Intervention Program for Improving Insulin Sensitivity and Ameliorating Adipokines altered Serum Levels in Obese and Type-2 Diabetic Children

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Abstract
Objectives: To evaluate therapeutic yield of lifestyle intervention program on body mass index (BMI), insulin resistance (IR) and estimated laboratory markers in obese and diabetic children.
Patients & Methods: Thirty-five obese non-diabetic, 35 type-II diabetic and 20 control children and adolescents were studied. All study children underwent 12-weeks intervention consisted of dieting regimen, aerobic exercise with curcumin as herbal therapy. All patients gave blood samples for ELISA estimation of serum insulin, progranulin (PGRN), tumor necrosis factor-α (TNF-α), adiponectin and YKL-40 levels. Insulin resistance was measured by homeostasis model assessment (HOMA-IR). Body weight (BW), BMI and HOMA-IR score and laboratory parameters were determined at start and end of the intervention.
Results: At end of intervention, BW and BMI, and HOMA-IR variables and score were significantly decreased compared to baseline measures. Patients had significantly higher baseline serum levels of PGRN, YKL-40 and TNF-α, but significantly lower serum adiponectin levels than controls and in diabetics compared...
to obese children. At end of intervention, serum PGRN and YKL-40 levels were significantly decreased compared baseline levels, despite being still significantly higher than control levels. Serum PGRN and YKL-40 levels were still significantly higher in diabetics than obese patients. Serum levels of TNF-α were still significantly higher in patients than in controls and in diabetics than in obese patients. In comparison to baseline levels, serum levels of TNF-α were significantly lower in obese but non-significantly lower in diabetics. Serum adiponectin levels were significantly lower in diabetics and non-significantly lower in obese compared to control levels, but were significantly higher in obese and non-significantly higher in diabetics compared to their baseline levels with significantly higher levels in obese compared to diabetics.

Conclusion: The proposed intervention program allowed reduction of BW and IR and could ameliorate disturbance of adipokines serum levels in obese and diabetic children.

Keywords: Obesity, Type-2 diabetes, Children, Adipokines, Exercise, Curcumin

Introduction

Obesity includes a subset of individuals that can be classified as having metabolically healthy obesity. Lower levels of abdominal obesity and insulin resistance are the most consistent predictors of prevalent metabolically healthy obesity status (1). Rapid infant weight gain is associated with increases in visceral adipose tissue and abdominal subcutaneous adipose tissue, as well as total adiposity and the risk of obesity in middle adulthood (2).

Inflammation process may underlie the development and maintenance of diverse chronic diseases, including diabetes and atherosclerosis. Diabetes can in turn increase the risk of cardiovascular events which can be considered as the most important cause of death in diabetic population (3).

Obesity-induced inflammation acts as a reflex to altered metabolic homeostasis secondary to nutrient overload on the metabolic cells. It involves up-regulation of the genes encoding for cytokines, chemokines and other inflammatory mediators through activated transcription factors (4).

White adipose tissue was recognized as an endocrine organ and an important source of biologically active substances with local and/or systemic action called adipokines (5). Increased adipocyte number and adipose-tissue mass have been found to result in increased plasma adipocytokine level except adiponectin, whose plasma
concentration is actually low in obesity \(^6\). Inappropriate secretion of several adipokines by the excessive amount of white adipose tissue participates in induction and progress of obesity-related complications \(^5\).

Circulating progranulin (PGRN) levels are elevated in patients with type 2 diabetes (T2DM) \(^7\). Increased plasma PGRN levels are associated with impaired glucose tolerance rather than impaired fasting glucose \(^8\). Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), besides its proinflammatory property, high TNF-\(\alpha\) levels inhibits insulin transduction mechanism, thus leading to inadequate glucose metabolism, insulin resistance (IR) and obesity \(^9\). Because visceral fat is a source of TNF-\(\alpha\), obesity leads to increased production of this cytokine, which aggravates obesity and a vicious cycle is established leading to predisposition, onset and progression of T2DM along with IR \(^10\). Circulating concentrations of the proinflammatory chitenase-like protein, YKL-40, were significantly higher in obese normoglycemic and T2DM patients compared to lean volunteers \(^11\) and a role of serum YKL-40 was suggested in obesity-related low grade inflammation \(^12\). Recently, in 2016, increasing body mass index (BMI) in adult offspring born to women with diabetes during pregnancy was found to be associated to YKL-40 \(^13\).

Adiponectin has remarkable insulin sensitizing property \(^14\) as well as antiatherogenic action \(^15\), thereby playing an important role in delaying and suppressing the metabolic derangements, which result in IR, T2DM, metabolic syndrome \(^16\) and complications of diabetes including vascular \(^15\) and cardiac \(^17\) complications.

The current prospective comparative study aimed to evaluate the therapeutic yield of a lifestyle intervention consisted of dieting regimen and aerobic exercise with curcumin as a herbal therapy on BMI, IR and estimated laboratory markers in obese and diabetic children.

**Patients & Methods**

The present study was conducted at Departments of Pediatrics, Medical Biochemistry and Clinical Pathology, Benha and Tanta Universities since Sep 2014 till March 2016. After approval of the study protocol by the Local Ethical Committee and obtaining written fully informed parents' consent; 35 obese non-diabetic (Obese group) children and adolescents and 35 proved type-II diabetic children and
adolescents (Diabetic group) irrespective of their body mass index were enrolled in the study.

All enrolled patients underwent determination of weight (kg) and height (cm) and body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters according to last update of calculation model provided by Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. Obesity was defined according to the percentile of BMI adjusted for age and gender as follows: <85th percentile= average healthy weight, >85th-90th= at risk of being over-weight, >90th-95th percentile= overweight and >95th percentile=obese (18). The study also included 20 control healthy weight children with BMI <85th percentile of BMI adjusted for age and gender and free of medical diseases or inflammatory conditions and without family history of diabetes especially for first-degree relatives (Control group). Diabetes mellitus was assured or excluded depending on estimation of fasting blood glucose (FBG) and fasting serum insulin (FSI).

**Intervention program**

During 12-weeks intervention program both diabetic and obese children underwent the following interventional items:

**Aerobic fitness assessment**

Subjects completed a continuous incremental V.O\(_{2}\)\(_{\text{max}}\) protocol on a bicycle ergometer (MedGraphics BreezeSuite Ultima CPX, St. Paul, MN; and Lode BV Corival Recumbent V2, Groningen, The Netherlands). Bicycle ergometer testing was selected because of the ease of administration, and maximal treadmill exercise is well tolerated in obese adolescents. Initial power output was 20 W, and was increased by 10-20 W/minute until volitional fatigue. Pedal rate was maintained between 60-100 rpm during the test. V.O\(_{2}\)\(_{\text{max}}\) was defined as the highest V.O\(_2\) attained during the test when at least two of criteria were satisfied: 1) respiratory exchange rate >1, 2) heart rate (HR) >95% of age-predicted maximum, or 3) a plateau of V.O\(_{2}\)\(_{\text{max}}\). HR and blood pressure were monitored continuously during the test.

**Exercise session**

Sessions consisted of structured exercise including both aerobic and strength training three times weekly. Exercise consisted of 5–10 min for warm-up and
stretching, followed by 15–30 min of cardiovascular exercise using treadmill or bicycle ergometer, 10–20 min of strength training using weight stack equipment, and 5–10 min of cool-down and stretching. Participants were started at 15 min of cardiovascular exercise and 10 min of strength training exercise and encouraged to progress by 2–3 min every week until 30 and 20 min, respectively, was achieved.

**Lifestyle intervention**

After baseline testing, all subjects began a structured 3-month lifestyle intervention consisting of dietary modification and exercise. Intensive dietary counseling was provided weekly for the first 4 wk of the intervention, monthly subsequently until 3 months. A target caloric deficit of ~250.500 cal/d was recommended throughout dietary counseling. Dietary regimen consisted of diets composed of nutrients contributing to total energy as 55% carbohydrate, 15% protein, and 30% fat. Other lifestyle changes included calorie restriction by exchanging high-calorie snacks with low-calorie and low-fat snacks; cutting down meal portions and frequency of snack consumption; limiting sugar-based carbonated drinks and limiting the duration of television watching (19).

**Herbal therapy**

During the 12-week intervention program both diabetic and obese children received herbal therapy in the form of administration of curcumin 20 mg mixed with honey as a pellet to be taken trice daily. Dose of curcumin was adjusted according to the instruction of the University of Michigan Health System (20).

**Laboratory measurements**

Fasting venous blood samples were obtained under complete aseptic conditions from the antecubital vein. Blood sample was divided into 2 parts:

1. The first part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ml blood) to prevent glycolysis and plasma was separated by centrifugation for estimation of fasting blood glucose (FBG) by glucose oxidase method (21).
2. The second part was put in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at –20°C till ELYSA estimation of insulin concentrations (Enzymuntest Insulin, ES 600, Boehringer Mannheim) (22), progranulin (Human
progranulin, AdipoGen Inc., Seoul, Korea) (23), TNF-α (ELISA kit from Pelikine™ Inc., Concord, USA) (24), adiponectin (Abcam’s Human Adiponectin ELISA, San Francisco, USA) (25) and YKL-40 levels (Human Chitinase 3-like 1/YKL-40 PicoKine™ ELISA Kit, Valley Ave, Pleasanton, USA) (26).

**Evaluation of insulin resistance (IR)**

Insulin resistance was measured by homeostasis model assessment (HOMA). The HOMA-IR score was calculated as (fasting serum insulin (µU/ml) x [fasting plasma glucose (mg/ml)/18])/22.5; HOMA-index >2 is considered abnormal (27).

**Follow-up**

Body weight (BW), calculated BMI and HOMA-IR score and laboratory investigations were determined at time of start of intervention and at the end of the 12-weeks intervention program.

**Statistical analysis**

Obtained data were presented as mean±SD, ranges, numbers and ratios. Considering gender and age difference of white adipose tissue secretion of adipokines (28), estimated serum levels of studied adipokines were represented by Median Interquartile range. Results were analyzed using One-way ANOVA with post-hoc Tukey HSD Test and Chi-square test (X² test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

**Results**

The study included 35 obese children; 23 males and 12 females and 35 diabetic children; 21 males and 14 females with mean age of 12±1.9; range: 7-17 years and 20 controls; 11 males and 9 females of mean age of 12±2; range: 8-15 years. There was non-significant inter-group difference as regards age and gender distribution.

Baseline data showed significantly higher BW and BMI of study children compared to control children with non-significantly higher measures of diabetic children compared to obese children. At the end of intervention, both obese and diabetic children had lost weight with significant difference compared to baseline BW.
Mean percentage of decrease of BMI was 13.8 and 12.8% of baseline BMI in obese and diabetic children, respectively. Details of BMI data and its changes are shown in table 1.

**Table (1): BMI of enrolled children determined at time of enrolment and at end of intervention and percentage of BMI change**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Obese</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>38.5±7.1</td>
<td>62.4±5.2</td>
<td>63.6±6.6</td>
</tr>
<tr>
<td>P1 = 0.001</td>
<td>P1 = 0.001</td>
<td>P2 = 0.003</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>142±11.3</td>
<td>147±9.3</td>
<td>144.3±8.9</td>
</tr>
<tr>
<td>P1 = 0.064</td>
<td>P1 = 0.821</td>
<td>P2 = 0.11</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19±2.3</td>
<td>29±3</td>
<td>30.7±3.5</td>
</tr>
<tr>
<td>P1 = 0.001</td>
<td>P1 = 0.001</td>
<td>P2 = 0.239</td>
<td></td>
</tr>
<tr>
<td><strong>End of intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>38.5±7.1</td>
<td>60.6±7</td>
<td>55.4±8.1</td>
</tr>
<tr>
<td>P1 = 0.001</td>
<td>P1 = 0.001</td>
<td>P2 = 0.029</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19±2.3</td>
<td>27.4±3.2</td>
<td>26.6±3</td>
</tr>
<tr>
<td>P1 = 0.001</td>
<td>P1 = 0.001</td>
<td>P2 = 0.482</td>
<td></td>
</tr>
<tr>
<td>% of change of BMI at end of intervention</td>
<td>13.8±5.8</td>
<td>12.8±6.3</td>
<td>P2 = 0.492</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD; P1: significance of difference versus control group; P2: significance of difference versus obese group; P3: significance of difference baseline data of each group.

Baseline insulin resistance (IR) parameters were significantly higher in patients compared to controls and in diabetic compared to obese patients. The applied intervention program significantly improved insulin sensitivity as manifested in both
groups by significant reduction of IR parameters determined at the end of 12-w intervention compared to baseline IR data, despite being still significantly higher compared to control data. The response to the intervention program was more pronounced in obese than in diabetic patients as manifested by significantly reduced IR parameters in obese than in diabetics. Also, at the end of 12-w intervention no obese children, but 16 diabetic children had HOMA-IR index >2 with significantly higher frequency of patients had HOMA-IR index >2 at enrolment compared to at the end of the 12-w intervention. Details of measurements of IR parameters are shown in table 2.

Table (2): HOMA-IR data of enrolled children determined at time of enrolment and at end of intervention and percentage of BMI change

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Obese</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline FBG (mg/dl)</td>
<td>82.9±8.4</td>
<td>116.9±5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
<tr>
<td></td>
<td>FI (μIU/L)</td>
<td>2.2±0.3</td>
<td>4.45±1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
<tr>
<td></td>
<td>HOMA-IR index</td>
<td>0.44±0.1</td>
<td>1.29±0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
<tr>
<td>End of intervention FBG (mg/dl)</td>
<td>82.9±8.4</td>
<td>113.9±3.4</td>
<td>138.2±9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
<tr>
<td></td>
<td>FI (μIU/L)</td>
<td>2.2±0.3</td>
<td>3.66±1.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
<tr>
<td></td>
<td>HOMA-IR index</td>
<td>0.44±0.1</td>
<td>1.04±0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1=0.001</td>
<td>P1=0.001</td>
</tr>
</tbody>
</table>
Mean baseline serum levels of PGRN, YKL-40 and TNF-α were significantly higher in patients compared to controls with significantly higher levels in diabetic compared to obese patients. On contrary, mean baseline serum adiponectin levels were significantly lower in patients compared to controls with non-significantly lower levels in diabetic compared to obese patients.

At the end of 12-weeks intervention, serum PGRN and YKL-40 levels were significantly decreased in comparison to their baseline levels, despite being still significantly higher than control levels. However, serum PGRN and YKL-40 levels were significantly lower in obese compared to diabetics. As regards, serum levels of TNF-α estimated at the end of 12-w intervention were still significantly higher in patients than in controls and in diabetics than in obese patients. In comparison to baseline levels, serum levels of and TNF-α estimated at the end of the intervention were significantly lower in obese but non-significantly lower in diabetics.

On the other hand, serum adeponectin levels estimated at the end of the intervention were significantly lower in diabetics and non-significantly lower in obese compared to control levels. However, serum adiponectin estimated at end of intervention were significantly higher in obese and non-significantly higher in diabetics compared to their respective baseline levels with significantly higher levels in obese compared to diabetics. Details of laboratory findings of studied groups are shown in table 3.
Table (3): Laboratory findings determined at time of enrolment and end of intervention

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Obese</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGRN (pg/ml)</td>
<td>185 (165-210)</td>
<td>215 (196.5-251.5)</td>
<td>295 (265-317.5)</td>
</tr>
<tr>
<td></td>
<td>P1=0.001</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
<tr>
<td>YKL-40 (pg/ml)</td>
<td>43.9 (42.53-51.9)</td>
<td>69.4 (58.85-75.1)</td>
<td>78.3 (74.1-82.7)</td>
</tr>
<tr>
<td></td>
<td>P1=0.001</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>12.15 (9.5-13.9)</td>
<td>16.9 (12.5-21)</td>
<td>20.6 (18.3-24)</td>
</tr>
<tr>
<td></td>
<td>P1=0.001</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>8 (6.75-9.25)</td>
<td>6 (5-7)</td>
<td>4 (4-7)</td>
</tr>
<tr>
<td></td>
<td>P1=0.0018</td>
<td>P2=0.001</td>
<td>P3=0.077</td>
</tr>
<tr>
<td><strong>End of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGRN (pg/ml)</td>
<td>185 (165-210)</td>
<td>179 (167.4-210.1)</td>
<td>255.1 (223.7-269.7)</td>
</tr>
<tr>
<td></td>
<td>P1=0.001</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
<tr>
<td></td>
<td>P4=0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKL-40 (pg/ml)</td>
<td>43.9 (42.53-51.9)</td>
<td>59.2 (49.8-65.35)</td>
<td>70.2 (66.4-73.1)</td>
</tr>
<tr>
<td></td>
<td>P1=0.001</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
<tr>
<td></td>
<td>P4=0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>12.15 (9.5-13.9)</td>
<td>13.2 (10.9-14.2)</td>
<td>18.6 (14.2-21.85)</td>
</tr>
<tr>
<td></td>
<td>P1=0.604</td>
<td>P2=0.001</td>
<td>P3=0.001</td>
</tr>
</tbody>
</table>
Adiponectin (µg/ml) | P4=0.001 | P4=0.053
---|---|---
8 (6.75-9.25) | 7.25 (6.125-8) | 5 (4.7-8)

Discussion

The current study detected significantly higher BMI and HOMA-IR index, and estimated serum levels of progranulin (PGRN), YKL-40 and TNF-α with significantly lower serum adiponectin levels in obese and diabetic children compared to control children. These findings were in line with previous literature detected significantly higher YKL-40 levels in type-2 diabetics and type-2 obese diabetics than normo-glycemic lean subjects and in obese children with insulin resistance (IR) than in non-IR obese children. Also, Youn et al. reported significantly higher PGRN serum levels in T2DM patients compared to normo-glycemics. Moreover, the obtained results were in line with previous work detected significantly higher YKL-40 and PGRN in complicated diabetics than in non-complicated diabetics.

Baseline levels of estimated serum markers showed significant correlations with HOMA-IR index; thus indicating a relationship between obesity and/or diabetes and disturbed serum levels of adipo-cytokines. In line with such relations; Nielsen et al. found plasma YKL-40 levels were associated with FBG and plasma interleukin(IL)-6 levels, Hempen et al. reported that YKL-40 was correlated with HOMA-IR variables (fasting insulin and FBG), thus indicating its role in developing IR and T2DM. Also, Catalán et al. found that level of YKL-40 was associated with variables of IR and inflammation and Kyrgios et al. found serum YKL-40 levels were positively correlated with age, BMI, HOMA-IR index and WBC count, but HOMA-IR index remained significantly associated with YKL-40 levels after adjustment for other factors.

Similarly, Youn et al. detected correlation between circulating PGRN serum levels and BMI, macrophage infiltration in omental adipose tissue, CRP and total cholesterol concentrations and Li et al. found serum PGRN levels were
correlated positively with BMI, waist circumference, IR variables, glycated hemoglobin A1c, triglyceride, and HOMA-IR, and were inversely related to HDL levels. Xu et al. (35) found serum PGRN levels were positively and markedly correlated with disease duration, BMI, and triglyceride, IL-6, and TNF-α serum levels.

Intervention 12-week program changed the picture with significant decrease of the elevated BMI, HOMA-IR index and PGRN, YKL-40 and TNF-α serum levels, but significantly elevated the decreased adiponectin serum levels. In line with these findings; Catalán et al. (30) found that elevated circulating levels of YKL-40 were decreased after weight loss following a conventional hypocaloric diet. Youn et al. (32) found physical training significantly reduces elevated PGRN levels in T2DM patients. Carrel et al. (37) suggested that the school-based fitness oriented curriculum resulted in improved insulin sensitivity with decreased serum levels of inflammatory markers. Blüher et al. (38) found adiponectin, HDL, high-sensitivity CRP and PGRN displayed continued, cumulative significant improvement compared with baseline measures.

Nemet et al. (39) reported that BW, BMI, and BMI percentiles of obese children were significantly reduced and endurance time significantly increased following the 3 months combined nutritional-behavioral-physical activity intervention. Wang et al. (40) documented that in obese children the addition of aerobic exercise training to caloric restriction increased plasma adiponectin concentrations significantly than caloric restriction alone.

Starting structural exercise in conjunction with dietary regimen during the applied intervention could abolish the deleterious effects of weight reduction on muscle mass and contribute to obtain acceptable body countering which alleviates the psychological impact of obesity so pushing the child to continue the program. In support of such policy; Chomentowski et al. (41) documented that diet-induced weight loss significantly decreased muscle mass, however, the addition of moderate aerobic exercise attenuated the loss of muscle mass. Sgro et al. (42) suggested that an 8-week resistance training program is sufficient time to significantly change body composition, strength, and power measures in overweight or obese children. Also, Carrel et al. (37) suggested that the school-based fitness oriented curriculum resulted in improved body composition and muscle mass.

Brambilla et al. (43) documented that both diet and physical activity contribute to fat loss, but only physical activity affects fuel metabolism through increased fat oxidation causing prevention of IR or restoration of insulin sensitivity and increases
muscle mass. You et al.\textsuperscript{(44)} documented that exercise training in obese individuals reduces chronic inflammation. Also, Garnett et al.\textsuperscript{(45)} reported that exercise program reduced BMI and percent of body fat with increased insulin sensitivity index in obese adolescents at risk of T2DM in dependent on the extent of diet restriction. Also, Blüher et al.\textsuperscript{(46)} found the one-year combined exercise/lifestyle program significantly improved markers of obesity with glycemic control.

In trial to explore the underlying mechanisms for the beneficial effect of the applied intervention program; Wang et al.\textsuperscript{(40)} found aerobic exercise training caused increased adiponectin release from abdominal and gluteal subcutaneous adipose tissue. You et al.\textsuperscript{(44)} attributed the beneficial effect of exercise training to its effect on generation of muscle-derived anti-inflammatory 'myokine', improved adipose tissue hypoxia and reduction of local adipose tissue inflammation, leukocyte adhesion and number of pro-inflammatory cells and pro-inflammatory cytokine production per cell.

Na et al.\textsuperscript{(47)} found curcuminoids supplementation of type-2 diabetics for 3-months led to significant decreases in serum levels of CRP, TNF-\(\alpha\) and IL-6. Panzhinskiy et al.\textsuperscript{(48)} attributed the alleviating effect of curcumin on obesity-induced glucose intolerance to a novel curcuminoid which was found to augment insulin signaling, lower the endoplasmic reticulum stress, reverse palmitate-induced impairment of insulin signaling and resulted in higher energy expenditure without altering the respiratory quotient. As another mechanism; Ghorbani et al.\textsuperscript{(49)} attributed the curcumin induced reduction of blood glucose level to reducing hepatic glucose production, suppression of hyperglycemia-induced inflammatory state, stimulation of glucose uptake by up-regulation of glucose transmitters' genes expressions, activation of AMP kinase, improvement in pancreatic cell function and stimulation of insulin secretion, thus reducing IR.

It could be concluded that obesity, T2DM and disturbed adipokines serum levels constitute a vicious circle entrapping children. The proposed intervention program consisting of dietary restriction, structured aerobic exercise and curcumin significantly reduced body weight and insulin resistance and ameliorated disturbance of adipokines serum levels in obese and diabetic children. Continued application of the program may be advocated for achieving progressive resolution of obesity and control of diabetes and pro-inflammatory adipokines.
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IMPACT OF AN INTENSIVE DYNAMIC EXERCISE PROGRAM ON OXIDATIVE STRESS AND ON THE OUTCOME IN PATIENTS WITH FIBROMYALGIA

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Abstract:
Objective: The aim is 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. 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 control (n=25) at presentation and after 12 weeks of intensive exercise program that is comprised of aerobic and strengthening exercises (lasting one hour three times per week). In the patients, pain was assessed using the visual analog scale (VAS), tender points count (TP), the fibromyalgia impact questionnaire (FIQ) and the Beck depression inventory (BDI) were undertaken 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), while the serum levels of antioxidant parameters were significantly lower (p<0.001) in patients with FM than in the controls. There was a higher significant decrease (p<0.001) in the oxidative stress parameters following the 12-week exercise regime, while the antioxidant parameters levels showed a higher significant increase (p<0.001) after the exercise treatment. TP, VAS, FIQ and BDI showed a higher
significant (p<0.001) improvement with exercise therapy. **Conclusion:** Twelve weeks of an 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:** Fibromyalgia; oxidative stress; fibromyalgia impact questionnaire (FIQ); exercise program.

1- **Introduction:**

Fibromyalgia syndrome (FMS) means a pain syndrome originating from the muscle and its connective tissues and it is characterized by widespread non-inflammatory pain, cognitive dysfunction, fatigue, sleep disturbance, and a heterogeneous complex of somatic symptoms [1]. It is more common in females 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 enzymatic (e.g., catalase, superoxide dismutase, glutathione peroxidase) and non-enzymatic (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 shift of 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]

Protein damage in response to the oxidative stress leads to the formation of protein carbonyl derivatives through either alpha-amidation pathway or by oxidation of the
glutamyl residue—which are considered markers of protein oxidation [7]. Also, increased carbonyl stress is associated with decreased protein thiol (t-SH) groups 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 radicals levels in many cell verities [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 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, increased energy phosphate level [17, 18].

The aim is 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.

2- Patients and methods:
Type of study: it is a case control study followed by an interventional prospective study
2.1. 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 in-
patients and out-patients’ 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 non-smoker females from the hospital personnel, medical and nursing staffs were also included as a control group. Certain inclusion criteria should be presented in all participants, such as ability to cycle, willing 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 have participated in regular exercise programs within 6 months prior to the study, those who take antioxidants or antidepressant medications.

Patients’ evaluation included full history taking with the recording of the disease duration, thorough clinical, physical and functional evaluation at presentation and after 12 weeks of the designated exercise program, with particular focus on body mass index (BMI), visual analog scales (VAS) to evaluate the pain intensity, 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 (BDI) [21] and the modified health assessment questionnaire (MHAQ)[22] were assessed in all the patients.

The FM 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. Higher value indicates more impairment [23].

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

2.2. The exercise program:

The exercises program was explained to patients to get their cooperation and consent. The patients were guided and carefully observed during sessions for any complaint. In
cases of extra pain lasting for more than 2 hours and occurring within 24 hours after training, the exercise load was temporarily decreased. The exercise program consisted of warming up for 10 minutes of peripheral and spinal range of motion exercises associated with walking, followed by cycling using a stationary bicycle for 15-20 minutes, the target heart rate was initially adjusted to 60–70 % of the age adjusted maximal heart rate (220-age in years), 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 to 2 kg and two sets of 8–10 repetitions. The exercise session was concluded by a cooling down period of -10-15 minutes of stretches followed by relaxing exercises. The program took up 45-60 minutes per session, three times per week for 12 week.

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

2.3. Laboratory Investigation

Blood samples were collected after an overnight fasting from patients and control group in heparinized and non heparinized tubes. Then, serum and plasma specimens were stored at -80°C until analysis. Serum and plasma specimens are collected at baseline and at the end of the exercise program and analyzed for:

**Measurement of Protein Carbonyl (PC) Levels**

Protein Carbonyl levels in plasma were measured using Cayman’s Protein Carbonyl Colorimetric Assay Kit. The kit utilized the DNPH reaction as described by Levine et al. [24].

**Measurement of thiobarbituric acid reactive substances (TBARS)**

TBARS were measured in plasma by colorimetric determination of malondialdehyde (MDA) the product of lipid peroxidation using Cayman’s TBARS Assay Kit according to manufacture instructions (Armstrong and Browne)[25].

**Measurement of Nitric Oxide (NO) 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 Research Product, USA) according to manufacture instructions.

**Measurement of Catalase Activity**

Catalase activity was measured in plasma by colorimetric method using catalase assay kit purchased from Biodiagnostic Co., Cairo, Egypt according to the method of Aebi [26].

**Measurement of Thiol (T-SH) Levels**

T-SH levels were measured in plasma using The SensoLyte® Thiol Quantitation Assay kit (Ana Spc, Inc.) utilizing the widely used Ellman’s reagent for colorimetric measurement of thiol concentrations according to manufacturer’s instructions of the kit (Dickinson et al)[27].

**Statistical analysis:** The collected data were analyzed using SPSS version 16 (Chicago, SPSS Inc. U.S.) Categorical data were presented as number and percentages while 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 is considered significant at p value <0.05.

**3- Results:**

Forty female patients with FMS (ages ranged from 23 to 55 years) with a mean of 39.3±9.1 years, and twenty five age matched apparently healthy females (ages ranged from 22 to 53 years) with a mean of 38.7±9.3 years were included in the study. Patients’ clinical and laboratory features are shown in (Table 1). The mean plasma and serum levels of oxidative stress parameters were significantly higher at baseline in the FM patients compared to their mean plasma levels in the control. The mean plasma and serum levels of NO, protein carbonyl and TBARS were found to be significantly higher in FMS group than the control group (p<0.001 and p< 0.001, respectively). The mean plasma levels of antioxidant capacity parameters were significantly lower in the FMS compared to their
mean plasma levels in the controls. The mean catalase, and T-SH plasma levels were found to be significantly lower in FMS group compared to the control group (p<0.001 and p<0.001, respectively); (Table 1).

Regarding the effect of the exercise program, all the clinical parameters significantly improved with exercise. There was a statistically significant decrease in the mean VAS (p<0.001), number of tender points (p<0.001), FIQ (p<0.001), BDI (p <0.001), Jenkins’ Sleep Questionnaire (p <0.001) and MHAQ (p <0.001) after the exercise program compared to their mean before the exercise program; (Table 2).

Regarding the effect of the exercise program on the oxidative stress parameters, there were statistically significant decrease in the mean serum and plasma levels of NO, protein carbonyl and TBARS (p<0.001) after the exercise program compared to their mean before after the exercise program, while there were statistically significant increase in the mean plasma levels of catalase (p<0.001) and T-SH (p<0.001) after the exercise program compared to their mean before the exercise program; (Table 2).

The plasma protein carbonyl 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), 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), 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), MHAQ (r= -0.46, p<0.05); (Table 3).

Table (1): Comparison between patients and control groups as regards clinical parameter and serum levels of Protein carbonyl, NO, Catalase and T-SH before 12 week exercise therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient group:</th>
<th>Control group:</th>
<th>P-value</th>
</tr>
</thead>
</table>

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<thead>
<tr>
<th></th>
<th>n=40</th>
<th>n=25</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
<td><strong>Mean±SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>39.3±9.1</td>
<td>38.7±9.3</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Disease duration (Year)</td>
<td>3.96±7.3</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2±4.1</td>
<td>27.1±1.8</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>TP</td>
<td>16.5±1.36</td>
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<td>------</td>
</tr>
<tr>
<td>VAS</td>
<td>6.11±1.44</td>
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</tr>
<tr>
<td>FIQ</td>
<td>57.44±16.2</td>
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<tr>
<td>BDI</td>
<td>23.65±12.50</td>
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<tr>
<td>Jenkins’ Sleep</td>
<td>9.14±4.11</td>
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<tr>
<td>Questionnaire</td>
<td></td>
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<tr>
<td>MHAQ</td>
<td>2.1±0.89</td>
<td>--------</td>
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<tr>
<td>TBARS (µM)</td>
<td>3.92±0.27</td>
<td>3.4±0.24</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>Protein carbonyl (mmol/mg)</td>
<td>1.5±0.62</td>
<td>0.72±0.32</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>NO</td>
<td>42.27±6.32</td>
<td>28.53±8.1</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>Catalase (kU/l)</td>
<td>39.03±8.03</td>
<td>50.65±9.84</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>T-SH(µM)</td>
<td>259.28±46.12</td>
<td>391.70±75.96</td>
<td>P&lt;0.001*</td>
</tr>
</tbody>
</table>

BMI = Body mass index, TP = tender points, VAS = Visual analog Scale, FIQ = Fibromyalgia Impact Questionnaire, BDI = beck depression inventory, MHAQ = modified health assessment questionnaire, TBARS = thiobarbituric acid reactive
substance, T-SH= thiol, NO= nitric oxide,* Highly significant (p<0.001). unpaired t-test is the statistical test used

Table (2): Comparison between FM patients as regards clinical parameter and serum levels of oxidative stress and anti-oxidant both groups before and after 12 week of exercise therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients group before exercise therapy</th>
<th>Patients group after exercise therapy</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>n=40</td>
<td>n=40</td>
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<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP</td>
<td>16.5±1.36</td>
<td>6.5±1.21</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>VAS</td>
<td>6.11±1.44</td>
<td>4.53 ± 1.33</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>FIQ</td>
<td>57.44±16.2</td>
<td>48.13 ± 7.61</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>BDI</td>
<td>23.65±12.50</td>
<td>19.50 ± 11.24</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>Jenkins’ Sleep Questionnaire</td>
<td>9.14± 4.11</td>
<td>5.4 ± 3.28</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>MHAQ</td>
<td>2.1±0.89</td>
<td>0.31±0.80</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>TBARS (μM)</td>
<td>3.92 ± 0.27</td>
<td>3.14 ± 0.52</td>
<td>P&lt;0.001*</td>
</tr>
</tbody>
</table>
Table (3): Correlation between oxidative stress parameters at baseline and different variables in FMS patients.

<table>
<thead>
<tr>
<th></th>
<th>Protein carbonyl</th>
<th>TBARS</th>
<th>NO</th>
<th>T-SH</th>
<th>Catalase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I) Demographic variables:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.23</td>
<td>0.21</td>
<td>0.21</td>
<td>-0.12</td>
<td>-0.17</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.26</td>
<td>0.18</td>
<td>0.24</td>
<td>-0.23</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI</td>
<td>0.09</td>
<td>0.46*</td>
<td>0.05</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>II) Disease related variables at baseline:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>0.22</td>
<td>-0.35</td>
<td>0.51</td>
<td>-0.12</td>
<td>-0.28</td>
</tr>
</tbody>
</table>

TP= tender points, BMI= Body mass index, VAS= Visual analog Scale, FIQ= Fibromyalgia Impact Questionnaire, BDI =beck depression inventory, TBARS= thiobarbituric acid reactive substance, T-SH= thiol, NO= nitric oxide MHAQ =modified health assessment questionnaire, * Highly significant (p<0.001). paired t-test is the used statistical test
<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>FIQ</th>
<th>BDI</th>
<th>Jenkins’ Sleep Questionnaire</th>
<th>MHAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>0.47  *</td>
<td>0.26</td>
<td>0.32</td>
<td>0.25</td>
<td>0.34</td>
</tr>
<tr>
<td>FIQ</td>
<td>0.42</td>
<td>0.48  *</td>
<td>0.38</td>
<td>0.32</td>
<td>0.52</td>
</tr>
</tbody>
</table>
| BDI            | 0.54  * | 0.52  * | 0.28  | 0.15                         | 0.53   *
| Jenkins’ Sleep Questionnaire | -0.25 | -0.34 | -0.096 | -0.25                         | -0.34  |
| MHAQ           | -0.45* | -0.32 | -0.18 | -0.17                         | -0.46* |

TP= tender points, BMI= Body mass index, VAS= Visual analog Scale, FIQ= Fibromyalgia Impact Questionnaire, BDI =beck depression inventory, TBARS= thiobarbituric acid reactive substance, T-SH= thiol, NO= nitric oxide MHAQ =modified health assessment questionnaire, * Spearman’s correlation coefficient (r) denote significant correlation.

4. Discussion:

Fibromyalgia syndrome (FMS) is a chronic condition characterized by evident pain and somatic symptoms that may be associated with possible disability in spite of normal physical examination, laboratory and radiological investigations.[28]. The underlying path physiology is multifactorial, potential etiologies may include central sensitization, alteration in the autonomic nervous system, genetic predisposition, neurotransmitters 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 macromolecules modification as lipids peroxidation and proteins oxidation. There is a dynamic relationship between production of Free radicals and antioxidant capacity. Oxidative stress occurs when the antioxidant capacity fail to neutralize the deleterious effect of Free radicals [32].

In our study, serum levels of the oxidative stress parameters were statistically significantly elevated in the FMS patients compared to their levels in the serum of healthy controls. Also, FMS patients had a significantly lower antioxidant capacity as compared to healthy controls. We also found these levels to be significantly correlated with the clinical and functional parameters of the disease especially pain, tender points 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. Also, 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 than 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]. Also, 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 to 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 the clinical parameters, such as pain, tender points, FIQ, sleep disturbance and depression showed a significant decrease (p<0.001) following the 12-week exercise regime as compared to 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 of reduction of pain perception and the increase in the accelerometer-monitored physical activity. The pain reduction related to aerobic exercises is usually termed (exercised-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 that strength and mixed exercises to be associated with marked improvements in the global well-being and physical function while they reported that the adverse events related to exercise such as pain and fatigue to be not uncommon.

On the other hand, 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, while no improvement was found regarding pain and depression. Also, Alentorn-Geli et al.[47] did not found any significant improvement regarding 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, Protein carbonyl, and NO following the 12-week exercise regime as compared to 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 to their levels at baseline. The same results were found by Sarıfakoğlu et al. [34], who found a decrease in the oxidative stress parameters following an exercise program applied to 30 patients with FMS.

Although free radicles production can be stimulated by acute exercises with a subsequent oxidative stress, many studies documented the up regulation 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 receptors expression. Also, Ji et al. [51] found trained individuals to have lower oxidative stress parameters at rest and post exercise as compared to 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 have 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, 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 an 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.

Conflict of interest: None

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