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Patients with Fibromyalgia Have Significant Autonomic Symptoms but Modest Autonomic Dysfunction

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Abstract

Background—Research suggests that disordered autonomic function may be one contributor to deconditioning reported in fibromyalgia, however no study to date has simultaneously assessed these variables utilizing comprehensive measures.

Objective—To characterize physical fitness and autonomic function using clinically validated measures and subjective questionnaires between patients with fibromyalgia and healthy controls.

Design—Cross-sectional, observational, controlled study

Setting—Community sample of patients with fibromyalgia and healthy controls

Participants—30 patients with fibromyalgia and 30 pain and fatigue-free controls
Methods: Participants completed a battery of self-report questionnaires and physiological measures including clinically validated measures of physical fitness and autonomic function.

Main Outcome Measurements—6 Minute Walk Test total distance, VO₂ max as assessed by cardiopulmonary exercise testing, total steps using activity monitor, Composite Autonomic Scoring Scale as assessed by Autonomic Reflex Screen, total metabolic equivalents per week using the International Physical Activity Questionnaire and self-reported autonomic symptoms using the 31-item Composite Autonomic Symptom Score questionnaire.

Results—Autonomic function, as assessed by self-report, was significantly different between patients and controls ($p < .0001$); in contrast, the only difference between patients and controls on the Autonomic Reflex Screen was in the adrenergic domain ($p = .022$), and these abnormalities

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were mild. Self-reported physical activity was not significantly different between patients and controls ($p=.99$), but levels of moderate and vigorous physical activity as measured by actigraphy, were significantly lower in patients ($p=.012$ and $p=.047$, respectively). Exercise capacity (6 Minute Walk) was poorer in patients ($p=.0006$), but there was no significant difference in maximal volume of oxygen consumption ($p=.07$).

Conclusions—Patients with fibromyalgia report more severe symptoms across all domains including physical activity and autonomic symptoms when compared to controls, but the objective assessments only showed modest differences. Our results suggest that patients with widespread subjective impairment of function have only modest objective measures of autonomic dysfunction. We recommend that the primary treatment goal should be focused on restoration of function which may also ameliorate symptoms.

Introduction

Fibromyalgia is a complex disorder characterized by chronic widespread pain, fatigue, and other associated symptoms (i.e., unrefreshing sleep, negative mood, and cognitive difficulties). Fibromyalgia is currently diagnosed based on subjective symptoms; there is no objective biomarker. In addition to these characteristic symptoms, patients with fibromyalgia also report a multitude of autonomic symptoms, including lightheadedness, palpitations, sensitivity to light and sounds, and gastrointestinal symptoms.^{1–3} As a result of all these symptoms, patients with fibromyalgia engage in more sedentary behavior, which may predispose them to be deconditioned.⁴ Objective studies evaluating autonomic function and physical activity suggest deficiencies in patients with fibromyalgia. Whether disordered autonomic function drives the physical inactivity, or whether it is physical deconditioning and chronic pain that results in disordered autonomic function, is currently unclear.

Studies of physical activity suggest that patients with fibromyalgia tend to predominantly engage in light physical activity, spend more time in sedentariness than healthy controls and are likely physically deconditioned.^{4–7} For example, using actigraphy, one study reported that although overall activity levels in patients with fibromyalgia did not differ from controls, patients with fibromyalgia engaged in less high-intensity physical activities.⁵ Another study reported that patients with fibromyalgia were, on average, sedentary 10 hours per day, or approximately 71% of their waking time.⁶ In regards to degree of deconditioning, one study reported that while patients with fibromyalgia had similar metabolic and cardiovascular responses to exercise as healthy controls, those with fibromyalgia had a reduced ability to reach the point of maximal oxygen consumption (VO_{2max}) and were insufficiently able to exercise above anaerobic threshold.⁷

Disordered autonomic function has been suggested as a possible mechanism for poor aerobic capacity in patients with fibromyalgia.⁸ In this study, impaired chronotropic reserve and delayed heart rate recovery with exercise, which is suggestive of dysautonomia, was thought to be responsible for the observed poor aerobic capacity. Other studies have also indicated disordered autonomic function in patients with fibromyalgia. In one study, patients with fibromyalgia had an increase in central cardiovascular sympathetic activity while recumbent and blunted sympathetic activity when upright when compared to controls⁹,

suggesting deficiencies in adrenergic function. Similarly, two other studies demonstrate altered autonomic responsiveness as assessed by heart rate variability parameters following acute resistance exercise¹⁰ and attenuated adrenergic response to repetitive isometric exercise.¹¹ More recently it was proposed that impaired neuroeffector mechanisms may initiate and perpetuate pain, physical deconditioning, and disordered autonomic function in patients with fibromyalgia.¹² Overall, these studies suggest some degree of autonomic dysfunction in fibromyalgia and that this dysfunction could be related to the decreased aerobic capacity commonly observed in patients with fibromyalgia.

Although there is preliminary support of the presence of deconditioning and impaired autonomic function in patients with fibromyalgia, no research has evaluated both of these variables using clinically validated tests in the same sample of patients with fibromyalgia. Our objective was to comprehensively characterize and compare subjective and objective measures of physical activity, physical fitness, and autonomic function using clinically validated measures in a well characterized sample of patients with fibromyalgia and healthy controls.

Methods

Study Design

We conducted a cross-sectional study of patients with fibromyalgia and healthy controls. This study was approved by the Institutional Review Board of the authors and all participants provided written informed consent. All participants were paid \$150 upon completion of study procedures.

Study Population

The study population consisted of women with fibromyalgia identified from an existing cohort of residents of Olmsted County¹³ and surrounding areas and pain- and fatigue-free controls. All data for this study were collected between 1/1/2012 – 6/31/2013.

Patients—The process of identifying Olmsted County residents with a diagnosis of fibromyalgia using the Rochester Epidemiology Project (REP) has been previously described.¹³ The Olmsted County cohort used in this study is composed of patients diagnosed with fibromyalgia by a medical provider in Olmsted County between 1/1/2005 and 12/31/2009. Patients meeting eligibility criteria were sent a letter of invitation to participate.

Controls—Healthy, pain- and fatigue-free controls were also identified using the REP and through local advertising. Potential controls were screened via medical record review to determine eligibility. Those meeting eligibility criteria were invited to participate.

Inclusion/Exclusion Criteria

All participants had a screening visit to ensure they met eligibility criteria. Exclusion criteria included uncontrolled diabetes, congestive heart failure, cardiac arrhythmias, chronic pulmonary disease, serious neurological illness, psychiatric disorders other than anxiety and

depression, chronic kidney or liver disease, pregnancy in last 12 months, current anemia, uncontrolled hypo or hyperthyroidism, uncontrolled hypertension, cancer within 5 years other than skin cancer, current chemotherapy, substance abuse problems in the last 2 years, anorexia or bulimia within the last 5 years, body mass index (BMI) ≥ 40 , or age < 18 or > 60 . Inclusion criteria were diagnosis of fibromyalgia (except controls, confirmed by a physician) and ability to speak and read English.

Additionally, for the cardiopulmonary exercise portion of the study, patients with conditions that placed them at risk for adverse reactions (including hypertension, asthma, and severe hip osteoarthritis) were excluded ($n=12$ patients, $n=2$ controls).

Testing and Measures

Physical Activity, Physical Fitness, and Autonomic Measures—Participants completed a battery of questionnaires and physiological tests. These included: International Physical Activity Questionnaire (IPAQ), Composite Autonomic Symptom Score (COMPASS-31), accelerometer to quantify physical activity, energy expenditure and sleep quality, 6 minute walk test, cardiopulmonary exercise testing on a recumbent bike, and autonomic reflex screen.

International Physical Activity Questionnaire (IPAQ)—The IPAQ is 27-item questionnaire that assesses type (i.e., work-related, housework, transportation, and recreation) and intensity (walking, moderate, and vigorous) of daily activities.¹⁴ The IPAQ also yields a total score that summarizes total metabolic equivalents (METs) per week. It has an internal consistency of 0.81.¹⁴

Accelerometer—Participants each wore a SenseWear Pro ArmBand (Body Media Fit, BodyMedia, Pittsburgh, PA) for 5 days to quantify active energy expenditure, activity time and type (light, moderate, vigorous), sedentary time, and sleep efficiency (percent of time asleep when lying down). The activity monitor recorded data from a 2-axis micro-electromechanical accelerometer, a galvanic skin resistance sensor, a heat flux sensor, a skin temperature sensor, and a near-body ambient temperature sensor. Data from the device were downloaded to a dedicated software package (InnerView Research Software v.2.2, BodyMedia, Pittsburgh, PA) for analysis.

6 Minute Walk Test (6MWT)—Participants each completed a 6MWT according to the American Thoracic Society guidelines.¹⁵ Testing was conducted in 67-foot corridor on a flat, firm surface. Heart rate, blood pressure, fatigue, and dyspnea were assessed prior to, immediately after, and every two minutes following the test for 10 minutes.

Cardiopulmonary Exercise Testing (CPET)—Participants underwent a CPET for measurement of maximal oxygen consumption and exercise recovery rates. Using an electronically braked recumbent bike, participants exercised while the workload was incrementally increased until participants achieved a VO_2 max or became too tired to continue. Heart rate was measured throughout the test using a 12-lead ECG and continuous blood pressures were also measured using a Finometer. At the completion of the test, participants engaged in an active 10-minute cool-down during which time heart rate and

blood pressure were recorded at two-minute intervals to allow for assessment of recovery. All participants were asked to abstain from caffeine, alcohol, and vigorous physical activity for 24 hours prior to the test, and avoid eating 3 hours prior to the test. In order to evaluate potential changes in pain after the CPET, patients and controls who completed the CPET were also asked to rate any changes in their pain 1 and 2 days following the test.

Chronotropic reserve was calculated as maximum heart rate achieved – heart rate at baseline, divided by predicted maximum heart rate (220-age) –heart rate at baseline, multiplied by 100.⁸ Heart rate recovery was calculated as the difference between the maximum heart rate achieved and recovery heart rate at 2, 4, 6, 8, and 10 minutes following the CPET.

Composite Autonomic Symptom Score-31 (COMPASS-31)—The COMPASS-31 was used for the subjective assessment of autonomic symptoms.¹⁶ The COMPASS-31 is a 31 item self-report questionnaire that assesses patient-reported autonomic symptoms across six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor. Total scores range from 0–100, with higher scores indicating worse self-reported autonomic symptoms. The COMPASS-31 has been previously reported in patients with fibromyalgia.^{2,3}

Autonomic Reflex Screen (ARS)—Autonomic function was objectively assessed using the ARS. The ARS is a clinically validated measure of autonomic function and includes quantitative sudomotor axon reflex test (QSART), heart rate response to deep breathing, heart rate and blood pressure responses to the Valsalva maneuver, and assessment of heart rate and orthostatic blood pressure response to postural tilt.¹⁷ Patients were instructed to hold anticholinergic medications, antidepressant, antihistamine and over-the-counter cough and cold medication, 9-a-fludrocortisone, diuretics, sympathomimetic (α - and β -agonists), and parasympathomimetic agents (which could interfere with the test results) for 24 hours prior to the test. A 10-point Composite Autonomic Scoring Scale (CASS) was generated from the results of the ARS, which takes into account participant age and sex. A CASS score 3 indicates no or mild autonomic failure, scores from 4 to 6 indicate moderate autonomic failure, and scores from 7 to 10 indicate severe autonomic failure.^{18,19} Baroreflex sensitivity and postural response to tilt were also computed.¹⁸

Testing and Measures

Additional Variables—Patients also completed an assessment of body composition. Percent body fat and index of fat distribution was assessed using a GE Lunar iDXA dual-energy x-ray absorptiometer (GE Healthcare, Madison, WI). For the testing, subjects wore a lightweight hospital gown and were asked to remove any jewelry or metal items. Participants who were not post-menopausal and had not undergone a hysterectomy completed a urine pregnancy screen prior to testing. As completion of a DXA scan was added as a mid-study modification, it was only available on n=19 patients. All controls completed a DXA scan. Percent body fat was calculated as weight of fat in grams divided by total body weight multiplied by 100. Index of fat distribution is the ratio of fat in legs to total body fat.

In addition to the above measures, patients also completed a battery of questionnaires that assessed common fibromyalgia symptoms including Brief Pain Inventory (BPI) (pain), Multidimensional Fatigue Inventory (MFI-20) (fatigue), Center for Epidemiologic Studies Depression Scale (CES-D) (depression), Generalized Anxiety Disorder questionnaire (GAD-7) (anxiety), Medical Outcomes Study Sleep questionnaire (MOS-Sleep) (sleep quality), Fibromyalgia Impact Questionnaire-Revised (FIQ-R) (fibromyalgia symptom severity), and Short Form 36 (SF-36) (overall physical and mental health).

Brief Pain Inventory (BPI)—The BPI is a 15-item, validated self-report measure of chronic, non-cancer pain and assesses presence of pain, pain severity, and pain interference.²⁰ Scores on the pain severity subscale range from 0–10, with higher scores indicating greater pain. The BPI is considered a valid and reliable measure of pain in fibromyalgia and has an internal consistency of 0.85.²¹

Multidimensional Fatigue Inventory (MFI-20)—The MFI-20 is a 20-item validated self-report measure of fatigue and assesses general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.²² Scores range from 20–100, with higher scores indicating greater fatigue. It is considered a valid and reliable measure of fatigue in fibromyalgia.^{23,24}

Center for Epidemiological Studies – Depression Scale (CES-D)—The CES-D is a widely used, 20-item validated questionnaire that measures the presence and severity of symptoms of depression.²⁵ Scores range from 0–60, with higher scores indicating more severe symptoms. The CES-D is considered a valid and reliable measure of depression in fibromyalgia and has an internal consistency of 0.85 in community samples and 0.90 in psychiatric samples.²⁵

Generalized Anxiety Disorder questionnaire (GAD-7)—The GAD-7 is a 7 item validated self-report questionnaire that measures presence and severity of symptoms of anxiety.²⁶ Scores range from 0–21, with higher scores indicating more severe symptoms. The GAD-7 has been used in multiple samples of patients with fibromyalgia as well as community samples has an internal consistency of 0.92.^{27,28}

Medical Outcomes Study Sleep Scale (MOS-Sleep)—The MOS-Sleep is a 12-item, validated, self-report measure that assesses 6 dimensions of sleep: 1) sleep disturbance, 2) sleep adequacy, 3) sleep quantity, 4) somnolence, 5) snoring, and 6) awakening with shortness of breath or headache.²⁹ The Sleep Problems Index II is a 9 item summary score capturing these dimensions. Scores on the sleep problems index II range from 0–100, with higher scores indicating poorer sleep. The MOS is considered a valid and reliable measure of sleep in fibromyalgia and has an internal consistency of 0.7 in patients with fibromyalgia.³⁰

Fibromyalgia Impact Questionnaire – Revised (FIQ-R)—The FIQ-R is a 21-item, validated self-report measure that assesses symptoms, physical functioning, and overall impact of fibromyalgia.^{31,32} Total scores on the FIQ-R range from 0–100, with higher scores indicating more severe fibromyalgia. The FIQ-R is the most widely used measure of

fibromyalgia symptom severity in fibromyalgia research studies.²⁴ This questionnaire was not completed by controls.

Short Form-36 (SF-36)—The SF-36 version 2.0 is a 36-item, validated self-report measure that assesses disease burden.^{33,34} It consists of 8 subscales and 2 summary scores: physical and mental component. Scores range from 0–100, with higher scores indicating better health. The SF-36 has been widely utilized in fibromyalgia.³⁵

To further characterize our sample, information regarding a selected list of comorbidities commonly associated with fibromyalgia that were not exclusionary conditions (headaches/migraines, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's, temporomandibular joint disorder, plantar fasciitis, interstitial cystitis, endometriosis, irritable bowel syndrome, gastroesophageal reflux disease, hypothyroidism, hypertension, peripheral neuropathy, autonomic disorders, insomnia, obstructive sleep apnea, restless legs/periodic limb movement disorder, anxiety, depression, and dysthymia) were also abstracted by chart review.

Data Analysis

Descriptive statistics (mean, standard deviation, and percent) were used to characterize the sample based on demographic characteristics, medical and psychiatric comorbidities, and self-report questionnaire scores. Demographic characteristics (age, race, ethnicity, BMI, and body fat percentage) were compared between patients and controls using two sample t-tests. Due to the significant difference in age between patients and controls, for all subsequent by group comparisons, both unadjusted (two sample t-test for continuous variables or chi square for categorical variables) and adjusted (multiple linear regression for continuous variables or logistic regression for categorical variables) analyses are reported. Pearson's correlation was used to evaluate the association between select measures of autonomic function (COMPASS-31 total, CASS domain and total scores) and physical fitness (6MWT total distance, VO2 max, mean steps).

Results

Thirty patients and thirty healthy controls were enrolled. Although our goal was to match patients and controls by age, a 1-to-1 match was not possible, and therefore we attempted to recruit controls with ages as close as possible to patients. Despite our efforts, there was a small but significant difference between patients and controls in regard to age (Table 1); therefore age was included as a covariate in all subsequent analyses. There were no significant differences between patients and control in regard to race, ethnicity, BMI, or body fat percentage. As expected, SF-36 physical and mental composite scores were lower, while BPI, MFI, MOS-Sleep, CES-D, and GAD-7 were significantly higher in patients than controls ($p < .01$) (Table 1). A higher proportion of patients had headaches, osteoarthritis, GERD, insomnia, RLS/PLMD, and depression when compared to controls (Table 2).

Autonomic symptoms, as assessed by self-report, were significantly different between patients and controls on all 6 domains of the COMPASS-31 (Table 3). In contrast, autonomic function as assessed by ARS was only different between patients and controls on

the adrenergic domain and all abnormalities fell within the mild category. Overall, 45% of patients and 67% of controls showed no evidence of autonomic dysfunction based on their CASS while mild abnormalities were present in 45% of patients and 33% controls. Only 3 patients (10%) showed moderate abnormality and no patients or controls showed severe abnormality. In regard to the adrenergic domain, there was a modest but significant difference between patients and controls ($p=.023$). The changes are likely modest since baroreflex sensitivity was intact ($ps>.17$). There was no correlation between self-report autonomic symptoms and CASS score in patients ($r = -0.0006$, $p = .997$).

Comparison of physical activity assessments between patients and controls revealed that patients reported significantly less vigorous activity conducted for leisure (IPAQ) ($p=.0002$), but did not differ in total METs per week ($p=.74$). In contrast, significant differences were noted in multiple domains of physical activity as measured by the accelerometer. Patients had significantly lower total energy expenditure ($p=.0174$), physical activity level ($p=.0074$), active energy expenditure ($p=.0029$), total number of steps ($p<.0001$), moderate activity time ($p=.0148$), and vigorous activity time ($p=.0467$) than controls. There were no significant differences in sedentary or light activity time or resting metabolic rate (all $ps>.15$).

Physical fitness as assessed by the 6MWT showed a statistically significant difference between patients and controls in regard to total distance covered (m) ($p=.0006$) (Table 4). Although mean VO2 max (mL/kg/min) did not significantly differ between patients and controls, there was a trend toward a lower VO2 max in patients ($p=.07$). Other CPET measures are summarized in Table 4. We found no difference in chronotropic reserve or heart rate recovery, except at two minutes, between patients and controls. Assessment of pain on day 1 and day 2 following CPET was not significantly different between patients and controls and only 1 patient reported worsening of pain following CPET. Patients did report significantly more fatigue both prior to and after the 6MWT, but when the post fatigue score was corrected for the baseline fatigue rating, scores were not significantly different between the two groups ($p=.19$). VO2 max was moderately correlated with total distance in the 6MWT ($r = .502$, $p=.0336$) among fibromyalgia patients. There was no correlation between self-report physical activity as measured by the IPAQ and 6MWT total distance ($r = -0.0206$, $p = .917$) while IPAQ and VO2 max showed a modest but not statistically significant correlation ($r = 0.4246$, $p = .0893$).

Assessment of correlation between autonomic function and physical fitness in patients demonstrated no significant correlations between objective physical fitness measures (6MWT, VO2 max, mean steps) and CASS total with correlation values of $r = -0.20$, $r = -0.18$, and $r = 0.06$, respectively. However, the CASS cardiovagal score was moderately correlated with both the 6MWT ($r = -0.44$, $p = 0.02$) and VO2 max ($r = -0.43$, $p = 0.07$).

Discussion

The main result of our study is that patients with fibromyalgia have widespread autonomic symptoms and significant impairment of physical activity, but with only modest autonomic dysfunction and deconditioning. Patients with fibromyalgia self-report a higher degree of symptoms across all domains when compared to controls. As expected, a substantially

higher proportion of medical and psychiatric comorbidities were observed in patients with fibromyalgia. Although patients and controls showed differences on some objective measures of physical activity and fitness and autonomic function, these differences were not uniform and were generally not of the same magnitude as the differences found in subjective measures.

Further, objective measures did not correlate with subjective measures. The findings with respect to subjective measures and comorbidities are well established and not surprising. This study however is the first to utilize clinically validated measures of physical fitness and autonomic function simultaneously for comparison between patients and controls and to the subjective measures.

This is the first study to evaluate autonomic function using the clinically validated autonomic reflex screen in fibromyalgia. Previous studies using the COMPASS, a validated self-report autonomic questionnaire, suggest that patients with fibromyalgia report autonomic symptoms across all autonomic domains¹⁻³, and our data in this study were consistent with these reports. Objective assessment of autonomic function in fibromyalgia has previously largely relied on the use of heart rate variability (HRV) measurements. A recent systematic review of HRV and fibromyalgia report that autonomic activity is altered in fibromyalgia, specifically, patients with fibromyalgia have reduced parasympathetic and increased sympathetic activity.³⁶ The review also cautioned against the effect of potential confounders in the measurement of HRV, including cardiac disorders, activity level of participants, testing conditions such as breathing rate and frequency, and use of medications. In contrast to HRV, ARS is a clinically validated measure done under standardized, reproducible conditions and is used in the diagnosis of autonomic disorders.^{18,19}

We observed moderate abnormalities on the CASS in 10% of patients but in none of the controls, although this difference did not reach the level of statistical significance. This may be reflective of sample size as the study was not powered to detect difference on the CASS total. A larger sample size will provide more insight into the possible presence of autonomic abnormalities in patients with fibromyalgia. Yet, our data suggest that a majority of fibromyalgia patients have no or only mild autonomic abnormalities as measured by CASS. The lack of consistency between the COMPASS-31 and CASS suggests that patient-reported autonomic symptoms may reflect somatic hypervigilance, rather than biological autonomic dysfunction. This is unlike correlations between COMPASS and CASS reported in samples of patients with autonomic disorders such as peripheral neuropathy, in which the two measures correlate very strongly.³⁷

Similarly, we found that the majority of fibromyalgia patients were not markedly deconditioned, as measured by the VO2 max. Despite the high level of symptoms reported by patients, all patients who participated in the CPET were able to complete the test and achieve an RER greater than 1.12, indicating adequate effort. It should be noted that despite adequate effort, there was a trend toward poorer maximal VO2 in patients when compared to controls, indicating some level of deconditioning. In addition, more patients than controls were excluded from testing due to comorbidities, and a clearer difference between patients and controls may have been apparent if all patients had been able to participate. In contrast

to the CPET testing, physical activity measures from the 6MWT and accelerometer showed that patients engaged in greater sedentariness and spent less time in vigorous physical activity as compared to controls. It should be noted that both 6MWT and accelerometry in this study were more effort dependent whereas with CPET, patients were encouraged and supported to achieve maximum effort. Our sample of patients and controls had similar BMI and body composition, so differences in physical activity and physical fitness are likely not due to these factors. Since patients reported significantly greater depression and anxiety, this may have influenced the degree of motivation and engagement in physical activity. Another factor that may be responsible for less engagement in vigorous physical activity is fear avoidance, which has been suggested by previous studies.^{38,39}

Regarding the suggested relationship between physical activity and autonomic dysfunction in fibromyalgia, our observation only suggested a moderate correlation between CASS cardiovagal score with VO2 max and with 6MWT. This is not surprising given the relationship between cardiovagal function and aerobic capacity. However, the fact that the majority of patients did not have markedly abnormal scores on CASS or on VO2 max suggests that the pervasive problem of inactivity of fibromyalgia is not primarily driven by autonomic dysfunction. Patients may be afraid to exercise due to pain exacerbation, although we did not observe significant increases in pain following VO2 testing in patients or controls.

In this prospective clinical study, we sought to perform a comprehensive assessment of both autonomic function and physical activity measures by both self-report and objective tests in patients with fibromyalgia. Use of clinically validated tests for assessment of autonomic function and physical activity is a strength, as is the use of both subjective and objective assessment methods for similar variables. Inclusion of healthy controls allowed us to compare self-report and objective measures between patients and controls at the same time and under similar testing conditions.

The main findings of the present study is reminiscent of prospective studies in postural orthostatic tachycardia syndrome, another condition associated with orthostatic intolerance and widespread autonomic symptoms, and has implications for design of treatment for fibromyalgia. These studies demonstrated that there was a discordance between symptoms and deficits.^{40,41} Patients improved in their functional status with treatment and time, but continued to have symptoms. The implication is that therapy for fibromyalgia should focus on measurable indices of function rather than on symptoms alone.

Our study has several limitations. First, we had a fairly small sample size, which may have limited our ability to detect difference between patients and controls. A large number of comparisons were performed between patients and controls, and we chose not to adjust for multiple comparisons due to already limited power provided by the small sample size and also our desire not to miss potential differences in objective measures between patients and controls since generally we found few differences in this regard. Because of the large number of significance tests, p-values should be interpreted with some caution and effect sizes examined for clinical significance. Second, our patient sample was composed of patients with moderate fibromyalgia severity (based on a mean FIQ-R score of 43), which

may influenced our results and the generalizability of our findings. Third, as we had a small sample size and little is known about the symptom experience of males with fibromyalgia, males were not included in this study. Therefore, we are unable to comment on physical activity and autonomic parameters in males with fibromyalgia.

Conclusion

Although patients with fibromyalgia report a high degree of symptoms across all domains, objective measures of autonomic function only showed a modest difference in adrenergic indices in our sample. In regard to assessments of objective physical activity, our sample of patients tended to be more sedentary when compared to controls. Our results suggest that clinically significant levels of autonomic dysfunction may not be present in patients with fibromyalgia with moderate symptom severity.

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Study data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic (UL1 TR000135). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

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Figure 1.

Table 1

Demographic and descriptive characteristics and comparison of self-report questionnaires between patients and controls.

Variable	<i>M(SD) or n[%]</i>		<i>p</i>	<i>p</i> (adjusted)*
	Patients	Controls		
Age (years)	47.0 (10.4)	41.1 (8.4)	.019	
Race (White) (n [%])	39 [96.7]	28 [93.3]	.25	.39
Ethnicity (Hispanic) (n [%])	0 [0]	1 [3.5]	.28	.27
BMI (kg/m ²)	25.8 (4.6)	26.0 (4.0)	.81	.47
No. of Tenderpoints	14.2 (3.2)	0.9 (1.8)	<.0001	<.0001
Percent Body Fat	37.5 (7.4)	35.5 (7.6)	.37	.94
Index of Fat Distribution	40.5 (7.3)	38.3 (5.8)	.26	.11
<i>SF-36</i>				
Physical Composite	36.8 (8.1)	57.4 (2.4)	<.0001	<.0001
Mental Composite	46.2 (7.1)	53.8 (6.7)	.0005	.0022
<i>FIQ-R</i>				
Function	10.0 (5.9)	NA		
Impact	8.5 (5.0)	NA		
Symptoms	25.1 (6.8)	NA		
Total	43.6 (14.7)	NA		
<i>BPI</i>				
Pain Severity	4.0 (1.5)	0.3 (0.5)	<.0001	<.0001
Pain Interference	4.6 (2.0)	0.2 (0.5)	<.0001	<.0001
<i>MFI</i>				
General	16.8 (2.8)	7.8 (2.5)	<.0001	<.0001
Physical	14.0 (3.6)	7.3 (3.3)	<.0001	<.0001
Mental	13.2 (4.2)	6.5 (3.0)	<.0001	<.0001
Reduced Motivation	10.9 (3.2)	6.3 (2.1)	<.0001	<.0001
Reduced Activity	12.5 (3.6)	5.3 (2.0)	<.0001	<.0001
Total Score	67.3 (14.1)	33.2 (10.4)	<.0001	<.0001
<i>MOS Sleep</i>				
Sleep Problems Index II	52.2 (15.2)	21.4 (15.0)	<.0001	<.0001

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Variable	<i>M(SD) or n[%]</i>		<i>p</i>	<i>p</i> <i>(adjusted)*</i>
	Patients	Controls		
<i>CES-D</i>	14.0 (7.6)	4.2 (6.0)	<.0001	<.0001
<i>GAD-7</i>	5.3 (4.3)	1.6 (3.3)	.0007	.0014

* multiple linear regression or logistic regression for categorical variables p-value adjusted for age

Table 2

Comparison of medical and psychiatric comorbidities and selected laboratory assessments of patients and controls.

Variable	N [%]		p	p (adjusted)*
	Patients	Controls		
Medical Comorbidities (n [%])				
Headaches/migraines	16 [53.3]	5 [16.7]	.0029	.0073
Osteoarthritis	6 [20.0]	0 [0]	.0098	.0117
Rheumatologic Conditions /	0 [0]	0 [0]	NA	NA
Temporomandibular joint disorder	2 [6.7]	0 [0]	.15	.14
Plantar fasciitis	1 [3.3]	1 [3.3]	1	.67
Interstitial cystitis	0 [0]	0 [0]	NA	NA
Endometriosis	1 [3.3]	0 [0]	.31	.27
Irritable bowel syndrome	4 [13.3]	1 [3.3]	.16	.18
Gastroesophageal reflux disease	10 [33.3]	1 [3.3]	.0027	.0088
Hypothyroidism	5 [16.7]	7 [23.3]	.52	.37
Hypertension	3 [10.0]	2 [6.7]	.64	.92
Peripheral neuropathy	1 [3.3]	0 [0]	.31	.58
Autonomic disorders	2 [6.7]	0 [0]	.15	.11
Insomnia	11 [36.7]	0 [0]	.0002	.0001
Obstructive sleep apnea	2 [6.7]	0 [0]	.15	.22
Restless legs/periodic limb movement disorder	5 [16.7]	0 [0]	.0195	.0135
Psychiatric Comorbidities (n [%])				
Anxiety	9 [30.0]	4 [13.3]	.12	.09
Depression	20 [66.7]	10 [33.3]	.0098	.0178
Dysthymia	5 [16.7]	1 [3.3]	.09	.17

[†] Rheumatic Conditions included rheumatoid arthritis, systemic lupus erythematosus, Sjögren's

* multiple linear regression or logistic regression for categorical variables p-value adjusted for age

Table 3

Comparison of COMPASS-31 and ARS between patients and controls.

Variable	M(SD)			
	Patients	Controls	p	p (adjusted) *
COMPASS 31				
Orthostatic Intolerance	9.2 (8.5)	2.9 (6.4)	.0020	.0008
Vasomotor	0.8 (1.3)	0.1 (0.3)	.0019	.0023
Secretomotor	4.9 (3.2)	1.1 (2.4)	<.0001	<.0001
Gastrointestinal	8.4 (4.4)	3.1 (2.7)	<.0001	<.0001
Bladder	1.8 (1.6)	0.5 (0.9)	.0003	.0044
Pupillomotor	2.4 (1.1)	1.2 (0.8)	<.0001	<.0001
COMPASS 31 Total	27.5 (14.2)	8.9 (8.7)	<.0001	<.0001
Autonomic Reflex Screen				
CASS Sudomotor			.20	.36
No Problem	16 [55.2]	22 [73.3]		
Mild	13 [44.8]	8 [26.7]		
Moderate	0 [0]	0 [0]		
Severe	0 [0]	0 [0]		
CASS Cardiovagal			.07	.14
No Problem	21 [72.4]	27 [90.0]		
Mild	8 [29.6]	3 [10.0]		
Moderate	0 [0]	0 [0]		
Severe	0 [0]	0 [0]		
CASS Adrenergic			.025	.023
No Problem	24 [82.8]	30 [100]		
Mild	5 [17.2]	0 [0]		
Moderate	0 [0]	0 [0]		
Severe	0 [0]	0 [0]		
CASS Total			.05	.10
No Problem	13 [44.8]	20 [66.7]		
Mild	13 [44.8]	10 [33.3]		

Variable	<i>M(SD)</i>		<i>p</i>	<i>p (adjusted) *</i>
	Patients	Controls		
Moderate	3 [10.3]	0 [0]		
Severe	0 [0]	0 [0]		
Baroreflex Sensitivity Down	4.52 (2.19)	5.55 (2.94)	.14	.17
Baroreflex Sensitivity Up	5.82 (2.19)	6.50 (2.82)	.32	.65
Postural Response to Tilt	2.10 (1.12)	1.79 (0.84)	.23	.53

* multiple linear regression or logistic regression for categorical variables p-value adjusted for age

Table 4

Comparison of physical activity assessments between patients and controls.

Variable	M(SD)		p	p (adjusted)*
IPAQ (METs)				
Work – Vigorous Activity	1191.4 (3264.3)	869.3 (2714.6)	.68	.29
Work – Moderate Activity	1560.0 (2580.1)	1395.3 (3418.5)	.84	.83
Work – Walking	823.8 (2003.1)	1439.9 (3330.1)	.40	.65
Transportation – Cycling	6.4 (34.0)	8.0 (43.8)	.88	.79
Transportation – Walking	397.2 (611.4)	752.4 (1362.3)	.21	.62
Domestic – Vigorous Activity	315.3 (853.8)	245.7 (436.8)	.69	.85
Domestic – Moderate Activity – Yard	985.7 (1400.7)	624.7 (951.1)	.25	.62
Domestic – Moderate Activity – Home	1051.1 (1239.4)	797.0 (1090.8)	.41	.52
Leisure – Walking	304.1 (600.1)	317.4 (392.9)	.92	.56
Leisure – Vigorous Activity	94.3 (266.1)	990.7 (1179.2)	.0002	.0023
Leisure – Moderate Activity	60.0 (189.0)	150.0 (272.3)	.15	.20
Total METs Per Week	6789.3 (8861.9)	7590.3 (9591.5)	.74	.99
Accelerometer (time in min)				
Sedentary	1103.7 (114.7)	1069.9 (110.2)	.26	.19
Light Activity	265.3 (104.9)	289.6 (89.3)	.34	.22
Moderate Activity	24.7 (20.7)	41.9 (28.8)	.0123	.0148
Vigorous Activity	1.2 (2.8)	5.4 (8.2)	.0127	.0467
6 Minute Walk Test				
Baseline Dyspnea	0.3 (0.7)	0 (0)	.0087	.0044
Baseline Fatigue	2.2 (1.3)	0.5 (0.9)	<.0001	<.0001
Post Dyspnea	2.3 (1.5)	1.7 (1.0)	.12	.15
Post Fatigue	3.2 (1.4)	1.2 (1.0)	<.0001	<.0001
Change in Fatigue	1.0 (1.3)	0.7 (1.3)	.37	.19
Total Distance (meters)	570.7 (51.9)	640.2 (65.7)	<.0001	.0006
CPET				
HR at Rest	76.9 (15.2)	71.5 (11.2)	.17	.16

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Variable	<i>M(SD)</i>		<i>p</i>	<i>p (adjusted)*</i>
	Patients	Controls		
HR at Max	165.5 (13.8)	169.6 (12.5)	.30	.83
SBP at Rest (mmHg)	113.8 (10.5)	115.8 (14.7)	.61	.31
SBP at Max (mmHg)	175.9 (22.8)	183.5 (23.9)	.30	.0404
VO ₂ max (mL/kg/min)	23.5 (5.2)	28.3 (6.9)	.0147	.07
Chronotropic Reserve	90.2 (10.7)	91.5 (11.2)	.69	.35
Heart Rate Recovery (deltaHRR)				
2 min	35.8 (14.7)	50.7 (18.5)	.0098	.0209
4 min	53.6 (17.2)	61.8 (10.9)	.06	.23
6 min	61.2 (14.9)	70.1 (11.6)	.0309	.13
8 min	65.5 (13.2)	73.4 (11.0)	.0349	.16
10 min	66.1 (12.4)	75.7 (11.1)	.0097	.06
Total Bike Time (min)	11.6 (2.0)	11.3 (1.9)	.93	.23

* multiple linear regression p-value adjusted for age