Arthritis & Rheumatism
ARTHRITIS CARE & RESEARCH 47:82–86, 2002
DOI 10.1002/art1.10240



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

STANLEY E. GEEL[1] AND ROBERT A. ROBERGS[2]

## 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 ($^{31}$P-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

Supported by the Clinical Research Center, University of New Mexico, Albuquerque, New Mexico.

[1]Stanley E. Geel, MS, PhD, PT: Center for Health and Human Services, California State University, Sacramento, California; [2]Robert A. Robergs, PhD: Center for Exercise and Applied Human Physiology, University of New Mexico, Albuquerque, New Mexico.

Address correspondence to Stanley E. Geel, MS, PhD, PT, 300 North Canyon Road, Camino, CA 95709.

Submitted for publication April 5, 2000; accepted in revised form August 21, 2001.

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 epicondyle, 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," and "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 weights, 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 (NaHP04) 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 $\mu$s rf pulse, every 5 seconds for 4 minutes. During exercise, FIDs were collected after a 0.15 $\mu$s 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:

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

$^{31}$P-MRS spectrums 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

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

| Variable | Study entry means (± SD) | Post study means (± SD) |
|---|---|---|
| Combined pain threshold | 15.6 (±2.9) | 21.2 (±6.4)* |
| FIQ | 53.1 (±18.6) | 28.3 (±15.0)§ |
| VAS | | |
| Pain | 5.2 (±2.2) | 2.6 (±1.8)‡ |
| Sleep | 6.0 (±2.7) | 3.4 (±2.6)‡ |
| SCL-90-R | | |
| GSI | 1.1 (±0.7) | 0.5 (±0.2)† |
| Somatization | 1.5 (±0.7) | 0.8 (±0.4)† |

Combined pain threshold represents combined algometer scores from 8 tender sites bilaterally (kg/cm$^2$). 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.
* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.005$.
§ $P < 0.0005$.

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 $\alpha$ 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-90R, 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 dampened 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.

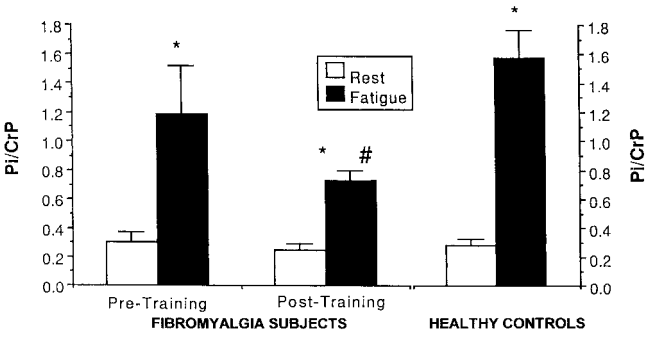


**Figure 1.** The change in Pi/CrP for the individuals with fibromyalgia and healthy controls. The incremental forearm exercise protocol caused typical increases in Pi/CrP compared to rest (*) for all subjects. Training dampened the increase in Pi/CrP in individuals with fibromyalgia (#) compared to healthy controls.

## 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).

$^{31}$P-MRS analysis of muscle high energy metabolism revealed a normal resting Pi/CrP ratio and intracellular muscle pH in FM compared to healthy individuals, which corroborates previous studies (28,29). On the other hand,

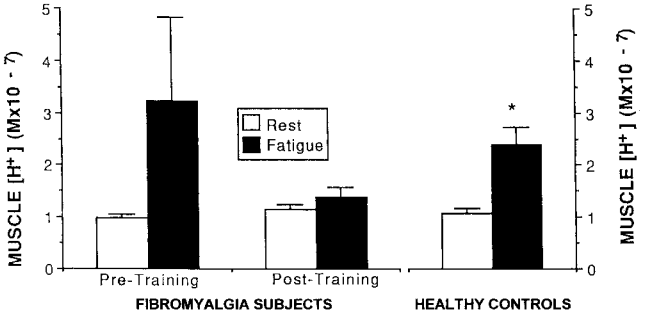


**Figure 2.** The change in intramuscular acidosis ([H+]) for the individuals with fibromyalgia and healthy controls. Exercise training reduced the metabolic acidosis accompanying the forearm incremental exercise in the fibromyalgia subjects (*) when compared to nonexercising healthy controls. The increased acidosis was more consistent for the control subjects than fibromyalgia subjects prior to exercise training.

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/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 $^{31}$P-MRS measurement because of subnormal voluntary drive (8,10), impaired strength (8–11), and/or exaggerated perception of effort (31). A post-hoc analysis (unpaired *t*-test) confirmed that power output at the point of fatigue during the MRS analysis was significantly lower in FM subjects compared with healthy controls.

Additional evidence exists for a relationship between physical deconditioning in FM and the rate of depletion of creatinine phosphate stores. Vestergaard–Poulsen and associates (30) observed that for dynamic exercise, muscle Pi/CrP values of FM subjects were lower than healthy active individuals and approached the level of sedentary subjects. Simms and coworkers (32) found that the depletion and recovery rate of creatinine phosphate was essentially identical to asymptomatic sedentary subjects with the same aerobic capacity, and concluded that muscle bioenergetic metabolism in FM is a reflection of detraining.

We were unable to draw any conclusions from the effect of 8 weeks of resistance training on muscle energy metabolism because of the variable response when MRS was conducted at baseline. Various degrees of pain and fatigue were prevalent at this stage that compromised toleration of 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 neuromodulators 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

Thanks are expressed to Eichii Fukushima of the Lovelace Institutes for access to the P-MRS equipment. Gratitude is also expressed to Jane Bentley, Sherri Miller, Mary Grabowski, and Joan Geel for assistance in exercise training and data collection.

## REFERENCES

1. Wolfe F. Fibromyalgia: the clinical syndrome. Rheum Dis Clin North Am 1989;15:1–18.
2. Boissevain MD, McCain GA. Toward an integrated understanding of fibromyalgia syndrome. I. Medical and pathophysiological aspects. Pain 1991;45:227–38.
3. Goldenberg DL. Clinical features of fibromyalgia. Advances in Pain Research and Therapy 1990;17:139–46.
4. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;33: 160–72.
5. Geel SE. The fibromyalgia syndrome: musculoskeletal pathophysiology. Semin Arthritis Rheum 1994;23:347–53.
6. Simms RW. Is there muscle pathology in fibromyalgia syndrome? Rheum Dis Clin North Am 1996;22:245–66.
7. Yunus MB, Kalyan-Raman UP. Muscle biopsy findings in primary fibromyalgia and other forms of nonarticular rheumatism. Rheum Dis Clin North Am 1989;15:115–34.
8. Jacobsen S, Wildschiodtz G, Danneskiold-Samsoe B. Isokinetic and isometric muscle strength combined with transcutaneous electrical muscle stimulation in primary fibromyalgia syndrome. J Rheumatol 1991;18:1390–5.
9. Jacobsen S, Danneskiold-Samsoe B. Dynamic muscular endurance in primary fibromyalgia compared with chronic myofascial pain syndrome. Arch Phys Med Rehabil 1992;73: 170–3.
10. Lindh M, Johansson G, Hedberg M, Grimby GL. Studies and maximal voluntary contraction in patients with fibromyalgia. Arch Phys Med Rehabil 1994;75:1217–22.
11. Norregaard J, Bulow PM, Vestergaard-Poulson P, Thomsen C, Danneskiold-Samsoe B. Muscle strength, voluntary activation and cross-sectional muscle area in patients with fibromyalgia. Br J Rheumatol 1995;34:925–31.
12. Bennett RM, Clark SR, Goldberg L, Nelson D, Bonafede RP, Porter J, et al. Aerobic fitness in patients with fibrositis: a controlled study of respiratory gas exchange and $^{133}$Xenon clearance from exercising muscle. Arthritis Rheum 1989;32: 454–60.
13. Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant control pain mechanisms with peripheral modulation. J Rheumatol 1992;19:846–9.
14. Russell IJ. A metabolic basis for fibromyalgia. Progress in fibromyalgia and myofascial pain. In: Vaeroy H, Mersky H, editors. Pain research and clinical management. New York: Elsevier; 1993. p. 283–309.
15. Yunus MB, Dailey JW, Aldag JC, Masi AT, Jobe PC. Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study. J Rheumatol 1992;19:90–4.
16. Russell IJ, Vaeroy H, Javors MA, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syn-

drome and rheumatoid arthritis. Arthritis Rheum 1992;35: 550–6.
17. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA. Platelet $^{3}$H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/ fibrositis syndrome. J Rheumatol 1992;19:104–9.
18. Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev 1992;72:165–229.
19. Tunks E, Crook J, Norman G, Kalaher S. Tender points in fibromyalgia. Pain 1988;34:11–20.
20. Mikkelsson M, Latikka P, Kautiainen H, Isomeri R, Isomaki H. Muscle and bone pressure pain threshold and pain tolerance in fibromyalgia patients and controls. Arch Phys Med Rehabil 1992;73:814–8.
21. McCain GA, Bell DA, Mai FM, Halliday PD. A controlled study of the effects of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia. Arthritis Rheum 1988;31:1135–41.
22. Wigers SH, Stiles TC, Vogel PA. Effects of aerobic exercise versus stress management treatment in fibromyalgia. Scand J Rheumatol 1996;25:77–86.
23. Martin L, Nutting A, Macintosh BR, Edworthy SM, Butterwick D, Cook J. An exercise program in the treatment of fibromyalgia. J Rheumatol 1996;23:1050–3.
24. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728–33.
25. Derogatis LR. SCL-90-R administration, scoring and procedures manual II. Towson (MD): Clinical Psychomatic Research; 1983.
26. Cheng HA, Robergs RA, Letellier JP, Caprihan C, Icenogle MV, Haseler LJ. Changes in muscle proton transfer relaxation times and acidosis during exercise and recovery. J Appl Physiol 1995;79:1370–8.
27. Portney LG, Watkins MP. Foundations of clinical research. Applications to practice. Norwalk (VA): Appleton & Lange; 1993. p. 525.
28. Jacobsen S, Jensen KE, Thomsen C, Danneskiold-Samsoe B, Henriksen O. $^{31}$P-magnetic resonance spectroscopy of skeletal muscle in patients with fibromyalgia. J Rheumatol 1992;19: 1600–3.
29. DeBlecourt AC, Wolfe RF, Van Rijswijk MH, Kamman RL, Knipping AA, Mooyaart EL. In vivo $^{31}$P-magnetic resonance spectroscopy (MRS) of tender points in patients with primary fibromyalgia syndrome. Rheumatol Int 1991;11:51–4.
30. Vestergaard-Poulsen P, Thomsen C, Norrregaard J, Bulow P, Sinkjaer T, Henriksen O. $^{31}$P NMR spectroscopy and electromyography during exercise and recovery in patients with fibromyalgia. J Rheumatol 1995;22:1544–51.
31. Miller T, Allen GM, Gandevia SC. Activation of elbow flexors assessed with sensitive twitch interpolation in fibromyalgia. J Rheumatol 1996;23:1621–7.
32. Simms RW, Roy SH, Hrovat M, Anderson JJ, Skrinar G, LePoole SR, et al. Lack of association between fibromyalgia syndrome and abnormalities in muscle energy metabolism. Arthritis Rheum 1994;37:794–800.
33. Chaouloff F. Effects of acute physical exercise on central serotonergic systems. Med Sci Sports Exerc 1997;29:58–62.
34. Meeusen R, DeMeirleir K. Exercise and brain neurotransmission. Sports Med 1995;20:160–88.
35. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39:1852–9.