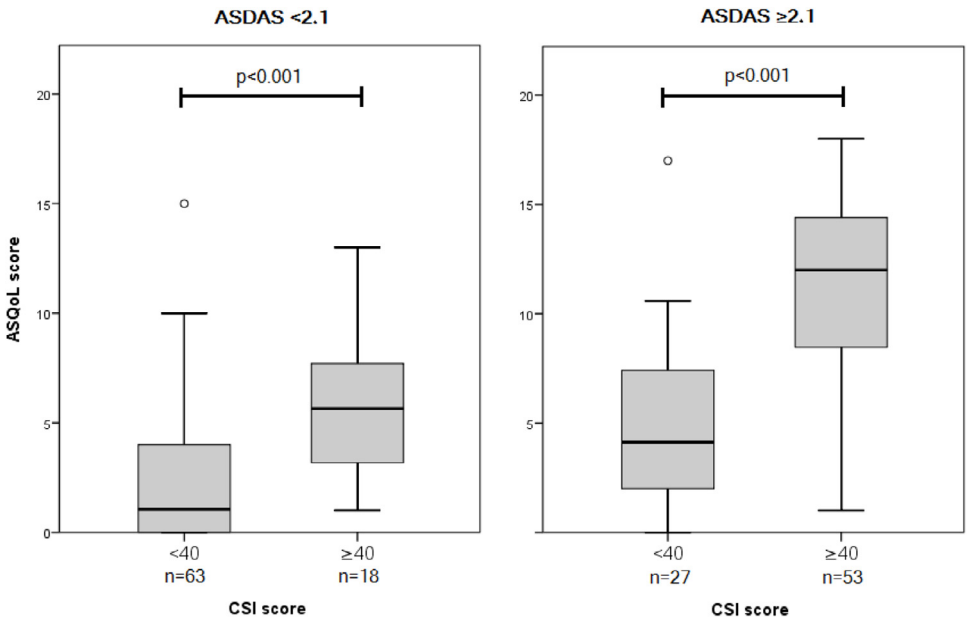

Fig. 1. ASQoL score in axSpA patients with CSI score <40 and ≥40, divided for $ASDAS_{CRP}$ (cutoff 2.1).
CSI: Central Sensitization Inventory, ASQoL: Ankylosing Spondylitis Quality of Life questionnaire, $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with CRP.

Table 2
Multivariable linear regression analysis for the association between CSI score and ASQoL (square root transformed, corrected for potential confounding variables).

Independent variable	B	Standardized β	95% CI for B	P
CSI score (0−100)	0.036	0.402	0.022 − 0.049	<0.001
$ASDAS_{CRP}$	0.417	0.340	0.228 − 0.605	<0.001
Female	0.413	0.164	0.040 − 0.786	0.030
Symptom duration	0.009	0.098	−0.004 − 0.023	0.187
Entheseal involvement	0.369	0.145	−0.004 − 0.742	0.052
Currently smoking	−0.118	−0.042	−0.474 − 0.2537	0.511
BMI categories:				
Overweight	0.215	0.083	−0.156 − 0.587	0.253
Obesity	0.231	0.075	−0.232 − 0.695	0.324
RDCI	0.069	0.067	−0.079 − 0.217	0.355
High educational level[1]	−0.080	−0.029	−0.459 − 0.300	0.677

[1] Higher education defined as International Standard Classification of Education (ISCED) level >4. CSI: Central Sensitization Inventory; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; HLA-B27: Human Leukocyte Antigen B27; RDCI: Rheumatic Disease Comorbidity Index; $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with C-reactive protein.

Supplementary Table S1
Multivariable linear regression analysis for the association between CSI score and ASQoL (square root transformed, corrected for potential confounding variables excluding educational level).

Independent variable	B	Standardized β	95% CI for B	P
CSI score (0−100)	0.035	0.397	0.024 − 0.047	<0.001
$ASDAS_{CRP}$	0.423	0.345	0.261 − 0.584	<0.001
Female	0.407	0.161	0.085 − 0.730	0.014
Symptom duration	0.010	0.106	−0.001 − 0.021	0.087
Entheseal involvement	0.378	0.148	0.056 − 0.700	0.022
Currently smoking	−0.118	−0.042	−0.427 − 0.191	0.451
BMI categories:				
Overweight	0.228	0.088	−0.090 − 0.546	0.158
Obesity	0.251	0.082	−0.143 − 0.645	0.210
RDCI	0.068	0.067	−0.060 − 0.197	0.294

CSI: Central Sensitization Inventory; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; HLA-B27: Human Leukocyte Antigen B27; RDCI: Rheumatic Disease Comorbidity Index; $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with C-reactive protein.

Rheumatology (ACR) criteria for fibromyalgia and ASQoL. Fibromyalgia is a disorder known to be strongly related to CS [28]. Subsequently, Rencber et al. reported that almost one-third of patients with axSpA fulfilling the ASAS criteria also fulfilled the 2010 ACR criteria for fibromyalgia. Additionally, they found a positive association between fulfilling the ACR criteria for fibromyalgia and ASQoL score (mean ASQoL 13.3 vs. 7.0) [29]. These studies are part of growing evidence showing the association between CS and QoL in axSpA. Current treatment recommendations for axSpA emphasize the importance of QoL as an outcome measure besides treating disease activity. However, the contribution of chronic pain as a result of CS to both patient-reported QoL and disease activity must be kept in mind [17].

Alongside CS and disease activity, gender was also independently associated with QoL. Disease phenotypes of axSpA differ between male and female patients. Overall male patients develop more structural damage, while female patients report higher average disease activity [30]. While reasons for these differences are still largely unclear, hormonal differences may play a role in pain processing [31]. Perhaps more importantly, men and women may also report symptoms differently, with women scoring higher on self-reported symptom intensity [32].

Somewhat surprisingly, symptom duration was not associated with CSI score. One explanation for this could be that, once established, it is hard to reduce the extent of CS without targeted (precise) management of CS. The average delay between symptom onset and diagnosis of axSpA is more than 6 years [33], allowing CS to develop through continuous peripheral nociceptive C-fiber input.

The CSI, including the cutoff score of $\geq$40, is developed and validated to recognize chronic (nociplastic) pain in patients suffering from chronic pain and has already been used, but not validated, in osteoarthritis, RA, SpA, and also in IBD [16,34,35]. In addition, the CSI is an indirect assessment for CS, inferring its presence from CS-related symptoms. In order to directly determine the presence and severity of CS, other direct methods such as quantitative sensory testing (QST) may be required [6,28]. In RA, higher pain pressure thresholds were shown to be associated with more intense reported pain levels [36]. So far, no studies have been performed exploring these methods in axSpA.

Data collection was part of our standardized GLAS protocol and therefore there were relatively few missing values. Only for educational level data was missing in 18%, but excluding educational level as potential confounder had no significant impact on the regression coefficients or the explained variance of the multivariable model. Another limitation of this study is that comorbidities were not assessed according to the Self-administered Comorbidity Questionnaire modified (mSCQ) for patients with SpA which represents comorbidities in axSpA better than the RDCI [37]. Since the RDCI has also been previously validated the impact on our results is expected to be minimal [22]. Finally, the cross-sectional design of our study means that no causal relationships can be inferred.

This study provides further evidence towards the theory that CS is a clinically relevant mechanism affecting chronic pain in rheumatic disease and also in axSpA. Our results indicate that clinicians should keep CS in mind during patient education and follow-up, especially in patients experiencing chronic pain. Furthermore, it is of importance to know if CS plays a role at the individual patient level to make the right treatment decisions and prevent unnecessary switching or dose escalation of pharmacological agents such as biological DMARDs. Future research should focus on finding treatment options for CS by identifying specific treatment targets. Potential treatment options may include pain neuroscience education, cognition-targeted exercise therapy and other behavior- and cognition-related neuroscience interventions as part of a multifactorial approach in the treatment of axSpA [38].

In conclusion, our cross-sectional study in long-term axSpA patients treated according to international standards in daily clinical practice demonstrated that CSI score indicative of CS has a major impact on disease-related QoL, also after correcting for potential confounders including disease activity. Awareness and treatment of CS in patients with axSpA has the potential to improve health-related QoL in these patients.

Funding and disclosure of interest

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: F.W. has received research grants from Novartis, and consulting fees from Pfizer. S.A. has received research grants from Pfizer. A.S. has received research grants from Abbvie, Pfizer, UCB and Novartis, and consulting fees from Abbvie, Pfizer, MSD, UCB, and Novartis. The other authors declare that they have no competing interests.

References

[1] Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70(6):896–904.
[2] Macfarlane GJ, Rotariu O, Jones GT, Pathan E, Dean LE. Determining factors related to poor quality of life in patients with axial spondyloarthritis: results from the British Society for Rheumatology Biologics Register (BSRBR-AS). Ann Rheum Dis 2020;79(2):202–8.
[3] Arends S, Brouwer E, Efde M, der Veer VE vanV, Bootsma H, Wink F, et al. Long-term drug survival and clinical effectiveness of etanercept treatment in patients with ankylosing spondylitis in daily clinical practice. Clin Exp Rheumatol 2017;35(1):61–8.
[4] Druce KL, Bhattacharya Y, Jones GT, Macfarlane GJ, Basu N. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford) 2016;55(10):1786–90.
[5] Macfarlane GJ, Pathan E, Siebert S, Packham J, Gaffney K, Choy E, et al. AxSpA patients who also meet criteria for fibromyalgia: identifying distinct patient clusters using data from a UK national register (BSRBR-AS). BMC Rheumatol 2019;3:19.
[6] den Boer C, Dries L, Terluin B, van der Wouden JC, Blankenstein AH, van Wilgen CP, et al. Central sensitization in chronic pain and medically unexplained symptom research: a systematic review of definitions, operationalizations and measurement instruments. J Psychosom Res 2019;117:32–40.
[7] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306(5944):686–8.
[8] Woolf CJ, American College of Physicians. American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140(6):441–51.
[9] Woolf CJ. Central sensitization: uncovering the relation between pain and plasticity. Anesthesiology 2007;106(4):864–7.
[10] Schaible H-G, Grubb BD. Afferent and spinal mechanisms of joint pain. Pain 1993;55(1):5–54.
[11] Brosschot JF. Cognitive-emotional sensitization and somatic health complaints. Scand J Psychol 2002;43(2):113–21.
[12] Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. Phys Ther 2011;91(5):700–11.
[13] Crombez G, Eccleston C, Van Damme S, Vlaeyen JWS, Karoly P. Fear-avoidance model of chronic pain: the next generation. Clin J Pain 2012;28(6):475–83.
[14] Nijs J, George SZ, Clauw DJ, Fernández-de-las-Peñas C, Kosek E, Ickmans K, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. The Lancet Rheumatology 2021;3(5):e383–92.
[15] Larrosa Pardo F, Bondesson E, Schelin MEC, Jöud A. A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain. Eur J Pain 2019;23(8):1563–73.
[16] Guler MA, Celik OF, Ayhan FF. The important role of central sensitization in chronic musculoskeletal pain seen in different rheumatic diseases. Clin Rheumatol 2020;39(1):269–74.
[17] Kieskamp SC, Paap D, Carbo MJ, Wink F, Bos R, Bootsma H, et al. Central sensitization, illness perception and obesity should be considered when interpreting axial spondyloarthritis disease activity. Rheumatology (Oxford) 2021;60(10):4476–85.
[18] Imkamp M, Lima Passos V, Boonen A, Arends S, Dougados M, Landewé R, et al. Uncovering the heterogeneity of disease impact in axial spondyloarthritis: bivariate trajectories of disease activity and quality of life. RMD Open 2018;4(2):e000755.
[19] Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68(1):18–24.
[20] 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(1):20–6.

[21] Godfrin-Valnet M, Prati C, Puyraveau M, Toussirot E, Letho-Gyselink H, Wendling D. Evaluation of spondylarthritis activity by patients and physicians: ASDAS, BASDAI, PASS, and flares in 200 patients. Jt Bone Spine 2013;80(4):393–8.
[22] England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res (Hoboken) 2015;67(6):865–72.
[23] Kregel J, Schumacher C, Dolphens M, Malfliet A, Goubert D, Lenoir D, et al. Convergent Validity of the Dutch Central Sensitization Inventory: associations with Psychophysical Pain Measures, Quality of Life, Disability, and Pain Cognitions in Patients with Chronic Spinal Pain. Pain Pract 2018;18(6):777–87.
[24] Kregel J, Vuijk PJ, Descheemaeker F, Keizer D, van der Noord R, Nijs J, et al. The Dutch Central Sensitization Inventory (CSI): factor Analysis, Discriminative Power, and Test-Retest Reliability. Clin J Pain 2016;32(7):624–30.
[25] Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, et al. The Central Sensitization Inventory (CSI): establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. J Pain 2013;14(5):438–45.
[26] Alkan H, Yildiz N, Ardiç F. The Correlations Between Disease Specific Quality of Life, Short Form-36 and Clinical Variables in Patients With Ankylosing Spondylitis. Arch Rheumatol 2020;35(x):i–ix.
[27] Machado PM, Landewé R, van der Heijde D. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77(10):1539–40.
[28] Eller-Smith OC, Nicol AL, Christianson JA. Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. Front Cell Neurosci 2018;12:35.
[29] Rencber N, Saglam G, Huner B, Kuru O. Presence of Fibromyalgia Syndrome and Its Relationship with Clinical Parameters in Patients with Axial Spondyloarthritis. Pain Physician 2019;22(6):E579–85.
[30] Van der Slik B, Spoorenberg A, Wink F, Bos R, Bootsma H, et al. Although female patients with ankylosing spondylitis score worse on disease activity than male patients and improvement in disease activity is comparable, male patients show more radiographic progression during treatment with TNF-α inhibitors. Semin Arthritis Rheum 2019;48(5):828–33.
[31] Craft RM, Mogil JS, Aloisi AM. Sex differences in pain and analgesia: the role of gonadal hormones. Eur J Pain 2004;8(5):397–411.
[32] Schneider S, Stona AA. Distinguishing between frequency and intensity of health-related symptoms from diary assessments. J Psychosom Res 2014;77(3):205–12.
[33] Zhao SS, Pittam B, Harrison NL, Ahmed AE, Goodson NJ, et al. Diagnostic delay in axial spondyloarthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2021;60(4):1620–8.
[34] Larice S, Ghiggia A, Di Tella M, Romeo A, Gasparetto E, Fusaro E, et al. Pain appraisal and quality of life in 108 outpatients with rheumatoid arthritis. Scand J Psychol 2020;61(2):271–80.
[35] Bennett EE, Walsh KM, Thompson NR, Krishnaney AA. Central Sensitization Inventory as a Predictor of Worse Quality of Life Measures and Increased Length of Stay Following Spinal Fusion. World Neurosurg 2017;104:594–600.
[36] Heisler AC, Song J, Dunlop DD, Wohlfahrt A, Bingham CO, Bolster MB, et al. Association of Pain Centralization and Patient-Reported Pain in Active Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2020;72(8):1122–9.
[37] Stolwijk C, Essers I, van den Bosch F, Dougados M, Etcheto A, van der Heijde D, et al. Validation of the self-administered comorbidity questionnaire adjusted for spondyloarthritis: results from the ASAS-COMOSPA study. Rheumatology (Oxford) 2020;59(7):1632–9.
[38] Nijs J, Leysen L, Vanlauwe J, Logghe T, Ickmans K, Polli A, et al. Treatment of central sensitization in patients with chronic pain: time for change? Expert Opin Pharmacother 2019;20(16):1961–70.