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Original Article

Does aerobic exercise affect the hypothalamic-pituitary-adrenal hormonal response in patients with fibromyalgia syndrome?

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Abstract. [Purpose] The hypothalamic-pituitary-adrenal (HPA) axis in the etiopathogenesis of fibromyalgia is not clear. This study aimed to analyze the effects of a 6-week aerobic exercise program on the HPA axis in patients with fibromyalgia and to investigate the effects of this program on the disease symptoms, patients' fitness, disability, and quality of life. [Subjects and Methods] Fifty fibromyalgia patients were randomized to Group 1 (stretching and flexibility exercises at home for 6 weeks) and Group 2 (aerobic exercise three times a week and the same at-home exercises as Group 1 for 6 weeks). Serum levels of cortisol, adrenocorticotropic hormone, insulin-like growth factor-1, and growth hormone were analyzed at baseline and at the end of, and 1 hr after an exercise stress test. [Results] Group 2 showed better improvement in morning stiffness duration and pain. Growth hormone levels significantly increased after intervention and cortisol levels significantly decreased at time-time interaction in both groups. No significant differences in adrenocorticotropic hormone and insulin-like growth factor-1 were found. [Conclusion] The results of this study seem to support the hypothesis that there is a dysregulation of the HPA axis in patients with FM, and that a six-week exercise program can influence symptoms and affect the HPA axis hormones.
Key words: Fibromyalgia, Aerobic exercise, Hypothalamic-pituitary-adrenal axis

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic pain disorder that is associated with fatigue, tender points, sleep disturbances, cognitive dysfunction and mood disorders[1)]. Although the exact cause of the disease is not known, several theories have been proposed. The role of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in the etiopathogenesis of FMS has been discussed[2–4)]. The HPA axis plays a major role in the regulation of stress responses. It has been shown that, cortisol levels switch from the normal diurnal cortisol pattern to constant time-independent levels in FMS patients, and that hormonal levels are low and that they are not suppressed by dexamethasone[5)]. Low serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels in FMS patients have also been reported[6)]. Exogenic and endogenic stresses, such as metabolic, physiological, infectious, inflammatory and emotional factors, activate the neuroendocrine system[7)]; however studies analyzing the stress responses of HPA axis alterations in FMS patients have reported conflicting results.

The management of FMS is difficult, and multifaceted treatment modalities are frequently required. Usually, the daily activities of patients are limited; thus, their physical and aerobic performance capacities decline. Aerobic exercise (AE) has positive effects on FMS through the alleviation of FMS symptoms[8, 9)]. The serum beta endorphin level, immunoreactivity, and euphoria increase after AE, eliciting positive emotional and mental effects, better sleep quality and decreased pain sensitivity. It is also well known that acute exercise is a potent modulator of the release of HPA hormones[10)]. In addition to this, high intensity exercise affects the HPA axis more than low intensity exercise[11)]. The improvements in the symptoms of FMS after an exercise program might be partially attributed to amelioration of disorder in the HPA axis[12)]. However, the manner by which exercise can benefit patients is still unclear[8, 13)]. Unfortunately, studies investigating the effect of exercise on HPA axis in FMS patients are scarce. Kurtais et al.[14)] analyzed the effects of a single exercise session on the HPA axis in patients with FMS, and their results of the study suggest that there might be a hormonal perturbation response to exercise in patients. Accordingly, the hypothesis of this study was

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that exercise training might improve HPA axis disturbances in patients with FMS and further ameliorate symptoms. To investigate this hypothesis, were investigated the effects of a 6-week AE program on the HPA axis in patients with FMS. Our secondary aim was to investigate the effects of this program on FMS symptoms, patients' fitness, disability, and quality of life.

SUBJECTS AND METHODS

This was a randomized, controlled study. Fifty-six female FMS patients who were admitted to the FMS Out-patient Clinic of the Physical Medicine and Rehabilitation Department of our institution were invited to participate in the study. The subjects had been diagnosed as having fibromyalgia according to clinicians' decisions considering both the 1990 American College of Rheumatology classification criteria[15] and clinical findings. Patients were excluded if they had any of the following: an endocrine, metabolic, infectious, or neurologic disease, cancer, connective tissue disorder, a cardiac, respiratory, or orthopedic disease that might have hindered AE, hormonal dysfunction, pregnancy, menopause, or a cognitive function that might have hampered the assessments. Patients who were receiving any sort of treatment such as psychological or physical therapy for FMS in the last 3 months and the patients who were in need of medication for anxiety or depression during the study were also excluded. The demographic and clinical characteristics were recorded.

Fifty-four consecutive patients, who were eligible for the study, were randomly assigned to Group 1 or Group 2 using a sequence of random numbers. Group 1 performed home exercises consisting of flexibility and stretching exercises twice a day in ten repetitions for 6 weeks. Group 2 performed the same at-home exercise program and an additional AE program comprised of walking on a treadmill three times a week for 6 weeks.

An illustrated card depicting flexibility and stretching training programs was given to patients, and all the motions were demonstrated and described in detail by physicians before the start of the study. This card had 12 flexibility (trunk, hips, ankle, shoulders, and wrist) movement and 12 stretching (neck, lateral side, chest, shoulder, arm, triceps, quadriceps, ankle, calf, hamstring stretch) movement illustrations. Exercise compliance of all the patients was checked by telephone once a week. In Group 2, each AE session was planned to last 40–50 min, including 5 min each for the warm-up and cool-down periods. The exercise intensity was adjusted to achieve a heart rate equivalent to 60–75% of the maximum heart rate. The heart rate was monitored using a pulse oximeter.

The use of paracetamol, was allowed if necessary; however, NSAIDs utilization was prohibited during this study since they cause significant changes in the HPA axis[16].

The patients were assessed for pain, tender point count, morning stiffness duration, fatigue, cardiovascular fitness, functional disability, and health-related quality of life (HRqOL). These measures were evaluated by the same examiner (AG) at baseline and at the end of the study.

Pain was assessed using a 100-mm visual analogue scale (VAS; 0 mm = no pain, 100 mm = worst possible pain). A digital tender point examination (tender point count) at the 18 sites specified in the American College of Rheumatology FMS classification criteria[15] was performed. The duration of morning stiffness was recorded in minutes. The sleep quality was assessed using questions including difficulty in falling asleep (the number of nights/week in which the patient experienced difficulty in falling asleep), frequent awakening during sleep (0=none, 1=some of the nights, 2=every night) and quality of sleep (0= good, 1= moderate, 2= unrefreshing). Functional disability was evaluated using the Fibromyalgia Impact Questionnaire (FIQ)[17]. The Turkish adaptation of the FIQ with validity and reliability studies of this scale was conducted by Sarmer et al[18]. The HRqOL was evaluated using the Turkish version of the SF-36[19, 20]. The SF-36 assesses eight dimensions, including physical functioning, physical role problems, bodily pain, general health perception, vitality, social functioning, emotional role problems, and mental health.

An ergospirometric exercise tolerance test was used not only to evaluate cardiovascular fitness (aerobic capacity) but also to serve as a physiological stressor to evoke HPA hormonal responses[14, 21]. Before each test, dynamic respiratory function tests were performed (Vmax29, Sensormedics, Yorba Linda, CA), a routine procedure of our laboratory, in order to exclude any major respiratory limitation for exercise, and the forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FVC/FEV1, and vital capacity were recorded. The patients were instructed to avoid heavy exercise 24 hours before the test and to abstain from any food, coffee, tea or cigarette smoking on the morning of the test day. The ergospirometric exercise tolerance test was conducted on a treadmill using the modified Bruce protocol. Twelve-lead electrocardiography (Marquette Case I; Marquette, Milwaukee, WI), blood pressure, and breath-by-breath analysis of respiratory gases (Vmax29, Sensormedics, Yorba Linda, CA, USA) were recorded during the exercise test. The resting and maximal heart rates (HR, beats per minute; bpm), exercise duration (minutes), systolic and diastolic blood pressure (SBP, DBP, mmHg), maximal oxygen consumption during exercise (VO_{2max}, ml/kg/min), oxygen consumption at the anaerobic threshold (AT) (ml/kg/min), and metabolic equivalent (MET) values were recorded. The ergospirometric exercise tolerance test was conducted twice for all patients. The objective of the first test was to determine the peak oxygen consumption (VO_{2peak}) and to establish an AT in both groups so that the second exercise test could be set to a level that was sufficient to exceed the AT for provoking the HPA axis. Therefore, for all patients, the ergospirometric exercise test to volitional exhaustion (symptom-limited termination) was performed at 8.30 a.m. The AT was determined using the V-slope technique on a VO_2/VCO_2 plot[22]. The second exercise test was performed a couple of days after the first test and at the same time in the morning. Prior to the second test, blood samples were drawn to measure the fasting basal levels of GH, IGF-I, adrenocorticotropic hormone (ACTH), and cortisol. Exercise testing was performed on a treadmill with 12-lead electrocardiography and respiratory gas analysis was conducted throughout the test. The exercise intensity of each subject was set above her AT, as guided by the HR and oxygen consumption. The

duration of the exercise was 15 minutes after reaching the AT, which is sufficient to provoke hormonal responses. Post-exercise blood samples were drawn to measure the levels of GH, ACTH, and cortisol immediately after the end of the exercise and at 30 and 60 minutes later. Since IGF-I is not secreted acutely after stimulation, it was only measured at 60 minutes after the end of exercise. At the end of the 6-week program period, both groups performed the two exercise tests again. All blood samples were stored at −80 °C until assayed.

Plasma ACTH, IGF-1, and GH levels were measured using immunoradiometric assays (Beckman Coulter, Immunotech, Marseille, France). Serum cortisol levels were also measured by a radioimmunoassay (Beckman Coulter, Immunotech, Prague, Czech Republic) method.

Statistical analyses were performed using SPSS 11.5. The frequency (percent) was used as a descriptive statistic for categorical variables, and the mean ± standard deviation [median (minimum-maximum)] was used for metric variables. To compare the metric variables of two independent groups, Student's t test or the Mann-Whitney U test was used. The χ^2 test was used to evaluate the differences between groups in categorical variables. To compare repeated measurements of independent groups, a two-way repeated measures ANOVA/linear mixed effects model was used to test the effects of time(s), group and their interactions. When the interaction between time and group was found to be statistically significant, a Bonferroni corrected one-way repeated measures ANOVA was used for each group and values of $p<0.025$ were considered as statistically significant. The linear mixed effects model analysis was performed for the analysis of nested longitudinal data with independent groups. In general, $p<0.05$ was considered as statistically significant.

This study was approved by the Ethical Committee of our institution. All patients provided their informed consent and the study was carried out in compliance with the Declaration of Helsinki.

RESULTS

Fifty-four patients who met the inclusion criteria were recruited for this study. During the study, two patients from both groups were excluded (Fig. 1). The mean ages of the patients in Group 1 and Group 2 were 36.9 years and 35.1 years, respectively. The mean durations of the disease in Group 1 and Group 2 were 62.2 months and 67.4 months, respectively. There was no significant difference between the two groups with respect to age (p=0.427), duration of disease (p=0.617), or the presence of comorbid conditions (p=0.463).

To evaluate pain a visual analog scale was used at the beginning and end of the 6 week exercise program. Pain decreased significantly in both groups ($p=0.008<0.025$ for Group 1, $p<0.001$ for Group 2), and there was a more significant improvement in Group 2 (p=0.011). The duration of morning stiffness significantly decreased only in Group 2 ($p=0.112>0.025$ for Group 1, $p=0.001<0.025$ for Group 2). The number of tender points, FIQ and sleep scores were significantly lower in both groups at the end of the study, but there were no statistically significant differences between the groups (Table 1).

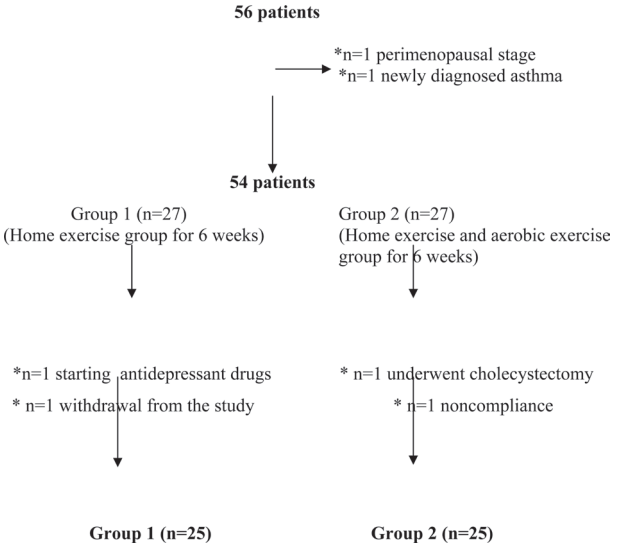


Fig. 1. Flow chart
*The reasons for exclusion from the study

The general health score was lower in Group 1 than in Group 2 (p=0.003), but it showed no significant time differences. Likewise, there were no significant differences in the other subscales of SF-36. Significant improvements in the bodily pain (BP) and social functioning (SF) subscales of the SF-36 were found in both groups ($p<0.001$ for BP, p=0.039 for SF) (Table 2).

Pulmonary function tests were within normal limits for all patients. Regarding the exercise test parameters, the overall difference between the groups was significant (mean score 13.75 and 15.33 for group 1 and 2, respectively) ($p<0.001$) and the duration of the exercise test after the exercise program significantly increased in both groups (p=0.002). The resting heart rate decreased after the exercise program in a statistically significant manner (p=0.006). As shown at Table 3, there were no statistically significant differences before and after the exercise program in either group in VO_{2max}, O_2 consumption at AT, maximal HR, SBP, DBP, or MET.

The time effect for before and after the exercise program (p=0.025) and the time-time interaction (before and after interaction with basal, 1st and 2nd measurements) (p=0.005) were statistically significant for the GH levels of both groups. The post-hoc comparisons showed that only the difference between the basal and 2nd measurements in the time period of before the exercise program was significant (p=0.003). The mean of the 2nd measurement was higher than the basal measurement (Table 4). For the cortisol levels, there were significant differences for the time effect of the basal, 1st and 2nd measurements (p=0.014) in both groups. Post-hoc comparisons indicated that the basal measurements (mean±SD: 158.22±35.76 nmol/l) were higher than the 1st measurements (mean±SD: 141.17±29.46 nmol/l) (p=0.012). There were no significant differences in ACTH and IGF-1 regarding either the time effect or between-group effects.

Table 1. Clinical parameters for FMS

	Factors			Group 1 (n=25)		Group 2 (n=25)	
	Group	Time	Group *Time interaction	BE	AE	BE	AE
VAS (0–100 mm)	0.382	<0.001	0.011	73.96±23.47 [80 (10–100)]	63.96±19.01 [65 (18–95)]	76.04±20.07 [79 (35–100)]	55.56±20.09 [52.2 (14–100)]
Morning stiffness (minute)	0.693	<0.001	0.038	47.80±45.53 [30 (0–180)]	39.80±36.41 [30 (0–120)]	61.80±59.07 [60 (0–240)]	35.60±40.35 [30 (0–150)]
Number of tender points (0–18)	0.506	<0.001	0.066	15.36±2.56 [16 (11–18)]	13.48±2.99 [14 (6–18)]	15.68±2.17 [16 (11–18)]	12.36±2.22 [12 (7–17)]
FIQ score (0–100)	0.916	<0.001	0.077	63.21±25.21 [68 (12–100)]	57.26±18.03 [60.1 (14–82.1)]	66.37±22.37 [61.3 (31.1–100)]	52.94±16.05 [53.6 (25.2–76.34)]
Sleep score (0–11)	0.732	0.037	0.081	8.46±3.51 [11 (3–11)]	8.02±2.91 [11 (0–11)]	9.41±2.34 [11 (3–11)]	8.24±3.37 [8 (2–11)]

Results are expressed as the mean±SD [median (minimum–maximum)]. BE: before exercise; AE: after exercise; VAS: visual analog scale; FIQ: Fibromyalgia impact questionnaire. The "group" column shows the main effect of group (home exercise vs. aerobic exercise), the "time" column shows the main effect of time (before exercise vs. after exercise), and the "group*time interaction" column shows the interaction between the groups and the time points.

Table 2. SF-36 health survey norm-based scores

	Factors			Group 1 (n=25)		Group 2 (n=25)	
	Group	Time	Group *Time interaction	BE	AE	BE	AE
Physical functioning	0.580	0.528	0.856	69.84±24.84 [80 (5.5–100)]	71.15±31.45 [85 (0–100)]	73.29±23.83 [72.2 (0–100)]	75.68±28.62 [85 (0–100)]
Role physical	0.741	0.077	0.248	33±44.32 [0 (0–100)]	36±44.53 [0 (0–100)]	24±34.97 [0 (0–100)]	38±38.27 [25 (0–100)]
Bodily pain	0.517	<0.001	0.300	31.74±21.1 [41 (0–67.5)]	38.52±21.16 [31 (0–84)]	32.52±17.48 [32.5 (0–62)]	44.48±20.97 [45 (0–74)]
General health	0.003	0.103	0.596	24.84±12.98 [25 (0–55)]	30±16.68 [25 (5–70)]	42.36±23.28 [42 (0–92)]	45.48±24.74 [40 (5–92)]
Physical component summary	0.993	0.842	0.102	42.56±18.89 [38.7 (24.7–100)]	39.95±8.91 [38.8 (24.4–55.1)]	39.57±8.11 [40 (19.5–51.6)]	42.89±10.18 [44.1 (19.9–57.5)]
Vitality	0.154	0.063	0.411	25.4±18.93 [20 (0–70)]	27.6±18.15 [25 (10–70)]	30±12.08 [25 (15–65)]	35.60±17.99 [40 (0–65)]
Social functioning	0.441	0.039	0.311	45.5±26.24 [50 (0–100)]	49±23.08 [50 (0–87.5)]	47±24.01 [50 (12.5–100)]	57±23.96 [62.5 (0–100)]
Role emotional	0.741	0.167	0.256	28±43.76 [0 (0–100)]	29.32±40.04 [0 (0–100)]	25.33±35.07 [0 (0–100)]	38.67±40.47 [33.3 (0–100)]
Mental health	0.191	0.537	0.723	40.64±24.07 [40 (8–90)]	41.12±18.46 [40 (12–84)]	46.24±14.15 [44 (16–92)]	48.01±12.27 [48 (24–88)]
Mental component summary	0.479	0.202	0.154	30.98±13.26 [25.8 (15.4–62)]	30.80±9.35 [27.7 (19.5–54.4)]	31.18±8.75 [29.3 (19.2–59.7)]	34.35±8.47 [33.4 (19.4–57.1)]

Results are expressed as the mean±SD [median (minimum–maximum)]. BE: before exercise; AE: after exercise The "group" column shows the main effect of group (home exercise vs. aerobic exercise), the "time" column shows the main effect of time (before exercise vs. after exercise), and the "group*time interaction" column shows the interaction between the groups and the time points.

DISCUSSION

Exercise has been fully recognized as an important part of FMS treatment following the European League against Rheumatism (EULAR) recommendations for the management of FMS syndrome[23]. Exercise at moderate-to-high intensity results in better improvements in functional capacity and in level of activity limitations[24]. The effects of aerobic, progressive-resistance stretching and flexibility exercises on FMS patients have been analyzed by several studies. Some of these studies demonstrated that AE has positive effects on sleep, quality of life, self-esteem, depression, pain, and some exercise test parameters[12, 24]. Bircan et al.[25] compared the effects of AE with a muscle-strengthening program, and

Table 3. Values of exercise test parameters by group

	Factors			Group 1 (n=25)		Group 2 (n=25)	
	Group	Time	Group *Time interaction	BE	AE	BE	AE
The duration of exercise (minute)	<0.001 (Means for group 1: 13.75 group 2: 15.33)	0.002	0.421	13.39±1.64 [13.3 (9.7–16.4)]	14.1±1.23 [14.2 (11.3–15.9)]	14.83±1.61 [15.4 (11.3–17.2)]	16.03±1.56 [15.8 (12.5–20)]
VO_2maximum (ml/kg/min)	<0.001 (Means for group 1: 24.19 group 2: 29.26)	0.704	0.583	24.53±3.72 [24.8 (14.7–31.1)]	24.09±4.87 [23.7 (12.4–32.6)]	30.11±3.90 [29.5 (22.1–40.3)]	29.14±8.12 [28 (15.6–53.5)]
O_2 consumption in AT (L/min)	0.727	0.283	0.320	1.02±0.36 [1 (0.3–1.6)]	1.02±0.22 [1 (0.7–1.5)]	1.09±0.20 [1.1 (0.6–1.5)]	1.02±0.19 [1 (0.7–1.5)]
Resting heart rate (BPM)	0.843	0.006	0.441	95.25±19.20 [94.5 (63–158)]	91.55±20.61 [86.5 (62–153)]	95.79±16.19 [99 (73–121)]	88.42±13.03 [83.5 (69–115)]
Maximal heart rate (BPM)	0.509	0.136	0.117	158.8±20.23 [165 (124–189)]	157.5±20.15 [155.5 (123–196)]	165.79±15.05 [164 (134–188)]	156.63±21.88 [162.5 (109–192)]
Systolic blood pressure (mmHg)	0.037 (Means for group 1: 115 group 2: 109.1)	0.692	0.883	114.5±12.76 [115 (100–130)]	114.5±8.87 [115 (100–130)]	108.54±11.18 [110 (90–140)]	109.58±11.6 [110 (90–130)]
Diastolic blood pressure (mmHg)	0.076	0.855	0.503	76.25±8.87 [80 (60–90)]	77.5±6.59 [80 (70–90)]	73.75±7.7 [70 (60–90)]	72.5±9.78 [70 (60–90)]
MET	0.027 (Means for group 1: 9.12 group 2: 10.28)	0.390	0.739	9.13±1.88 [10.1 (4.4–11.6)]	9.31±2.1 [9.5 (4.4–12)]	10.21±1.55 [9.8 (6.9–12.1)]	10.56±2.59 [11.8 (4.1–14.8)]

Results are expressed as the mean±SD [median (minimum-maximum)]. BE: before exercise; AE: after exercise; AT: anaerobic threshold; BPM: beats per minute; MET: metabolic equivalent. The "group" column shows the main effect of group (home exercise vs. aerobic exercise), the "time" column shows the main effect of time (before exercise vs. after exercise), and the "group*time interaction" column shows the interaction between the groups and the time points.

Table 4. Growth hormone (mIU/L) levels

	BE			AE		
	Basal	1st measurement	2nd measurement	Basal	1st measurement	2nd measurement
Group 1	2.81±6.37 [0.6 (0–28.2)]	2.89±4.73 [1.3 (0–21.6)]	6.79±8.33 [2.9 (0.2–32.4)]	9.61±12.41 [4 (0.3–56.3)]	5.64±13.7 [0.8 (0–65.8)]	5.41±11.38 [2 (0–56.7)]
Group 2	1.27±2.29 [0.7 (0–11.1)]	4.9±8.66 [0.7 (0.1–31.4)]	6.49±8.22 [1.7 (0.3–26.1)]	8.64±10.27 [4.4 (0.2–30.9)]	3.89±6.97 [0.7 (0–22.2)]	6.06±8.96 [1.5 (0.1–30.8)]
Overall	2.04±4.8 [0.6 (0–28.2)]	3.89±6.98 [0.8 (0–31.4)]	6.64±8.19 [2.3 (0.2–32.4)]	9.13±11.28 [4.1 (0.2–56.3)]	4.77±10.79 [0.7 (0–65.8)]	5.74±10.14 [2 (0–56.7)]

Results are expressed as the mean±SD [median (minimum–maximum)].
BE: before exercise; AE: after exercise

found that both exercise modalities were similarly effective at improving symptoms, tender point count, fitness, depression, and quality of life. On the other hand, Mengshoel et al.[26] found that AE did not show any advantages over no exercise treatment for the physical functions of FMS patients. In the present study, AE was determined to be superior to the stretching and flexibility exercises in relation to pain and morning stiffness duration. Although stretching and flexibility exercise was performed daily, it was well tolerated by both groups. This may have been because exercises were divided into two daily sessions with low numbers of repetitions. All clinical parameters of FMS except morning stiffness duration (number of tender points, FIQ score, pain levels, and length of exercise), the BP and SF subscales of the SF-36, and resting heart rate improved similarly with both exercise programs.

Approximately one third of FMS patients are estimated to suffer from GH deficiency. This condition can lead to reduced IGF-1[6]. Ross et al. suggested that GH dysfunction was associated with increased pain and poor muscle

performance in FMS patients[27]. Nearly fifty percent of GH secretion occurs during the third and fourth non-REM sleep stages[28], and FMS patients have non-REM sleep disturbances[29]. This may be one of the reasons why there are low levels of these hormones in FMS patients. Furthermore, there is not always a correlation between GH and IGF-1 release. It is well known that an exercise intensity of 25% VO_{2max} increases GH levels[10]. Exercise is believed to stimulate GH release via cholinergic activation, and in acute stress conditions, exercise first enhances growth hormone releasing hormone (GHRH), which then triggers an increase in GH levels[30]. On the other hand, some authors have reported there are no significant differences in GH and IGF-1 values between FMS patients and healthy control groups[31, 32]. The reasons for these discrepancies might be due to the pulsatile release of GH and/or differences in the duration of disease and/or chronic stress level[14]. As for IGF-1, regular exercise is expected to increase the resting level of the hormone in healthy individuals[33], but Jones et al.[34] reported there was no increase in patients with FMS who exercised regularly for a long time. In our study, GH levels increased in all patients after a 6-week exercise program and AE was not superior to flexibility and stretching exercises regarding the changes in GH levels. Moreover; IGF-1 levels were not changed by the exercise program, and there was no correlation between GH and IGF-1 levels. This finding was in agreement with previous studies. Lack of changes in IGF-1 levels with exercise suggests the existence of a disorder in the hypothalamus-GH-IGF-1 axis in FMS patients.

If exercise intensity reaches to 30–40% of $VO_{2max,}$ or if an individual exercises over the anaerobic threshold, ACTH also increases, and after a 10-minute interval, the cortisol level also increases. The critical exercise level that triggers cortisol release is 60% of VO_{2max}. Low-intensity exercises may lead to a decrease in blood cortisol levels by increasing clearance[10]. Several stimulating agents such as GHRH, luteinizing hormone releasing homone, corticotropin releasing hormone, clonidine, levodopa, metyrapone, exercise, or several tests such as the dexamethasone suppression test, or the insulin tolerance test have been used to analyze hormonal changes in FMS patients by many studies[4, 14, 27, 33–38]. The ACTH and cortisol responses to these stimulants are somewhat conflicting. Increased basal cortisol levels were reported by one study[39], whereas other studies reported decreased 24-hour urinary free cortisol and low morning cortisol release in fibromyalgia[2, 40]. Normal 24-hour cortisol and diurnal patterns of ACTH and cortisol secretion have been reported as well[38, 41, 42]. In the present study, while no significant difference was detected in the ACTH levels after the exercise program, cortisol levels significantly decreased with only a time effect. Therefore, the proposed this discordancy in the HPA axis may be associated with insufficient exercise intensity and/or duration.

The main limitation of this study was short exercise duration, since it has been reported that the positive effects of aerobic exercise become apparent from the 6th week of exercise[43]. Extension of the exercise period to 8–12 weeks would possibly allow better monitoring of the effects of exercise. The lack of increase in VO_{2max} levels after the 6-week exercise program in both groups is possibly a result of insufficient exercise intensity during the intervention period. There may be several reasons for this such as: insufficient pain relief, short exercise time, and/or mild-moderate exercise intensity. Furthermore, it is known that patients with FMS cannot perform high intensity exercises due to pain and tiredness. Only the use of paracetamol was allowed during this study because NSAIDs utilization can cause significant changes in the HPA axis. Insufficient pain relief may have resulted in decreased exercise tolerance and discordance in HPA axis hormones. To relieve pain and increase exercise capacity pharmacological agents, physical treatment, biofeedback and cognitive behavioral therapy should be started before all treatments, and exercise programs should be started afterwards to soothe pain and fatigue.

The findings of the present study, especially the absence of correlation between GH and IGF-1, and between ACTH and cortisol, seem to support our hypothesis of a perturbation of the HPA axis resulting from exercise by FMS patients; however, they do not exactly support our assumption that this program would provide specific effects on the HPA axis, other than improvement of FMS symptoms. The increase in GH observed in this study might indicate a possible link between them. Nonetheless, the findings do verify our hypothesis that exercise can decrease FMS symptoms. Confirmation of this hypothesis was our secondary objective. AE programs with stretching and flexibility exercises were found to be similarly effective with regard to many of the clinical parameters assessed.

It is our belief that more accurate findings can be obtained by randomized controlled studies of larger samples and if possible more prolonged or higher intensity exercise.

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