LACK OF ASSOCIATION BETWEEN FIBROMYALGIA SYNDROME AND ABNORMALITIES IN MUSCLE ENERGY METABOLISM

ROBERT W. SIMMS, SERGE H. ROY, MIRKO HROVAT, JENNIFER J. ANDERSON, GARY SKRINAR, STEVEN R. LePOOLE, CRISTIANO A. F. ZERBINI, CARLO De LUCA, and FERENC JOLESZ

Objective. To compare parameters of muscle energy metabolism in patients with fibromyalgia syndrome (FMS) and sedentary controls.

Methods. Thirteen female FMS patients and 13 female sedentary controls underwent a standardized clinical assessment (including dolorimeter measurements of the upper trapezius and tibialis anterior muscles) and a standardized aerobic fitness test including measurement of maximum oxygen uptake (VO_{2max}). Phosphorus (^{31}P) magnetic resonance spectroscopy studies of the upper trapezius and tibialis anterior muscles were then performed in FMS patients and controls, at rest and during and following a muscle-fatiguing exercise protocol.

Results. FMS patients and controls had similar levels of VO_{2max} and of maximum voluntary contraction (MVC) of the upper trapezius and tibialis anterior muscles. After controlling for VO_{2max} and MVC, measurements of phosphocreatine (PCr), inorganic phosphate (P_i), and intracellular pH in these muscles were not significantly different in FMS patients versus sedentary controls either at rest, during exercise, or during recovery. In the patients with FMS, no correlation was found between overall or local pain severity and the principal muscle metabolic parameter, PCr/P_i. Inverse correlations between dolorimeter scores at 2 muscle sites and tibialis anterior PCr/P_i were found both in patients and in controls.

Conclusion. This study demonstrates that under the conditions studied, muscle energy metabolism in FMS is no different than that in sedentary controls. These findings do not support the hypothesis that detectable defects in muscle energy metabolism occur in FMS.

Fibromyalgia syndrome (FMS) is a common chronic musculoskeletal pain syndrome which has been recently defined in a multicenter study (1), although its cause remains unknown (2). A number of studies using invasive and noninvasive techniques have suggested that patients with FMS have abnormalities in muscle energy metabolism (3–8). Several histologic studies appeared to demonstrate histopathologic changes consistent with tissue anoxia, including "moth-eaten" and "ragged-red" muscle fibers at the sites of tenderness (4–6). More recent studies appeared to confirm these findings, with the demonstration of local hypoxia and reduced high-energy phosphate levels at sites of tenderness, compared with normal controls (7,8). It has also been recently recognized, however, that patients with FMS are relatively deconditioned when compared with normal subjects (9). Furthermore, increases in high-energy phosphate levels in skeletal muscle may occur in response to physical training (10). It is therefore possible that studies demonstrating lower levels of high-energy phosphate compounds in muscles of FMS patients compared with normal controls reflect only a disuse effect. Nevertheless, no studies of muscle metabolism in FMS to date have taken into account the level of deconditioning in study subjects.

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) has provided a noninvasive approach to measure important metabolites in muscle energy metabolism, such as phosphocreatine (PCr), inorganic phosphate (P_i), ATP, and intracellular muscle pH (11–15). Two preliminary studies using this technology suggested that muscle energy metabolism was abnormal in patients with FMS (16,17). A more recent ^{31}P-MRS study of the trapezius muscle in FMS patients showed no differences in high-energy metabolites compared with healthy controls (18). Jacobsen and colleagues recently found similar values for P_i and PCr in the calf muscles of patients with FMS and healthy controls (19). No studies using ^{31}P-MRS, however, have yet compared FMS patients with sedentary controls under dynamic conditions at characteristic sites of tenderness where focal abnormalities in muscle energy metabolism may occur. To further investigate the role of muscle energy metabolism in FMS, we utilized the noninvasive technology of ^{31}P-MRS to study typically tender and nontender muscle sites of FMS patients, both at rest and during and after an exercise protocol, and compared them with a sedentary control group, taking into account the level of aerobic conditioning.

PATIENTS AND METHODS

Study participants. Thirteen female patients with FMS and 13 normal sedentary female controls were evaluated. Eligible patients were required to meet American College of Rheumatology criteria for fibromyalgia syndrome and to have global pain symptoms scored at least 4 on a scale of 0–10 (with 10 representing the most severe pain). The control group consisted of 13 healthy female volunteers. All study participants reported that they did not perform regular aerobic exercise at any time prior to or during the study. Patients were recruited from an academic rheumatology practice with an interest in FMS and were permitted to continue their usual medications during the study. Controls were recruited by advertisement. Due to the size of the NMR magnet (60 cm bore diameter), only nonobese subjects (generally, body weight <175 pounds) could be studied.

Clinical assessment. Both patients and controls underwent a standardized physician-administered questionnaire with assessment of fibromyalgia symptom activity (severity of pain over the past week, overall illness severity, and location of pain symptoms). Patients and controls also underwent a standardized physical examination consisting of an assessment of tender points on both sides of the body using manual palpation and a pressure-gauge algometer (dolorimeter). Bilateral tender point sites were assessed by manual palpation and included the occiput, low cervical area, mid-upper trapezius, supraspinatus, paraspinous, second rib, lateral pectoralis, lateral epicondyles, posterior

superior iliac crest, greater trochanter, anserine bursa, distal third of forearm, thumbnail, midpoint of third metatarsal, and mid–tibialis anterior. The findings of the manual tender point examination were scored in the following manner: 0 = no tenderness, 1 = mild tenderness expressed but no withdrawal, 2 = moderate tenderness expressed plus withdrawal, and 3 = severe pain expressed with immediate and exaggerated withdrawal. Sites assessed by dolorimeter included the occiput, paraspinous, midpoint of the trapezius, second rib, lateral epicondyle, distal forearm, thumbnail, anserine bursa, tibialis anterior, and midpoint of third metatarsal. The method of application of the dolorimeter was as described previously (20).

Fitness measurement. Patients and controls underwent a standard aerobic fitness measurement within 4 weeks before the ^{31}P-MRS procedure. The aerobic measurement was carried out using a Monarch cycle ergometer with 1-minute stages of 15W increases, beginning with 0 W for the first minute. Subjects were then exercised to volitional exhaustion with continuous monitoring of pulse, blood pressure, inspired oxygen, and expired carbon dioxide. The following standard physiologic variables were then calculated: maximal oxygen uptake (VO_{2max}), respiratory exchange ratio, and minute ventilation. Subject rating of perceived exertion was determined at 1-minute intervals during the fitness measurement, according to the method of Borg (21).

MRS. ^{31}P-MRS was performed at 2 sites in each patient and control subject: 1) the midpoint of the right upper trapezius (typically a symptomatic muscle) and 2) the midpoint of the right tibialis anterior muscle (typically an asymptomatic muscle). Measurements were obtained at 1.5 Tesla in a 60-cm bore IBM/MIT research magnet system utilizing a 3 cm–diameter surface coil placed over the muscle of interest. MR spectra were derived from muscle tissue in an approximately 3 × 3 cm cylinder directly under the coil placed on the skin surface. From a prior study of tender points in FMS, we estimated that 3 cm in diameter was required to minimize potential areas of overlapping tenderness (20). Field homogeneity and radio frequency transmitter power were optimized on each subject prior to study.

Spectral measurements were made with the subject at rest, during a muscle-fatiguing exercise protocol of repeated isometric contractions, and during recovery. The muscle of interest was isolated by a constraining device to minimize movement artifact. For the trapezius, the limb-restraining device consisted of a forearm splint to prevent flexion of the elbow. Isometric contraction of the trapezius then consisted of a static "shoulder-shrug" against a low-compliance-force transducer attached to the wrist via a cable. For the tibialis anterior, a specially constructed lower limb–restraining device, which immobilized the knee and permitted dorsiflexion of the ankle against a low-compliance-force transducer at the medial and lateral aspect of the ankle, was used. For each muscle, the subject first performed a maximal voluntary contraction (MVC) for 5 seconds. Preliminary studies of normal volunteers and FMS patients (data not shown) were conducted to determine the optimal muscle-fatiguing protocol which would be tolerated by patients and provide changes in the metabolic parameters. The final exercise protocol consisted of a 4.5-minute period of

intermittent contractions at 60% MVC, immediately followed by 4.5 minutes of intermittent contractions at 50% MVC. This duty cycle format consisted of 6 seconds of contraction followed by 6 seconds of rest. Measurements of intracellular PCr, P_i, and pH were derived from ^{31}P-MR spectra obtained continuously, at baseline, during each phase of the fatiguing protocol and during an 11-minute period of recovery. Fourier-transformed spectra were processed (without knowledge of the subject's status) and spectral peak integration was carried out by means of semiautomated routines to minimize operator bias. A piecewise baseline deconvolution routine was used to eliminate baseline variation. Spectra were obtained every 2.5 seconds and averaged over 0.5-minute epochs with standard phasecycling techniques. Spectral widths were set to 2 KHz. Integrals for regions corresponding to PCr, P_i, and ATP were then used as a database for further statistical analysis by SAS software (see below). Measurements of intracellular pH were derived from relative spectral peak shifts of P_i and PCr using pH titration curves constructed from spectra of model solutions containing KCl, NaCl, PCr, ATP, $MgSO_4$, and P_i.

The data for each variable were grouped into 6 periods reflecting the phases of the experimental protocol. Period 1 consisted of 5 minutes of baseline acquisition; period 2, 1.5 minutes early in the 60% MVC exercise protocol (0–1.5 minutes); period 3, the final 1.5 minutes of 60% MVC; period 4, 4 minutes of the 50% MVC exercise protocol (4.5–8.5 minutes); period 5, early recovery (9.5–11.0 minutes); and period 6, late recovery (11.0–18.0 minutes).

Mean PCr/P_i (reflecting the thermodynamic state of the muscle) and pH were then plotted over time for both the upper trapezius and the tibialis anterior muscles. PCr, P_i, and pH values normalized to the initial measurement at rest were also calculated over time.

Statistical methods. Baseline and other univariate comparisons were performed using t-tests. Repeated-measures analysis of variance and F tests were used to compare FMS and control PCr/P_i and pH over time for each muscle. The repeated-measures analysis of variance was also performed with adjustment for both VO$_{2max}$ and MVC. Pearson correlation coefficients between PCr/P_i levels at the end of period 3 and measures of overall pain, right shoulder girdle pain, right tibialis anterior pain, and dolorimeter scores in the patients with FMS were also calculated.

With the sample sizes used in this study, there is >50% power for detecting a difference of at least 0.80 SD in PCr/P_i between patients and controls in a 2-sided test at $\alpha = 0.05$ in univariate analysis, and ~80% power for detecting this difference in a repeated-measures analysis.

RESULTS

The patients with FMS had a mean ± SEM symptom duration of 5.2 ± 2.3 years and rated their overall symptom severity at 5.5 ± 1.7 (visual analog scale; 0 = no symptoms, 10 = most severe symptoms), and 9 of the 13 were receiving medication (tricyclics agents in 5, cyclobenzaprine in 2, fluoxetine in 1,

Table 1. Characteristics of the fibromyalgia syndrome (FMS) patients and sedentary controls*

	FMS patients (n = 13)	Controls (n = 13)	P
Age, years	39.9 ± 5.5	34.2 ± 10.8	0.10
Height, inches	63.2 ± 2.8	63.2 ± 5.4	0.98
Weight, kg	59.0 ± 10.6	57.0 ± 4.9	0.76
Maximum heart rate, beats/minute	176 ± 8.5	179 ± 13.9	0.59
Minute ventilation, liters/minute	49.3 ± 16.9	54.8 ± 9.3	0.32
Respiratory exchange ratio	1.01 ± 0.2	1.06 ± 0.4	0.23
VO$_{2max}$, ml/minute/kg	29.7 ± 8.1	32.1 ± 7.2	0.43
MVC, pounds			
Tibialis anterior	20.9 ± 5.7	21.4 ± 3.3	0.82
Upper trapezius	50.1 ± 22	55.8 ± 17.5	0.47
Overall Borg rating of perceived exertion†	15.2 ± 0.5	15.8 ± 0.6	0.88
First time period intracellular pH			
Tibialis anterior	7.08 ± 0.01	7.07 ± 0.02	0.64
Upper trapezius	7.12 ± 0.03	7.20 ± 0.02	0.04
First time period PCr/P_i			
Tibialis anterior	10.21 ± 0.63	9.17 ± 0.56	0.23
Upper trapezius	9.10 ± 0.90	8.98 ± 0.57	0.91

* Values are the mean ± SEM. VO$_{2max}$ = maximum oxygen uptake; MVC = maximum voluntary contraction; PCr/P_i = phosphocreatine/inorganic phosphate.
† The Borg rating of perceived exertion (ref. 21) is a 15-point rating scale (range 6–20) and is reported at high exercise intensity (105W).

alprazolam in 1). The patient group and the sedentary control group were similar in terms of age, height, weight, and parameters of aerobic fitness, including age-adjusted maximum heart rate, minute ventilation, respiratory exchange ratio, VO$_{2max}$, and MVC of both the tibialis anterior and upper trapezius muscles (Table 1). Patients and controls also had similar ratings of perceived exertion at high exercise intensity (Table 1).

The ratio of PCr/P_i recorded over time at both the tibialis anterior and upper trapezius muscles showed no significant difference between patients and controls at baseline, during the exercise protocol, or during recovery (Figure 1). This was the case for the comparison of measurements for each time period and for the analysis of variance reflecting the overall metabolic profile over time after adjusting for VO$_{2max}$ and MVC. Similarly, intracellular muscle pH measurements during the different time periods for both the upper trapezius and tibialis anterior muscles showed no difference between patients and controls (Figure 1), except that the pH value for the upper trapezius during period 1 was significantly lower in patients compared with controls by the univariate comparison ($P = 0.02$). No significant difference in the pH values between
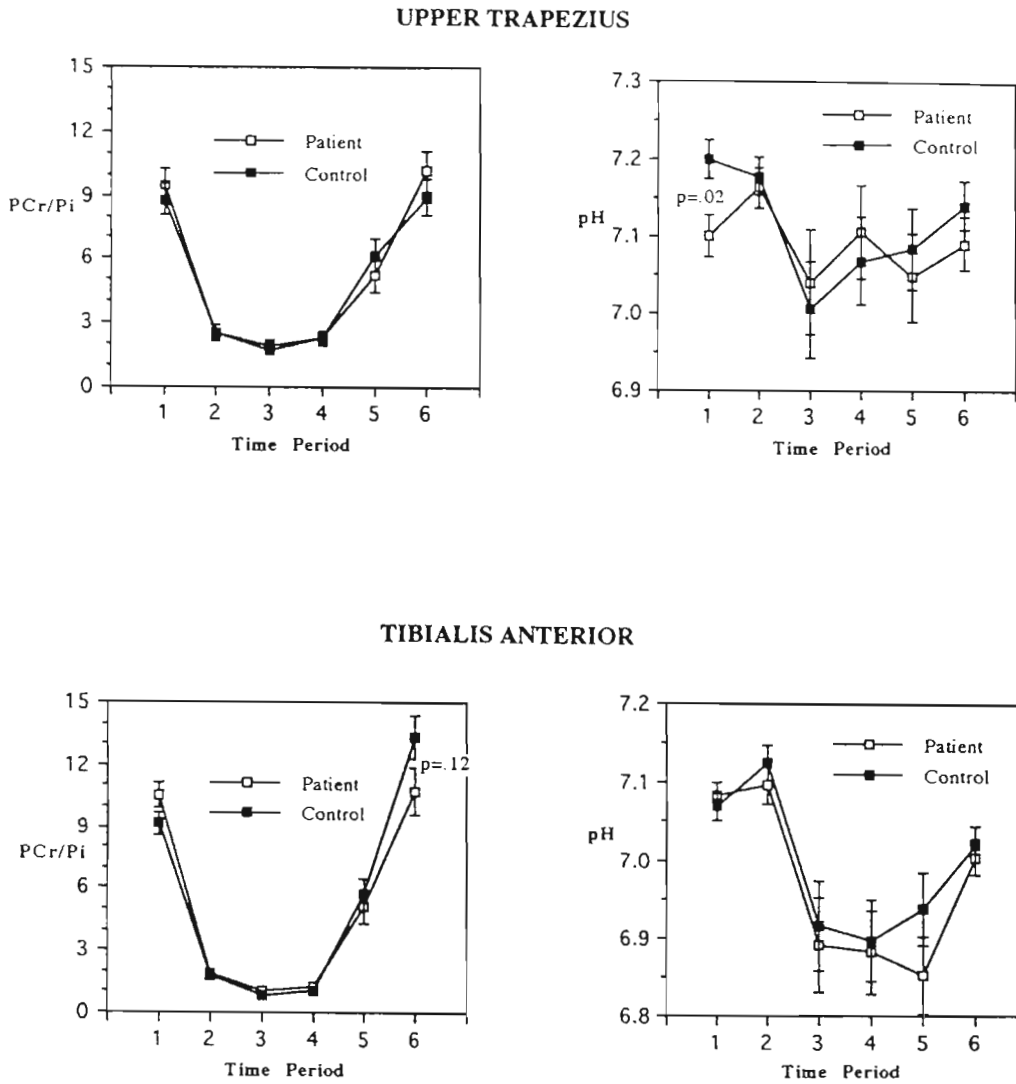
UPPER TRAPEZIUS

TIBIALIS ANTERIOR

Figure 1. Comparison of phosphocreatine/inorganic phosphate (PCr/P$_i$) ratios and intracellular muscle pH by time period (see Patients and Methods for description of time periods) between patients with fibromyalgia syndrome and sedentary controls, during tibialis anterior and upper trapezius muscle fatiguing experiments.

patients and controls, however, was seen in the repeated-measures analysis of variance of pH in either muscle. There was also no difference between patients and controls in the PCr and pH normalized to baseline values for each variable (data not shown).

In patients with FMS, correlations between PCr/P$_i$ at the end of the 60% MVC period and symptoms of pain (either global or local) or dolorimeter scores failed to reach significance except for the correlation between tibialis anterior PCr/P$_i$ and paraspinal and right tibialis anterior dolorimeter scores (Table 2). In these 2 muscles, higher dolorimeter scores (less tenderness) correlated with lower PCr/P$_i$ values. Similar, in fact stronger, negative correlations occurred between PCr/P$_i$ and dolorimeter score at both the right and left tibialis anterior muscles in the control group (Table 2).

DISCUSSION

Prior studies of muscle metabolism in fibromyalgia using a variety of techniques have suggested that there may be a metabolic basis for the musculoskeletal pain symptoms in this disorder (3–8,16,17). These

Table 2. Correlations (r) between PCr/P$_i$ levels followed 60% MVC exercise protocol and clinical measurements in FMS patients and controls*

	Upper trapezius PCr/P$_i$		Tibialis anterior PCr/P$_i$	
	Patients	Controls	Patients	Controls
Pain measure				
Overall pain	0.008	NA	−0.473	NA
Right shoulder girdle pain	−0.191	NA	−0.054	NA
Right tibialis anterior pain	−0.083	NA	0.047	NA
Dolorimeter score				
Occiput	0.094	0.238	−0.105	0.013
Paraspinal	0.435	0.068	−0.811†	−0.068
Trapezius				
Right	−0.083	0.067	−0.459	−0.182
Left	0.091	−0.043	−0.369	−0.205
Second rib	−0.031	0.331	0.373	−0.153
Lateral epicondyle	0.007	0.123	−0.122	0.082
Distal forearm	0.217	0.114	0.378	−0.520
Thumbnail	−0.103	0.013	0.240	−0.397
Anserine bursa	0.226	0.213	0.216	−0.547
Tibialis anterior				
Right	−0.060	−0.100	−0.553†	−0.831†
Left	−0.088	−0.120	−0.427	−0.838†
Mid–third metatarsal	−0.265	0.231	0.050	−0.456

* NA = not applicable; see Table 1 for other definitions.
† Statistically significant correlation ($P < 0.05$).

studies have utilized a number of methods to determine muscle energy metabolism, including histochemical studies, oxygen probes, and more recently MRS. Bengtsson and coworkers, using histochemical measurements of muscle biopsy specimens, found lower levels of ATP, ADP, and PCr at the tender point sites in FMS patients compared with normal controls (8). That same group also found lower muscle oxygen tension at tender point sites in FMS patients compared with normal controls and hypothesized that muscle hypoxia (an "energy crisis") may be of pathogenic significance in patients with FMS (7).

More recent studies utilizing MRS have yielded conflicting results. Mathur and coworkers found abnormally low PCr/P$_i$, PCr/ATP, and resting pH levels in the forearm muscles of FMS patients compared with controls (16). Bach-Anderson and colleagues found that patients with FMS did not have a depletion of PCr below 30% of the resting value during exercise but had normal P$_i$/PCr ratios at rest (17). Csuka et al studied 4 patients and normal controls with ^{31}P-MRS sampling the suprascapular and anterior tibial muscles, but found no significant differences in metabolic parameters between patients and controls (22). DeBlécourt

et al recently reported the results of ^{31}P-MRS of 10 patients and 6 normal controls at the trapezius tender point site (18). Those investigators found no difference between patients and controls using this approach, although they noted that their studies were not performed under dynamic conditions and that a dynamic stress test may be needed to reveal any changes in muscle metabolism (18). Jacobsen and colleagues reported similar P$_i$/PCr ratios in the calf muscles of FMS patients when compared with controls, although they conceded that they could not rule out focal ischemia at more typical sites of tenderness (19).

The present study represents the first attempt to utilize ^{31}P-MRS to measure parameters of muscle energy metabolism at rest and under dynamic conditions in both tender and nontender muscle sites in fibromyalgia patients compared with sedentary controls. Our data indicate that measurements of phosphocreatine metabolism at rest, during muscle-fatiguing exercise, and during recovery, at either the upper trapezius or the tibialis anterior muscle sites, are not substantially different between patients with FMS and sedentary controls. These results suggest that muscle energy metabolism in FMS patients is not different from that in sedentary controls, and that the findings in prior studies which have indicated abnormalities in muscle metabolism may have been confounded by muscle deconditioning.

The similarity in metabolic parameters between FMS patients and sedentary controls was not the result of an exercise protocol which incompletely fatigued the muscles studied, since depletion of PCr and sizeable accumulation of P$_i$ occurred in both subject groups in the muscles studied. With our sample sizes, there was sufficient statistical power (80% at the 0.05 level of significance) to detect a difference of 13–20% of initial PCr/P$_i$ between patients and controls at the end of the 60% MVC contraction at each muscle site. Since differences of this magnitude in ^{31}P-MRS parameters have been described in patients with at least one example of a confirmed metabolic myopathy when compared with controls (myophosphorylase deficiency) (23), we believe that this study has sufficient statistical power to detect clinically meaningful differences between the study groups.

The pattern of pH change over time was different for each muscle studied, likely reflecting differences in muscle fiber type and the degree of vascular engorgement. The tibialis anterior has a higher proportion of type II fibers than does the upper trapezius (24) and is therefore capable of generating higher levels of

lactate, hence the greater depression in pH for the tibialis anterior at 60% and 50% MVC. When pH measurements in FMS patients were compared with those in controls, the intracellular muscle pH in the upper trapezius during rest was slightly higher for controls than for patients in the univariate comparison (mean ± SEM 7.12 ± 0.03 versus 7.20 ± 0.02; $P =$ 0.04) (Table 1). No difference was seen during exercise or recovery, and the repeated-measures analysis for pH in the upper trapezius showed no difference between patients and controls. DeBlécourt et al found resting levels of intracellular pH in the upper trapezius of FMS patients (mean ± SEM 7.14 ± 0.05) and controls (7.13 ± 0.01) that were similar to those in our patients, suggesting that the controls in our study had relatively high initial levels of intracellular pH (18). The precise explanation for this high initial pH in our control group is uncertain, but may have been the result of transient, relative intracellular alkalinization induced by the MVC test performed before beginning the exercise protocol.

It remains possible that a localized metabolic defect in high-energy muscle metabolism in FMS produces a similar change in PCr, P_i, and pH with exercise as is seen in deconditioned muscle. We believe that this is unlikely, however, since both the magnitude and the pattern of change in PCr, P_i, and pH occurring during exercise and recovery for each subject group were virtually superimposable. Furthermore, we found no correlation between the principal muscle metabolic parameter, PCr/P_i, and overall pain severity or local pain in the patients with FMS. An inverse correlation was found between the right tibialis anterior and paraspinal muscle dolorimeter scores and the tibialis anterior PCr/P_i ratio in patients with FMS. Stronger inverse correlations between right and left tibialis anterior dolorimeter score and tibialis anterior PCr/P_i were found in the control group, suggesting that more tender (and presumably more deconditioned) muscles in both patients and controls generated lower amounts of inorganic phosphorus during the greatest energy expenditure of the 60% MVC protocol.

Interestingly, we found that isometric muscle strength in both the tibialis anterior and upper trapezius muscles of the FMS patients, as determined by measurement of MVC, was not different from that in sedentary controls (Table 1). These results should be contrasted with data from Jacobsen and Danneskiold-Samsøe, in which isometric and isokinetic quadriceps muscle strength was significantly reduced in FMS patients compared with age-, sex-, and height-matched

normal controls (25). Although we did not test quadriceps MVC, our data suggest that it is necessary to compare muscle parameters in FMS patients with those in sedentary controls who possess similar VO_{2max} levels.

In summary, these data show no appreciable differences in parameters of muscle metabolism between patients with fibromyalgia syndrome and sedentary controls, during a muscle-fatiguing exercise protocol. Thus, the results do not support the hypothesis that localized defects in muscle metabolism (an "energy crisis") occur in fibromyalgia syndrome.

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