

Impact of an intensive dynamic exercise program on oxidative stress and on the outcome in patients with fibromyalgia

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Objective

The aim of this study was to investigate the effectiveness of intensive dynamic exercises on the oxidative status in patients with primary fibromyalgia (FM) and to explore the importance of these effects on the outcome of FM.

Patients and methods

We measured levels of stress oxidants (protein carbonyls, nitric oxide, and thiobarbituric acid reactive substances) and antioxidant parameters (thiols and catalase) in blood samples from 40 FM patients and from healthy controls ($n = 25$) at presentation and after 12 weeks of intensive exercise program that comprised aerobic and strengthening exercises (lasting 1 h three times per week). In the patients, pain was assessed using the visual analog scale and tender points counts, and the Fibromyalgia Impact Questionnaire and the Beck Depression Inventory were applied at presentation and after 12 weeks of exercise therapy.

Results

At presentation, the serum levels of the oxidative stress parameters were significantly higher ($P < 0.001$), whereas the serum levels of antioxidant parameters were significantly lower ($P < 0.001$) in patients with FM than in controls. There was a higher significant decrease ($P < 0.001$) in the oxidative stress parameters following the 12-week exercise regime, whereas the antioxidant parameter levels showed a higher significant increase ($P < 0.001$) after the exercise treatment. Tender points, visual analog scale, Fibromyalgia Impact Questionnaire, and Beck Depression Inventory showed a higher significant ($P < 0.001$) improvement with exercise therapy.

Conclusion

Twelve weeks of intensive dynamic exercise program should be recommended to patients with FM as it was effective in decreasing the oxidative stress parameters, increasing the antioxidant parameters, and improving the clinical outcome of this disease.

Keywords:

exercise program; fibromyalgia; Fibromyalgia Impact Questionnaire; oxidative stress

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Introduction

Fibromyalgia syndrome (FMS) is a pain syndrome originating from the muscle and its connective tissues and it is characterized by widespread noninflammatory pain, cognitive dysfunction, fatigue, sleep disturbance, and a heterogeneous complex of somatic symptoms [1]. It is more common in women, with an estimated prevalence of 1–2% in the adult population [2]. FMS is still a disease of unknown etiology. There are many pathologic mechanisms, which are postulated as a possible etiology of FMS; one of them is local hypoxia, which is suggested to play a potential role in the pathophysiology of disease manifestations [3].

Free radicals are synthesized as a product of redox reactions and normally antagonized by means of enzymatic (e.g. catalase, superoxide

dismutase, and glutathione peroxidase) and nonenzymatic (e.g. vitamin E, vitamin A, vitamin C, glutathione, and uric acid) antioxidative mechanisms [4]. In some pathological conditions, free radicals may be present in excess as a result of increased protein degradation and lipid peroxidation, leading to tissue damage and altered membrane permeability. Oxidative stress refers to the shift in the balance between free oxygen species and antioxidant levels in favor of oxidation and may contribute to the pathogenesis of many diseases, including chronic fatigue syndrome and FMS [5,6].

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Protein damage in response to the oxidative stress leads to the formation of protein carbonyl (PC) derivatives, through either the α -amidation pathway or oxidation of the glutamyl residue, which are considered markers of protein oxidation [7]. Moreover, increased carbonyl stress is associated with decreased protein thiol (T-SH) group levels, which are considered a marker of antioxidant capacity [8].

Nitric oxide (NO) is an intracellular messenger molecule that is incorporated in many biological processes such as neurotransmission, vascular regulation, and metabolic regulation of exercise [9]. NO is found to modulate free radical levels in many cell varieties [10]. NO is suggested to play an important role in pain pathway and is believed to have a potential role in the pathogenesis of chronic pain syndromes [11].

Treatment of FMS includes patient education, exercise, cognitive behavioral therapy, and medications [12]. No definite individual or combined therapy has been proven to cause definite resolution of disease symptoms. However, exercise may have beneficial role in the management of FMS [13] as many patients are found to have impaired aerobic fitness and poor muscle strength [14,15].

Exercise was defined in a Cochrane review of exercise for the treatment of FMS to include aerobics, such as stepping and walking, and strengthening exercises such as resistance training and weight lifting and stretching for flexibility [13].

Many studies showed a relief of pain and fatigue and improvements in fatigue, mood, and sleep quality in patients with FMS treated with regular physical exercise [13,15,16]. Possible mechanisms of improved disease manifestation were attributed to improved tissue oxygenation and increased energy phosphate level [17,18].

The aim of this study was to investigate the effectiveness of intensive dynamic exercises on the oxidative status in patients with primary fibromyalgia (FM) and to explore the importance of these effects on the outcome of FM.

Patients and methods

This is a case-control study, followed by an interventional prospective study.

Participants

Forty-three female patients fulfilling the revised American College of Rheumatology (ACR) criteria for

FMS [19] were included as the study group from the inpatient and outpatient clinic of the Rheumatology, Rehabilitation and Physical Medicine Department of Benha University Hospitals between December 2014 and June 2015. Twenty-five age-matched apparently healthy nonsmoker women from the hospital personnel and medical and nursing staffs were also included as a control group. Inclusion criteria were as follows: ability to cycle; willingness to exercise three times weekly on a fixed schedule; having no serious psychiatric disease; and acceptance to complete a questionnaire.

We excluded patients with secondary FMS, smokers, patients with any condition that can interfere with exercising, such as severe chest, cardiac, neurological, or musculoskeletal diseases, those who had participated in regular exercise programs within 6 months before the study, and those who were taking antioxidants or antidepressant medications.

Patients' evaluation included full history taking, with the recording of the disease duration and thorough clinical, physical, and functional evaluation at presentation and after 12 weeks of the designated exercise program with particular focus on BMI. Visual analog scales (VASs) were used to evaluate pain intensity, and the tenderness points (TP) were evaluated and recorded over 18 specific body points by applying pressure (4 kg/cm²). Four-item Jenkins' Sleep Questionnaire to assess the sleep disturbance [20], Beck Depression Inventory [21], and the Modified Health Assessment Questionnaire (MHAQ) [22] were applied to all patients.

The Fibromyalgia Impact Questionnaire (FIQ) to assess the severity of FMS symptoms and the functional status was also used. It is a multidimensional instrument composed of 10 items (physical impairment, feel good, work missed, interference in job, pain, fatigue, morning tiredness, stiffness, anxiety, and depression) with a maximal total score of 100. A higher value indicates more impairment [23].

The local ethical committee of our institution (at Faculty of Medicine, Benha University) approved the study and all participants provided written informed consent before being enrolled into the study.

The exercise program

The exercise program was explained to patients to obtain their consent. The patients were guided and carefully observed during sessions for any complaint. In cases of extra pain lasting for more than 2 h and occurring within 24 h after training, the exercise load was temporarily decreased. The exercise program consisted of warming up for 10 min with peripheral

and spinal range of motion exercises associated with walking, followed by cycling using a stationary bicycle for 15–20 min. The target heart rate was initially adjusted to 60–70% of the age-adjusted maximal heart rate ($220 - \text{age in years}$), and then strengthening exercises to the upper limb, lower limb, and trunk muscles were performed using dumbbells, shoulder press, elevation of the shoulder against resistance, hip flexion and extension, and standing hip exercises using weights of 1–2 kg and two sets of 8–10 repetitions. The exercise session was concluded with a cooling-down period of 10–15 min of stretches, followed by relaxing exercises. The program took up to 45–60 min/session, three times per week for 12 week.

Three patients refused to complete exercise program and so were excluded from the study. Only 40 patients completed the exercise therapy and assessments at the allocated time.

Laboratory investigation

Blood samples were collected after overnight fasting from patients and controls in heparinized and nonheparinized tubes. Thereafter, serum and plasma specimens were stored at -80°C until analysis. Serum and plasma specimens were collected at baseline and at the end of the exercise program and analyzed for the following.

Measurement of protein carbonyl levels

PC levels in plasma were measured using Cayman's (Cayman chemical Michigan USA) Protein Carbonyl Colorimetric Assay Kit. The kit utilized the DNPH=2,4-dinitrophenyl hydrazine (DNPH) reaction as described by Levine *et al.* [24].

Measurement of thiobarbituric acid reactive substances

Thiobarbituric acid reactive substances (TBARSs) were measured in plasma by means of colorimetric determination of malondialdehyde, the product of lipid peroxidation, using Cayman's TBARS Assay Kit according to manufacturer's instructions [25].

Measurement of nitric oxide levels

NO production was determined by measuring total nitrate/nitrite, the stable end product of NO metabolism, in serum in a two-step process using BioVision's Nitric Oxide Colorimetric Assay Kit (#K262-200; Biovision Milpitas Blvd, Ca, USA) according to manufacturer's instructions.

Measurement of catalase activity

Catalase activity was measured in plasma using colorimetric method with catalase assay kit purchased

from Biodiagnostic Co. (Cairo, Egypt), according to the method of Aebi [26].

Measurement of thiol levels

T-SH levels were measured in plasma using the SensoLyte Thiol Quantitation Assay Kit (Anaspec inc, San Francisco USA) utilizing the widely used Ellman's reagent for colorimetric measurement of thiol concentrations according to manufacturer's instructions [27].

Statistical analysis

The collected data were analyzed using SPSS (version 16; SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages, whereas continuous variables were presented as mean and SD. Paired *t*-test, unpaired *t*-test, and Pearson's correlation coefficients were used as tests of significance. The results were considered significant at *P* value less than 0.05.

Results

Forty female FMS patients with a mean age of 39.3 ± 9.1 years (range: 23–55 years) and 25 age-matched apparently healthy women with a mean age of 38.7 ± 9.3 years (range: 22–53 years) were included in the study. Patients' clinical and laboratory features are shown in Table 1. The mean plasma and serum

Table 1 Comparison between the patient and control groups as regards clinical parameter and serum levels of protein carbonyl, nitric oxide, catalase and thiol before 12-week exercise therapy

Parameters	Patient group (n=40) (mean±SD)	Control group (n=25) (mean±SD)	<i>P</i> value
Age (years)	39.3±9.1	38.7±9.3	>0.05
Disease duration (years)	3.96±7.3	-	-
BMI (kg/m ²)	27.2±4.1	27.1±1.8	>0.05
TP	16.5±1.36	-	-
VAS	6.11±1.44	-	-
FIQ	57.44±16.2	-	-
BDI	23.65±12.50	-	-
Jenkins' Sleep Questionnaire	9.14±4.11	-	-
MHAQ	2.1±0.89	-	-
TBARS (μmol/l)	3.92±0.27	3.4±0.24	<0.001*
Protein carbonyl (mmol/mg)	1.5±0.62	0.72±0.32	<0.001*
NO	42.27±6.32	28.53±8.1	<0.001*
Catalase (kU/l)	39.03±8.03	50.65±9.84	<0.001*
T-SH (μmol/l)	259.28±46.12	391.70±75.96	<0.001*

BDI, Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; MHAQ, Modified Health Assessment Questionnaire; NO, nitric oxide; TBARS, thiobarbituric acid reactive substance; TP, tender points; T-SH, thiol; VAS, visual analog scale. *Highly significant (*P*<0.001). Unpaired *t*-test is the statistical test used.

levels of oxidative stress parameters were significantly higher at baseline in FM patients compared with their mean plasma levels in controls. The mean plasma and serum levels of NO, PC, and TBARSs were found to be significantly higher in the FMS group than in the control group ($P < 0.001$ and < 0.001 , respectively). The mean plasma levels of antioxidant capacity parameters were significantly lower in the FMS group compared with the control group. The mean catalase and T-SH plasma levels were found to be significantly lower in the FMS group compared with the control group ($P < 0.001$ and < 0.001 , respectively) (Table 1).

As regards the effect of the exercise program, all clinical parameters significantly improved with exercise. There was a statistically significant decrease in the mean VAS ($P < 0.001$), number of TP ($P < 0.001$), FIQ ($P < 0.001$), Beck Depression Inventory ($P < 0.001$), Jenkins' Sleep Questionnaire ($P < 0.001$), and MHAQ ($P < 0.001$) after the exercise program compared with their mean before the exercise program (Table 2).

As regards the effect of the exercise program on the oxidative stress parameters, there was a statistically significant decrease in the mean serum and plasma levels of NO, PC, and TBARS ($P < 0.001$) after the exercise program compared with their mean before the exercise program, whereas there was a statistically significant increase in the mean plasma levels of catalase ($P < 0.001$) and T-SH ($P < 0.001$) after the exercise program compared with their mean before the exercise program (Table 2).

The plasma PC levels at baseline showed a statistically significant positive correlation with TP ($r = 0.47$, $P < 0.05$), and plasma TBARS levels at baseline showed a statistically significant positive correlation with BMI ($r = 0.46$, $P < 0.05$), FIQ ($r = 0.48$, $P < 0.05$), and MHAQ ($r = 0.52$, $P < 0.05$) (Table 3).

Serum NO levels at baseline showed a statistically significant positive correlation with VAS ($r = 0.51$, $P < 0.05$), TP ($r = 0.54$, $P < 0.05$), FIQ ($r = 0.52$, $P < 0.05$), and MHAQ ($r = 0.53$, $P < 0.05$). There was a statistically significant negative correlation between catalase level at baseline and TP ($r = -0.45$, $P < 0.05$) and MHAQ ($r = -0.46$, $P < 0.05$) (Table 3).

Discussion

FMS is a chronic condition characterized by evident pain and somatic symptoms that may be associated with possible disability despite normal physical examination and laboratory and radiological investigations [28]. The underlying pathophysiology is multifactorial; potential

Table 2 Comparison between fibromyalgia patients as regards clinical parameter and serum levels of oxidative stress and antioxidant both before and after 12 week of exercise therapy

Parameters	Patients group before exercise therapy (n=40) (mean±SD)	Patients group after exercise therapy (n=40) (mean±SD)	P value
TP	16.5±1.36	6.5±1.21	<0.001*
VAS	6.11±1.44	4.53±1.33	<0.001*
FIQ	57.44±16.2	48.13±7.61	<0.001*
BDI	23.65±12.50	19.50±11.24	<0.001*
Jenkins' Sleep Questionnaire	9.14±4.11	5.4±3.28	<0.001*
MHAQ	2.1±0.89	0.31±0.80	<0.001*
TBARS (µmol/l)	3.92±0.27	3.14±0.52	<0.001*
Protein carbonyl (mmol/mg)	1.5±0.62	1.04±0.23	<0.001*
NO	42.27±6.32	31.53±5.1	<0.001*
Catalase (kU/l)	39.03±8.03	53.05±13.89	<0.001*
T-SH (µmol/l)	259.28±46.12	342.40±55.96	<0.001*

BDI, Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; MHAQ, Modified Health Assessment Questionnaire; NO, nitric oxide; TBARS, thiobarbituric acid reactive substance; TP, tender points; T-SH, thiol; VAS, visual analog scale. *Highly significant ($P < 0.001$). Paired *t*-test is the used statistical test.

Table 3 Correlation between oxidative stress parameters at baseline and different variables in fibromyalgia syndrome patients

	Protein carbonyl	TBARS	NO	T-SH	Catalase
Demographic variables					
Age	0.23	0.21	0.21	-0.12	-0.17
Disease duration	0.26	0.18	0.24	-0.23	0.12
BMI	0.09	0.46*	0.05	0.12	0.14
Disease-related variables at baseline					
VAS	0.22	-0.35	0.51*	-0.12	-0.28
TP	0.47*	0.42	0.54*	-0.25	-0.45*
FIQ	0.26	0.48*	0.52*	-0.34	-0.32
BDI	0.32	0.38	0.28	-0.096	-0.18
Jenkins' Sleep Questionnaire	0.25	0.32	0.15	-0.25	-0.17
MHAQ	0.34	0.52*	0.53*	-0.34	-0.46*

BDI, Beck Depression Inventory; FIQ, Fibromyalgia Impact Questionnaire; MHAQ, Modified Health Assessment Questionnaire; NO, nitric oxide; TBARS, thiobarbituric acid reactive substance; TP, tender points; T-SH, thiol; VAS, visual analog scale. *Spearman's correlation coefficient (*r*) denote significant correlation.

etiologies may include central sensitization, alteration in the autonomic nervous system, genetic predisposition, neurotransmitter imbalance, dysfunction of the hypothalamic–pituitary–adrenal axis, pain modulation, and oxidative stress [9].

Oxygen radicals, such as superoxide anion and hydrogen peroxide, are produced mainly in the mitochondria [29]. About 1–4% of oxygen that react with the respiratory chain is involved in the production of superoxide radicals (O_2^-) [30]. Free radicals can play both beneficial as well as deleterious

roles. At low physiological levels, it plays a potential role as a messenger in some of the intracellular signal transduction pathways [31]. However, when produced in excess, it can cause oxidative damage to many cellular components through macromolecule modification such as lipid peroxidation and protein oxidation. There is a dynamic relationship between production of free radicals and antioxidant capacity. Oxidative stress occurs when the antioxidant capacity fails to neutralize the deleterious effect of free radicals [32].

In our study, serum levels of the oxidative stress parameters were statistically significantly elevated in FMS patients compared with their levels in the serum of healthy controls. Moreover, FMS patients had a significantly lower antioxidant capacity as compared with healthy controls. We also found these levels to be significantly correlated with the clinical and functional parameters of the disease, especially pain, TP, and FIQ. Our results confirmed the results reported by other studies [4,33,34].

Wang *et al.* [35] suggested that peripheral and central sensitization can be mediated by the oxidative stress that can cause hyperalgesia at both local and spinal levels. In addition, isoprostanes, a product of lipid peroxidation, can cause increased excitability of type C nociceptors [36].

Cells of the central nervous system may be more sensitive to the deleterious effect of free radicals compared with other body organs due to their high rate of metabolic activity and a low level of antioxidant capacity, and the high concentrations of oxidizable unsaturated fatty acids in their cell membranes [37]. Moreover, free radicals and NO disturb the permeability of blood-brain barrier and increase excitability of dorsal root ganglion [9].

Not all studies reported increases in the oxidative stress parameters in FMS patients. Chung *et al.* [38] measured F2-isoprostane in the urine of 48 FMS patients for evaluation of the oxidative stress and found no significant difference as compared with the control group. They attributed this discrepancy to the difference in the molecule (F2-isoprostanes) measured to assess the oxidative stress.

In our study, all clinical parameters, such as pain, TP, FIQ, sleep disturbance, and depression showed a significant decrease ($P < 0.001$) following the 12-week exercise regime as compared with their levels at baseline. Many studies have shown the benefit of different types of exercises in the management of FMS with improvement of the quality of life and reduction of pain in patients with FMS [34,39,40].

McLoughlin *et al.* [41] confirmed the association between reduction in pain perception and the increase in the accelerometer-monitored physical activity. The pain reduction related to aerobic exercises is usually termed exercise-induced analgesia, which can be explained by activation of the sympathetic nervous system, which may be linked to supraspinal pain modulatory mechanism [42] as endogenous opioids may be released along adrenaline, leading to temporary analgesic effect [43].

Dinler *et al.* [44] found aerobic exercises to reduce pain and fatigue due to increased peak oxygen uptake, and Busch *et al.* [45] reported strength and mixed exercises to be associated with marked improvements in the global well-being and physical function and they reported that the adverse events related to exercise such as pain and fatigue to be not uncommon.

Redondo *et al.* [46] applied an 8-week program consisting of aerobic, strength, and stretching exercises to FMS patients and they found improvement only in the FIQ and fatigue, whereas no improvement was found with regard to pain and depression. Alentorn-Geli *et al.* [47] also did not find any significant improvement with regard to FIQ, pain, fatigue, and depression following a 6-week program of aerobic and stretching exercises plus patient education. This discrepancy can be related to the shorter duration of their exercise program.

In our study, there was a significant decrease in the oxidative stress parameters TBARS, PC, and NO following the 12-week exercise regime as compared with their levels at baseline. T-SH and catalase levels also showed a significant increase ($P < 0.001$) following the 12-week exercise regime as compared with their levels at baseline. The same results were found by Sarıfakıoğlu *et al.* [34], who found a decrease in the oxidative stress parameters following an exercise program applied to 30 patients with FMS.

Although free radical production can be stimulated by means of acute exercises with a subsequent oxidative stress, many studies documented the upregulation of the antioxidant capacity as a result of repeated exercise training in an attempt to avoid future free radical increase [34,48,49].

Peake *et al.* [50] found skeletal muscles to be capable to adapt in response to repeated exercise by a process termed 'repeated bout effect' through modification of their cellular structure to become less susceptible to injury after repetition of the same exercise as noticed by decreased leukocyte cell surface receptor expression. Moreover, Ji *et al.* [51] reported that trained individuals

have lower oxidative stress parameters at rest and after exercise as compared with untrained individuals.

Previous studies investigated the effect of exercise on FMS and other studies evaluated stress oxidant levels in FMS patients. Only a previous study has assessed the relationship between exercise treatment and oxidative stress parameters in FMS patients [34].

In the current study, we found that a 12-week intensive exercise therapy is effective in improving the severity of the FMS symptoms and the functional status as well as reduction of the oxidative load in FMS patients, and so exercise regimen should be recommended and encouraged in these patients and we should focus on reducing oxidative stress in the treatment of FMS. Further studies are recommended with different exercise programs to obtain more results and select the best exercise regime that can reduce the oxidative stress.

In conclusion, 12 weeks of intensive dynamic exercise program should be recommended to patients with FM as it was effective in decreasing the oxidative stress parameters, increasing the antioxidant parameters, and improving the clinical outcome of this disease.

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Conflicts of interest

There are no conflicts of interest.

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