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Original article

Central sensitization, illness perception and obesity should be considered when interpreting disease activity in axial spondyloarthritis

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Abstract

Objectives. Many patients with axial spondyloarthritis (axSpA) report persistent pain even when treated with anti-inflammatory agents. Our aim was to explore the presence of central sensitization (CS) and different types of illness perceptions in patients with axSpA, and to assess their associations with disease activity assessments.

Methods. Consecutive outpatients from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort were included. Besides standardized assessments, patients filled out the Central Sensitization Inventory (CSI), Illness Perception Questionnaire (IPQ-R) and Pain Catastrophizing Scale (PCS). Univariable and multivariable linear regression analyses were used to investigate the association between questionnaire scores, patient characteristics and disease activity assessments $ASDAS_{CRP}$, BASDAI and CRP.

Results. We included 182 patients with a mean symptom duration of 21.6 years. Mean $ASDAS_{CRP}$ was 2.1, mean BASDAI 3.9, and median CRP 2.9. Mean CSI score was 37.8 (scale 0–100) and 45% of patients scored $\geq$40, indicating a high probability of CS. CSI score, IPQ-R domain identity (number of symptoms the patient attributes to their illness), and IPQ-R domain treatment control (perceived treatment efficacy), and obesity were significantly and independently associated with both $ASDAS_{CRP}$ and BASDAI, explaining a substantial proportion of variation in these disease activity scores (R^2=0.35 and R^2=0.47, respectively). Only obesity was also independently associated with CRP.

Conclusion. CS may be common in patients with long-term axSpA. CS, as well as specific illness perceptions and obesity were all independently associated with the widely used (partially) patient-reported disease activity assessments $ASDAS_{CRP}$ and BASDAI. Treating physicians should take this into account in the follow-up and treatment of their patients.

Key words: Axial spondyloarthritis, disease activity, central sensitization, illness perceptions, obesity

CLINICAL SCIENCE

Rheumatology key messages

- Central sensitization indicated with the Central Sensitization Inventory seems common in long-term axSpA.
- Central sensitization, specific illness perceptions and obesity are associated with disease activity assessments.
- Central sensitization and illness perceptions may become additional targets in more patient-tailored treatment of axSpA.

Introduction

Axial spondyloarthritis (axSpA) is characterized by chronic inflammation of especially the sacroiliac joints and the spine, causing symptoms such as back pain and stiffness. The burden of disease is high and is related to disease activity [1, 2]. The cornerstone of therapy for axSpA is a combination of patient education, physical exercise and treatment with NSAIDs [3]. If treatment response is insufficient, biological agents such

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as TNF-α inhibitors and IL-17 inhibitors are the next step in pharmacological therapy [4]. These agents have shown to be effective in improving disease activity as well as disease-related outcome [5–8]. Generally, disease activity in axSpA is assessed with the Ankylosing Spondylitis Disease Activity Score ($ASDAS_{CRP}$), which is a combination of patient-reported items about pain and stiffness from the BASDAI and the inflammatory marker, CRP. Both $ASDAS_{CRP}$ and BASDAI are used in daily clinical practice and research.

Interestingly, 40% of patients who still received etanercept after 7 years of follow-up reported persistent pain defined by a pain score of >4 on a scale of 0–10 [5]. Therefore, it can be hypothesized that this persistent pain may not always be entirely of inflammatory origin and additional pain mechanisms may play a role. For example, patient perceptions about their disease might contribute to persistent pain. Also, central sensitization (CS) may play a role. The central mechanism of CS is hyper-excitability of the central nervous system [9]. This is an important non-nociceptive pain mechanism that is the result of altered pain processing of the central nervous system, and it may be present independently from peripheral injury or inflammation [10]. Clinically, CS can be inferred from signs such as hyperesthaesia and allodynia. However, CS can present within a wide range of cognitive, emotional and physical symptoms [11]. Therefore, it is particularly important to approach CS within its entire biopsychosocial context, both in clinical practice and in research.

The prevalence of CS is unknown in axSpA [12–14]. Previous research has shown that patients with ankylosing spondylitis (AS) rate disease activity based on their complaints, whereas physicians rate disease activity based on disease aspects related to inflammation while including the patient's opinion [15], indicating that illness perception is associated with patient-reported disease activity. In patients with RA, pain catastrophizing has been shown to be associated with the severity of experienced pain, patient-reported disease activity and patient-reported global health, but not with CRP or signs of articular inflammation on ultrasound [16]. No data are available on the relationship between pain catastrophizing and patient-reported disease activity in axSpA [16].

Therefore, our objective was to explore, in daily clinical practice, the presence of CS and different types of illness perceptions, including pain catastrophizing, and to assess their associations with disease activity assessments in patients with axSpA.

Methods

Consecutive outpatients from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort visiting the outpatient clinic between April and September 2019 were included in this observational cross-sectional study. GLAS is a prospective long-term observational cohort study of patients with axSpA from a tertiary (UMCG) and secondary (MCL) referral center in the Netherlands with follow-up visits according to a standardized protocol. This study complies with the Declaration of Helsinki. The GLAS cohort was approved by the ethics committees of the Medical Centre Leeuwarden (MCL) and the University Medical Centre Groningen (UMCG). Informed consent was obtained from all participating patients prior to enrolment.

Since 2004, the GLAS cohort included consecutive AS outpatients who started TNF-α blocking therapy due to active disease [17]. Since the development of the ASAS classification criteria in 2009 [18], this inclusion was extended to all consecutive axSpA patients irrespective of treatment regimen. All participating patients were ≥18 years old and met the modified New York criteria for AS and/or the Axial SpondyloArthritis International Society (ASAS) classification criteria for axSpA.

Patient and disease-related assessments were collected, including age, gender, symptom duration, time since diagnosis, HLA-B27 status, current smoking status, educational level (categorized according to the cutoff value of International Standard Classification of Education level >4 [19]), BMI (absolute and categorized into three subclasses: normal weight <25 kg/m^2, overweight 25–30 kg/m^2, obese ≥30 kg/m^2), history of extra-articular manifestations (uveitis, psoriasis, IBD, according to ASAS guidelines [20]), presence of peripheral arthritis (≥1 swollen joint), entheseal involvement (Maastricht Ankylosing Spondylitis Enthesitis Score ≥1) and current medication use (NSAIDs and biological agents). Disease activity assessments were $ASDAS_{CRP}$, BASDAI and CRP. Patients included in this study were asked to fill out three additional questionnaires concerning the presence of symptoms of CS and illness perception including pain catastrophizing: the Central Sensitization Inventory (CSI) [11], the Pain Catastrophizing Scale (PCS) [21] and the Revised Illness Perception Questionnaire (IPQ-R) [22]. The combination of these assessments allows a broad view on CS and related cognitive and emotional factors beyond just centralized pain.

The CSI is composed of two parts. The first part consists of 25 items on a 5-point Likert scale about the presence of symptoms associated with CS, with a total sum score ranging from 0 to 100. A score of ≥40 is associated with a high likelihood of CS in patients with chronic pain [23]. In case of ≤4 missing answers, these items were substituted by the average of the other items, and for >4 missing answers, the total score was coded as missing. The second part inquires after previous diagnoses possibly associated with CS.

The PCS consists of 13 items on a 5-point Likert scale about the presence of catastrophizing thoughts concerning pain, with a total sum score ranging from 0 to 52. In case of ≤2 missing answers, these items were substituted by the average of the remaining items and if more items were missing, the total score was coded as missing.

The IPQ-R is composed of three parts. We used the first two parts for our analyses. The first part consists of

14 items, where the patient is asked whether they experience any of the symptoms as a result of axSpA: joint stiffness, pain, fatigue, sleep difficulties, loss of strength, sore eyes, headaches, breathlessness, dizziness, upset stomach, nausea, wheeziness, weight loss or sore throat. This 'identity' domain score ranges from 0 to 14 and is calculated by counting the number of symptoms the patient attributes to their illness. In case of $\leq$2 missing answers, these items were substituted by the average score of the remaining items and if more, the score was coded as missing. The second part of the IPQ-R consists of 38 items on a 5-point Likert scale divided in seven domains: (i) timeline acute/chronic (perceived chronicity of the disease; 6–30); (ii) consequences (perceived impact of the disease; 6–30); (iii) personal control (perceived personal control over the disease; 6–30); (iv) treatment control (perceived efficacy of treatment; 5–25); (v) illness coherence (extent to which patients feel they understand their disease; 5–25); (vi) timeline cyclical (perceived variability of the disease; 4–20); and (vii) emotional representations (experienced negative emotions due to the disease; 6–30). For domains with no more than one missing answer, this item was substituted by the average of the remaining items and otherwise, the domain score was coded as missing.

Statistical analysis

Descriptive statistics are shown as numbers of patients (%), mean (S.D.) or median (interquartile range; IQR) for categorical, normally distributed and non-normally distributed variables, respectively.

Univariable linear regression analyses were used to investigate the association of CSI total score, PCS total score, domain scores of the IPQ-R, and patient characteristics with disease activity assessments ($ASDAS_{CRP}$, BASDAI and CRP).

All CS and illness perception variables that were significantly associated with disease activity in the univariable analysis were entered into a forward stepwise multivariable regression model. In addition, we tested the following patient characteristics: gender, symptom duration, BMI class, educational level, smoking status and HLA-B27 status. We also performed the same analyses using the enter model to check robustness of the results. Regression assumptions including linearity of relationship (scatterplots), normal distribution of residuals (QQ-plots), homoscedasticity (plotting residuals *vs* predicted values), and absence of multicollinearity (variance inflation factor $<$5), were tested. Multivariable logistic regression analysis was also performed using the validated dichotomized variables for high and low disease activity for $ASDAS_{CRP}$ (cutoff value $\geq$2.1), BASDAI (cutoff value $\geq$4.0) and CRP (cutoff value $\geq$5.0).

In order to explore whether specific symptoms of the IPQ-R identity domain were related to disease activity assessments, disease activity was compared between patients with and without these symptoms using Mann–Whitney U tests. All statistical analysis was performed using IBM SPSS Statistics 25.0.0. *P*-values of $<$0.05 were considered statistically significant.

Results

Patient characteristics

Between April 2019 and September 2019, 184 consecutive patients with axSpA were included. Two patients were excluded due to missing disease activity assessments. Therefore, 182 patients were eligible for analyses, of which 104 (57%) patients were male. Median symptom duration was 21 years (IQR 10–32), 135 (79%) patients were HLA-B27 positive and 91 (50%) patients were using biological agents. Mean $ASDAS_{CRP}$ was 2.1 (1.0) with 82 patients (49.7%) scoring $<$2.1, mean BASDAI 3.9 (2.2) with 93 patients (52.8%) scoring $<$4.0, and median CRP 2.9 mg/l (IQR 1.1–7.0) with 116 patients (65.5%) scoring $<$5.0. All patient characteristics are presented in Table 1.

CSI, PCS and IPQ-R scores and the associations with disease activity assessments

The mean CSI score was 38.0 (14.1) (scale of 0–100) and 80 (45%) patients scored $\geq$40, indicating presence of CS [23]. A total of 25 (14%) and 16 (9%) patients reported a former diagnosis of depression or fibromyalgia, respectively (for all CSI comorbidities, see Supplementary Table S1, available at *Rheumatology* online).

Median PCS score was 15 (IQR 8–22, scale of 0–52). For IPQ-R domain scores, see Table 1. As expected, the IPQ-R domain 'timeline acute/chronic' showed strong clustering of the results towards the 'chronic' end of the scoring range (Table 1) due to the evident chronicity of the disease and was therefore excluded from further analysis. Individual questionnaire domains showed correlations with each other ranging in strength from weak to moderate (Supplementary Table S2, available at *Rheumatology* online).

$ASDAS_{CRP}$

In univariable linear regression analysis, CSI, PCS, all IPQ-R domain scores, gender and BMI class were significantly associated with $ASDAS_{CRP}$. In the multivariable regression model, four variables were independently associated with $ASDAS_{CRP}$: CSI, IPQ-R identity, IPQ-R treatment control and BMI class (Table 2). In this multivariable model, 35% of the ASDAS score was accounted for by these four variables (R^2 of 0.35), and each association remained significant after correcting for patient characteristics (Supplementary Table S3, available at *Rheumatology* online). Correcting the model for the individual comorbidities from the second part of the CSI, or the prior diagnosis of at least one of these comorbidities, did not significantly affect the model (data not shown).

Logistic regression analyses using the cutoff value of $\geq$2.1 for $ASDAS_{CRP}$ to discriminate between low and high disease activity showed similar results

TABLE 1 Patient characteristics of axSpA study population ($n = 182$)

Characteristics	
Age, years	47.6 (14.0)
Male	104 (57)
Ankylosing spondylitis	116 (65)
Symptom duration, years	21.6 (13.6)[2]
Time since diagnosis, years	13.1 (11.6)[1]
HLA-B27 positive	135 (79)[1]
Current smoker	46 (28)[1]
High education level[a]	83 (70)[3]
BMI, kg/m2	26.7 (5.0)
BMI ≤25 kg/m2 (normal weight)	73 (42)
BMI 25–30 kg/m2 (overweight)	63 (37)
BMI >30 kg/m2 (obese)	36 (21)
History of IBD	27 (15)
History of uveitis	47 (26)
History of psoriasis	24 (13)
Current peripheral arthritis[b]	10 (6)[1]
Current entheseal involvement[c]	66 (40)[1]
NSAID use	88 (48)
Biological use[d]	91 (50)
$ASDAS_{CRP}$	2.1 (1.0)[1]
BASDAI, 0–10	3.9 (2.2)
CRP, mg/ml	2.9 (1.1–7.0)
CSI total score, 0–100	38.0 (14.1)
PCS total score, 0–52	15.7 (10.5)
IPQ-R:	
Identity, 0–14	3 (2–4)
Timeline acute/chronic, 6–30	28 (25–30)
Consequences, 6–30	17 (13–21)
Personal control, 6–30	21 (18–24)
Treatment control, 5–25	18 (16–20)
Illness coherence, 5–25	20 (18–24)
Timeline cyclical, 4–20	14 (11–16)
Emotional representations, 6–30	13 (10–18)

Values are presented in: *n* (%), mean (S.D.) or median (IQR). All % values exclude missing items for their respective characteristic. All missing values <5% unless otherwise specified: [1]5–10% missing; [2]10–20% missing; 35% missing. [a]Defined as International Standard Classification of Education (ISCED) level >4. [b]Defined as a swollen joint count of ≥1. [c]Defined as Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) ≥1. [d]Biologicals include TNF-α inhibitors and the IL-17A inhibitor secukinumab. $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with CRP; ASQoL: Ankylosing Spondylitis Quality of Life questionnaire; AxSpA: axial spondyloarthritis; CSI: Central Sensitization Inventory; IPQ-R: Revised Illness Perception Questionnaire; PCS: Pain Catastrophizing Scale.

(Supplementary Table S4, available at *Rheumatology* online).

BASDAI

Univariable linear regression analysis for BASDAI showed the same associations as for $ASDAS_{CRP}$, with the exception of IPQ-R personal control. Also, the same four variables as for $ASDAS_{CRP}$ were independently associated with BASDAI in the multivariable regression model (Table 3). This model accounted for 47% of the variability of the BASDAI (R^2 of 0.47), which is substantially higher than for $ASDAS_{CRP}$. Each association remained significant after correcting for patient characteristics (see Supplementary Table S5, available at *Rheumatology* online). Again, correcting the model for the individual comorbidities from the second part of the CSI, or the prior diagnosis of at least one of these comorbidities, did not significantly affect the model (data not shown).

Logistic regression analyses using the cutoff value of ≥4.0 for BASDAI to discriminate between low and high disease activity showed similar results (Supplementary Table S6, available at *Rheumatology* online).

CRP

Univariable linear regression analyses using the log transformed CRP showed only significant associations with IPQ-R treatment control and BMI class (Table 4). Only BMI class was significant in the multivariable model. Univariable logistic regression analyses with the cutoff value of ≥5.0 for CRP to discriminate between low and high disease activity only showed a significant association with BMI class (data not shown).

IPQ-R identity and disease activity

Concerning the IPQ-R identity domain, patients who believed that joint stiffness, pain, fatigue, loss of strength, sleep difficulties and headaches could be attributed to axSpA had a significantly higher median $ASDAS_{CRP}$ and BASDAI score. A significantly higher BASDAI was also found for the symptom breathlessness. None of the symptoms in the identity domain were significantly associated with CRP (Table 5).

Discussion

In this cross-sectional study within a long-term observational cohort of axSpA patients, we found moderate to strong independent associations of CSI score, the illness perceptions identity and treatment control, and obesity with disease activity assessments $ASDAS_{CRP}$ and BASDAI. Interestingly, we did not find a significant association between CSI score and IPQ-R domain scores, and CRP, indicating that only the patient-reported responses of the $ASDAS_{CRP}$ and the BASDAI are influenced by illness perception and the presence of CS. However, in axSpA, CRP is elevated only in part of the patients with active inflammation of the sacroiliac joints and/or spine on MRI [24]. Therefore, until now, $ASDAS_{CRP}$ is the best possible tool to measure disease activity in axSpA.

The mean CSI score in this study was comparable to the average scores in study populations of patients with chronic (low back) pain from the same geographic region [25–27], but lower than scores found in an American chronic pain population [11], which might be explained by lifestyle, genetics or sociocultural

Table 2 Univariable and multivariable linear regression analysis exploring the associations of CS, illness perceptions, patient characteristics with $ASDAS_{CRP}$ in patients with axSpA ($n = 148$)

	Univariable			Multivariable[a]	
Independent factor	R^2	*B*	95% CI	*B*	95% CI
CSI score (0–100)	0.23	0.04***	0.03, 0.04	0.02***	0.01, 0.03
PCS score (0–52)	0.10	0.03***	0.02, 0.04		
IPQ-R:					
Identity (0–14)	0.14	0.17***	0.10, 0.24	0.10**	0.03, 0.17
Consequences (6–30)	0.10	0.06***	0.04, 0.09		
Personal control (6–30)	0.03	−0.04*	−0.07, 0.00		
Treatment control (5–25)	0.09	−0.09***	−0.13, −0.04	−0.06**	−0.10, −0.01
Illness coherence (5–25)	0.03	−0.04*	−0.08, 0.00		
Timeline cyclical (4–20)	0.07	0.07**	0.03, 0.11		
Emotional representations (6–30)	0.06	0.05**	0.02, 0.08		
Gender (female *vs* male)	0.04	0.41*	0.09, 0.72		
Symptom duration (years)	0.00	0.00	−0.02, 0.01		
BMI class (reference: $\leq 25\ kg/m^2$)	0.10				
Overweight (25–30 kg/m^2)		0.10	−0.25, 0.45	0.07	−0.24, 0.38
Obesity ($>30\ kg/m^2$)		0.84***	0.44, 1.26	0.56**	0.19, 0.93
Educational level (high *vs* low)	0.02	−0.31	−0.73, 0.11		
Smoking status (yes *vs* no)	0.00	0.10	−0.26, 0.47		
HLA-B27 status (pos. *vs* neg.)	0.00	−0.04	−0.45, 0.36		

[a]Order of inclusion: (1) CSI score (R^2=0.23); (2) BMI class (R^2=0.29); (3) IPQ-R identity (R^2=0.32); (4) IPQ-R treatment control (R^2=0.35). *P <0.05; **P <0.01; ***P <0.001. $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with CRP; CSI: Central Sensitization Inventory; IPQ-R: Revised Illness Perception Questionnaire; PCS: Pain Catastrophizing Scale.

Table 3 Univariable and multivariable linear regression analysis exploring the associations of CS, illness perceptions, patient characteristics with BASDAI in patients with axSpA ($n = 158$)

	Univariable			Multivariable[a]	
Independent factor	R^2	*B*	95% CI	*B*	95% CI
CSI score (0–100)	0.38	0.10***	0.08, 0.11	0.07***	0.05, 0.09
PCS score (0–52)	0.11	0.07***	0.04, 0.10		
IPQ-R:					
Identity (0–14)	0.20	0.46***	0.32, 0.60	0.24***	0.11, 0.37
Consequences (6–30)	0.17	0.18***	0.12, 0.24		
Personal control (6–30)	0.02	−0.07	−0.14, 0.00		
Treatment control (5–25)	0.06	−0.15**	−0.25, −0.06	−0.08*	−0.16, 0.00
Illness coherence (5–25)	0.03	−0.09*	−0.17, −0.01		
Timeline cyclical (4–20)	0.09	0.17***	0.09, 0.25		
Emotional representations (6–30)	0.10	0.14***	0.08, 0.20		
Gender (male/female)	0.06	1.08**	0.43, 1.72		
Symptom duration (years)	0.01	−0.02	−0.04, 0.01		
BMI class (reference: $<25\ kg/m^2$)	0.08				
Overweight (25–30 kg/m^2)		0.21	−0.53, 0.95	0.19	0.39, 0.78
Obesity ($>30\ kg/m^2$)		1.58***	0.71, 2.45	0.90*	0.20, 1.60
Educational level (low/high)	0.01	−0.60	−1.49, 0.28		
Smoking status (yes/no)	0.00	0.11	−0.65, 0.88		
HLA-B27 status (pos/neg)	0.00	0.02	−0.82, 0.86		

[a]Order of inclusion: (1) CSI score (R^2=0.38); (2) IPQ-R identity (R^2=0.43); (3) BMI class (R^2=0.45); (4) IPQ-R treatment control (R^2=0.47). *P <0.05; **P <0.01; ***P <0.001. CSI: Central Sensitization Inventory; IPQ-R: Revised Illness Perception Questionnaire; PCS: Pain Catastrophizing Scale.

Table 4 Univariable and multivariable linear regression analysis exploring the associations of CS, illness perceptions, patient characteristics with log(CRP) in patients with axSpA ($n = 176$)

		Univariable		Multivariable	
Independent factor	**R^2**	**B**	**95% CI**	**B**	**95% CI**
CSI score (0–100)	0.01	0.002	−0.002, 0.005		
PCS score (0–52)	0.02	0.004	0.000, 0.009		
IPQ-R:					
Identity (0–14)	0.00	0.007	−0.018, 0.031		
Consequences (6–30)	0.00	0.003	−0.007, 0.013		
Personal control (6–30)	0.01	−0.006	−0.018, 0.006		
Treatment control (5–25)	0.03	−0.017*	−0.032, −0.002		
Illness coherence (5–25)	0.01	−0.009	−0.021, 0.004		
Timeline cyclical (4–20)	0.01	0.007	−0.006, 0.020		
Emotional representations (6–30)	0.00	0.002	−0.008, 0.013		
Gender (male/female)	0.01	0.063	−0.040, 0.166		
Symptom duration (years)	0.00	0.001	−0.003, 0.005		
BMI class (reference: <25 kg/m^2)	0.06				
Overweight (25–30 kg/m^2)		0.010	−0.106, 0.125	0.010	−0.106, 0.125
Obesity (>30 kg/m^2)		0.211**	0.074, 0.348	0.211**	0.074, 0.348
Educational level (low/high)	0.00	0.026	−0.166, 0.114		
Smoking status (yes/no)	0.00	0.014	−0.133, 0.106		
HLA-B27 status (pos/neg)	0.00	0.042	−0.169, 0.086		

*P <0.05; **P <0.01. CSI: Central Sensitization Inventory; IPQ-R: Revised Illness Perception Questionnaire; PCS: Pain Catastrophizing Scale.

Table 5 Prevalence of individual symptoms of the IPQ-R identity domain and their association with $ASDAS_{CRP}$, BASDAI and CRP in axSpA patients with and without these symptoms

Symptom	**Patients who believed symptom to be associated with axSpA, *n* (%)**	**Median $ASDAS_{CRP}$ (IQR)**		**Median BASDAI (IQR)**		**Median CRP (IQR)**	
		with symptom	**without symptom**	**with symptom**	**without symptom**	**with symptom**	**without symptom**
Joint stiffness	122 (67%)	2.2 (1.3–3.0)	1.6 (1.0–2.6)**	4.3 (2.4–5.9)	2.7 (1.4–4.0)***	3 (1–7)	3 (1–6)
Pain	119 (65%)	2.3 (1.6–3.1)	1.3 (0.9–2.4)***	4.6 (2.6–6.0)	2.3 (1.2–3.7)***	3 (1–7)	2 (1–6)
Fatigue	112 (62%)	2.2 (1.6–3.1)	1.5 (0.9–2.6)***	4.3 (2.6–6.1)	2.4 (1.4–4.6)***	3 (1–7)	3 (1–7)
Sleep difficulties	44 (24%)	2.4 (2.1–3.3)	1.8 (1.2–2.7)**	4.8 (3.2–6.9)	3.0 (1.8–5.4)***	4 (2–8)	3 (1–6)
Loss of strength	41 (23%)	2.8 (2.2–3.3)	1.9 (1.2–2.6)***	5.6 (4.3–6.8)	2.8 (1.7–4.9)***	3 (1–7)	3 (1–7)
Sore eyes	40 (22%)	2.1 (1.1–3.0)	2.0 (1.2–2.8)	3.7 (1.8–5.0)	3.7 (2.0–5.7)	3 (1–7)	3 (1–7)
Headaches	18 (10%)	2.8 (2.0–3.5)	2.0 (1.2–2.8)*	5.2 (3.7–6.9)	3.3 (1.9–5.6)*	4 (1–7)	3 (1–7)
Breathlessness	18 (10%)	2.9 (1.5–3.3)	2.0 (1.2–2.7)*	5.7 (3.5–7.4)	3.5 (1.9–5.5)**	3 (1–6)	3 (1–7)
Dizziness	9 (5%)	2.2 (1.2–2.5)	2.0 (1.2–2.9)	3.8 (2.7–6.5)	3.7 (2.0–5.7)	3 (1–5)	3 (1–7)
Upset stomach	8 (4%)	2.8 (1.8–3.3)	2.0 (1.2–2.8)	5.6 (3.3–6.8)	3.7 (1.9–5.6)	2 (1–7)	3 (1–7)
Nausea	6 (3%)	2.9 (1.9–3.5)	2.0 (1.2–2.8)	5.2 (3.5–6.3)	3.7 (1.9–5.7)	3 (1–15)	3 (1–7)
Wheeziness	6 (3%)	3.0 (1.8–3.3)	2.0 (1.2–2.8)	5.6 (4.9–7.5)	3.6 (1.9–5.6)*	2 (1–6)	3 (1–7)
Weight loss	3 (2%)	N/A	N/A	N/A	N/A	N/A	N/A
Sore throat	3 (2%)	N/A	N/A	N/A	N/A	N/A	N/A

Significance levels determined by Mann–Whitney U test. *P <0.05; **P <0.01; ***P <0.001. P-values compared with patients who did not report having these symptoms due to their axial spondyloarthritis; for all significant symptoms the patient's attribution of the symptom to axSpA correlated with a higher disease activity score. $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with CRP; axSpA: axial spondyloarthritis.

differences [28]. Strikingly, 45% of the patients with axSpA in our study had a CSI score ≥40. Therefore, patients suffering long-term from axSpA seem to have an increased risk of developing CS. This is in accordance with an earlier study in 200 axSpA patients with even a short mean symptom duration of 5.9 years and a mean $ASDAS_{CRP}$ of 3.2, in which a disproportionate number of patients (24%) fulfilled the 2011 American College for Rheumatology criteria for fibromyalgia [29]. Fibromyalgia is a disorder in which CS is considered to be one of the main contributing mechanisms of the experienced symptoms [30]. On the other hand, CS encompasses a wider range of clinical manifestations than fibromyalgia alone, as is also shown in our study. The outcome of our multivariable model did not significanlty change when correcting for the CS-related clinical syndromes (including fibromyalgia).

Our results are also consistent with findings from previous studies in RA, where CS has been studied more extensively [31, 32]. Although, in RA, more objective markers reflecting disease activity are availabe such as CRP, swollen joint count by the physician and joint inflammmation on ultrasound. This makes it easier to detect if chronic widespread pain may still be a result of active disease or is related to non-nociceptive pain mechanisms in case of abcense of objective signs of inflammation.

We found significant associations for CSI/PCS/IPQ-R domains and $ASDAS_{CRP}$, as well as for CSI/PCS/IPQ-R domains and BASDAI, but not for CSI/PCS/IPQ-R domains and CRP. This indicates that the disease activity assessment scores cannot fully discriminate between nociceptive pain caused by inflammation, and nociplastic pain, which is clinically characterized by allodynia and hyperalgesia due to CS. This also indicates that patients with axSpA who have developed CS can retain a high disease activity score even if the underlying inflammation is adequately treated.

CS is affected by two main mechanisms. Firstly, it can be induced by peripheral-to-central, nociceptive C-fiber input [33, 34], of which there is an abundance in axSpA [35]. However, another important factor in the development and persistence of CS is top-down modulation originating from the central nervous system, which may encompass malfunction of descending pain-inhibitory pathways or enhanced pain facilitation by psychosocial factors. Psychosocial factors contributing to CS and somatosensory changes are depression, anxiety, stress, and cognitive factors, including catastrophizing and maladaptive illness perception [36–38]. In accordance with this mechanism, we found that illness perceptions such as identity (the number of individual complaints experienced by patients that they believed were caused by axSpA) and patient's expected treatment efficacy were both independently associated with the disease activity assessments $ASDAS_{CRP}$ and BASDAI.

In our study, perceived treatment control was negatively correlated with both PCS and CSI (Supplementary Table S2, available at *Rheumatology* online), which indicates that a more strongly perceived treatment control reduces catastrophizing thoughts, possibly resulting in a lower degree of CS. Former studies have found that positive expectations of treatment outcome improve this outcome through promoting beneficial coping strategies [39], reducing treatment-related anxiety and inducing physiological changes through reward mechanisms [40]. This may in turn mean that framing the expectations of treatment and illness perceptions positively could improve patient reported aspects of disease activity [39].

We also found that obesity was strongly associated with higher CRP, $ASDAS_{CRP}$, and even BASDAI, confirming results from previous research [41]. Adipose tissue is an active endocrine organ excreting adipocytokines or adipokines like TNF-α, which may be responsible for a more proinflammatory state in obese patients [42].

In our models, we also found that gender was associated with $ASDAS_{CRP}$ and BASDAI, although not independently from CS and illness perceptions. Earlier research showed that females with axSpA on average score higher on patient-reported disease activity assessments than males [43, 44]. Suggested explanations for these differences in males and females are differences in sex hormone distribution, coping strategies and manner of reporting symptoms [45, 46]. Our finding that gender was not independently associated with the disease activity assessments may indicate that the more common occurrence of CS in women is caused by higher disease activity scores in female patients [47].

Implications and limitations

CS is strongly associated with the scores of the widely used disease activity assessments $ASDAS_{CRP}$ and BASDAI in patients with axSpA, which implies that more attention should be paid to the role of pain mechanisms in individual patients to be able to reach treatment goals. In the upcoming 11th Revision of the International Classification of Diseases, a defined classification for chronic musculoskeletal pain that is secondary to another disease will be added [48], which is beneficial for the recognition of nociplastic pain in rheumatic diseases. In this way, treatment becomes more tailored to patient-specific needs and context. Possibly, treatment may focus on pain neuroscience education, cognition-targeted exercise therapy and other behaviour- and cognition-related interventions [49] rather than on adjusting pharmacological agents.

As mentioned earlier, an important difficulty in interpreting disease activity in axSpA is that CRP is neither a sensitive nor specific biomarker for active disease in axSpA [24]. Unfortunately, up to now, no other biomarkers are available to objectively assess inflammation in axSpA. Although it is not optimal, $ASDAS_{CRP}$ is the best available assessment combining patient-reported symptoms and an objective assessment of inflammation (CRP). It is important for clinicians to have knowledge of the associations of CS and illness perceptions with $ASDAS_{CRP}$, when interpreting disease activity.

The main limitation of our study is that our results explore the associations between CS, illness perception, patient characteristics and disease activity, but do not properly illustrate the complex interrelationships between all these involved factors influencing disease activity assessments in axSpA. Further research is needed to study these interactions; for example, through qualitative studies utilizing patient interviews. Additionally, studies are needed to determine whether interventions aimed towards improving CS-related symptoms and illness perceptions improve disease activity and other disease-related outcomes.

Furthermore, some of the questions of CSI and especially BASDAI have overlapping constructs such as pain and fatigue, which therefore may be a confounding factor. However, fatigue-related items of the CSI such as 'waking unrefreshed' and 'low energy' not only correlated moderately with BASDAI but also with $ASDAS_{CRP}$. Additionally, CSI items not included in BASDAI and $ASDAS_{CRP}$ and not directly related to axSpA such as 'memory problems' and 'restless legs' also showed moderate correlations with both $ASDAS_{CRP}$ and BASDAI, which are more indicative for CS.

The CSI cut-off value of 40, indicating a high likelihood of CS, is not based on patients with axSpA, but has been previously studied in other pain-related conditions instead. The 2016 revision of American College of Rheumatology criteria for fibromyalgia has often been used for investigating CS; however, a large part of this instrument involves widespread pain, which may be clinically indistinguishable from axSpA-related tendinopathy. Studies employing methods such as quantitative sensory testing (QST) including pressure pain thresholds and conditioned pain modulation testing are needed to better investigate the aspect of CS-related pain in axSpA, including the relationship with CSI scores and disease activity assessments in axSpA. QST assesses altered somatosensory function related to CS [50], and it is able to identify central nervous system mechanisms such as dysfunction and adaptions of the endogenous (facilitatory and inhibitory) pain systems indicative of CS [51]. Although a consented gold standard to assess CS is still unavailable, QST is one of the most reported and appreciated methods to measure altered somatosensory function related to CS and is considered closest to a gold standard.

Conclusion

This is the first dedicated study investigating CS and illness perception in relation to disease activity in long-term axSpA. We found that CS indicated with the CSI seems to commonly occur in axSpA. CS as well as specific illness perceptions and obesity were all independently associated with widely used disease activity assessments. Treating physicians should take this into account in the follow-up and treatment of their patients. Our results may indicate new perspectives for more patient tailored treatment of chronic pain in axSpA patients.

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This study complies with the Declaration of Helsinki. The GLAS cohort was approved by the ethics committees of the Medical Centre Leeuwarden (MCL) and the University Medical Centre Groningen (UMCG). Informed consent was obtained from all participating patients prior to enrolment.

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Data availability statement

Data are available from the University of Groningen UMCG Institutional Data Access for researchers who meet the criteria for access to confidential data. Detailed information concerning data requests and metadata of our dataset can be found on DataverseNL through https://doi.org/10.34894/RXAROZ.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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