The Effect of Graded Resistance Exercise on Fibromyalgia Symptoms and Muscle Bioenergetics: A Pilot Study

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Introduction

The fibromyalgia (FM) syndrome is a chronic pain disorder that primarily affects middle-aged women. Individuals with FM generally report a broad spectrum of symptoms, with the main features including diffuse musculoskeletal pain, fatigue, stiffness, disordered sleep, and the presence of multiple “tender points” at anatomically distinct sites (1–3). The primary mechanisms underlying the expression of these symptoms have not been identified.

In view of the significance of musculoskeletal tender points as a criterion in clinical diagnosis (4), attention has focused in the past on skeletal muscle function in the phenomenology of FM. However, contemporary evidence for the role of skeletal muscle in the pathogenesis of FM is inconclusive (5,6). For example, structural abnormalities of skeletal muscle are generally nonspecific (7), and cannot account for the diverse symptoms. It is reasonable to suggest that observed deficits in skeletal muscle are a reflection of deconditioning (8–11) and a below-average fitness level (12), secondary to pain and fatigue-induced inactivity.

Attention has recently shifted to a dysfunction in FM of central neuroregulatory pathways and associated neurotransmitters that modulate sleep physiology and pain perception (13,14). For example, an abnormal metabolism of the neurotransmitter serotonin (15–17), which functions prominently in those behaviors adversely affected by FM such as pain, mood, and sleep (18), has received considerable attention. Furthermore, the observation that pain threshold is lowered at sites other than anatomically distinct tender points (19,20) supports the existence of a generalized aberration of pain modulation of central origin.

The contribution of, and distinction between, peripheral and central mechanisms in the pathogenesis of FM has not been resolved. Cardiovascular fitness training is reported to alleviate some of the FM symptoms (21–23), which can be interpreted as evidence for either a central mechanism through augmentation of neurotransmitter levels, or the stimulation of muscle metabolism causing acute and perhaps longterm changes in neuromuscular function. The favorable response of individuals with FM to exercise merits closer scrutiny to assist in identifying the pathophysiologic mechanism(s) involved in mediating the symptoms and distinguishing between peripheral and central pathways.

The purpose of this study was to investigate the effect of graded resistance exercise as a treatment for key symptoms representative of the FM disorder. In addition, the response of muscle metabolism, as determined by phosphorus magnetic resonance spectroscopy (31P-MRS) was assessed. We reasoned that attenuation of symptoms without a corresponding change in muscle metabolism would implicate a central mechanism in the rehabilitation of individuals with FM.

Methods

Individuals with FM were sequentially recruited through referral from primary care practitioners at the University School of Medicine medical, family practice, and rheumatology clinics, and from a local FM support group. Subjects were assessed by the same physician to confirm the presence of FM according to the criteria established by the American College of Rheumatology (4). Patients with other myofascial pain syndromes, inflammatory rheumatic disease, or untreated endocrine disorders, determined from history or laboratory tests, were excluded.

Of the 12 subjects included in the study at baseline, 2 withdrew because of orthopedic complications and illness. The remaining 9 women and 1 man had a mean age of 48.0 years (± 8.3 SD; range 27–55 years), and a mean duration of symptoms of 8 years (range 3–25 years). Data derived from pilot studies established that the sample size

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was adequate for at least a power of 0.8 for detecting a change of approximately 40% at an alpha level of <0.05. Six subjects volunteered for the $^{31}$P-MRS study. Healthy sedentary subjects served as control subjects, but did not exercise. Written informed consent was provided in accordance with the Medical School Human Research Review Committee.

Musculoskeletal tender points at 8 bilateral sites, equally distributed between upper and lower quadrants (upper trapezius, lateral epicondyly, greater trochanter, and medial fat pad of the knee), were identified according to the American College of Rheumatology criteria (4). Pain threshold was measured with a pressure algometer (Model DPP10, Chatillon and Sons, Greensboro, NC) fitted with a 1.2 cm diameter footplate. Pressure was applied at a constant rate of approximately 1 kg/second and the patients were instructed to respond verbally when the sensation of pressure first became painful. Sites were identified as tender when threshold values were <4 kg. The tender point pain thresholds were summed to represent a combined score. Measurements were conducted by the same investigator and were repeated after 2 weeks during the baseline period to establish test–retest reliability.

Patients completed a Fibromyalgia Impact Questionnaire (FIQ) (24) at weekly intervals, beginning at baseline. This self-assessment instrument, which has proven reliability and validity, provided a composite score based on responses to 10 scaled measures of physical functioning and symptom severity. Estimates of pain severity and sleep disturbance were reported using information from a 10 cm visual analog scale (VAS) included in the FIQ. Limiting descriptors for pain intensity and restful sleep were “no pain,” “very severe pain,” and “awoke well rested,” and “awoke very tired,” respectively.

Psychological symptom status was assessed with a Symptom Checklist-90-Revised (SCL-90-R) administered at baseline and again at the conclusion of the exercise program (25). This instrument is a 90-item self-report symptom inventory consisting of 9 primary symptom dimensions and 3 global indices of psychological distress. The test is a sensitive measure of distress in pain patients and has been shown to possess excellent validity in extensive clinical use. Raw scores were compared to a normative cohort and converted to T scores.

The FM subjects participated in an exercise program 2 days per week for 8 consecutive weeks. The twice-a-week exercise frequency was adopted in order to avoid the risk of exacerbating symptoms and to ensure adherence. Subjects were instructed in the correct technique for a series of resistive exercises which included leg press, shoulder press, latissimus dorsi pull down, bicep curl, and military press. All exercises were performed with wall pulley widths, with the exception of the seated leg press, which was conducted on a machine.

Training load was based on the maximum weight lifted in one repetition through the complete range of motion with appropriate form (one repetition maximum, [1 RM]) established for each exercise. The initial training intensity was set at 60% of the 1RM, and patients performed three sets of 10 repetitions for each exercise, with a one minute rest between sets. To accommodate for strength gains, the 1 RM was retested at weeks 2 and 6. In addition, the percent 1 RM was increased to 70% after 4 weeks. All weight training sessions were preceded by a 5 minute warm-up on a cycle ergometer, followed by a series of upper and lower body stretching exercises.

The individuals with FM completed trials of incremental forearm wrist flexion exercise before training, and during the week following their final training session. The control subjects did not train, and only performed one trial. Subjects performed exercise within the bore of a superconducting magnet, using a man-made exercise apparatus (26). The exercise consisted of continuous incremental forearm wrist flexion and extension at a rate of 11.2 contractions/minute, resulting in a power increment of 0.1 W/stage.

$^{31}$P-MRS was performed using a NMR spectrometer (Quest 4400, Nalorac, Martinez, CA) and a 1.9 Tesla superconducting magnet with a 31 cm bore (Oxford Instruments, Oxfordshire, UK) operating at 32.5 MHz. The arm of each subject was placed within the magnet so that the skin over the flexor carpi radialis and palmaris longus muscles rested over a 3.5 cm diameter, two-turn surface coil made of 14 gauge copper wire, mounted in a shielded probe and covered by an acrylic sheet. Magnetic field homogeneity was optimized by shimming on protons in a forearm-sized phantom containing a solution of 20 mmol/L sodium phosphoric acid (NaHPO4) with the coil tuned to 80.35 MHz. A minimum proton line width at half height of 10–12 Hz (magnitude spectrum) was required before data collection could begin.

During rest conditions, free induction decays (FIDs) were collected after a 45 μs rf pulse, every 5 seconds for 4 minutes. During exercise, FIDs were collected after a 0.15 μs rf pulse every 0.5 seconds throughout the 5 minutes of exercise at each stage. Data from the final 4 minutes of each stage were summed and analyzed.

The averaged FIDs were multiplied by an exponential function (5 Hz line broadening) before fast fourier transformation. All spectra were manually phased using zero-and first-order corrections. A 7 peak Lorenzian fit was calculated for each spectrum to isolate the inorganic phosphate (Pi), creatinine phosphate (CrP), and the alpha, gamma, and beta ATP peaks. The height area, and chemical shift of each peak relative to CrP were computed. Muscle intracellular pH was calculated from the chemical shift difference in ppm (t) between Pi and CrP using the following equation:

$$\text{pH} = 6.75 + \log[(t - 3.27)/(5.69 - t)]$$

$^{31}$P-MRS spectra were analyzed by converting the Pi and CrP areas to Pi/CrP.

Due to the need to compare both control and FM subjects across exercise intensities and training status, multiple two-way repeated measure analyses of variance (ANOVAs) were performed on the MRS data. The control subjects were compared to the FM subjects pre-training and post-training for each of the resting and fatigue conditions for the variables Pi/CrP and muscle [H+]. A Bonferroni adjustment was used for each dependent variable to correct for multiple comparisons, resulting in a significance level of $P < 0.025$. When required, post-hoc analyses
were performed using one-way ANOVAs and specific repeated factor error terms, and Tukey’s test. The test–retest reliability of the pain threshold measurement using a hand-held algometer was computed as method error and expressed as a percentage using the coefficient of variance, (27). Paired t-tests were conducted on change scores after exercise training to test for significance at an α level of P < 0.05. Data are presented as means ± SD.

**Results**

Dynamic strength, assessed by shoulder and leg press 1 RM, increased by 43% and 51% respectively after 8 weeks of resistance exercise. The pain threshold determined by pressure algometry at 8 bilateral sites and presented as a combined score increased by 36% at the conclusion of the study (P < 0.05) (Table 1). The pain threshold of individual sites was in the range of 2–3 kg/cm at baseline. The coefficient of variation for repeat measures of pain threshold was calculated to be 11%.

The subjective self-report of symptom variables (Table 1) all responded favorably by approximately the same magnitude. The pain and disordered sleep rating on a 10 cm VAS declined by 49% and 43% (P < 0.005, P < 0.005) respectively. The FIQ composite score, which reflects the degree of physical functioning and severity of symptoms, declined by 47% from baseline (P < 0.0005). Finally, the raw score for the Global Severity Index (GSI), which represents a summary measure of psychological distress on the SCL-90-R, declined by 52% (P < 0.01) and the Somatization subscale raw score improved by 44% (P < 0.01). The t-scores for both Somatization and the GSI were elevated at baseline (> 60) and returned to normal values representative of a non-patient population following the exercise program.

Data on the changes in Pi/CrP and intramuscular acidosis during fatiguing exercise are presented in Figures 1 and 2, respectively. Resting values for Pi/CrP ratios were equivalent for control and FM subjects. Incremental wrist flexion exercises elicited a significant increase in this ratio from rest at maximal exertion in both FM and control groups. Control subjects exhibited a significantly greater metabolic response to maximal exertion compared to FM individuals at the post-training interval. The increased response in FM subjects was reflected in the significantly lower muscle acidosis at the post-training interval compared with controls. The change in muscle acidosis was inconsistent between individuals within the FM group at the onset of the training program.

**Discussion**

The results of this study demonstrate that a treatment program of resistance exercise attenuates the major clinical symptoms characteristic of FM. Patients voluntarily reported on the favorable response to the exercise regimen, and in particular emphasized diminished fatigue and improved mood and sleep. These findings support and extend earlier studies employing either aerobic exercise alone (21,22) or in combination with conditioning (23) in FM patients compared to those receiving flexibility exercises (21,23), or a program of stress management (22).

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\text{Pi/CrP} = \frac{\text{PPI}}{\text{CrP}}
\]

**Table 1. Changes in outcome variables in 10 patients with fibromyalgia following an 8-week resistance exercise program**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study entry means (± SD)</th>
<th>Post study means (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined pain threshold</td>
<td>15.6 (±2.9)</td>
<td>21.2 (±6.4)*</td>
</tr>
<tr>
<td>FIQ</td>
<td>55.1 (±18.6)</td>
<td>28.3 (±15.0)#</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5.2 (±2.2)</td>
<td>2.6 (±1.8)#</td>
</tr>
<tr>
<td>Sleep</td>
<td>6.0 (±2.7)</td>
<td>3.4 (±2.6)#</td>
</tr>
<tr>
<td>SCL-90-R</td>
<td>1.1 (±0.7)</td>
<td>0.5 (±0.2)†</td>
</tr>
<tr>
<td>GSI</td>
<td>1.5 (±0.7)</td>
<td>0.8 (±0.4)†</td>
</tr>
</tbody>
</table>

Combined pain threshold represents combined algometer scores from 8 tender sites bilaterally (kg/cm²). FIQ = Fibromyalgia Impact Questionnaire (cumulative score); VAS = Visual Analog Scale (cm); SCL-90-R = Symptom Checklist-90 Revised Questionnaire (raw scores); GSI = Global Severity Index.

* P < 0.05.
† P < 0.01.
‡ P < 0.005.
§ P < 0.0005.
there was a significantly lower metabolic response to fatiguing exercise in FM subjects, which is in agreement with similar trends observed by others (28–30). Jacobsen and coworkers (28) demonstrated that the tendency for a lower Pi/creatine phosphate (CrP) ratio exists in anaerobic but not for aerobic exercise.

A reasonable interpretation of the lower depletion of phosphate stores is that FM subjects may not have exercised at the same intensity as asymptomatic individuals during the 31P-MRS measurement because of subnormal creatinine phosphate stores. Vestergaard and coworkers (28) demonstrated that the tendency for a normal workload and conceivably contributed to the inconsistent results. In light of the evidence that muscle energy metabolism is unaltered in FM and a reflection of detraining, an appealing consideration is that the attenuation of symptoms by exercise is mediated through the enhancement of neurotransmitters of central origin. Exercise has been shown to promote the synthesis and turnover of brain serotonin (33,34), and the alleviation of FM symptoms through resistance exercise is paralleled by a rise in blood serotonin levels (Geel and I.J. Russell, unpublished observations). Several lines of evidence have recently contributed to the confirmation of a disordered serotonin metabolism that may underlie FM symptoms (15–17) including the treatment effectiveness of pharmacologic agents that enhance levels of the neurotransmitter (35). Focusing attention on central mechanisms, provides a rational explanation for the diverse symptoms of FM that cannot be accounted for by a localized somatic abnormality.

A limitation of this study is the lack of inclusion of a non-exercising group to control for confounding psychosocial effects such as peer support, encouragement, and attention afforded subjects. However, the magnitude of the symptom abatement is far in excess of any placebo reported in other studies conducted under similar experimental conditions. Moreover, this study was designed to test the response of a group of patients to exercise. In addition, concerns about maturational or history effects were considered negligible because patients reported having FM for a protracted period prior to the study, without resolution of symptoms.

The small sample size is a further limitation that precludes strict interpretation of the data. Nevertheless, the findings provide valuable insight into the pathogenesis of the disorder and raise provocative questions that merit further attention.

**ACKNOWLEDGMENTS**

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