Arthritis Care & Research
Vol. 70, No. 2, February 2018, pp 197–204
DOI 10.1002/acr.23266

ORIGINAL ARTICLE

Association Between Pain Sensitization and Disease Activity in Patients With Rheumatoid Arthritis: A Cross-Sectional Study

YVONNE C. LEE,[1] CLIFTON O. BINGHAM III,[2] ROBERT R. EDWARDS,[1] WENDY MARDER,[3] KRISTINE PHILLIPS,[3] MARCY B. BOLSTER,[4] DANIEL J. CLAUW,[3] LARRY W. MORELAND,[5] BING LU,[1] ALYSSA WOHLFAHRT,[1] ZHI ZHANG,[1] AND TUHINA NEOGI[6]

Objective. **Pain sensitization may contribute to pain severity in rheumatoid arthritis (RA), impacting disease activity assessment. We examined whether pain processing mechanisms were associated with disease activity among RA patients with active disease.**

Methods. **The study included 139 subjects enrolled in the Central Pain in Rheumatoid Arthritis cohort. Subjects underwent quantitative sensory testing (QST), including assessment of pressure pain thresholds (PPTs) at multiple sites, conditioned pain modulation, and temporal summation. RA disease activity was assessed using the Clinical Disease Activity Index (CDAI) and its components. We examined cross-sectional associations between QST measures and disease activity using linear regression.**

Results. **Low PPTs (high pain sensitization) at all sites were associated with high CDAI scores ($P \leq 0.03$) and tender joint counts ($P \leq 0.002$). Associations between PPTs and patient global assessments were also seen at most sites. High temporal summation at the forearm (also reflecting high pain sensitization) was significantly associated with high CDAI scores ($P = 0.02$), patient global assessment scores ($P = 0.0006$), evaluator global assessment scores ($P = 0.01$), and tender joint counts ($P = 0.02$). Conversely, conditioned pain modulation (a measure of descending inhibitory pain pathways) was associated only with tender joint count ($P = 0.03$).**

Conclusion. **High pain sensitization is associated with elevations in disease activity measures. Longitudinal studies are underway to elucidate the cause–effect relationships between pain sensitization and inflammatory disease activity in RA.**

INTRODUCTION

Pain is often considered a surrogate marker for inflammatory disease activity in rheumatoid arthritis (RA). It is the single largest determinant of patient assessment of global disease activity (1,2). It is also a prominent component of the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for remission (3,4). However, pain does not always equal inflammation. Evidence of this was seen in one study, in which the majority of established RA patients with pain (median 3 of 10 in intensity) had a minimum number of swollen joints (5).

Several studies indicate that individuals with RA have abnormalities in peripheral and central nervous system

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or of Harvard Catalyst or Harvard University and its affiliated academic health care centers.

Supported by the NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (grants R01-AR-064850, P60-AR-47785, and R01-AR-062506), Harvard Catalyst/The Harvard Clinical and Translational Science Center (NIH UL1-TR-001102), Harvard University and its affiliated academic health care centers, the Rheumatic Diseases Research Core Center (P30-AR-053503), and the Camille Julia Morgan Arthritis Research and Education Fund.

[1]Yvonne C. Lee, MD, MMSc, Robert R. Edwards, PhD, Bing Lu, MD, DrPH, Alyssa Wohlfahrt, BA, Zhi Zhang, MS: Brigham and Women's Hospital, Boston, Massachusetts; [2]Clifton O. Bingham III, MD: Johns Hopkins University, Baltimore, Maryland; [3]Wendy Marder, MD, Kristine Phillips, MD, Daniel J. Clauw, MD: University of Michigan Medical School, Ann Arbor; [4]Marcy B. Bolster, MD: Massachusetts General Hospital, Boston; [5]Larry W. Moreland, MD: University of Pittsburgh, Pittsburgh, Pennsylvania; [6]Tuhina Neogi, MD, PhD: Boston University School of Medicine, Boston, Massachusetts.

Dr. Lee has received grant support from Pfizer and owns stock in Express Scripts. Dr. Bolster has received research support from Amgen and Eli Lilly. Dr. Clauw has received consulting fees from Eli Lilly, Nuvo, Cerephex, Tonix, Abbott, Forest Labs, Johnson & Johnson, Merck, Purdue Pharma, Sammumed, Zynerba, Astellas Pharma, Williams & Connolly LLP, and Therevance (less than $10,000 each) and from Pfizer (more than $10,000), and has received research support from Pfizer, Cypress Biosciences, Forest, Merck, Nuvo, and Cerephex.

Address correspondence to Yvonne C. Lee, MD, MMSc, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, 60 Fenwood Road, Boston, MA 02115. E-mail: ylee9@partners.org.

Submitted for publication July 20, 2016; accepted in revised form April 18, 2017.

Significance & Innovations

- This is the largest study to comprehensively assess pain sensitization in rheumatoid arthritis (RA), using pressure pain thresholds, temporal summation, and conditioned pain modulation, in a study population that draws from 5 academic medical centers across the US.
- Associations between temporal summation at the forearm (a measure of central sensitization) and Clinical Disease Activity Index score, tender joint count, evaluator global assessment score, and patient global assessment score are reported for the first time.
- Associations between conditioned pain modulation (a measure of descending analgesic pain mechanisms) and measures of disease activity in an RA population are described for the first time.

pain processing, resulting in widespread pain sensitivity. Four cross-sectional studies have examined the relationship between pain thresholds and validated measures of disease activity in RA (6–9). All 4 studies were small (n ≤59), limiting the ability to examine differences in associations between subgroups of patients, such as those with secondary fibromyalgia. Two of the studies included only women, thereby limiting generalizability to men (8,9). In this study, we enrolled 139 patients across 5 sites, including 23 men. In addition, we also assessed conditioned pain modulation as a measure of descending analgesic pain mechanisms. We hypothesized that low pressure pain thresholds (PPTs), low conditioned pain modulation and high temporal summation would be associated with high Clinical Disease Activity Index (CDAI) scores, tender joint counts, and patient global health assessment scores, whereas the association between pain sensitization and measures that emphasize direct assessment of inflammation would be low.

PATIENTS AND METHODS

Study population. The study includes baseline data from the first 139 subjects with complete data on disease activity measures in the Central Pain in Rheumatoid Arthritis (CPIRA) study. CPIRA is a multicenter, prospective, observational study designed to examine the relationship between pain and treatment response in RA. Participants were recruited from 5 US academic medical centers beginning in January 2014. The inclusion criteria were as follows: diagnosis of RA based on the ACR/EULAR 2010 classification criteria (10); starting or switching to a disease-modifying antirheumatic drug (DMARD) due to active RA; and ability to participate in a study visit before taking the first dose of the new DMARD. An exception was made for participants starting methotrexate therapy. These individuals were able to participate after taking 1 dose of medication if they were able to come in for their study visit before taking a second dose. Pharmacodynamic studies indicate that the onset of action of oral methotrexate for RA is between 3 and 6 weeks, so a single dose of methotrexate should not alter the results of our study (11). For individuals switching to a different DMARD, no washout period was required.

Exclusion criteria were as follows: changing doses of centrally acting pain medications (e.g., amitriptyline, gabapentin, or duloxetine) within 3 months of enrollment; corticosteroid treatment of >10 mg of prednisone or its equivalent; chronic opioid use or any opioid use within 24 hours of testing; diagnosis of a systemic autoimmune disease other than RA; severe Raynaud's phenomenon requiring pharmacologic treatment; severe peripheral vascular disease manifested by claudication or ischemic rest pain; and peripheral neuropathy. All subjects provided written informed consent. The institutional review boards at each site approved the study.

Quantitative sensory testing (QST). All assessors attended a 1-day training session and received in-person instruction on the use of QST. Two of the authors (YCL and RRE) supervised these sessions and ensured that testing measures were standardized across all sites. Site visits were conducted approximately 1 year into the study to ensure that standardized protocols were being followed. Assessments of interrater reliability were performed among a subgroup of assessors (n = 4), and the intraclass correlation coefficients (ICCs) ranged from 0.71 to 0.90 for the PPT and temporal summation measures. The ICC for conditioned pain modulation was 0.45. As per Cicchetti (12), ICCs 0.40–0.59 were defined as fair, 0.60–0.74 as good, and 0.75–1.00 as excellent. A comparison of QST measures across sites is shown in Supplementary Table 1 (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23266/abstract).

PPTs. Using a Wagner Force 10 FDX algometer, we obtained PPTs at joint sites (bilateral wrists and knees) and nonjoint sites (bilateral trapezius muscles and thumbnails) in random order, with 3 trials at each site. The 1-cm^2 rubber algometer probe was placed in the center of each anatomic site by the study staff. The pressure was increased at a rate of 0.50 kgf/second until the stimulus first became painful. The pressure at this point was defined as the PPT. To obtain the mean PPT for each site, we averaged the PPTs obtained on both sides of the body during all 3 trials. Low PPTs at joint sites were considered markers of peripheral sensitization, whereas low PPTs at both joint and nonjoint sites were considered markers of central sensitization (13).

Mechanical temporal summation. Consistent with previous literature (14), temporal summation was assessed using a set of 6 probes, with weighted, flat-end wire tips measuring 0.2 mm in diameter (University of North Carolina, Chapel Hill). The weights ranged 8–256 mN. The probes were tested on the participants by slowly touching the full weight of the probe against the subject's skin at the middle of the wrist (joint site) and then the forearm (nonjoint site). Test taps were performed, beginning with the probe of least weight and sequentially increasing the probe weight until the subject reported a pain rating of 30–40/100 or until the heaviest probe was used. Using this probe, temporal summation was measured by tapping the probe against the skin at the test site 10 times, with each

tap lasting approximately 0.5 seconds and with 1 second between stimuli. The subject was asked to rate his/her pain level on a scale of 0–100 after the first, fifth, and tenth taps. Temporal summation was defined as the difference between the pain level at the tenth tap and the pain level at the first tap for each trial. Three trials were performed at each site. Mean temporal summation measurements at the wrist and the forearm were calculated by averaging the results of the 3 trials. Higher measures of temporal summation were considered to reflect greater central sensitization.

Conditioned pain modulation. Conditioned pain modulation was assessed using a procedure that incorporates a conditioning stimulus (painful stimulus that activates the descending analgesic pain pathways) and a test stimulus (painful stimulus to test the analgesic response to the conditioning stimulus) (15,16). The conditioning stimulus was immersion of the right hand in a cold water bath, maintained between 5°C and 7°C. The test stimulus was pressure applied by an algometer at the left trapezius muscle. An initial PPT was obtained before immersion of the hand in the cold water bath. The subject was then instructed to place his/her hand in the water. After 20 seconds, the PPT at the left trapezius muscle was obtained a second time, immediately before the participant removed his/her hand from the water. If the participant was unable to keep the hand in the water for 20 seconds, the second PPT was measured immediately after the removal of the hand from the water. Conditioned pain modulation was defined as the ratio of the PPT at the second time point over the PPT at the first time point, multiplied by 100 (17). A result of 100 meant that there was no difference between the PPT before the subject was exposed to the conditioning stimulus versus the PPT after the subject was exposed to the conditioning stimulus. Values greater than 100 were indicative of conditioned pain modulation, reflecting increases in PPTs at the second time point compared to PPTs at the first time point. Conversely, lower values were considered to reflect abnormalities in descending pain inhibition.

Assessment of clinical variables. Overall RA disease activity was assessed using the CDAI, a composite measure that includes tender joint count, swollen joint count, patient global assessment, and assessor global assessment (18). We used the CDAI as the primary measure of RA disease activity because serum inflammatory markers (required for the calculation of other validated disease activity measures) will be measured after the full cohort is assembled and are not currently available. Joint counts and assessor global assessments were performed by trained study staff members. For the patient global assessment score, participants were asked to assign a number, using a 100-point numeric rating scale, in response to the question, "Considering all the ways in which your arthritis has affected you, how do you feel your arthritis is today?" Demographic information and RA disease characteristics were obtained using self-report questionnaires. Rheumatoid factor (RF) and anti–cyclic citrullinated peptide (anti-CCP) seropositivity were obtained using a standardized chart review process. Body mass index (BMI) was calculated from height and weight obtained at the time of the study visit. Depression, anxiety, and sleep disturbance were assessed using Patient-Reported Outcomes Measurement Information System (PROMIS) computerized adaptive tests (19,20). Catastrophizing was assessed using the Pain Catastrophizing Scale (21). Fibromyalgia status was determined according to the ACR 2010 modified preliminary diagnostic criteria, which include meeting a score of: ≥7 on the Widespread Pain Index and ≥5 on the Symptom Severity Scale or 3–6 on the Widespread Pain Index and ≥9 on the Symptom Severity Scale (22,23).

Statistical analysis. The primary outcome was RA disease activity, measured by the CDAI. Secondary outcomes included the components of the CDAI, specifically, the tender joint count, swollen joint count, patient global assessment, and assessor global assessment. The main predictors were PPTs at the wrists, knees, trapezius muscles, and thumbnails; temporal summation at the forearm and the wrist; and conditioned pain modulation. Potential confounders included age, sex, BMI, RA disease duration, RF or anti-CCP seropositivity, depression, sleep disturbance, and catastrophizing.

Unadjusted associations between QST measures and clinical disease activity were identified using Pearson correlation coefficients. We examined the association between

Table 1. Participant characteristics (n = 139)*

Characteristic	Value
Age, mean ± SD years	54.2 ± 13.6
Female	83.5
Body mass index, mean ± SD kg/m^2	30.9 ± 17.3
Seropositive	83.5
Disease duration, mean ± SD years	9.3 ± 12.7
CDAI score, mean ± SD	24.4 ± 14.0
Tender joint count in 28 joints, mean ± SD	11.4 ± 9.2
Swollen joint count in 28 joints, mean ± SD	5.5 ± 5.1
Patient global assessment score (0–10), mean ± SD	5.3 ± 1.8
Assessor global assessment score (0–10), mean ± SD	3.7 ± 2.3
Any DMARD use†	61.2
Biologic DMARD use†	25.2
Synthetic DMARD use†	46.0
NSAID use	48.9
Corticosteroid use	43.2
Pain (0–10 NRS), mean ± SD	5.1 ± 2.3
PROMIS depression (T score), mean ± SD	50.5 ± 9.1
PROMIS anxiety (T score), mean ± SD	53.7 ± 8.7
PROMIS sleep disturbance (T score), mean ± SD	54.2 ± 9.2
Pain Castastrophizing Scale, mean ± SD	18.4 ± 13.4
Fibromyalgia‡	31.7

* Values are percentages unless otherwise indicated. CDAI = Clinical Disease Activity Index; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; NRS = numeric rating scale; PROMIS = Patient-Reported Outcomes Measurement Information System.
† Numbers reflect DMARD use within 6 weeks of the baseline assessment, prior to starting their new DMARD.
‡ Defined by the American College of Rheumatology 2010 modified preliminary diagnostic criteria.

QST measures and disease activity using multivariable linear regression, after adjusting for the covariates listed above. The strength of association was assessed using regression coefficients (β). In exploratory analyses, we also examined the role of fibromyalgia as an effect modifier of the relationship between QST measures and disease activity. These analyses were performed using models stratified by fibromyalgia status, as well as models including a QST measure × fibromyalgia interaction term. The threshold for statistical significance was set as a 2-tailed P value of less than 0.05. We did not adjust for multiple comparisons because this was an observational, hypothesis-screening study, and adjustments for multiple testing limit the ability to identify potentially important findings (24). All analyses were performed using SAS, version 9.4.

RESULTS

Patient characteristics and PPTs. There were 139 RA patients included in the analysis. The mean ± SD age was 54.2 ± 13.6 years, and 83.5% were women (Table 1). The mean ± SD baseline CDAI score was 24.4 ± 14.0, and 31.7% met the ACR 2010 modified preliminary diagnostic criteria for fibromyalgia. The mean ± SD PPT was lowest at the wrists and trapezius muscles (2.9 ± 1.6) and highest at the knees (5.3 ± 2.7) (Table 2). PPTs were inversely associated with the CDAI, with beta coefficients ranging from −1.29 at the thumbnail to −3.30 at the trapezius ($P \leq 0.03$) (Table 3). PPTs were also significantly associated with the tender joint count, with beta coefficients ranging from −1.09 at the thumbnail to −1.98 at the trapezius ($P \leq 0.002$). PPTs at all sites except the thumbnail were significantly associated with patient global assessment scores ($P \leq 0.04$). In contrast, PPTs were not significantly associated with the swollen joint count.

In stratified analyses, beta coefficients for the association between PPTs and both the CDAI and tender joint counts were generally higher among RA patients who met the 2010 ACR modified preliminary criteria for fibromyalgia (β range = −1.07, −5.72), compared with those who did not meet the 2010 ACR modified preliminary criteria for fibromyalgia (β range = −0.81, −3.11). To assess the statistical significance of these differences, we performed exploratory analyses using multivariable linear regression models including an interaction term for PPT × fibromyalgia. None of the interaction terms were found to be statistically significant.

Table 2. Quantitative sensory testing measures (n = 139)*

Measure	Mean ± SD	Median (IQR)
PPT at wrist, kgf	2.9 ± 1.6	2.5 (1.9–3.8)
PPT at knee, kgf	5.3 ± 2.7	4.9 (3.0–7.3)
PPT at thumbnail, kgf	3.6 ± 1.9	3.1 (2.4–4.4)
PPT at trapezius, kgf	2.9 ± 1.6	2.5 (1.9–3.5)
Temporal summation at wrist†	15.0 ± 15.3	10.0 (2.7–23.3)
Temporal summation at forearm†	14.0 ± 13.8	11.3 (1.7–22.0)
Conditioned pain modulation‡	142.3 ± 39.4	132.6 (117.7–155.7)

* IQR = interquartile range; PPT = pressure pain threshold.
† Calculated as the difference between the maximum pain rating at the tenth tap minus the pain rating at the first tap.
‡ Calculated as PPT2/PPT1 × 100.

Temporal summation. The mean ± SD values for temporal summation at the wrist and forearm were 15.0 ± 15.3 and 14.0 ± 13.8, respectively (Table 2). Temporal summation at the forearm was significantly associated with the CDAI score (β = 0.19; $P = 0.02$), tender joint count (β = 0.11; $P = 0.02$), patient global assessment score (β = 0.05; $P = 0.0006$), and assessor global assessment score (β = 0.04; $P = 0.01$), whereas temporal summation at the wrist was significantly associated only with patient global assessment (β = 0.04; $P = 0.003$) (Table 4). In analyses stratified by fibromyalgia status, beta coefficients for the association between temporal summation and CDAI score were lower among those with RA and fibromyalgia (β = −0.02 in forearm and β = −0.01 in wrist), compared with those with RA alone (β = 0.25 in forearm and β = 0.23 in wrist). The interaction terms for temporal summation × fibromyalgia were not statistically significant.

Conditioned pain modulation. The mean ± SD conditioned pain modulation ratio was 142.3 ± 39.4 (Table 2). Conditioned pain modulation was associated with tender joint count (β = 0.04; $P = 0.03$) but not with any other disease activity measure (Table 4). Analyses stratified by fibromyalgia status did not reveal significant differences in the beta coefficients for the associations between conditioned pain modulation and disease activity measures. Interaction terms for conditioned pain modulation × fibromyalgia were not statistically significant.

DISCUSSION

This study confirms previous findings showing associations between PPTs and composite measures of RA disease activity, tender joint count, evaluator global assessment, and patient global assessment (6,8,25). This study is also the first to report associations between temporal summation at the forearm and CDAI, tender joint count, evaluator global assessment, and patient global assessment. These findings suggest that pain sensitization, reflected by low PPTs and high temporal summation, may contribute to the amplification of patient assessment of disease activity and tender joint count, as well as a perception of higher activity by the evaluator.

To provide clinical context, we compared our results to published data using the same techniques (e.g., same test stimulus and same conditioning stimulus). The median PPT in this population (2.5–4.9 kgf) was lower than that in the general population (6.2–9.4 kgf) and lower than that observed in an RA population with lower disease activity (5.2–8.4 kgf) (15). Temporal summation at the forearm (mean ± SD 14.0 ± 13.8) was higher in our population compared to healthy controls (mean ± SD 10.6 ± 11.3) (26). These comparisons should be interpreted with caution, given possible differences in study populations beyond the differences in disease state and disease activity levels.

The observation that low PPTs were associated with high CDAI scores, high tender joint counts, and high patient global

Table 3. Relationship of pressure pain thresholds to RA disease activity*

	TJC	SJC	PtGA	EGA	CDAI
Overall study cohort					
Wrist, adj. β	−1.65	−0.46	−0.25	−0.30	−2.66
P	< 0.0001†	0.09	0.04†	0.01†	< 0.0001†
Knee, adj. β	−1.12	−0.17	−0.16	−0.13	−1.58
P	< 0.0001†	0.32	0.03†	0.09	0.0001†
Thumbnail, adj. β	−1.09	0.02	−0.10	−0.11	−1.29
P	0.002†	0.95	0.32	0.31	0.03†
Trapezius, adj. β	−1.98	−0.47	−0.40	−0.44	−3.30
P	< 0.0001†	0.12	0.002†	0.0009†	< 0.0001†
RA patients without FM (n = 95)					
Wrist, adj. β	−1.94	−0.53	−0.33	−0.31	−3.11
P	< 0.0001†	0.09	0.03†	0.03†	< 0.0001†
Knee, adj. β	−0.81	−0.06	−0.16	−0.06	−1.09
P	0.001†	0.73	0.06	0.46	0.009†
Thumbnail, adj. β	−0.99	0.08	−0.13	−0.03	−1.08
P	0.004†	0.76	0.28	0.79	0.07
Trapezius, adj. β	−1.68	−0.30	−0.41	−0.38	−2.78
P	< 0.0001†	0.32	0.005†	0.005†	< 0.0001†
RA patients with FM (n = 44)					
Wrist, adj. β	−1.07	−0.21	−0.08	−0.28	−1.64
P	0.25	0.70	0.73	0.23	0.22
Knee, adj. β	−1.66	−0.06	−0.08	−0.23	−2.02
P	0.009†	0.88	0.62	0.16	0.03†
Thumbnail, adj. β	−1.63	−0.40	−0.04	−0.41	−2.48
P	0.08	0.48	0.86	0.07	0.06
Trapezius, adj. β	−3.79	−0.96	−0.29	−0.68	−5.72
P	0.009†	0.29	0.40	0.07	0.006†

* Adjusted for age, sex, seropositivity, RA disease duration, body mass index, depression, sleep disturbance, and pain catastrophizing. RA = rheumatoid arthritis; TJC = tender joint count; SJC = swollen joint count; PtGA = patient global assessment; EGA = evaluator global assessment; CDAI = Clinical Disease Activity Index; adj. = adjusted; FM = fibromyalgia.
† Statistically significant.

assessment scores, but not with swollen joint counts, is consistent with studies showing that individuals with RA and fibromyalgia score higher on composite disease activity measures and the individual components of tender joint count and patient global assessment (27–30). In our study, beta coefficients for the associations between PPTs and CDAI scores indicated that a 1-unit difference in PPT was associated with a 1.29–3.30 difference in CDAI score. The magnitude of this association was not high, given that the minimum clinically important difference for the CDAI is 6 for individuals with moderate disease activity and 12 for individuals with high disease activity (31). The strength of this association was higher among individuals with both RA and fibromyalgia, with a beta coefficient of −5.72 for the association between trapezius PPT and CDAI. However, the interaction terms between fibromyalgia and PPTs were not statistically significant when fibromyalgia was examined as a dichotomous variable or as a continuous measure of fibromyalgia symptom

Table 4. Relationship of temporal summation and conditioned pain modulation to RA disease activity in the overall study cohort (n = 139)*

	TJC	SJC	PtGA	EGA	CDAI
Temporal summation (forearm), adj. β	0.11	−0.009	0.05	0.04	0.19
P	0.02†	0.80	0.0006†	0.01†	0.02†
Temporal summation (wrist), adj. β	0.07	−0.02	0.04	0.02	0.11
P	0.10	0.56	0.003†	0.10	0.12
Conditioned pain modulation, adj. β	0.04	−0.001	−0.001	−0.004	0.03
P	0.03†	0.91	0.77	0.47	0.27

* Adjusted for age, sex, seropositivity, RA disease duration, body mass index, depression, sleep disturbance, and pain catastrophizing. RA = rheumatoid arthritis; TJC = tender joint count; SJC = swollen joint count; PtGA = patient global assessment; EGA = evaluator global assessment; CDAI = Clinical Disease Activity Index; adj. = adjusted.
† Statistically significant.

severity. The lack of statistical significance may reflect limited statistical power, given the small number of individuals with fibromyalgia.

High temporal summation at the forearm was significantly associated with high CDAI scores, tender joint counts, evaluator global assessment scores, and patient global assessment scores, but temporal summation at the wrist was associated only with patient global assessment. The beta coefficients for the association between temporal summation and CDAI score ranged from 0.07 at the wrist to 0.11 at the forearm, indicating that a 1-unit difference in temporal summation was associated with an increase in CDAI score of 0.07–0.11. Thus, a large difference in temporal summation is needed to see a relatively small difference in CDAI score.

It was surprising that temporal summation at the wrist was not associated with disease activity measures, because the wrist is a site commonly affected by inflammation in RA. Thus, if anything, we expected stronger associations between temporal summation at the wrist and disease activity measures. One explanation could be that our measure of temporal summation was not sufficiently sensitive. Many subjects did not find the punctate probes to be painful, and the distribution of temporal summation, both at the forearm and the wrist, was right-skewed. We were not able to use a higher-weight probe due to skin fragility in a number of subjects. Compared to other study populations, in this RA population skin fragility may be a larger problem due to chronic corticosteroid use.

To our knowledge, only one other study has examined the association between temporal summation and disease activity measures in RA. Using a temporal summation protocol involving cuff pressure algometry, Vladimirova et al assessed temporal summation at the leg in 38 women with active RA and found no association between the temporal summation index and tender joint count, swollen joint count, or Disease Activity Score in 28 joints (9). A study of 1,111 individuals in the Multicenter Osteoarthritis Study, however, found differences in associations between temporal summation of mechanical stimuli at affected versus unaffected body sites and magnetic resonance imaging–based evaluation of inflammation (32). Over 24 months, this study noted a stronger association between knee effusions and incident temporal summation at the affected site than between knee effusions and incident temporal summation at an unaffected site. Additional studies, using a different method of temporal summation, may be helpful in further elucidating the association between temporal summation and disease activity measures in RA.

Contrary to the associations observed between PPTs and disease activity measures and temporal summation and disease activity measures, conditioned pain modulation was associated with tender joint count and not with any other disease activity measure. The lack of association may be due to several factors, including statistical chance (false negative) and/or technical issues in the assessment of conditioned pain modulation. The ICC for conditioned pain modulation was 0.45, which was lower than the ICCs for the other QST measures, indicating a lower level of reproducibility compared to the other QST measures. In addition, the magnitude of conditioned pain modulation may have been affected by the choice of test and conditioning stimuli. For example, using cold as the test stimulus may be more sensitive than pressure, given that the cold pressor task was also used as the conditioning stimulus. However, a meta-analysis of conditioned modulation paradigms in populations with chronic pain did not find that the type of test or conditioning stimulus type significantly influenced the effect size (33). Additional studies, using different conditioned pain modulation paradigms, are needed to replicate this finding.

Another possibility for the lack of association between conditioned pain modulation and disease activity measures is that conditioned pain modulation reflects a different type of pain pathway (34). While temporal summation is thought to reflect the facilitation of ascending nociceptive processing, conditioned pain modulation is considered a measure of the descending inhibitory pain pathways (35). We expected impaired conditioned pain modulation to be associated with heightened measures of disease activity due to enhanced pain sensitivity. However, among individuals with high inflammatory disease activity, peripheral inflammation may serve as an endogenous conditioning stimulus that activates the descending analgesic pain mechanisms. Thus, in some individuals, impairments in conditioned pain modulation may be associated with elevations in disease activity measures, while, in others, heightened conditioned pain modulation may be associated with decreases in disease activity measures. Longitudinal assessment of conditioned pain modulation before and after the onset of inflammation would be useful in disentangling these relationships. We are continuing to follow the individuals in this study longitudinally, as they are started on new DMARDs, which provides an opportunity to identify changes in conditioned pain modulation with improvements in inflammation.

Strengths of this study include the comprehensive assessment of PPTs, temporal summation, and conditioned pain modulation. To our knowledge, this is the largest study of QST in RA, and the only study to assess PPTs, temporal summation, and conditioned pain modulation, while also characterizing inflammatory disease activity and psychosocial factors. An additional strength is the assessment of secondary fibromyalgia in this RA cohort. However, misclassification may exist since the ACR 2010 modified preliminary diagnostic criteria for fibromyalgia are based on self-reported pain in 19 areas, fatigue, nonrestorative sleep, and cognitive symptoms (22). Although the 19 areas are nonjoint sites, RA patients may find it difficult to distinguish between pain at different locations.

Limitations of this study include the cross-sectional design, which precludes conclusions involving the directionality of associations between QST measures and disease activity. Longitudinal data collection is ongoing, and analyses to examine associations between baseline QST measures and changes in inflammatory serum markers and composite RA disease activity measures in response to DMARD therapy are planned. The heterogeneity in the assessment of QST measures across sites may be another limitation. These assessments can be sensitive to variations in study procedures. We have made efforts to standardize protocols, including an intensive training session before the start of the study and visiting each site approximately 1 year into the study to ensure that there was no drift in technique.

ICCs between the master study assessor and 3 other study assessors were in the fair to excellent range. When comparing QST measurements across sites, PPTs at the knee and trapezius were the only measures that differed significantly across sites (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23266/abstract). This may reflect variations in testing procedures across sites. Alternatively, this difference may reflect differences in study populations across sites. To address these concerns, we included study site as a covariate in all analyses.

Although we included many potential confounders of the relationship between QST measures and inflammatory disease activity in our models, the potential for residual confounding remains. While we performed a large number of statistical analyses, we avoided adjustment for multiple comparisons in accordance with what has been advocated in epidemiologic research (24). We made a conscious effort to highlight only the associations that were consistent across the majority of body sites or disease activity measures.

In conclusion, pain sensitization, demonstrated by low PPTs and high temporal summation values at the forearm, were associated with high CDAI scores. These findings highlight the importance of understanding pain sensitization in RA, particularly as it relates to inflammatory disease assessment. Additional studies are needed to better understand the clinical impact of pain sensitization on the efficacy of RA treatment.

ACKNOWLEDGMENTS

The authors thank the study coordinators at all of the sites, including Cassandra Corrigan, Agnes Zak, and Dee Luo (Brigham and Women's Hospital); Malini Moni and Grazyna Purwin (Johns Hopkins University); Alieysa Patel and Melanie Woods (University of Michigan); Joyce Goggins (Boston University); and Laurie Hope and Kelly Reckley (University of Pittsburgh). The authors also acknowledge all of the referring physician and patient participants.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lee, Bingham III, Edwards, Phillips, Bolster, Clauw, Moreland, Neogi.

Acquisition of data. Marder, Wohlfahrt.

Analysis and interpretation of data. Lee, Bingham III, Edwards, Marder, Phillips, Bolster, Clauw, Moreland, Lu, Zhang, Neogi.

REFERENCES

1. Furu M, Hashimoto M, Ito H, Fujii T, Terao C, Yamakawa N, et al. Discordance and accordance between patient's and physician's assessments in rheumatoid arthritis. Scand J Rheumatol 2014;43:291–5.
2. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in the perception of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.
3. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.
4. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
5. Lee YC, Frits ML, Iannaccone CK, Weinblatt ME, Shadick NA, Williams DA, et al. Subgrouping of patients with rheumatoid arthritis based on pain, fatigue, inflammation, and psychosocial factors. Arthritis Rheumatol 2014;66:2006–14.
6. Joharatnam N, McWilliams DF, Wilson D, Wheeler M, Pande I, Walsh DA. A cross sectional study of pain sensitivity, disease activity assessment, mental health and fibromyalgia status in rheumatoid arthritis. Arthritis Res Ther 2015;17:11.
7. Konttinen YT, Honkanen VE, Gronblad M, Keinonen M, Santavirta N, Santavirta S. The relation of extraarticular tenderness to inflammatory joint disease and personality in patients with rheumatoid arthritis. J Rheumatol 1992;19:851–5.
8. Lee YC, Chibnik LB, Lu B, Wasan AD, Edwards RR, Fossel AH, et al. The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2009;11:R160.
9. Vladimirova N, Jespersen A, Bartels EM, Christensen AW, Bliddal H, Danneskiold-Samsoe B. Pain sensitisation in women with active rheumatoid arthritis: a comparative cross-sectional study. Arthritis 2015;2015:434109.
10. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
11. Williams HJ, Willkens RF, Samuelson CO Jr., Alarcón GS, Guttadauria M, Yarboro C, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1985;28:721–30.
12. Cicchetti DV. Guidelines, cirteria and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994;6:284–90.
13. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6:599–606.
14. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
15. Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, et al. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain 2008;136:142–9.
16. Lee YC, Lu B, Edwards RR, Wasan AD, Nassikas NJ, Clauw DJ, et al. The role of sleep problems in central pain processing in rheumatoid arthritis. Arthritis Rheum 2013;65:59–68.
17. Edwards RR, Mensing G, Cahalan C, Greenbaum S, Narang S, Belfer I, et al. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. J Pain Symptom Manage 2013;46:30–42.
18. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
19. Pilkonis PA, Yu L, Dodds NE, Johnston KL, Maihoefer CC, Lawrence SM. Validation of the depression item bank from the Patient-Reported Outcomes Measurement Information System (PROMIS) in a three-month observational study. J Psychiatr Res 2014;56:112–9.
20. Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, et al. Development and validation of patient-reported outcome

measures for sleep disturbance and sleep-related impairments. Sleep 2010;33:781–92.
21. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995;7: 524–32.
22. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 2011;38:1113–22.
23. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–72.
24. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology 1990;1:43–6.
25. Pollard LC, Ibrahim F, Choy EH, Scott DL. Pain thresholds in rheumatoid arthritis: the effect of tender point counts and disease duration. J Rheumatol 2012;39:28–31.
26. Campbell CM, Carroll CP, Kiley K, Han D, Haywood C Jr., Lanzkron S, et al. Quantitative sensory testing and pain-evoked cytokine reactivity: comparison of patients with sickle cell disease to healthy matched controls. Pain 2016; 157:949–56.
27. Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (fibromyalgia) in rheumatoid arthritis. J Rheumatol 1984;11:814–8.
28. Coury F, Rossat A, Tebib A, Letroublon MC, Gagnard A, Fantino B, et al. Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. J Rheumatol 2009;36:58–62.
29. Duran J, Combe B, Niu J, Rincheval N, Gaujoux-Viala C, Felson DT. The effect on treatment response of fibromyalgic symptoms in early rheumatoid arthritis patients: results from the ESPOIR cohort. Rheumatology (Oxford) 2015;54:2166–70.
30. Lee YC, Hackett J, Frits M, Iannaccone CK, Shadick NA, Weinblatt ME, et al. Multibiomarker disease activity score and C-reactive protein in a cross-sectional observational study of patients with rheumatoid arthritis with and without concomitant fibromyalgia. Rheumatology (Oxford) 2016;55: 640–8.
31. Curtis JR, Yang S, Chen L, Pope JE, Keystone EC, Haraoui B, et al. Determining the minimally important difference in the Clinical Disease Activity Index for improvement and worsening in early rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2015;67:1345–53.
32. Neogi T, Guermazi A, Roemer F, Nevitt MC, Scholz J, Arendt-Nielsen L, et al. Association of joint inflammation with pain sensitization in knee osteoarthritis: the Multicenter Osteoarthritis Study. Arthritis Rheumatol 2016;68:654–61.
33. Lewis GN, Heales L, Rice DA, Rome K, McNair PJ. Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. Pain Res Manag 2012;17:98–102.
34. Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156 Suppl 1:S24–31.
35. Suzan E, Midbari A, Treister R, Haddad M, Pud D, Eisenberg E. Oxycodone alters temporal summation but not conditioned pain modulation: preclinical findings and possible relations to mechanisms of opioid analgesia. Pain 2013;154:1413–8.