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Characteristics of Fibromyalgia Independently Predict Poorer Long-Term Analgesic Outcomes Following Total Knee and Hip Arthroplasty

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Objective. **While psychosocial factors have been associated with poorer outcomes after knee and hip arthroplasty, we hypothesized that augmented pain perception, as occurs in conditions such as fibromyalgia, may account for decreased responsiveness to primary knee and hip arthroplasty.**

Methods. **A prospective, observational cohort study was conducted. Preoperative phenotyping was conducted using validated questionnaires to assess pain, function, depression, anxiety, and catastrophizing. Participants also completed the 2011 fibromyalgia survey questionnaire, which addresses the widespread body pain and comorbid symptoms associated with characteristics of fibromyalgia.**

Results. **Of the 665 participants, 464 were retained 6 months after surgery. Since individuals who met criteria for being classified as having fibromyalgia were expected to respond less favorably, all primary analyses excluded these individuals (6% of the cohort). In the multivariate linear regression model predicting change in knee/hip pain (primary outcome), a higher fibromyalgia survey score was independently predictive of less improvement in pain (estimate −0.25, SE 0.044; $P < 0.00001$). Lower baseline joint pain scores and knee (versus hip) arthroplasty were also predictive of less improvement ($R^2 = 0.58$). The same covariates were predictive in the multivariate logistic regression model for change in knee/hip pain, with a 17.8% increase in the odds of failure to meet the threshold of 50% improvement for every 1-point increase in fibromyalgia survey score ($P = 0.00032$). The fibromyalgia survey score was also independently predictive of change in overall pain and patient global impression of change.**

Conclusion. **Our findings indicate that the fibromyalgia survey score is a robust predictor of poorer arthroplasty outcomes, even among individuals whose score falls well below the threshold for the categorical diagnosis of fibromyalgia.**

The estimated lifetime risk of symptomatic knee osteoarthritis is ~45% (1). Between 1991 and 2010 the number of total knee arthroplasties (TKAs) per capita

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among US Medicare beneficiaries nearly doubled, and there was a 59% increase in revision TKA (2). Based on temporal trends in aging and obesity, the numbers of TKA and total hip arthroplasties (THAs) are anticipated to increase substantially in the coming years (3,4). Although TKA and THA have been shown to improve chronic pain and function (5), studies estimate that ~20% of TKA and 10% of THA patients fail to derive the desired analgesic benefit (6–9). Cross-sectional studies of long-term pain outcomes have identified pain in other locations, as well as negative affect and cognitions (i.e., depression and catastrophizing, respectively) as independent risk factors for lack of improvement in pain following TKA and THA (7,8,10,11).

One possible explanation for the differences in long-term analgesic outcomes may be mechanistic. There is a growing appreciation of the importance of augmented central nervous system pain processing and other symptoms in many chronic pain states (12,13). A number of pain disorders without clear peripheral pathology have been given specific names, such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis. The most "systemic" of these conditions, fibromyalgia, is characterized by widespread body pain and comorbid somatic symptoms (i.e., fatigue, poor sleep, depression, and memory difficulties), all of which are thought to be of central nervous system origin (12). Research has demonstrated that these patients have alterations in central neurotransmitters that, at least in part, lead to both augmented pain and sensory processing and the comorbid symptoms. Opioids, nonsteroidal antiinflammatory drugs, surgical procedures, and other peripherally directed interventions are generally thought to be less effective for central pain states (12). Our group recently showed that patients with higher fibromyalgia survey scores consumed substantially more opioids in the acute postoperative period after TKA and THA (14). Most importantly, the fibromyalgia survey score is not just a dichotomous label; rather, it appears relevant as a continuous variable within the population (15). For example, every 1-point increase in the fibromyalgia survey score from 0 to 31 was associated with consuming an adjusted 9 mg more oral morphine equivalents to treat postoperative pain following THA and TKA (14).

Additional support for the hypothesis of poorer outcomes in patients who have characteristics of fibromyalgia comes from earlier studies. For example, poorer long-term analgesic outcomes in arthroplasty patients have been associated with multifocal pain, one of the hallmarks of fibromyalgia (6–8,10,16). One of the physiologic correlates for fibromyalgia and other conditions where pain is thought to have become centralized is diffuse hyperalgesia (12). Two recent cross-sectional postoperative studies using quantitative sensory testing showed that patients with pain after revision TKA have more widespread body pain and lower pain thresholds (17,18). To date, no prospective study has been performed to show that measures of centralized pain are associated with poorer arthroplasty outcomes, nor has any previous study compared the predictive value of these measures versus classic measures of negative affect (depression and anxiety) or cognitions (catastrophizing) already known to be associated with poor outcomes.

Given the current utilization and future projections for arthroplasty (2–4), the ability to predict poorer outcomes and triage patients to alternate analgesic therapies that might be more effective (e.g., centrally acting analgesics) has enormous socioeconomic implications. Thus, the objective of this prospective, observational cohort study was to assess the associations between fibromyalgia survey scores and chronic pain outcomes after primary TKA and THA. We hypothesized that patients with higher fibromyalgia survey scores would report less long-term pain reduction following arthroplasty.

PATIENTS AND METHODS

Study design. University of Michigan Institutional Review Board approval was obtained. The reporting of this prospective, observational cohort study conforms to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement (19). Between July 27, 2010 and May 31, 2013, adult patients (≥18 years old) who were scheduled for primary, unilateral TKA or THA were prospectively recruited prior to surgery. Patients were excluded if they were undergoing bilateral arthroplasty, were undergoing revision arthroplasty, did not speak English, were unable to provide written informed consent, or were incarcerated. All patients provided written informed consent. Acute postoperative outcomes (anesthesia/acute pain) from a portion of this cohort were published earlier (14), but the long-term surgical outcomes explored herein have not been presented previously.

Phenotyping battery. Patients completed validated self-report questionnaires prior to surgery, and other relevant data were obtained from surgical and anesthesia medical records. Additional details of the preoperative phenotyping battery have been described previously (14).

Fibromyalgia survey criteria. The fibromyalgia survey is a validated self-report measure consisting of 2 scales, with one assessing widespread body pain and the other evaluating comorbid symptoms (12,15). First, the Widespread Pain Index (WPI) was calculated using the Michigan Body Map to assess the 19 specific body areas described in the measure (score 0–19). The second aspect of the criteria was evaluated using the comorbid Symptom Severity (SS) scale (score 0–12). The

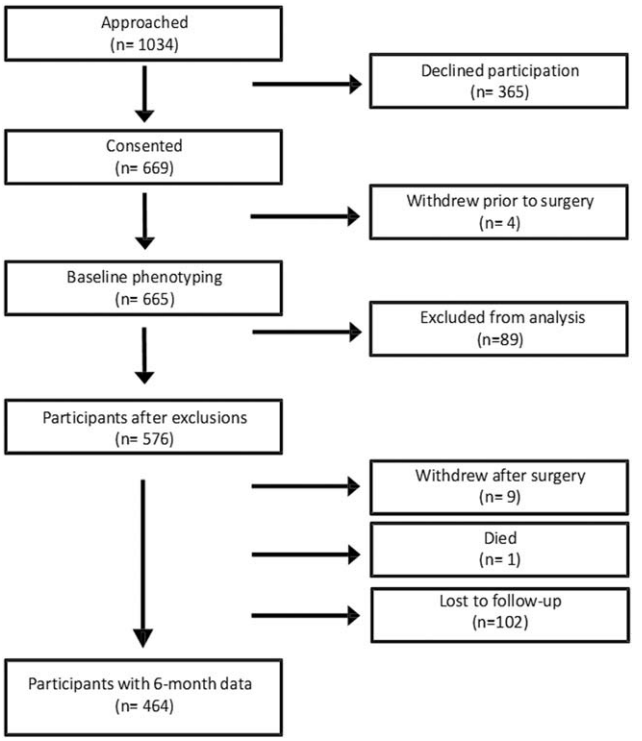

Figure 1. Flow diagram showing the recruitment and retention of the patients.

resulting total fibromyalgia survey score ranged from 0 to 31. Previously described cut points were used to categorize patients as "fibromyalgia positive" (15). Specifically, patients were classified as fibromyalgia positive if they had a WPI of ≥ 7 and SS score of ≥ 5 or a WPI of 3–6 and SS score of ≥ 9 (20).

Knee and hip measures. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used for knee/hip-specific pain severity (5 questions, score 0–20), stiffness (2 questions, score 0–8), and functional status (17 questions, score 0–68) (21).

Pain severity. The 4 pain severity questions from the Brief Pain Inventory (BPI) (worst, least, average, and right now; with a numeric rating scale of 0–10, where 0 = no pain and 10 = pain as bad as you can imagine) were used to create a single composite score (0–10) for severity of overall body pain (22).

Pain descriptors. The PainDETECT Questionnaire is a 9-item screening tool used to detect descriptors of neuropathic pain. Scores of ≥19 suggest that a neuropathic component is likely (23). The neuropathic pain assessment was specific to the surgical site (knee or hip) (23).

Psychological measures. The Hospital Anxiety and Depression Scale (HADS) contains 7 questions about anxiety and 7 questions about depression, with a score range of 0 to 3 for each question (score 0–21 for each measure, with higher scores indicating more depressive symptoms and anxiety) (24). The Coping Strategies Questionnaire-Catastrophizing contains a subscale for pain catastrophizing, which is a valid and reliable measure of this cognition. Scores range from 0 to 36, with higher scores indicating more catastrophizing (25).

In addition, research assistants recorded all opioid use as an average daily dose. Each opioid was then converted to oral morphine equivalents using previously described conversions (26) (Palliative Care Consortium [http://www.gha.net.au/Uploadlibrary/406205172GRPCC-CPG002_1.0_2011-Opioid.pdf] and The Hopkins Opioid Program [www.hopweb.org]). Body mass index (BMI) and the American Society of Anesthesiologists (ASA) physical function score (an ordinal measure of comorbidities with a range of 1 to 5 [https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system]) were queried from the anesthesia electronic medical record (Centricity; General Electric Healthcare). The primary anesthetic was categorized as general anesthesia alone, general anesthesia plus femoral nerve block, general anesthesia plus neuraxial anesthesia (spinal or epidural), or neuraxial anesthesia alone. In a review of patient records, it was noted that only 4.2% of the cohort had radiographic evidence of arthritis rated as something other than "severe" (0.52% mild and 3.65% moderate). Due to the low variability, radiographic evidence of arthritis was not included as a covariate in the outcomes analyses.

Longitudinal assessment. Patients were evaluated 6 months after arthroplasty using the same questionnaires that were assessed in the baseline phenotyping noted above. The outcomes assessments were sent and returned by postal mail.

Postoperative record review. The medical records of all included participants were reviewed for potential complications or nonphenotypic factors that might explain more pain or disability in the 6-month followup period (reviews conducted by AGU, BRH, and NIW). Patients who had additional arthroplasty (i.e., THA or TKA for a different joint), hardware fracture, revision surgery, postoperative joint infection requiring incision and drainage surgery, and/or other significant surgery or postoperative outcomes (e.g., coronary artery bypass, subdural hematoma) prior to their 6-month outcomes assessment were excluded from the long-term analyses. These exclusions are displayed in the patient flow diagram (Figure 1) and further detailed in the Results section below.

Primary and secondary outcomes. Primary outcomes analyses were conducted excluding the patients who met the criteria for being "positive" for fibromyalgia to ensure that the results were not driven by this small subset of patients. All analytic models were also conducted with the entire cohort (including fibromyalgia-positive patients) minus the exclusions previously noted (data not shown). Patients who had fibromyalgia symptoms but did not satisfy the previously defined thresholds are referred to as having "subclinical" disease.

The 6-month change in knee/hip pain (WOMAC pain subscale) was used for the primary outcome. Secondary outcomes included change in the composite measure of the BPI (mean of the current, worst, least, and average pain response [range 0–10]) and the patient's global assessment of change.

Statistical analysis. Data were entered into the APOLO Electronic Data Capture system (27). Missing data for the validated instruments were handled as follows. Catastrophizing, fibromyalgia survey score, and WOMAC scales were computed with complete data only. BPI scales were calculated as the mean of all items or the mean of 3 items if 1 item was missing. If more than 1 item was missing, no scale score was computed. The PainDETECT Questionnaire score

was calculated as the sum of all 9 items or the sum of 8 items if 1 item was missing. If more than 1 item was missing, the PainDETECT Questionnaire score was not calculated. HADS subscales were calculated using the sum of all subscale items. If 1 item was missing, the missing value was imputed with the mean of the remaining items. The scale score was then computed as the sum of all items. If more than 1 item was missing, no scale scores were computed. Data were analyzed using R software version 3.1.1.

The cohort was divided into thirds based on the preoperative fibromyalgia survey score for preoperative descriptive data. These tertiles were not based on previously defined cut points. The continuous score from the fibromyalgia survey criteria was used for linear and logistic regression outcomes models, with the models presented excluding fibromyalgia-positive patients. Additional models included these patients for comparison (data not shown). The change in knee/hip pain (WOMAC pain subscale) and overall body pain (BPI) were analyzed as a continuous score using multivariate linear regression models. Both knee/hip and overall pain were also analyzed using a multivariate logistic regression model with a successful outcome defined as a 50% improvement in pain 6 months after arthroplasty. The patient's global assessment of change was dichotomized as patient responses of "very much improved" or "much improved" versus all other responses for a multivariate logistic regression model. Given the invasive nature of arthroplasty, the "slightly improved" response on the patient's global assessment of change was not deemed a successful outcome. All of the baseline covariates were included in the regression models. Age, BMI, and self-report measures were analyzed as continuous variables, and other demographic responses, primary anesthetic type, ASA score, and knee versus hip surgery were either dichotomized or treated as categorical variables as appropriate.

Model-based hypotheses testing and backwards variable selection were conducted using likelihood ratio tests. Briefly, we identify a set of all potential explanatory variables as the first step. The second step in building a regression model is to identify the best combination of explanatory variables to include in the model. The model is first calculated with all potential explanatory variables (full model), then recalculated after dropping the variable with the least significant association with the response variable. Significance is assessed by the likelihood ratio test. The process continues until all variables remaining in the model are statistically significant (28,29). For transparency, the fibromyalgia survey score results in the full model prior to backwards selection are presented in the results.

RESULTS

Recruitment and retention. A total of 1,034 patients were approached for participation, of whom 665 agreed to participate (64.3%). The mean ± SD age of the cohort was 62.3 ± 11.3 years, and 52.3% were women. The cohort was predominantly white (91.4%), and 41.6% had TKA (versus THA). There were no differences in age ($P = 0.76$) or sex ($P = 0.34$) when comparing participants to nonparticipants; however, there was a significantly higher proportion of nonwhites in the nonparticipant group when compared to participants (86.3% of the nonparticipants were white and 93.2% of the participants were white; $P = 0.001$). Some patients were excluded from the analysis, due to additional arthroplasty during the followup period (n = 50), hardware fracture (n = 27), joint infection (n = 25), revision of the same joint during the followup period (n = 6), and other medical adverse events recorded during the followup period (n = 7). Some patients were excluded for multiple reasons. After postsurgical exclusions withdrawals, and loss to followup, there were 464 patients with 6-month outcome data (80.6% of eligible participants retained) (Figure 1). Patients lost to followup reported a significantly worse preoperative phenotype (e.g., greater pain, more anxiety and depressive symptoms, lower function, etc.).

Higher fibromyalgia survey scores predictive of poorer outcomes regardless of whether individuals met criteria for fibromyalgia. There was a wide distribution of fibromyalgia survey scores (mean ± SD 6.35 ± 4.18, median 6, range 29, interquartile range 6). A total of 6.2% of the patients scored at or above the previously defined cut points for meeting the criteria for being "fibromyalgia positive" (15). These patients were excluded from the outcomes analyses unless otherwise noted. Higher fibromyalgia scores were associated with higher preoperative pain severity and use of neuropathic pain descriptors, more negative affect (i.e., depression, anxiety), increased tendency to catastrophize pain, worse physical function, and more opioid use (Table 1).

All of the covariates listed in Table 1 were included in the multivariate regression models. Seventy-three patients (18.2%) did not meet the threshold of at least 50% improvement in the WOMAC pain subscale for the logistic regression model. The outcome was best predicted by the fibromyalgia survey score ($P = 0.00032$), as well as the baseline WOMAC pain score and THA (versus TKA) (Figure 2). The fibromyalgia survey score was predictive of failing to meet the threshold for improvement, with the odds increasing by 17.8% for every 1-point increase on the scale. The same covariates were predictive in the multivariate linear regression model for the WOMAC pain subscale (continuous measure) (Table 2).

The fibromyalgia survey score was also predictive of robust change in all of the secondary outcomes. The fibromyalgia survey score independently predicted reduced improvement in overall pain (BPI). For every 1-point increase in the fibromyalgia survey score, patients reported an adjusted 0.19 points less improvement

Table 1. Baseline phenotype by FM survey score tertile*

	FM score			*P*			
	Low (0–4) (n = 220)	Moderate (5–8) (n = 238)	High (9–29) (n = 177)	Regression for overall group	Low vs. moderate†	Low vs. high†	Moderate vs. high†
Age	64.1 ± 10	62 ± 11.8	59.7 ± 11.5	0.00052	0.041	0.0001	0.043
Sex, % female	49.5	48.7	63.3	0.0055	0.86	0.006	0.0031
Ethnicity, % Hispanic	1.4	1.26	1.13	0.98	0.92	0.84	0.9
Race, % white	92.3	92.4	89.8	0.58	0.69	0.62	0.26
Preoperative pain, affect, and function							
Surgical site pain	4.15 ± 2.22	4.51 ± 1.96	5.72 ± 2.03	<0.0001	0.062	<0.0001	<0.0001
Overall body pain	4.13 ± 2.09	4.58 ± 1.77	5.84 ± 1.95	<0.0001	0.013	<0.0001	<0.0001
Neuropathic pain symptoms	7.29 ± 4.88	8.53 ± 5.59	12.8 ± 6.46	<0.0001	0.022	<0.0001	<0.0001
Depressive symptoms	3.09 ± 2.36	4.81 ± 3.07	7.06 ± 3.77	<0.0001	<0.0001	<0.0001	<0.0001
Anxiety symptoms	3.86 ± 2.92	5.61 ± 3.36	7.43 ± 4.16	<0.0001	<0.0001	<0.0001	<0.0001
Catastrophizing, median (IQR)	1 (0–4)	3 (1–6)	7 (3–13)	<0.0001	0.004	<0.0001	<0.0001
WOMAC							
Pain subscale	9.82 ± 3.43	10.9 ± 3.38	12.8 ± 3.03	<0.0001	0.00096	<0.0001	<0.0001
Stiffness subscale	4.26 ± 1.84	4.75 ± 1.73	5.31 ± 1.55	<0.0001	0.0026	<0.0001	0.0016
Function subscale	34 ± 10.9	37.6 ± 11.1	42.4 ± 9.6	<0.0001	0.0005	<0.0001	<0.0001
Total score	48.1 ± 14.8	53.2 ± 14.9	60.5 ± 12.8	<0.0001	0.00023	<0.0001	<0.0001
% taking preoperative opioids	20.9	27.8	51.7	<0.0001	0.0841	<0.0001	<0.0001
Preoperative opioids, median (IQR) OME	0 (0–0)	0 (0–2.15)	0.71 (0–30)	0.415	0.188	0.441	0.647
Medical, anesthetic, and surgical variables							
Body mass index, kg/m^2	29.2 ± 5.14	30.9 ± 5.68	30.1 ± 5.67	0.003	0.00065	0.11	0.11
ASA physical function score, %							
1	3.6	4.2	4.5	0.156	0.542	0.058	0.176
2	67.7	63.9	56.5				
3	28.6	31.9	40				
Primary anesthetic, %							
General anesthesia	38.6	42.4	48	0.316	0.855	0.084	0.31
General anesthesia + nerve block	2.3	2.5	4				
General anesthesia + neuraxial	13.6	13	14.7				
Neuraxial	45.5	42	33.3				
Surgery, % knee arthroplasty	49.1	42	31.6	0.0019	0.13	0.00042	0.03

* The cohort was divided into tertiles based on the preoperative fibromyalgia survey score for comparisons of preoperative characteristics. Statistics and *P* values are regression model–based with fibromyalgia tertile group as a categorical covariate. The model is linear for continuous response, logistic for binary, multinomial logistic for nominal, and proportional odds for ordinal variables. FM = fibromyalgia; IQR = interquartile range; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OME = 24-hour total oral morphine equivalents (measured in mg); ASA = American Society of Anesthesiologists.

† Adjusted for multiple comparisons by Holm's procedure.

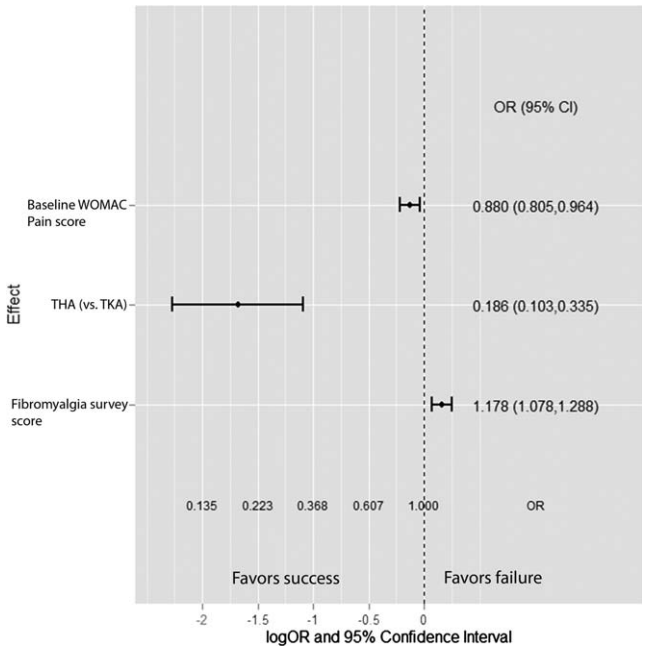

Figure 2. Predictors of failure to meet the threshold for knee or hip pain improvement (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain subscale). In this multivariate logistic regression model, patients describing less than 50% improvement in pain on the WOMAC pain subscale 6 months after total knee arthroplasty (TKA) or total hip arthroplasty (THA) were considered to have failed to have met the threshold. The fibromyalgia survey score was predictive, with the odds of failing to meet the threshold increased by 17.8% for every 1-point increase on the scale. Higher preoperative WOMAC pain score and THA (versus TKA) were predictive of improved outcomes. Values are the odds ratio (OR) ± 95% confidence interval (95% CI). Area under the curve 0.74. Values >1 indicate higher odds of failure.

on the 11-point pain scale (Table 3). A total of 157 patients (37.7%) failed to derive 50% improvement in overall body pain. As with the multivariate linear regression model, the fibromyalgia survey score was predictive, with the odds of failing to meet the threshold increased by 30% for every 1-point increase on the scale (logistic regression odds ratio [OR] 1.30 [95% confidence interval (95% CI) 1.19–1.42], $P < 0.00001$). In addition to the other independent predictors in the multivariate linear regression model of change in overall pain (Table 3), the ASA physical function score and depression were predictive in the multivariate logistic regression model.

Thirty-seven patients (8.4%) did not meet the patient's global assessment of change threshold for success, and the fibromyalgia survey score was again predictive of failed outcomes. The odds of failing to meet the threshold for success for the patient's global assessment of change increased by ~18% for every 1-point increase in fibromyalgia survey score (OR 1.18 [95% CI 1.05–1.31], $P = 0.0038$). The higher tertiles of the fibromyalgia survey score had higher rates of failure to meet the thresholds for change in knee/hip pain (WOMAC knee/hip pain severity [difference not significant]), overall body pain (BPI), and patient's global assessment of change (Table 4).

The models were also conducted with the fibromyalgia-positive patients included, and fibromyalgia survey scores remained predictive of change in linear and logistic regression models for knee/hip pain and overall body pain, as well as the patient's global assessment of change logistic model (data not shown).

No measure of negative affect (depression, anxiety), negative cognitions (catastrophizing), or neuropathic pain consistently remained in the best models presented, suggesting that these covariates have less predictive power than the fibromyalgia survey score. In the full multivariate models with all of the candidate predictors (prior to backwards selection), the fibromyalgia survey score was a significant predictor for failure to meet the threshold for knee or hip pain improvement on the

Table 2. Multivariate linear regression best model for change in knee/hip pain (WOMAC)*

Variable	Estimate	SE	*P*
(Intercept)	−1.46	0.46	0.0015
Fibromyalgia survey score	−0.25	0.044	<0.00001
Baseline WOMAC pain	0.92	0.042	<0.00001
THA (vs. TKA)	1.96	0.27	<0.00001

* Independent predictors of change in pain using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (dependent measure) over the 6-month followup period are shown. Negative numbers indicate less improvement in pain. Patients categorized as fibromyalgia positive were excluded from the analysis. $R^2 = 0.58$. THA = total hip arthroplasty; TKA = total knee arthroplasty.

Table 3. Multivariate linear regression best model for change in overall pain (BPI)*

Variable	Estimate	SE	*P*
(Intercept)	−0.26	0.25	0.30
Fibromyalgia survey score	−0.19	0.029	<0.00001
Preoperative opioids (OME)	−0.015	0.0047	0.0016
Other race†	−1.49	0.58	0.011
Baseline overall pain	0.80	0.049	<0.00001
THA (vs. TKA)	0.96	0.18	<0.00001

* Independent predictors of change in pain using the Brief Pain Inventory (BPI) over the 6-month followup period are shown. Negative numbers indicate less improvement in pain. Patients categorized as fibromyalgia positive were excluded from the analysis. $R^2 = 0.44$. OME = 24-hour total oral morphine equivalents (measured in mg); THA = total hip arthroplasty; TKA = total knee arthroplasty.
† Nonwhite, non–African American race.

Table 4. Failure rates in the FM tertiles*

	All patients	Patients with low FM survey score	Patients with moderate FM survey score	Patients with high FM survey score	*P*			
					Overall group	Low vs. moderate	Low vs. high	Moderate vs. high
Failed to achieve 50% improvement in knee/hip pain (WOMAC)	19.87 (16.3–23.45)	16.76 (11.29–22.23)	19.77 (13.91–25.64)	25.42 (17.57–33.28)	0.2	0.46	0.071	0.25
Failed to achieve 50% improvement in overall pain (BPI)	40.89 (36.56–45.23)	26.97 (20.45–33.49)	43.24 (36.1–50.38)	60.68 (51.83–69.53)	<0.00001	0.0011	<0.00001	0.0031
Failed to achieve change of "much improved" or "very much improved" (patient's global assessment)	9.79 (7.237–12.34)	6.77 (3.217–10.32)	9.14 (4.998–13.28)	17.21 (10.51–23.91)	0.014	0.39	0.0042	0.037

* Values are the percentage (95% confidence interval) of all patients and patients in each tertile of preoperative fibromyalgia (FM) survey score. Both patients who underwent total hip arthroplasty and those who underwent total knee arthroplasty are included. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; BPI = Brief Pain Inventory.

WOMAC in the linear multivariate models (estimate -0.20, $P = 0.00014$) and logistic multivariate models (OR 1.17, $P = 0.0058$), as well as on the BPI in the linear models (estimate -0.20, $P < 0.00001$) and logistic models (OR 1.37, $P < 0.00001$).

DISCUSSION

In this large, prospective, observational cohort study of arthroplasty outcomes, patients with higher preoperative fibromyalgia survey scores were less likely to report improvement in pain in the affected knee or hip (Table 2 and Figure 2), overall body pain (Table 3), and global impression of change. To our knowledge, this is the first study to describe the fibromyalgia survey criteria (15) as a predictor of long-term pain outcomes after surgery. Most importantly, this measure showed this predictive ability across the entire cohort, not just in the 6% of the individuals studied who met the categorical criteria for fibromyalgia. This single, simple-to-administer measure was a powerful predictor of a poor outcome and was the only preoperative phenotypic measure to consistently show predictive utility across the different outcome domains. As such, the measure may have value in screening for appropriateness for arthroplasty in the clinical setting.

Patients with higher fibromyalgia survey scores had higher levels of pain in the affected knee or hip, as determined by WOMAC scores, and higher levels of overall body pain, as determined by BPI, preoperatively (Table 1). As is often noted in trials of analgesic therapies (16), patients with higher baseline pain have more room to improve and are thus more likely to improve when change in pain is assessed as the primary outcome (Table 2 and Figure 2). Nonetheless, despite starting with higher baseline pain, patients with higher fibromyalgia survey scores were still less likely to meet the threshold for change in overall pain and change in affected knee or hip pain.

The findings of this study provide some additional mechanistic rationale for a portion of the failures following TKA and THA. Total joint replacement addresses what has long been thought to be an exclusively or predominantly peripheral disease. The current conceptualization of fibromyalgia is that the central sensitivity inherent to this and related conditions leads to pain augmentation/amplification (12). Despite the overwhelming data supporting this conceptualization, there are some that contest these ideas. Patients with fibromyalgia survey scores that were elevated but still subclinical (e.g., not meeting previously described cut points to be fibromyalgia positive) demonstrated poorer outcomes. We suggest that augmented central nervous system pain processing is likely more prominent in patients with moderate and higher fibromyalgia survey scores when compared to those with lower scores; however, future studies are needed to assess this concept. Individuals in this study all had severe enough radiographic evidence of arthritis to qualify for arthroplasty, so they did all presumably have some ongoing peripheral nociceptive input that might benefit from arthroplasty. However, these data suggest that in

some individuals with arthritis or other peripheral nociceptive input, this superimposed pain amplification is clinically relevant and might even be playing a more prominent role in a given individual's overall pain experience as opposed to what is occurring solely in the knee or hip (12,13).

The notion that there is a subset of individuals with osteoarthritis, or any other chronic pain condition, that has centralized pain augmentation is well supported by quantitative sensory testing and neuroimaging studies (30,31). This study, however, is the first large prospective study to show that it may be very important to use simple screening tools such as the 2011 fibromyalgia survey criteria to identify clinical or subclinical fibromyalgia in medical practice (17,18,31). Combined with our recent study showing that this same measure was also predictive of markedly increased opioid requirements in the immediate postoperative period (14), it now appears that individuals with this phenotype respond differentially to treatments for both acute (i.e., opioids) and chronic (i.e., surgery) pain. Additional research is needed to identify the precise biologic underpinnings of the poorer outcomes associated with higher fibromyalgia survey scores, as well as whether this measure might finally allow us to move toward the elusive "personalized analgesia" sought for acute and chronic pain. It is possible that patients with higher fibromyalgia survey scores would be more likely to benefit from therapies targeting centralized pain, including medications (e.g., serotonin and norepinephrine reuptake inhibitors, gabapentinoids), exercise, and cognitive behavioral therapy (12). These findings could have implications for other pain therapies, including minimally invasive interventions and surgery for spine pain (32).

Other measures and concepts have been studied and described as predictive of chronic postsurgical pain outcomes. Of these, measures of affect, catastrophizing, and neuropathic pain descriptors have gained a great deal of interest (7); however, none of these measures was retained in the best models for the outcomes analyzed, suggesting that these are at least weaker predictors of the outcomes assessed when compared to the fibromyalgia survey score. Wylde et al (7) described depression as independently predicting poorer pain status in a cross-sectional study after TKA and THA. Whereas meeting criteria for depression was predictive, the adjusted OR for depression (categorical variable) was only 1.27–1.29. By comparison, they found that the adjusted OR for having higher pain scores after arthroplasty in patients with widespread body pain (pain at $\geq$5 locations) was 11.8 for TKA and 14.8 for THA.

These data are derived from a single, academic center cohort and therefore may not be generalizable. In fact, one manner by which we know this cohort to be unusual is the low overall rate of categorical fibromyalgia; only 6% of study participants met the criteria for fibromyalgia, whereas in other osteoarthritis cohorts this is generally found to be 10–20% (33). Also, the cohort was followed up for 6 months after surgery, and it is possible that some patients may have continued to improve after that time point. There are limited data to support continued improvement after 6 months; however, there are multiple postoperative, cross-sectional studies showing a high proportion of the population with continued moderate to severe pain (6–8,10). Hence, we believe that a 6-month time point allowed for sufficient time to evaluate outcomes and also avoided additional attrition. In its favor, this study included the core components recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group (34). The retention rate was very high; however, the group lost to followup reported a worse overall pain phenotype, which could have influenced the results.

The fibromyalgia survey score was a robust predictor of poorer arthroplasty outcomes. Fibromyalgia-like features suggest the presence of augmented central nervous system pain processing and may provide a mechanistic explanation for the failure of a peripherally driven intervention in some patients.

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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. Brummett 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.

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