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RESEARCH ARTICLE

The Utility of the Central Sensitivity Score as a Predictor of Disease Activity in a Cohort of Stable Rheumatoid Arthritis

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ABSTRACT

Objective: To assess the impact of central sensitisation as measured by the 'Central Sensitivity Score' on rheumatoid arthritis disease activity change.

Methods: This was a prospective cohort study of rheumatoid arthritis patients receiving routine clinical care. At baseline, participants had assessment of rheumatoid arthritis disease activity from a 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate, symptoms of central sensitisation (from central sensitivity score, the numerical score derived from the 2016 American College of Rheumatology Fibromyalgia diagnostic criteria), demographic and clinical variables. A follow up 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate was collected on the next routine clinic appointment (median 3 months). The association of central sensitivity score and change in rheumatoid arthritis disease activity was assessed using a multivariate linear regression analysis.

Results: Data were obtained from 82 participants. The median baseline 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate across the cohort was 2.44. On multivariate linear regression a higher baseline central sensitivity score independently predicted improvement in 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate (regression coefficient=-0.02, 95% CI [-0.08 to -0.01]). A higher C-Reactive Protein was also an independent predictor of improvement in 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate (regression coefficient -0.02, 95% CI [-0.04 to 0.01]). Exposure to a higher number of biologics predicted worsening in 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate (regression coefficient=0.28, 95% CI [0.08 to 0.48]).

Conclusion: In this closely monitored cohort with relatively well controlled disease, a higher baseline central sensitivity score was predictive of a small but not clinically meaningful change in objective rheumatoid arthritis disease activity.

Key Indexing Terms: Arthritis, Rheumatoid, Central Nervous System Sensitization, Prognosis, Fibromyalgia, Surveys and Questionnaires

Introduction

Rheumatoid arthritis (RA) is a painful chronic inflammatory condition primarily affecting the musculoskeletal system. The central pathophysiology involves activation of the immune system leading to infiltration of the synovial membrane with B cells, T cells and monocytes.[1] Whilst the disease is incurable, disease modifying anti-rheumatic drugs (DMARDs) which target inflammatory molecules have revolutionised treatment and prognosis and led to significant symptom alleviation and inhibition of progressive joint damage.[1] The aim is to obtain remission or low disease activity by a validated measure, which translates to better functional and structural outcomes.[2]

Despite the advancements in RA treatment, a significant proportion of patients (up to 20%) have persistent pain and difficult to treat disease.[3, 4] Whilst some have truly resistant inflammatory disease, other factors such as non-inflammatory pain and psychosocial factors can lead to a persistent high burden of symptoms.[5, 6] The cause of pain in RA is multidimensional and includes not only local intra-articular factors but also sensitised peripheral nociceptors as well as augmented central processing also known as central sensitisation.[6, 7] Central sensitisation has been shown to be an independent contributor to pain intensity, independent of intra-articular inflammation.[8, 9] Fibromyalgia is the prototypical syndrome characterised by central sensitisation, and it has a higher prevalence of approximately 21% in RA compared to a population prevalence rate of 2-4%.[10] Whilst the best methods to treat non-inflammatory pain in RA are not clear, the use of psychological therapy, exercise and pharmacological agents targeting the central nervous system (CNS) may each play a role.[6, 9]

Numerous studies have shown that comorbid fibromyalgia or central sensitisation is associated with higher patient-reported RA disease activity measures and a lower likelihood of achieving sustained remission.[11-15] The few studies examining the impact of fibromyalgia or non-inflammatory pain on longitudinal RA disease activity outcomes have consistently shown worse RA disease activity measures.[13, 16, 17] In an attempt to target presumed persistent inflammation, this has resulted in a greater use of DMARDs and glucocorticoids as well as reduced response to escalating anti-inflammatory treatment.[18-21] More longitudinal studies are needed to assess the impact of central sensitisation on RA disease activity progression in different groups, such as those with significantly active disease or established cohorts with well-controlled RA. It is also important to gauge differences in the influence of fibromyalgia on RA outcomes by using objective RA disease activity measures.

There is no universal method to easily identify comorbid fibromyalgia and/or central sensitisation. Furthermore, it has been shown that fibromyalgia symptoms exist on a continuum and should not be assessed as a binary outcome.[22] The self-report fibromyalgia severity (FS) score, also referred to as the 'central sensitivity score (CSS)',[23] was introduced in the 2010/2011 American College of Rheumatology (ACR) Fibromyalgia criteria and enabled fibromyalgia symptoms to be measured on a continuum, assess severity and monitor response to treatment.[24] The CSS has been suggested as a proxy tool to measure level of central sensitisation and has also shown predictive utility.[25, 26] A higher CSS has predicted glucocorticoid persistence and long-term worse functional status in RA cohorts.[27, 28]

The objective of this study was to assess the impact of level of central sensitisation as measured by the CSS on RA disease activity change in a RA cohort undergoing standard of care. We hypothesised that a higher CSS would predict lack of improvement of RA disease activity, as measured by routine clinical methods, in RA patients.

Methods

STUDY DESIGN AND PATIENTS

This was a prospective observational cohort study based at tertiary hospital in Melbourne, Australia. Patients attending a specialised RA clinic were consecutively approached to participate in this study. The study enrolled adult English-fluent patients (≥18 years old) with a diagnosis of RA based on opinion of the treating rheumatologist. There were no exclusion criteria. Baseline data were obtained between May 2019 and March 2020. Follow-up data were collected on the next routine assessment. Data were collected by direct interaction with participants, medical records and a self-report questionnaire. Monash Health human research ethics committee (HREC) (13019A) approved the collection of de-identified clinic data as part of usual care for quality research purposes. Individual consent was not required for the study.

Demographic and clinical variables were collected. Clinical variables included smoking status, comorbidities, medication use and RA disease variables. Information on treatment regimens, which were at the discretion of the treating rheumatologist, was recorded.

The CSS is the numerical score derived from 2016 ACR Fibromyalgia diagnostic criteria.[29] This validated self-report questionnaire includes the wide spread pain index (WPI) and the symptom severity (SS) scale and can be used to assist fibromyalgia diagnosis as well as measure fibromyalgia symptoms on a continuum (sum of WPI and SS scale).[30] The WPI (score 0-19) measures the number of painful bodily regions and the SS scale (score 0-12) incorporates key symptoms seen in fibromyalgia such as fatigue, cognition and sleep disturbances.

This study used a 3-variable Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate (DAS28-3) to measure RA disease activity.[31] It is derived from the Disease Activity Score with 28 Joint Count Erythrocyte Sedimentation Rate (DAS28ESR), a validated tool to measure RA disease activity which consists of the tender joint count (TJC), swollen joint count (SJC), ESR and patient global assessment (PtGA). The DAS28-3 does not include the Patient Global Assessment and clinically meaningful change is defined by a change of 1.2.[31]

STATISTICAL ANALYSIS

The primary outcome was change in DAS28-3. Positive numbers indicate an increase i.e. worsening in DAS28-3 and negative numbers a decrease.

All data were entered directly into a Research Electronic Data Capture (REDCap) platform managed by Monash University.[32, 33] REDCap is a secure web-based software platform designed to support data capture for research studies. The data were assessed for missing or incomplete assessments and a final complete dataset was defined, which included baseline demographic and clinical information, complete CSS questionnaires and two complete DAS28-3 assessments. Data were analysed using STATA SE version 16.1.

Baseline variables were summarised using summary statistics. Continuous parametric data are presented by mean and standard deviation, continuous non-parametric data by median and interquartile range and categorical data by prevalence (percentage).

Spearman's correlation between baseline CSS and DAS28-3 measures were calculated. Linear regression analysis was used to examine for associations between CSS and clinical and demographic variables with the endpoint of change in DAS28-3. All baseline variables were included in univariate regression analysis. Variables with a P value ≤ 0.1 on univariate regression were included in a multivariate regression model and likelihood ratio test was used to select for inclusion from collinear pairs. Secondary analyses compared CSS measures within the subgroup of higher RA disease activity (DAS28ESR-3>3.1). Patients receiving RA treatment escalation were compared to those with no treatment change, and patients with improved RA disease activity compared to those with no RA improvement. RA disease activity improvement was defined as change in DAS28-3<0 and no improvement was defined as change in DAS28-3≥0.

Statistical significance was defined as a P value < 0.05.

Results

A complete dataset of 82 patients was included in the analysis. The study population was majority female (73%) with median age 63 years observed over median 3 months. Seventeen percent of patients had a clinical diagnosis of fibromyalgia recorded in the medical record and the median CSS was 9. The most frequently prescribed analgesia was a non-steroidal anti-inflammatory drug (NSAID) (Table 1).

Table 1: Baseline demographics and clinical characteristics, N=82	
Age, median [IQR] (range)	63 [17] (23-82)
Observation (months)*, median [IQR] (range)	3 [2.04] (1.44-7.56)
Gender, female n (%)	60 (73.17)
Smoker, n (%)	12 (14.63)
No. Comorbidities, median [IQR] (range)	2 [2] (0-6)
Anxiety, n (%)	3 (3.66)
Depression, n (%)	7 (8.54)
No. analgesia medications, median [IQR] (range)	0 [1] (0-5)
NSAID analgesia, n (%)	23 (28)
Opioid analgesia, n (%)	11 (13.41)
Neuropathic analgesia, n (%)	8 (9.76)
CSS, median [IQR] (range)	9 [8] (1-26)
Fibromyalgia clinical diagnosis, n (%)	14 (17.07)
*= Period of observation (months) between clinic visits IQR = Interquartile Range, No. = Number, NSAID= Non-steroidal Anti-inflammatory Drugs, CSS= Central Sensitivity Score	

Most participants (78%) fulfilled the 2010 ACR/EULAR criteria for rheumatoid arthritis. On average, participants had longstanding RA (median 11 years), with low disease activity (median DAS28ESR-3 2.44, median CRP 3.6mg/L. At the baseline visit, 16 participants (20%) were prescribed RA treatment escalation (Table 2).

Table 2: Baseline RA disease variables, N=82	
ACR/EULAR criteria positive, n (%)	64 (78.05)
Disease duration (years), median [IQR] (range)	11 [12] (2-47)
Rheumatoid factor, n (%)	49 (59.76)
CCP, n (%)	51 (62.20)
Erosions, n (%)	17 (20.73)
No. RA medications, mean [SD] (range)	2.16 [1.05] (0-5)
Steroids, n (%)	21 (25.61)
No. total biologics exposure, median [IQR] (range)	0 (2) (0-5)
Failed biologics, n (%)	22 (26.83)
Baseline DAS28ESR-3, median [IQR] (range)	2.44 [1.49] (0.16-7.72)
TJC, median [IQR[(range)	0 [2] (0-27)
SJC, median [IQR[(range)	0 [2] (0-23)
ESR, median [IQR[(range)	11 [17] (1-68)
CRP, median [IQR] (range)	3.6 [9.8] (0.2-125.3)
RA treatment escalation, n (%)	16 (19.51)
ACR/EULAR = American College of Rheumatology/ European Alliance of Associations for Rheumatology, CCP= Anti-cyclic citrullinated peptides, DAS28ESR-3= Three Variable Disease Activity Score 28 Erythrocyte Sedimentation Rate, TJC= Tender joint count, SJC= swollen joint count, CRP = C-Reactive Protein, RA = Rheumatoid Arthritis	

At baseline, there was no correlation between CSS and DAS28-3 (r=0.1, P=0.35). Patients were followed for a median (range) of 3 (1.44 to 7.56) months. All variables listed in table 1 and 2 were included in univariate linear regression to examine predictors of DAS28-3 change. Significant predictors of a reduction in DAS28-3 between baseline and follow up visit included the use of NSAIDs, higher baseline DAS28-3, higher SJC and TJC, higher CRP and a higher CSS. Previous exposure to a higher number of biologic DMARDs predicted increasing DAS28-3 over the study period (Table 3).

Table 3: Univariate Linear Regression of DAS28-3 change*		
	Coefficient (95% CI)	P value**
Age	0.02 (-0.01 to 0.04)	0.1
Total Biologics Exposure	0.27 (0.04 to 0.49)	**0.02**
Biologics Failure	0.52 (-0.08 to 1.12)	0.09
NSAID	-0.59 (-1.18 to 0.01)	**0.05**
CSS	-0.05 (-0.09 to -0.01)	**0.05**
SJC	-0.12 (-0.19 to -0.05)	**0.01**
TJC	-0.1 (-0.15 to -0.04)	**0.01**
Baseline DAS28-3	-0.51 (-0.7 to -0.32)	**0.01**
CRP	-0.03 (-0.04 to -0.01)	**0.01**
Period of observation***	2.13 (-0.14 to 4.41)	0.07
RA treatment escalation	-0.61 (-1.28 to 0.07)	0.08
*Predictors of change in DAS28-3 over median 3 months are shown, variables with P value ≤0.1 presented. **Significant P values bolded ***=Period of observation between clinic visits A positive coefficient indicates an increase (therefore worsening) in DAS28-3 and a negative coefficient indicates a decrease (therefore improvement) in DAS28-3. All baseline variables were included on univariate regression analysis. CI= Confidence Interval; DAS28-3= Three Variable Disease Activity Score 28 Erythrocyte Sedimentation Rate; NSAID= Non-steroidal anti-inflammatory drug; CSS= Central sensitivity score; SJC= Swollen Joint Count, TJC = Tender Joint Count, CRP= C-reactive protein; RA= Rheumatoid arthritis		

On multivariate linear regression, higher CRP, use of NSAID and a higher CSS each independently predicted DAS28-3 reduction. A higher number of previous biologic DMARDs independently predicted increase in DAS28-3 (Table 4).

Table 4: Multivariate Linear Regression best model for DAS28-3 change*		
	Coefficient (95% CI)	P value**
Total biologics exposure	0.28 (0.08 to 0.48)	**0.01**
NSAID	-0.55 (-1.09 to -0.16)	**0.04**
CSS	-0.02 (-0.08 to -0.01)	**0.02**
CRP	-0.02 (-0.04 to -0.01)	**<0.001**
Period of observation***	1.32 (-0.76 to 3.4)	0.21
RA treatment	0.08 (-0.56 to 0.72)	0.8

*Independent predictors of change in DAS28-3 over median 3 months are shown. Negative numbers indicate a reduction (therefore improvement) in DAS28-3. All baseline variables were included on univariate regression analysis. Variables with a P value of ≤0.1 on univariate regression were included in the multivariate regression model and likelihood ratio test was used to select for inclusion from collinear pairs.
R^2=0.33
**Significant P values bolded
***=Period of observation between clinic visits
CI= Confidence Interval; NSAID = Non-steroidal anti-inflammatory drug; CSS= Central Sensitivity Score; CRP= C-Reactive Protein; RA = Rheumatoid Arthritis

Secondary analyses examined differences in CSS measures within the subgroup of patients with higher baseline RA disease activity. In those with DAS28-3>3.1 (n=26), there was no significant difference in median CSS measures between those who had RA treatment escalation versus no treatment change (Figure 1).

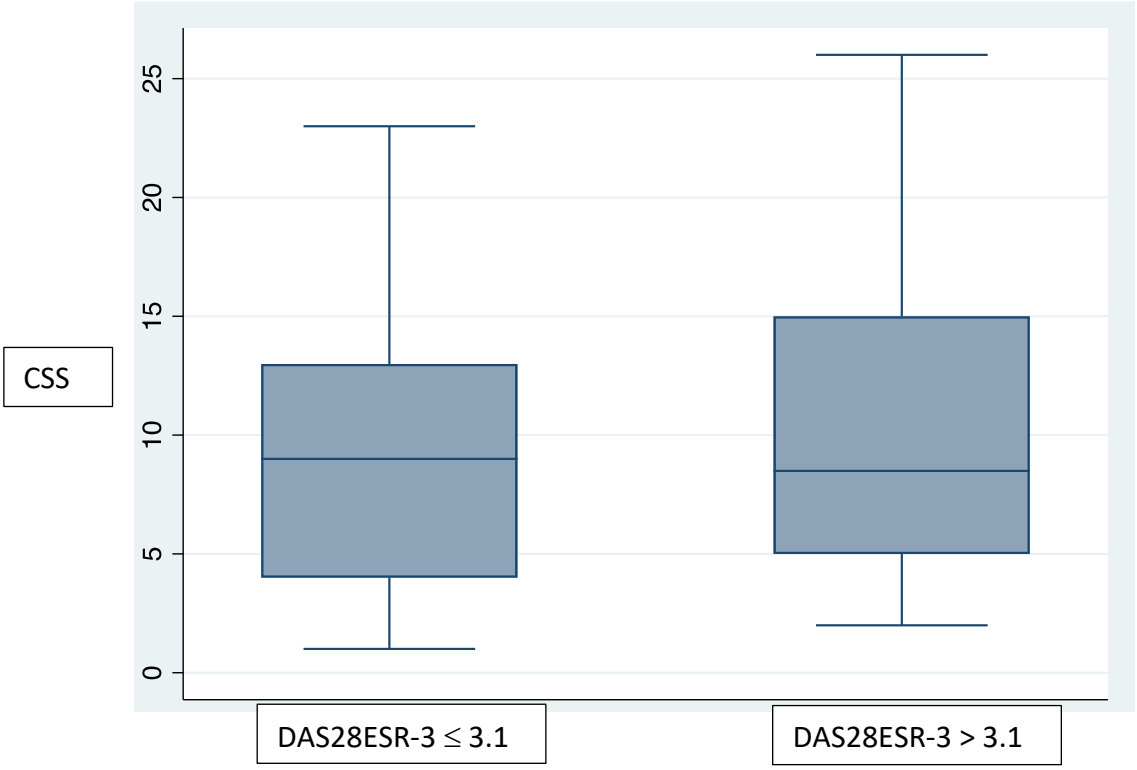

Figure 1. This boxplot compares central sensitivity score (CSS) measures between those with baseline active rheumatoid arthritis (RA) disease (3-variable disease activity score 28 erythrocyte sedimentation rate [DAS28ESR-3 >3.1]) compared to inactive RA disease (DAS28ESR-3≤3.1). There was no difference between median CSS values between the two categories (DAS28ESR-3≤3.1 median CSS=9, DAS28ESR-3 >3.1 median CSS=8.5, P=0.39).

Similarly, in this same subgroup there was no difference in CSS comparing patients who had disease activity improvement versus no improvement (Table 5).

Table 5: CSS in DAS28ESR-3>3.1, based on RA disease activity change*			
	RA worsening, N=18	RA Improvement, N=8	P Value
CSS (median/IQR/range)	7 [7] (2-26)	11.5 [10] (3-25)	0.18
*Improvement RA disease activity was defined as a negative change in DAS28-3 (<0), worsening in RA disease activity was defined as no change or a positive change in DAS28-3 (≥0) CSS= Central Sensitivity Score; IQR= interquartile range			

Discussion

This real-world longitudinal study in a cohort of largely stable RA patients with well-controlled disease found that a higher CSS was not associated with higher concurrent RA disease activity, nor with worsening in RA disease activity over time as measured by DAS28-3.

At baseline, higher CSS did not correlate with higher DAS28-3. This is the first study to show that a higher CSS was not associated with higher RA disease activity, when measured using DAS28-3 which excludes the patient global aspect of the assessment. Cross-sectional studies have shown that a higher CSS and/or the presence of fibromyalgia are associated with higher RA disease activity, potentially driven by subjective components and patient reported outcomes that are possibly confounded by the clinical features of fibromyalgia.[14, 34-36]. Previous studies have shown that features of central sensitisation as measured by CSS and neurodiagnostic measures contribute to higher patient-reported RA disease activity.[11, 12] However, a recent study showed only a weak correlation between the CSS and central sensitisation detected by quantitative sensory testing (QST) in an active RA cohort.[37] Only one study has shown an association between presence of fibromyalgia and disease activity measured using DAS28-3, while another has shown a weak association between increasing CSS and physician outcomes (swollen joint count and physician global assessment).[18, 36] Whilst it may be that the CSS does not accurately identify central sensitisation in RA cohorts, it does not appear to be associated with objective measures of RA disease activity.

This study showed that a higher CSS was not associated with worsening in RA disease activity over time within the study period as measured by change in DAS28-3. Conversely, higher CSS was associated with improvement, although not a clinically meaningful change in DAS28-3. Other longitudinal studies exploring the impact of presence of fibromyalgia, a higher CSS, or non-nociceptive pain on long-term prognosis all showed a worse outcome including higher RA disease activity, lower likelihood of achieving remission, worse function, reduced response to DMARDs and a higher odds of steroid persistence.[13, 15-17, 21, 27, 28, 38] However, none of these studies used measures of RA disease activity that excluded PtGA. Moreover, some specified that it was the potentially more subjective components of RA disease activity (TJC and PtGA) that were the drivers of higher RA disease activity in patients with higher CSS or fibromyalgia.[13, 17] Other studies have shown that the tender-swollen difference and the DAS28-P (TJC and visual analogue scale score) both predicted worse pain outcomes in RA cohorts.[39, 40] Therefore, the potentially subjective components of RA disease activity appear to be important in capturing non-inflammatory drivers such as central sensitisation that impact aspects of RA prognosis. In this study, higher CSS was associated with statistically significant but modest improvement in RA disease activity, measured with the potentially more objective markers. It may be that the CSS captures aspects of active RA inflammation and/or the CSS is measuring central sensitisation that is driven by peripheral RA inflammation and is thus responsive to RA treatment.[41] Nonetheless the effect size of the association of CSS with change in DAS28-3 was smaller than the change of DAS28 of 1.2, considered to be clinically meaningful.[31] A study assessing RA trajectory over 24 months found that after 3 months post-diagnosis, disease activity remains stable.[42] This is consistent with our study which included a cohort with overall well-controlled RA disease activity of long duration. Overall, in a well-controlled RA cohort the CSS does not appear to impact on RA disease progression particularly when using more objective markers of disease activity.

In the subgroup that had higher disease activity, there was no relationship between CSS and escalation of RA treatment. Nor was there association between CSS and either improvement or worsening of RA disease activity over time. This may also be influenced by the omission of the PtGA in the assessment of disease activity, as discussed above. Whilst the PtGA does capture some aspects of inflammatory disease, in particular pain and fatigue, and is sensitive to change with RA treatment, it doesn't correlate with more objective markers of swollen joint count and CRP.[43, 44] The PtGA is also influenced by non-RA factors including

psychological distress and fibromyalgia.[43] Thus, whilst the PtGA is important in predicting functional outcomes, a 3-variable DAS28 is predictive of radiographic outcomes and is suggested to be used as the target for immunosuppression.[45] Additionally, in established long-standing RA, the PtGA has been shown to correlate with pain and functional disability and not inflammatory variables.[46]

A higher baseline C-reactive protein (CRP) was also associated with meaningful improvement in RA disease activity with standard of care management. Previous studies have shown that a higher CRP correlates with worse prognostic markers including a high disease activity trajectory, radiological damage and progression, lower likelihood of remission and extra-articular comorbidities.[42, 47, 48] On the contrary, CRP has shown to be predictive of treatment response to tumour necrosis factor inhibitors, anti-interleukin-6 monoclonal antibodies and as part of a multiple biomarker disease activity score.[47, 49] This is the first study to suggest that CRP is a predictor of disease activity improvement independent of treatment intervention. CRP has been shown to have direct effects on inflammation and potentially bone destruction but it has also been identified to have different isoforms with different properties, [47] wherein the pentametric isoform is thought to act as an immune regulator whereas the monomeric isoform is pro-inflammatory.[47] No distinction between these isoforms is measured in clinical testing and this may contribute to the conflicting observations. Nonetheless the effect size was small and therefore no clinically meaningful conclusions can be made. Further longitudinal studies will be helpful to elucidate the role of CRP both as a prognostic marker and predictor of treatment response in well-established RA.

In contrast, a higher number of biologic DMARDs previously used was associated with worsening of RA disease activity over time, suggesting this metric appropriately identified patients whose arthritis was treatment-resistant. Surprisingly this is the only longitudinal study that we are aware of to show that increased numbers of biological therapies is a poor prognostic marker in a RA cohort, independently predicting worsening of RA disease activity over time. The European Alliance of Associations for Rheumatology (EULAR) guidelines include those failing more than 2 biologic or targeted synthetic DMARDs with different mechanisms of actions in part of the definition for difficult to treat (D2T) RA.[50] The reasons for exposure to a greater number of biological DMARDs in this cohort was not documented but may be affected by both truly resistant inflammatory disease and non-inflammatory factors. A previous study has shown multiple contributing factors to D2T RA such as lower socioeconomic factors, comorbidities, fibromyalgia and poorer coping amongst others.[4] It identified 3 subgroup of patients including non-adherence, patients with pain syndromes and obesity and finally true treatment resistance.[4] Previous cross-sectional studies have also shown that concomitant fibromyalgia is associated both with more frequent more frequent switching of biologic DMARDs.[18, 19] Additionally, RA patients with concomitant fibromyalgia on conventional or biological DMARDs were less likely to achieve remission compared to those without fibromyalgia.[15] Therefore, as outlined in the EULAR guidelines, it is important to consider the heterogenous factors that may influence the increased use of biological therapy to optimise disease outcome.[50]

While this is the first longitudinal real-world cohort study to examine the effect of the CSS on RA disease activity progression, there are several limitations that impact interpretation of these data. The cohort was small and from a single centre. Only one follow-up timepoint was assessed, which may not capture the overall trajectory of disease. Additionally, there was no follow up CSS measurement to assess change in CSS alongside DAS28-3. It would be useful in future studies to assess the direction of change of the CSS in comparison to the DAS28-3.
The cohort assessed had established disease with low disease activity and therefore the results may not be generalisable to those with early or more active disease. Larger and longer longitudinal studies are required to assess the influence of the CSS on RA disease progression in cohorts with higher disease activity and whether it impacts objective measures of RA disease activity.

Conclusion

This longitudinal cohort study found that a higher CSS, as a measure of central sensitisation, did not predict a meaningful objectively-measured change in RA disease activity measured without patient-reported measures, in patients with established well-controlled rheumatoid arthritis.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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