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ORIGINAL ARTICLE

Association Between Pain, Radiographic Severity, and Centrally-Mediated Symptoms in Women With Knee Osteoarthritis

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Objective. **To examine the relationship between pain, radiographic severity, and a common set of co-occurring centrally-mediated symptoms (fatigue, sleep quality, and depression) in women with knee osteoarthritis.**

Methods. **Participants underwent knee radiographs, and had repeated assessments of pain severity and other centrally-mediated symptoms during a 5-day home monitoring period. To examine associations between pain severity (the average of pain over the home monitoring period), measures of osteoarthritis radiographic severity (Kellgren/Lawrence grade, minimum joint space width), centrally-mediated symptoms, and demographics (age) were used. Symptoms of fatigue, sleep efficiency, and depression were used in a composite measure representing centrally-mediated symptoms.**

Results. **Using a series of linear regression models in which each variable was entered hierarchically (n = 54), the final model showed that 27% of the variance in pain severity was explained by age, radiographic severity, and centrally-mediated symptoms. Centrally-mediated symptoms explained an additional 10% of the variance in pain severity after the other 2 variables were entered.**

Conclusion. **Both radiographic severity and centrally-mediated symptoms were independently and significantly associated with pain severity in women with knee osteoarthritis. In addition to more severe radiographic features, women with higher centrally-mediated symptoms had greater pain severity. Treatments for women with symptomatic knee osteoarthritis may be optimized by addressing both peripheral and central sources of pain.**

INTRODUCTION

Osteoarthritis is a leading cause of disability among older adults (1) and is often characterized by pain, the most common symptom for which people with osteoarthritis seek treatment. Pain in osteoarthritis affects the ability to engage in activities of daily living, work, and other meaningful activities, and is associated with a reduced quality of life (2–4). Knee pain due to osteoarthritis in particular is a main cause of impaired mobility among older adults (5). Women with arthritis have more functional deficits than men, reporting more severe joint pain, more psychological distress, and greater limitations on activity (6).

Despite the negative impact of osteoarthritis pain, its underlying causes are not well understood. Pain in osteoarthritis has been hypothesized to be complex and caused by both peripheral and central sources (7–9). Although treatment for knee osteoarthritis is typically targeted at peripheral sources (i.e., alleviating joint pain), population-based studies have shown that radiographic severity of knee osteoarthritis and pain are only weakly associated (10,11). In some studies, however, this relationship was found to be stronger, for instance, when methods were used that controlled for between-person effects (using a

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Significance & Innovations

- A cluster of centrally-mediated symptoms (representing the manifestation of central pain) explained a small but significant amount of variance in pain severity, even after age and radiographic severity were taken into account.
- The co-occurrence of pain severity with centrally-mediated symptoms supports the idea that osteoarthritis treatment needs to be broadened to impact all potentially modifiable factors.

within-person matched knee design) (12), and when the more functionally-based Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale was used (13). Nevertheless, the association between radiographic severity in osteoarthritis and pain remains imperfect and requires further examination. There are still many individuals who have radiographic evidence of osteoarthritis in the absence of pain (11,14) and there are those who have little radiographic evidence of osteoarthritis with moderate to severe pain.

There is growing evidence that central nervous system factors may be playing a prominent role in maintaining osteoarthritis pain in certain individuals. In animal studies, central sensitization in osteoarthritis has been noted by altered spinal nociceptive processing (15,16). In clinical studies, compared to controls, participants with knee osteoarthritis had more diffuse hyperalgesia to mechanical or heat stimuli (17,18). Furthermore, pharmacologic studies have demonstrated that compounds that alter pain neurotransmitters centrally such as serotonin and norepinephrine (e.g., duloxetine, tricyclics) are efficacious in knee osteoarthritis (19,20).

Central involvement in pain is often accompanied by non–region-specific symptoms that are systemically mediated, such as fatigue, cognitive problems, sleep problems, and perturbations of mood (21–23). In fact, in a recent cluster analysis of older adults with symptomatic knee or hip osteoarthritis, one-third of the sample had a high level of these types of "centrally-mediated" symptoms (24). Many of these symptoms are associated with increased pain severity in osteoarthritis. For instance, pain in osteoarthritis is a predictor of sleep disturbance (25), was found to mediate a large amount of the relationship between arthritis and sleep problems (26), and was most associated with having any sleep problem in combination with having radiographic evidence of osteoarthritis (27). Pain is also associated with higher levels of depression in several studies (25,26,28–34) and with fatigue (35,36). In 1 study, fatigue was the strongest predictor of pain on the WOMAC scale (36), and fatigue is also correlated with both sleep disturbance and depression (33,35,37).

Although many of these centrally-mediated symptoms are interrelated and associated with increased pain severity, no studies to our knowledge have examined these symptoms in aggregate along with their combined contribution to pain severity in osteoarthritis above and beyond peripheral factors. The purpose of this study was to examine the associations of central and peripheral factors with osteoarthritis pain. We hypothesized that central factors (represented by centrally-mediated symptoms other than pain) would explain additional variance in pain severity, after controlling for demographics (age) and radiographic severity.

PATIENTS AND METHODS

Participants. For this analysis, participants came from 2 samples. In sample 1, participants consisted of women between the ages of 55 and 80 years who were involved in a cross-sectional study that examined the relationship between pain, fatigue, and physical activity (38). Participants were recruited through fliers, a research participant registry maintained by the University of Michigan's Claude D. Pepper Center, and a clinical studies web site at the University of Michigan. There were 65 people in the original sample. Five participants had data collected only to pilot our procedures but had complete data and were therefore included in this analysis, and the remaining 60 (40 with knee or hip osteoarthritis and 20 age-matched controls) have been described previously (38). In this analysis, we included only participants who had symptomatic knee osteoarthritis that was defined as radiographic evidence of osteoarthritis (Kellgren/Lawrence score $\geq$2) and at least mild reported pain on the WOMAC pain scale. They also needed to report having knee pain for at least 3 months in duration. The resulting sample size was 41. Sample 2 had 42 participants ages 50 years and older who were randomized into 1 of 2 intervention arms of a pilot randomized controlled trial and who completed a baseline assessment involving assessment of pain and other symptoms and physical function (39). Participants were recruited through fliers and advertisements in senior center newsletters. Participants were eligible for the study if they had definitive radiographic evidence of knee or hip osteoarthritis (Kellgren/Lawrence score $\geq$2), had joint pain for at least 3 months in duration, and reported mild to moderate joint pain on the WOMAC pain scale. From these 42, we excluded people with hip osteoarthritis or who were men, and 3 people whose home monitoring data were deemed unusable, leaving 14 people in sample 2. The combined sample in this study was 55.

Individuals in both samples were excluded from participating if they were nonambulatory, had medical conditions other than osteoarthritis that interfered with activity performance or caused pain and fatigue, had a joint replacement or surgery of the knee or hip in the previous 6 months, had inadequate cognition (by Mini-Mental State Examination or 6-Item Screener), or could not operate the wrist-worn accelerometer used in the study protocols. Participants in the pilot randomized controlled trial (sample 2) also were excluded if they were undergoing current nonpharmacologic treatment for osteoarthritis (e.g., rehabilitation, injections).

Measures. *Radiographic assessment.* Semiflexed bilateral standing radiographs were taken of the knees in an

Table 1. Baseline characteristics of the sample (n = 55)*

Variable	Total sample	Sample 1 (n = 41)	Sample 2 (n = 14)
Age, mean ± SD years	62.63 ± 7.50	62.83 ± 7.39	61.29 ± 7.64
White, no. (%)	43 (78.2)	34 (82.9)	9 (64.3)
Married, no. (%)	27 (49.0)	22 (53.7)	5 (35.7)
BMI, mean ± SD kg/m^2	31.12 ± 5.67	31.14 ± 5.68	31.89 ± 6.42
Kellgren/Lawrence grade (n = 53)			
1	4	4	0
2	27	22	6
3	16	12	4
4	6	2	4
MJSW, mean ± SD	3.03 ± 1.85	3.34 ± 1.85†	2.11 ± 1.52
Average weekly pain, mean ± SD‡		0.95 ± 0.79†	3.42 ± 1.57
Average weekly fatigue, mean ± SD‡		1.02 ± 0.74†	3.28 ± 1.57
Geriatric Depression Scale (n = 53), mean ± SD	1.89 ± 2.20	2.00 ± 2.33	1.50 ± 1.70
Sleep efficiency, mean ± SD %	88.00 ± 5.09	88.41 ± 5.31	85.87 ± 5.09

* BMI = body mass index; MJSW = minimum joint space width.
† Significantly different from sample 2 at $P < 0.05$.
‡ Average weekly pain and fatigue were rated on a scale of 0–4 for sample 1 and on a scale of 0–10 in sample 2, and these values are shown above. The independent *t*-tests between samples for pain and fatigue were performed using the Z-scored variables.

anteroposterior view. Radiographs were graded using the Kellgren/Lawrence scale (range 0–4) in each study by a radiologist, and measurement of minimum joint space width (MJSW) was done by a rheumatologist on our study team (KP). Both had expertise in reading radiographs and were blinded to the participants' symptom levels.

Pain. Pain was assessed in 2 ways in each study. Pain was assessed repeatedly over a 5-day home monitoring period in which participants rated their pain severity 6 times per day. They input responses into a wrist-worn accelerometer (Actiwatch-Score; Philips Respironics-Mini Mitter) that also concurrently measured physical activity levels. Pain was assessed on a scale of 0–4 by sample 1 and on a scale of 0–10 by sample 2. Because of the different scaling, a Z score was calculated for each participant in order to compare pain severity across studies. The ratings were averaged over the 5 days to generate an average pain severity score for each participant. Pain was also assessed using the WOMAC scale administered to participants with osteoarthritis at the baseline visit. Because of our interest in multifocal pain mechanisms, we chose to use the assessment of pain severity as the outcome in this analysis rather than the WOMAC pain scale, as we think it better captures global pain experience compared to a disease-specific, more functionally-based instrument.

Centrally-mediated symptoms. Non–region-specific symptoms accompanying pain such as fatigue, cognitive problems, sleep problems, and perturbations of mood are systemically-mediated symptoms that may index more central nervous system involvement in the maintenance of illnesses, such as pain (21–23). Therefore, we chose all available symptom measures that may indicate the presence of central involvement, i.e., fatigue, sleep efficiency, and depressive symptoms. Fatigue was measured similar to pain severity, in which participants in samples 1 and 2 rated fatigue severity 6 times per day over 5 days on scales of 0–4 and 0–10, respectively. To accommodate for the scale differences, fatigue severity ratings were averaged and Z scored per participant. Sleep efficiency was measured using the Actiwatch-Score that measures daytime and nighttime activity from which sleep and wake patterns can be derived. The data were collected over a series of 24-hour days via a small wrist-worn accelerometer. This method is widely used and validated (40,41), and there is strong concordance between accelerometry and polysomnography on parameters such as total sleep time, wake after sleep onset, number of awakenings, and sleep efficiency (42). Although polysomnography is the accepted measure of sleep architecture, accelerometry may better tap sleep-related behaviors and routines because it can occur in the home and is less obtrusive (40,43). For this analysis, we used sleep efficiency, which indicates the percentage of time spent asleep relative to the time spent in bed. Depressive symptoms were measured in both studies using the Geriatric Depression Scale (44). Measures of fatigue, sleep efficiency, and depressive symptoms were formed into a composite for analysis by Z scoring the measures and summing them for each participant.

Statistical analysis. We first examined the bivariate correlations among all of the variables to examine the interrelationships. Then we performed a hierarchical series of linear regressions to determine how each variable contributed to pain severity. We examined contributions of age, radiographic features of osteoarthritis (MJSW, Kellgren/Lawrence grade), and centrally-mediated symptoms. Missing values were replaced with the group mean for that variable. For the radiographic features of osteoarthritis, we used the values from each participant's designated joint, i.e., the joint chosen by the participant as having the most pain.

RESULTS

The baseline characteristics of the sample are shown in Table 1. The 2 samples were similar with respect to age

Table 2. Correlations between pain severity and factors included in regression models*

	K/L grade	MJSW	Centrally-mediated symptoms	Pain severity
Age	0.14	−0.15	−0.07	−0.01
K/L grade		−0.36†	0.29‡	0.32‡
MJSW			−0.10	−0.35‡
Centrally-mediated symptoms				0.39†

* K/L = Kellgren/Lawrence; MJSW = minimum joint space width.
† $P \leq 0.01$.
‡ $P \leq 0.05$.

and body mass index, and sample 2 had a greater proportion of African American participants compared to sample 1. There were differences in radiographic severity between the 2 samples in that sample 2 presented significantly greater joint space narrowing ($P = 0.03$); however, the percentages of individuals with Kellgren/Lawrence grades of 3 or 4 versus grades 1 or 2 were similar between the 2 samples ($\chi^2 = 2.85$, Fisher's exact test $P = 0.11$). Sample 2 was also more symptomatic than sample 1, presenting with greater levels of both pain and fatigue. Samples 1 and 2 did not differ significantly on sleep efficiency, and their levels were relatively high (88% and 86%, respectively).

Correlations were examined to determine how pain severity related to age, radiographic severity, and centrally-mediated symptoms (Table 2). Variables representing radiographic severity and centrally-mediated symptoms had small to moderate associations with pain severity. Of the predictor variables, small to moderate relationships were found between centrally-mediated symptoms and Kellgren/Lawrence grade (r = 0.29) and between Kellgren/Lawrence grade and MJSW (r = −0.36).

In performing the linear regressions, predictors were entered in separate steps in a hierarchical manner: 1) age, 2) radiographic severity variables of Kellgren/Lawrence grade and MJSW, and 3) centrally-mediated symptoms. The steps were chosen in this order because it was of particular interest to determine the added contribution of centrally-mediated symptoms to pain severity in a model with factors that physicians may more commonly consider when treating osteoarthritis pain (i.e., demographics and osteoarthritis disease severity). We first evaluated the model diagnostics. The residuals were normally distributed, although an analysis of the Cook's D confirmed that 1 participant had the potential for undue influence on the overall model. This particular participant had an average pain rating that was >4 SDs from the sample mean. We removed this participant from the data set and reran the analysis (n = 54). Although the betas in both series of regressions with and without this participant were similar, the series without the participant was the best-fitting model and is summarized in Table 3. Radiographic severity variables and centrally-mediated symptoms added a significant proportion of variance in pain severity. Controlling for age, radiographic severity explained 17% ($F[2,50] = 5.10$, $P = 0.01$) of the variance in pain severity. Including centrally-mediated symptoms in the model added another 10% of the variance ($F[1,49] = 6.51$, $P = 0.01$). Overall, more than one-quarter of the variance ($R^2 = 0.27$) in pain severity was predicted by the 4 independent variables. In these models, increasing radiographic severity (increasing Kellgren/Lawrence grade or decreasing joint space width) was associated with greater pain severity; however, centrally-mediated symptoms were most strongly independently associated with pain severity (standardized $\beta = 0.33$, 95% confidence interval 0.04–0.34).

DISCUSSION

This study found that in a group of community-dwelling adults ages ≥50 years, both radiographic severity and centrally-mediated factors contributed to pain severity. In support of our hypothesis, centrally-mediated symptoms explained additional variance in pain severity beyond age and radiographic severity. This was a small but significant addition to the model.

The association between pain severity and radiographic features of osteoarthritis in population-based samples is typically weak (10,11), although it is stronger in a study controlling for between-person differences (12). In our study, radiographic severity was independently associated with pain severity and contributed 17% of variance to the model. This relatively strong relationship between radiographic severity and pain may be due in part to how sample 1 was selected, in that people with radiographic osteoarthritis needed to have at least minimal pain (≥5 on the WOMAC pain scale). We also used 2 parameters of

Table 3. Factors associated with pain severity in women with knee osteoarthritis (n = 54)*

Measure	Total R^2	F ratio for R^2	Cumulative R^2 by step	F ratio by step	Unstandardized β	Standardized β	P
Average pain severity	0.27	4.46†					
Age			0.000	0.01	−0.01	−0.10	0.44
Osteoarthritis severity			0.17	5.10†			
K/L grade					0.15	0.14	0.32
MJSW					−0.13†	−0.28	0.05
Centrally-mediated symptoms			0.10	6.51‡	0.19‡	0.33	0.01

* df 4,49. K/L = Kellgren/Lawrence; MJSW = minimum joint space width.
† $P < 0.05$.
‡ $P < 0.01$.

radiographic severity, both the Kellgren/Lawrence score and MJSW narrowing, which may have increased our ability to explain variance in the model. Other markers of osteoarthritis severity from radiographs, such as number of osteophytes, have been inconsistently associated with knee pain (32,36). However, in studies using magnetic resonance imaging of the knee joint, factors that have been associated with knee pain severity include flattening of articular surfaces and bone marrow lesions (45) as well as subchondral bone plate exposure (46). To more fully understand the peripheral contribution of pain in knee osteoarthritis, it appears important to consider these types of factors.

The findings from this study show that additional variance in the model was explained by a cluster of centrally-mediated symptoms. Separately, each of these symptoms has been associated with pain severity and there are strong associations between pain severity and sleep disturbance (25–27) and depression (25,26,28–34). Kim et al (34) found that the relationship between depression and pain severity was stronger for people with less radiographic severity (Kellgren/Lawrence grade of 0 or 1) compared to those with greater levels of radiographic severity, suggesting that depression may be one explanatory factor for discrepancies in the relationship between pain and radiographic severity. We examined whether one symptom, such as depression, was driving the effect of centrally-mediated symptoms in the model. However, this does not appear to be the case as the frequency of the most severe symptom reported (as denoted by the largest absolute value of each Z score in the composite) was somewhat evenly distributed: 37% had the most severe depression in the composite, 37% had the most severe sleep disturbance, and 26% had the most severe fatigue.

The main limitation of this study was the highly select sample that had symptomatic knee osteoarthritis and did not report other medical conditions known to cause pain and fatigue that may be centrally mediated (such as fibromyalgia and low back pain). Exclusion of people without these comorbid conditions could have led to an underestimation of the association between centrally-mediated symptoms and pain severity. Replication is needed to determine whether the estimates found in the model are reliable. In addition, generalizability of the study findings are limited to women and it is not clear if these findings would be replicated in male samples, as men tend to report lower levels of symptoms (6). The cross-sectional design of this study limits the ability to examine causality. However, the centrally-mediated symptoms in aggregate help to explain the variance in pain beyond demographic or disease severity factors. While the small sample size limited the ability to build a model with many predictors, other demographic factors may also be important to include, such as body mass index, as it has been associated with a measure of pain severity in an adjusted model (32). It should be noted that pain severity (averaged over a 5-day period) was measured differently in this study than in most other studies. However, compared to recall-based measures, this measure of pain severity is considered to be more ecologically valid and does not have the weakness of being biased by peak or recent experiences (47). Lastly, although this study provides support for the contribution of centrally-mediated symptoms as a symptom cluster influencing pain severity, we did not have data from quantitative sensory testing to examine pain threshold or sensitivity in these participants. These latter measures would provide an index of patients' inherent sensitivity to painful stimuli in addition to the amount of clinical pain they were experiencing.

Despite limitations, this study is the first to our knowledge that examined the unique contributions of peripheral and central factors on pain severity in women with knee osteoarthritis. It also adds to a knowledge base on the heterogeneity in knee osteoarthritis pain (7,48). Given this heterogeneity, there are some potential clinical implications of this study. The majority of osteoarthritis pharmacologic and rehabilitation treatments are geared toward alleviating pain due to disease severity in the joint; therefore, it appears important to optimize treatment for people who have pain beyond peripheral sources. Because women with higher pain severity in this study also had a greater presence of centrally-mediated symptoms, high reported pain severity may be one way to identify patients who should be further screened for the presence of depression, fatigue, and sleep disturbance. Furthermore, the cooccurrence of pain with these other symptoms provides support for the development of multifaceted interventions that could impact these potentially modifiable symptoms. In 1 study, Lin et al found that an intervention to reduce depression also reduced arthritis pain interference in people with osteoarthritis, providing support for these types of interventions (49). In addition, we found that fatigue inference was significantly improved by an occupational therapist–led activity pacing intervention in a pilot study of people with symptomatic knee and hip osteoarthritis (39).

Future studies should be done to examine the underlying pain mechanisms in people who present with centrally-mediated symptoms in knee osteoarthritis. While we have used a proxy measure for central sensitization in this study, more sophisticated aggregated indices of central mechanisms are needed to examine the relationship between this clinical symptom presentation and pain severity. One way to better understand the role of central sensitization in osteoarthritis pain is to examine the response to treatments that target central pain processing. In addition to the studies of pharmacologic treatments, such as duloxetine (19,20), nonpharmacologic approaches should also be examined for their effect on central sensitization and centrally-mediated pain. Several rehabilitative strategies, such as manual therapy, behavioral therapy, and transcutaneous electrical nerve stimulation, should be examined as potential ways to target central sensitization (50).

Due to the growing evidence of osteoarthritis as a mixed peripheral/central pain state, we examined associations between pain severity and variables representing peripheral and central factors that could contribute to osteoarthritis pain. We found significant independent associations between pain severity, radiographic severity, and centrally-mediated symptoms. Centrally-mediated symptoms added significant additional variance in the model

after controlling for age and radiographic features and may need to be addressed in osteoarthritis management strategies.

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 published. Dr. Murphy 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. Murphy, Lyden, Phillips, Clauw, Williams.

Acquisition of data. Murphy, Lyden, Phillips.

Analysis and interpretation of data. Murphy, Lyden, Phillips, Clauw, Williams.

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