Knee Extensor Strength Is Associated with Pressure Pain Thresholds in Adults with Fibromyalgia

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Abstract

Objective: Individuals with fibromyalgia (FM) have lower muscle strength and lower pressure pain thresholds (PPT). The primary aim of this study was to determine the associations between muscle strength and PPT in adults with FM to test the hypothesis that greater measures of muscle strength would be associated with greater values of PPT. Secondary aims included determining the effects of pain severity and the peak uptake of oxygen (Vo2) on the associations between muscle strength and PPT.

Methods: Knee extensor and flexor strength (N = 69) was measured in the dominant leg using a dynamometer, and PPT was assessed using an electronic algometer. Pain severity was determined using the Multidimensional Pain Inventory, and peak Vo2 uptake was quantified using an electronically braked cycle ergometer.

Results: Univariable linear regression analysis demonstrated a significant association between PPT (dependent variable) and isometric knee extensor (P < .001), isokinetic (60°/s) knee extensor (P = .002), and isokinetic (60°/s) knee flexor strength (P = .043). In a multiple variable linear regression analysis adjusted for age, sex, pain severity, body mass index and peak Vo2 uptake, a significant association was found between PPT and isometric knee extensor strength (P = .008). In a similar multiple variable analysis, a significant association was found between PPT and isokinetic knee extensor strength (P = .044).

Conclusion: Greater measures of isometric and isokinetic knee extensor strength were significantly associated with greater values of PPT in both univariable and multiple variable linear regression models.

Trial Registration: ClinicalTrials.gov NCT01253395.

Introduction

Individuals with fibromyalgia (FM) have been recognized to have lower knee extensor and flexor strength [1,2,3], and lower pressure pain thresholds (PPT) [4,5,6]. In previous experimental studies, patients with FM have been observed to have lower PPT during and immediately following muscle contraction [7,9]. However, the associations between measures of muscle strength and values of PPT obtained independent of active muscle testing have not been fully investigated. Fibromyalgia is also associated with widespread pain [10] and lower levels of aerobic conditioning [11,12], both of which could potentially influence the associations between muscle strength and PPT [2,13,14].

In a previous randomized equivalence trial, measures of knee extensor and flexor strength, PPT, peak uptake of oxygen (Vo2), and pain severity were assessed in a cohort of adults with FM undergoing interdisciplinary pain treatment [15]. In this previous study, maximum voluntary isometric knee extensor, isokinetic knee extensor and isokinetic knee flexor strength were assessed using a dynamometer which provided measures of maximum voluntary strength for both the hamstring and quadriceps muscle groups. Although endurance plays an important role in muscle performance, differences in muscle endurance among adults with FM compared to controls have not been consistently reported [16,17,18,19]. However, dynamometric measures of maximum voluntary knee extensor and flexor strength have been widely used to investigate alterations in muscle strength among adults with FM despite the potential confounding effects of motivation and pain perception [3,20,21,22]. Therefore, the primary aim of this study was to determine the associations between isometric knee extensor, isokinetic knee extensor, and isokinetic knee flexor strength and PPT in adults with FM to test the hypothesis that greater measures of muscle strength would be associated with greater values of PPT. A secondary aim was to determine the influence of pain severity, as measured by the Multidimensional Pain Inventory, and peak Vo2 uptake on the associations between muscle strength and PPT. The current study represents a secondary analysis of previously published data [15].
Methods

Study Participants
The study was approved by the Mayo Foundation Institutional Review Board, and written informed consent was obtained from all study participants. All patients were recruited at admission to the 3-week outpatient interdisciplinary pain treatment program from April 2006 through February 2008. Upon admission to the interdisciplinary pain treatment program and prior to study recruitment, all patients were fully ambulatory and able to independently maintain all activities of daily living. Inclusion criteria included an established diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) 1990 diagnostic criteria [23] and age greater than 18 years. Exclusion criteria included cardiovascular (e.g., ischemic heart disease, cardiomyopathy), pulmonary (e.g., chronic obstructive pulmonary disease), orthopedic (e.g., severe osteoarthritis) or other systemic disease (e.g., rheumatoid arthritis, lupus) that could limit the assessment of knee extensor or flexor strength. Other exclusion criteria included pregnancy, and a diagnosis of schizophrenia, schizoaffective disorder, or dementia. Informed consent was obtained on the day of admission, strength testing and PPT were assessed on day 1 following admission, and peak VO₂ uptake was assessed on day 2 following admission. During the study period, 72 patients were recruited and 69 completed the baseline assessment.

Baseline demographic and clinical characteristics were collected at admission including age, gender, ethnicity, body mass index (kg/m²), employment status, pain duration, marital status, years of education, and prescription opioid use.

Determination of Morphine Equivalent Dose
At admission, the daily opioid dose of each study subject was determined by self-report and review of pharmacy records, as previously described [24,25]. The daily opioid dose was converted to daily morphine equivalents using an equianalgesic conversion software program [26] that has been used extensively at our outpatient treatment center [27,28,29].

Pressure Pain Threshold
Musculoskeletal tender points at 18 sites were identified according to ACR criteria [23] on day 1 after admission in a purpose-designated examination room located at the interdisciplinary pain treatment center. The method for assessing PPT has been previously described [15]. In brief, PPT at all 18 specified sites were measured by the same investigator (WMH) using an electronic algometer (JTECH Medical, Salt Lake City, UT, U.S.A.) fitted with a 1.0 cm diameter pressure plate. The peak pressure was applied at a constant rate of 1 kg/sec. Study participants were instructed to indicate when the pressure sensation became painful. Each site was tested 3 times in immediate succession, and the mean pressure pain threshold of each site was calculated using software designed specifically for the algometer. The mean pressure pain threshold of the 18 sites was then calculated for each patient. The interrater and intrarater reliability of this particular algometer has been shown to be 0.89 and 0.92, respectively [30]. This method of assessing pressure pain thresholds is similar to that reported by Harden et al [4].

Muscle Strength
All study participants underwent knee strength testing on day 1 after admission in a test session that was independent of the assessment of PPT. Strength testing was conducted in a purpose-designed biomechanics laboratory, as previously described [15]. Isometric knee extensor strength, isokinetic knee extensor strength, and isokinetic knee flexor strength were measured in the dominant leg of each subject using a dynamometer (Biodex Medical Systems, Shirley, NY, U.S.A.). This particular device has been shown to provide a reliable and valid measure of isometric and isokinetic strength [31,32]. Subjects were seated with a hip joint angle between 90 and 100 degrees of flexion and stabilizing straps were placed over the chest, hips and thighs [33]. The knee joint was aligned with the axis of the lever arm and the leg was attached to the lever arm just above the ankle. Each subject was familiarized with the test protocol, and a brief warm-up session was conducted prior to testing. Isokinetic strength testing was performed at a speed of 60 degrees per second (°/s) from a starting point of 90° of knee flexion. Subjects were instructed to perform maximal force voluntary contraction of knee extendors followed immediately by contraction of knee flexors in a continuous manner. For the isometric test, the lower leg position was fixed at 60° of knee flexion and subjects were instructed to perform a maximal force voluntary contraction of the knee extensors. A series of five consecutive contractions was performed for each strength measure with an intervening 1 minute rest period between series. The maximum torque production recorded from the five attempts was used for data analysis, and gravity correction was performed.

Peak Uptake of Oxygen (VO₂)
All study subjects had testing of peak aerobic capacity in a purpose-designated human physiology laboratory under the direct supervision of a physician on day 2 following admission. Oxygen uptake was measured using an incremental protocol on an electronically braked cycle ergometer [33]. After an initial 3-min stage at 25 to 50 W, the workload was increased by 10 to 25 W every minute until volitional fatigue was achieved. All subjects were encouraged by the research staff throughout the test session to give maximal effort. Peak VO₂ uptake was defined as the greatest oxygen uptake recorded during the last 30 s of exercise. Continuous monitoring of 12-lead electrocardiogram and blood pressure were performed, and expired gases were analyzed with a mass spectrometer (Perkin Elmer, Walthman, MA). The peak VO₂ uptake per kilogram was used for data analysis.

Pain Severity
Pain severity was assessed on the day of admission using the pain severity subscale of the Multidimensional Pain Inventory (MPI) [34]. This self-report questionnaire has proven reliability and construct validity [35]. The pain severity subscale is a composite measure of pain calculated from the responses to the following three questions: 1) “Rate the level of your pain at the present moment;” 2) “On average, how severe has your pain been during the last week;” and 3) “How much suffering do you experience because of your pain.” Responses to each question are scored on a 7-point Likert scale where 0 indicates no pain or suffering, and 6 indicates extreme pain or suffering. Raw scores from the pain severity subscale were converted to standardized T-scores using the means and standard deviations from a group of over 700 patients with chronic pain [36]. The standardized subscale has a mean of 50 (range 0 to 100) and a standard deviation (SD) of 10, where higher scores indicate greater pain severity. This standardized measure of clinical pain has been used previously to assess the outcomes of patients with fibromyalgia admitted to our pain treatment program [28,29].
Data Analyses

Demographics (age, sex, ethnicity, marital status, educational status, employment status) and clinical characteristics (pain duration, pain severity, frequency of opioid use, daily morphine equivalent dose) were summarized. Mean and standard deviation (SD) were reported for continuous variables, and count and proportion were reported for categorical variables.

Univariable linear regression analysis was performed with PPT as the dependent variable and measures of muscle strength (isometric knee extensor, isokinetic knee extensor, isokinetic knee flexor) as the independent variables. Multiple variable linear regression analyses were then performed and adjusted for age, sex, pain severity, BMI and peak Vo2 uptake. These demographic and clinical characteristics were included as cofactors because they have been previously associated with alterations in pain perception, physical functioning, and pain severity in patients with FM [2,12,13], and in patients admitted to our interdisciplinary treatment program [28,29,37,38,39]. The level of significance for all statistical tests was set at \( P < 0.05 \), and all analyses were completed using PAWS (IBM, Inc., Chicago, Il, Version 18.0).

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics have been summarized in Table 1. The majority of study participants were Caucasian females who were married and not currently employed. The average pain duration exceeded 12 years, and 28% of the group was using prescription opioids. The morphine equivalent dose ranged from 5 mg/day to 442 mg/day.

Associations between PPT and Muscle Strength

Table 2 contains the mean values for muscle strength, PPT, pain severity, and peak Vo2 uptake. In univariable linear regression analyses, a significant association was found between PPT (dependent variable) and isometric knee extensor (\( P < 0.001 \)), isokinetic knee extensor (\( P = 0.002 \)), and isokinetic knee flexor strength (\( P = 0.043 \)) (Table 3). Figure 1 displays a graph of the significant associations between PPT and isometric knee extensor, and isokinetic knee flexor strength.

In a multiple variable linear regression analysis adjusted for age, sex, pain severity, BMI and peak Vo2 uptake, a significant association was found between PPT (dependent variable) and isometric knee extensor strength (independent variable) \( (P = 0.008) \), where every one point (Nm) increase in isometric knee extensor strength was associated with an 13 g increase in PPT (Table 3). A significant factor in the regression model included pain severity (B coefficient = –0.061; \( P = 0.016 \)), where every one point increase in pain severity was associated with an approximate 6 g decrease in PPT.

In a similar multiple variable linear regression analysis adjusted for age, sex, pain severity, BMI and peak Vo2 uptake, a significant association was found between PPT (dependent variable) and isokinetic knee flexor strength (independent variable) \( (P = 0.577) \). Significant factors in the regression model included pain severity (B coefficient = –0.058; \( P = 0.027 \)) and sex (B coefficient = –1.7, \( P = 0.023 \)) where greater pain severity and female sex were associated with a lower PPT.

In a multiple variable linear regression analysis adjusted for age, sex, pain severity, BMI, and peak Vo2 uptake, no significant association was found between PPT (dependent variable) and isokinetic knee flexor strength (independent variable) \( (P = 0.785) \). Significant factors in the regression model included pain severity (B coefficient = –0.036; \( P = 0.547 \)) and sex (B coefficient = –2.0, \( P = 0.048 \)), where greater pain severity and female sex were associated with a lower PPT.

Discussion

The main findings of this study were that greater measures of isometric and isokinetic knee extensor strength were significantly associated with greater values of PPT in both univariable and multiple variable regression models adjusted for age, sex, opioid use, pain severity, BMI, and peak Vo2 uptake. In all multiple variable regression models, greater pain severity scores were associated with lower values of PPT, but no significant associations were observed between peak Vo2 uptake and PPT.

Previous studies have consistently found lower values of PPT, assessed using an algometer, during and up to 5 minutes following assessment of isometric knee extensor strength in patients with FM compared to healthy controls [7,8,9]. More specifically, lower values of PPT have been observed over the quadriceps and resting homologous contralateral muscle groups [40,41,42]. Dysfunction in pain inhibitory and activation of pain facilitatory mechanisms have been posited to explain, in part, lower values of PPT obtained over painful and distant non-painful muscle groups, respectively [43]. The methods used in our study were distinct from those used in previous investigations. First, the values of PPT were obtained independent of strength testing. Second, the mean PPT of the 18 ACR tender point sites [23] was used to assess pain perception compared to PPT obtained over a single muscle group. Using different methods, our findings extend the observations of previous studies and suggest that greater measures of muscle strength could influence the peripheral mechanisms implicated in the maintenance of central sensitization in patients with FM [44,45]. For example, various metabolic factors including alterations in ATP, phosphocreatine, and nitric oxide levels could lead to alterations in tissue oxygenation, and contribute to the development and maintenance of peripheral sensitization.

Table 1. Demographic and clinical characteristics.

| Characteristic                      | (N = 69) |
|-------------------------------------|----------|
| Sex (N, %)                          |          |
| Female                              | 63 (91.3)|
| Male                                | 6 (8.7) |
| Age (M ± SD)                        | 46.7 ± 10.5|
| Ethnicity (N, %)                    |          |
| Caucasian                           | 66 (95.7)|
| African American                    | 1 (1.4) |
| Hispanic                            | 1 (1.4) |
| Other                               | 1 (1.4) |
| Body mass index (kg/m²) (M ± SD)    | 30.2 ± 6.8|
| Married (N, %)                      | 46 (66.7)|
| Currently employed (N, %)           | 21 (30.4)|
| Frequency of opioid use (N, %)      | 19 (27.5)|
| Years of education (M ± SD)         | 14.9 ± 3.2|
| Pain duration, years (M ± SD)       | 12.2 ± 12.9|
| Morphine equivalent dose (mg/day)   | 89.5 ± 132.2|
However, the specific mechanisms by which greater muscle strength could effect peripheral and central sensitization have not been elucidated.

Greater pain severity was associated with lower PPT in all multiple variable models. This is consistent with previous studies where greater measures of clinical pain have been associated with lower PPT and greater tender point counts [49,50]. Furthermore, the occurrence of pain impairs muscle function due, in part, to the input of joint nociceptors on motor neurons which can reduce the capacity to activate and coordinate muscle contractions [51,52,53]. More recent findings also suggest that motor unit recruitment can be independently altered by descending inputs related to the cognitions of pain anticipation without concomitant nociceptive discharge [54]. The observations from our study suggest that the influence of muscle strength on PPT occurred independent of pain severity, which further supports the supposition that muscle strength could play an important role in peripheral sensitization among individuals with FM. However, peak Vo2 uptake was not associated with PPT. Although an association between peak Vo2 uptake and tender point counts has been reported in some, but not all studies [12,20,55,56], the effect of peak Vo2 uptake on PPT has not been widely investigated. The findings from this study suggest that peak Vo2 uptake does not have a direct effect on peripheral sensitization in FM.

The findings from this study have potential implications for the use of isometric and isokinetic knee extensor strength in ongoing clinical research and practice. First, greater isometric and isokinetic knee extensor strength was associated with lower values of PPT at a single time point in the multiple variable regression models, but further research is needed to determine if immediate changes in these measures of knee extensor strength following strength training would be predictive of greater values of PPT. Although it is not entirely clear why knee extensor but not knee flexor strength was associated with lower values of PPT, previous investigators have postulated that the greater torque generating capacity of knee extension and nociceptive input from the patello-femoral joint may be contributing factors [57,58]. Second, further research is also needed to determine if repeated assessments of isometric and isokinetic knee extensor strength over time would be a useful indicator of sustained improvements in PPT among patients engaged in maintenance strength training programs. If these lines of research prove successful, the assessment of isometric and isokinetic knee extensor strength could be a useful, noninvasive tool for investigating the immediate and long-term effects of various strength training interventions on PPT in adults with FM.

The study has limitations. Study participants were specifically referred for interdisciplinary pain treatment at a tertiary medical center, and the majority of participants were Caucasian women. Therefore, referral bias may limit the generalization of the study findings to other populations of adults with FM. However, the clinical characteristics of patients admitted to the pain program were comparable to a random sample of community pain patients from the catchment area of our medical center [59]. Similarly, the study was conducted exclusively at a specialized outpatient pain treatment center which could limit the generalization of the study observations to other ambulatory care settings. Although patients recruited for study participation were screened for underlying medical and surgical conditions that could limit the assessment of knee extensor and flexor strength, the assessment of maximal voluntary strength would not be expected to identify individual patients who may have had unrecognized muscle dysfunction due, in part, to reduced muscle mass or abnormal strength production capacity. However, the mean maximal voluntary strength values

**Table 2.** Mean values of pressure pain threshold, muscle strength, peak Vo2 uptake, and pain severity.

| Variable                        | (N = 69)         |
|---------------------------------|------------------|
| Pressure pain threshold (kg)    | 4.5±1.8          |
| Isometric knee extensor (Nm)    | 130.7±45.0       |
| Isokinetic knee extensor 60/s (Nm) | 92.9±40.3     |
| Isokinetic knee flexor 60/s (Nm) | 53.7±23.0       |
| Pain severity*                 | 47.7±8.2         |
| Peak Vo2 uptake (ml/kg/min)     | 16.5±4.2         |

*pain severity subscale of the Multidimensional Pain Inventor.

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and replication of our results in other muscle groups would further widespread changes in PPT that occur in patients with FM. Lastly, point sites should be a more representative measure of the specific body region. Therefore, the PPT from the 18 FM tender reductions in PPT as opposed to lower PPT localized to any one lower extremity region. The PPT of the 18 FM tender point sites not measured. The mean PPT of the 18 FM tender point sites was used rather than a measure of PPT derived from the knee or other body region. The PPT from the 18 FM tender point sites should be a more representative measure of the widespread changes in PPT that occur in patients with FM. Lastly, the strength of the quadriceps and hamstring groups was tested, and replication of our results in other muscle groups would further verify the observed associations between muscle strength and PPT.

The findings reported herein extend the results of previous experimental studies and suggest that greater isometric and isokinetic knee extensor strength were associated with greater values of PPT in both univariable and multiple variable linear regression analyses. Ongoing research is needed to further elucidate the immediate and long-term clinical effects of strength training on values of PPT in adults with FM.

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Author Contributions

Conceived and designed the experiments: WMH WQ. Performed the experiments: WMH. Analyzed the data: WMH CJR JSE. Contributed reagents/materials/analysis tools: WMH. Wrote the paper: WMH CJR JSE WQ.

of our cohort were comparable to mean normative values for women age 30 to 50 years where isokinetic knee extensor, isokinetic knee extensor (60°/s) and isokinetic knee flexor (60°/s) strength have been reported to range from 123–147 Nm, 99–113 Nm, and 66–93 Nm, respectively [60,61,62,63]. Although peak VO₂ uptake was assessed using an incremental protocol on an electronically braked cycle ergometer, other physiological measures of peak aerobic capacity, including maximal heart rate, were not correlated with muscle strength, and serum lactate levels were not measured. The mean PPT of the 18 FM tender point sites was used rather than a measure of PPT derived from the knee or other lower extremity region. The PPT of the 18 FM tender point sites was used because FM is clinically characterized by widespread reductions in PPT as opposed to lower PPT localized to any one specific body region. Therefore, the PPT from the 18 FM tender point sites should be a more representative measure of the widespread changes in PPT that occur in patients with FM. Lastly, the strength of the quadriceps and hamstring groups was tested, and replication of our results in other muscle groups would further verify the observed associations between muscle strength and PPT.

Table 3. Linear regression analyses with pressure pain threshold as the dependent variable.

| Variable | B coefficient univariable analysis (95% CI) | P Value | B coefficient multiple variable analysis (95% CI)* | P Value |
|----------|---------------------------------------------|---------|--------------------------------------------------|---------|
| Isometric knee extensor | .018 (.009 to .027) | <.001 | .015 (.004 to .026) | .008 |
| Isokinetic knee extensor 60°/s | .017 (.006 to .027) | .002 | .012 (.000 to .024) | .044 |
| Isokinetic knee flexor 60°/s | .020 (.010 to .039) | .043 | .006 (−.016 to .028) | .577 |

*adjusted for age, sex, pain severity, BMI and peak VO₂ uptake.

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