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Effect of aerobic exercise on inflammatory markers in polycystic ovary syndrome: a randomized controlled trial

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Abstract. – OBJECTIVE: Chronic low-grade inflammation has emerged as a key contributor to the pathogenesis of Polycystic Ovary Syndrome (PCOS). In this regard, the present study examined the potential effects of aerobic exercise on interleukin-6 (IL6), tumor necrosis factor (TNF), and C-reactive protein (CRP) in PCOS women.

PATIENTS AND METHODS: This was a randomized clinical trial that included 40 females aged 25-35 years diagnosed with PCOS. The participants were divided into two groups equal in number: the aerobic exercise group (AEM), and the metformin group (M). The AEM group performed aerobic exercise three times a week for 12 weeks in addition to metformin treatment. The M group received metformin only. Participants were assessed for IL-6, TNF-α, and CRP at baseline and after 12 weeks of intervention.

RESULTS: The findings showed a significant reduction in IL-6, TNF-α, and CRP values in both AEM and M groups (p=0.001, p=0.01, respectively) after the end of the 12 weeks of the intervention. However, the participants who received aerobic exercise plus metformin, group AEM, showed a greater reduction in IL-6, TNF-α, and CRP (p=0.01, p = 0.01 and p=0.001, respectively).

CONCLUSIONS: Aerobic exercise is effective in lowering IL-6, TNF-α, and CRP in polycystic ovarian women. Further clinical trials are recommended to assess the potential effects of aerobic exercise on PCOS-associated risk factors.

Key Words:
PCOS, Aerobic exercise, Inflammation, IL-6, TNF-α, CRP.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive age, affecting 15-20% of women. Women present with two of the following three signs/symptoms-hyperandrogenism, persistent anovulation/oligomenorrhea, and polycystic ovaries in the absence of other diseases that promote these symptoms[1].

Women with PCOS have a clustering of cardiovascular risk factors such as insulin resistance, inflammatory markers, hypertension, impaired cardiopulmonary and autonomic function, and metabolic syndrome[2]. The metabolic syndrome is characterized by a group of cardiovascular risk factors such as arterial hypertension, insulin resistance, hyperinsulinemia, glucose intolerance/diabetes type II, and dyslipidemia (high LDL-cholesterol, high triglycerides, and low HDL-cholesterol)[3]. Women with PCOS have higher levels of inflammatory factors in their blood, like CRP and interleukin-6 (IL-6), compared to women who do not have the condition[4,5].

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A healthy lifestyle that includes exercise has been found to be effective in the treatment of polycystic ovary syndrome. Moderate aerobic exercise for more than or equal to three months decreases numerous cardio-metabolic risk factors in women with polycystic ovarian syndrome. Some of these factors include CRP and TNF[6].

Aerobic exercise has been shown to reduce inflammation[7]. However, very few studies have focused on how exercise affects adipose tissue inflammation[8]. Exercise training may induce a significant improvement in inflammatory marker levels[9]. There are several plausible mechanisms by which exercise could reduce inflammation. Long-term exercise has been shown to significantly increase antioxidant capacity in both humans and experimental animals, reduce the susceptibility of LDL-C to oxidation, reduce age-related impairment in nitric oxide availability, improve endothelial dysfunction, and decrease the expression of adhesion molecules on leucocytes[10,11].

Metformin was the first insulin-sensitizing drug used in PCOS to investigate the role of insulin resistance in the pathogenesis of this syndrome[12]. Metformin has been shown to play a critical role in improving insulin sensitivity and low-grade inflammation in PCOS (Diamanti-Kandarakis et al[13], 2006; Sirmans and Pate[14], 2013). The aim of this study was to examine the potential effects of aerobic exercise on IL6, TNF, and CRP in PCOS women.

Patients and Methods

Participants

Forty normal-weight women with PCOS [mean age of 26.7±2.3, body mass index (BMI) of 23.6±3.5 kg/m^2] were recruited from the Outpatient Clinic of Gynecology, Kasr Al-Aini University Hospital. The diagnosis of PCOS was assessed by the Rotterdam criteria[15]. Women with PCOS had to meet two of the following criteria: a medical history of hyperandrogenic oligo/amenorrhea (8 menses per year) and PCO on ultrasonography of more than 10 ovarian follicles 2-9 mm in diameter, or clinical hirsutism (a modified Ferriman-Gallwey score of 8 or higher was considered diagnostic of hirsutism)[16]. No participation in an exercise training program in the last 3 months had to be present with the exclusion of other disorders known to cause hyperandrogenism, such as congenital adrenal hyperplasia, thyroid dysfunction, and hyperprolactinemia. Additional exclusion criteria for this study were renal or hepatic dysfunction.

Study Design

Participants were randomized into a two-group, parallel, controlled clinical trial to assess the efficacy of a supervised aerobic exercise training intervention on interleukin 6, TNF-α, and C-reactive protein in women with PCOS, either in the anaerobic exercise group (AEM) or the metformin group (M). Outcomes were measured pre- and post-intervention.

Sample Size and Randomization

Based on prior studies[17,18], with a statistical power of 80% and an alpha of 5%, a total of 16 participants per group was needed for the study. We aimed for 20 individuals in each group, assuming a dropout rate of 20% (Figure 1). Randomly, the participants were placed in one of two groups: one that did aerobic exercise, and one that took metformin.

The Modified Ferriman-Gallwey

The original Ferriman-Gallwey system involved the scoring of 11 body regions, including the lip, chin, chest, upper abdomen, lower abdomen, upper arm, forearm, thigh, lower leg, upper back, and lower back. This was later modified (i.e., the modified Ferriman-Gallwey or mF-G method) to include only 9 body areas, thus excluding the forearm and lower leg, as these areas were found not to be correlated to androgen excesses. The clinical evaluation of hirsutism entails the use of visual scoring tools, of which the most widely used is the modified Ferriman-Gallwey (mFG) score. A score of 0 represents the absence of terminal hair growth, and a score of 4 represents extensive growth. A total score of 8 or higher constitutes hirsutism[14]. Hirsutism scores were assessed by a single investigator for all the subjects.

Transvaginal Ultrasonography

Transvaginal ultrasonography using a Toshiba Xario (Toshiba Medical Systems Corporation, Japan) equipped with a curved array transducer and a 3.5- to 5- MHz convex probe was systematically performed by the same investigator before the beginning of the study. The presence of multiple cysts (12 small follicles in each ovary, 2-9 mm in diameter) arranged peripherally and scattered throughout the dense core of stroma (the necklace

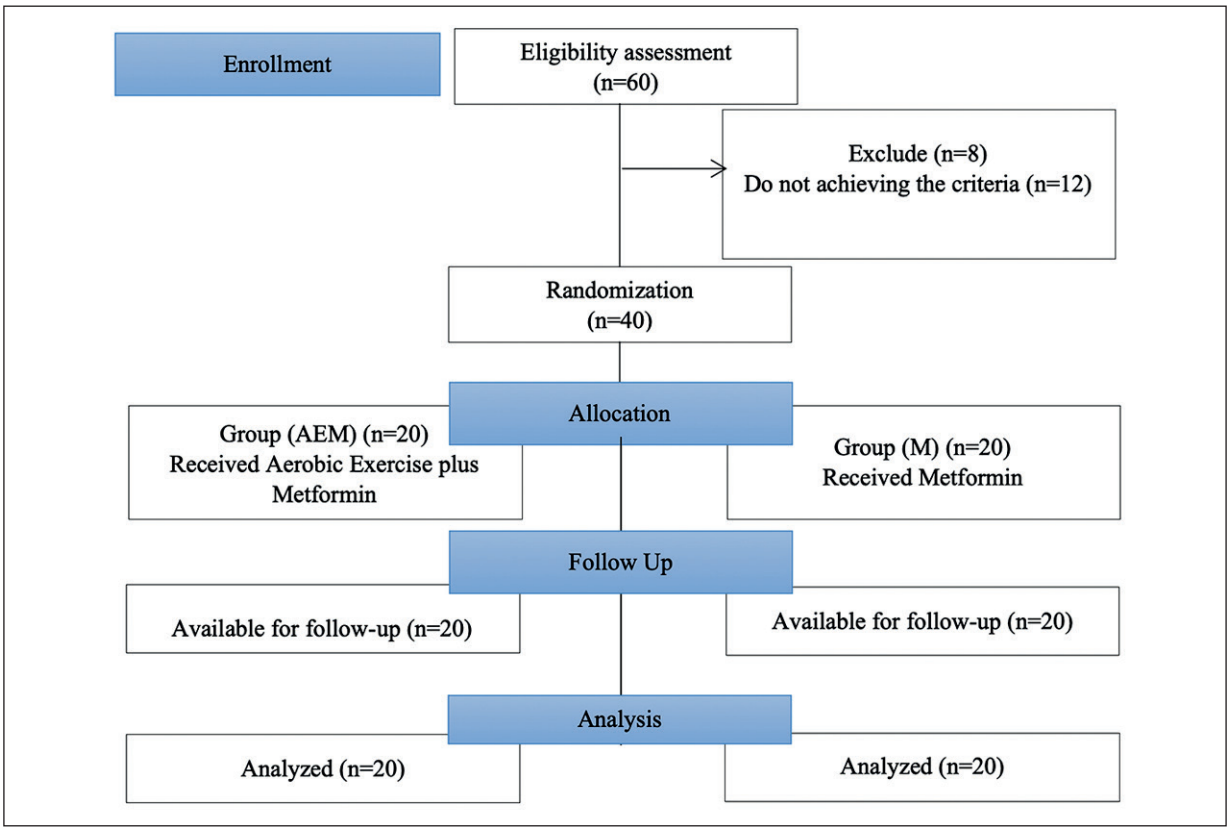

Figure 1. Flowchart demonstrates the experimental design of the study.

appearance of follicular cysts and/or increased ovarian volume > 10 mL) on pelvic or vaginal ultrasound examination was used to diagnose polycystic ovaries[19].

Biochemical Assays

In the morning, between 8 and 10 a.m. and after a 12-hour fast, blood samples were taken and placed in tubes containing EDTA. Plasma was separated by centrifugation at 4°C within 15 minutes at each clinic. Aliquots of plasma were immediately frozen at -80°C for measurements of CRP, IL-6, and TNF-α. IL-6 was measured with a high-sensitivity ELISA (Human IL-6 ELISA Kit; Medical and Biological Laboratories Co., Nagoyai, Japan). C-reactive protein (CRP) was determined by immunoassay (Immulite 2000™, Siemens Healthcare Diagnostics, Deerfield), and tumor necrosis factor-alpha (TNF-α) by immunoassay (Luminex 100™, Austin, TX, USA).

Procedures

All participants underwent a physical examination, transvaginal ultrasonography, and anthropometrical measurements, including height, weight, and body mass index (BMI), the ratio between the weight and the square of the height; the presence of hirsutism was recorded before the beginning of the study.

Participants who met the inclusion criteria were randomly assigned to one of the two groups. A computer-generated random table was used for randomization. At the baseline and after 12 weeks of the intervention, only one independent investigator, who was blinded to group allocation, conducted the testing procedures. Participants were randomly divided into two groups: the AEM group, who received aerobic exercise training on a treadmill in addition to metformin, and the M group, who received metformin only.

Supervised Aerobic Exercise for the AEM Group

Participants were given a separate familiarization session prior to the aerobic training session, during which they were introduced to the aerobic exercise protocol as well as all measurement procedures. A treadmill (Track Star, Incheon,

Table I. Patients demographic data.

	Group (AEM) (n = 20)	Group (M) (n = 20)	*t*-value	*p*-value
Age (yrs.)	29.4 ± 3.45	30.66 ± 2.96	-1.07	0.29^{NS}
BMI (kg/m^2)	28.55 ± 1.36	28.62 ± 2.20	1.05	0.93^{NS}
mFG Score	11.65 ± 3.42	10.69 ±2.52	1.43	0.82^{NS}
No. menses per year	6.23 ± 3.45	7.32 ± 2.66	1.03	0.89^{NS}

Note: Data are expressed as mean ±SD; NS: not significant; No.: number; yrs: years.

Korea) was used for walking aerobic exercise. All participants were allowed to hold a support bar if necessary. Participants assigned to the aerobic exercise group were invited to undertake three sessions of supervised exercise training each week for 12 consecutive weeks. Each session lasted approximately 60 min.

The aerobic exercises consisted in walking on the treadmill for 30 minutes at a 0% slope, including three phases: the warming-up phase, which consisted in walking on the treadmill for 5 minutes at low intensity (30% of MHR), the actual phase, which consisted in walking on the treadmill for 20 min at moderate intensity (60-70% of MHR), and the cooling phase, which consisted in walking on the treadmill for 5 minutes at low intensity (30% of MHR). The MHR was calculated according to the equation (220-age).

Metformin for AEM and M Groups

Both the AEM and M groups received metformin 1,500 mg daily for 12 weeks.

Statistical Analysis

The data are presented as mean±SD. Shapiro-Wilk test confirmed the normal distribution of the data. The baseline differences between groups were assessed using an independent samples *t*-test. The statistical analysis was performed using the Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). An unpaired *t*-test was performed to compare the mean values of different parameters between the two groups. A comparison between pretreatment and post-treatment data in the same group was performed using a paired *t*-test. A *p*-value lower than or equal to .05 was considered significant. Cohen's *d* was used for within group comparisons, where values of 0.20, 0.50, and 0.80 represented small, moderate, and large effect sizes[20].

Results

Baseline Characteristics of the Participants in Both Groups (AEM and M)

Table I shows the general characteristics of women in both groups, AEM and M, when enrolled in the study.

The Mean Values of IL-6 (pg/mL) Counted Before and After Intervention for Both Groups (AEM and M)

Mean values of IL-6 before and after intervention for both groups (AEM and M) showed statistically significant decreases in the AEM group (4.91±1.1 pg/mL, p=0.001, d=0.645) and the M group (5.05±1.22 pg/mL, p=0.01, d=0.533) after treatment compared with the corresponding value before treatment (6.33±1.15, 6.93±1.28 pg/mL). As shown in Table II, a comparison between both groups AEM and M showed a statistically non-significant difference in IL-6 (pg/mL) before the treatment (t=0.06, p=0.95) and a statistically

Table II. Mean values of IL-6 (pg/mL) for AEM and M groups before and after intervention.

	Group (AEM) (n = 20)	Group (M) (n = 20)	*t*-value	*p*-value
Before treatment	6.33 ± 1.15	6.93 ± 1.28	0.06	0.95^{NS}
After treatment	4.91 ± 1.1	5.05 ± 1.22	-5.03	0.01^{S}
t--value	10.9	8.6		
p-value	0.001^{s}	0.01^{s}		
d-value	0.645	0.533		

Note: Data are expressed as mean ± SD; *t*-value: unpaired *t*-test; *t*-- value: paired *t*-test; s: significant.

Table III. Mean values of TNF-α (pg/m) for AEM and M groups before and after intervention.

	Group (AEM) (n = 20)	Group (M) (n = 20)	*t*-value	*p*-value
Before treatment	12.14 ± 2	12.27 ± 1.66	-0.19	0.84^{NS}
After treatment	8.78 ± 1.3	11.11 ± 1.66	-6.09	0.01^{S}
t--value	14.06	1.48		
p-value	0.001s	0. 01^{s}		
d-value	0.554	0.522		

Note: Data are expressed as mean ± SD; *t*-value: unpaired *t*-test; *t*--value: paired *t*-test; s: significant; NS: non-significant.

significant difference after the treatment in favor of the AEM group (*t*=-5.03, *p*=0.01), as shown in Table II.

TNF-(pg/mL) Levels in the AEM and M Groups Before and After the Intervention

TNF-(pg/mL) mean values before and after intervention for both groups (AEM and M) demonstrated statistically significant decreases in the AEM group (8.78±1.3 pg/mL, *p*=0.001, *d*=0.554) and the M group (11.11±1.66 pg/mL, *p*=0.01, *d*=0.522) after treatment, compared to the corresponding value before treatment (12.14±2, 12.27±1.66 pg/mL). As shown in Table III, a comparison of both groups AEM and M revealed a statistically non-significant difference in TNF-α before treatment (*t*=-0.19, *p*=0.04) and a statistically significant difference after treatment in favor of group AEM (*t*=-6.09, *p*=0.01).

CRP (mg/L) for AEM and M Groups Before and After Intervention

The mean values of CRP (mg/L) before and after intervention for both groups (AEM and M) showed statistically significant decreases in AEM group (6.68±1.77 mg/L, *p*=0.001, *d*=0.640) and M group (8.28±2 mg/L, *p*=0.01, *d*=0.542) after treatment, compared with the corresponding values before treatment (10.14±2.39, 9.76±1.93 mg/L). The comparison between both groups AEM and M showed a statistically non-significant difference in CRP (mg/L) before the treatment (*t*=0.06, *p*=0.63) and a statistically significant difference after the treatment in favor of group AEM (*t*=1.67, *p*=0.001), as shown in Table IV.

Discussion

PCOS is a pro-inflammatory condition. TNF-α, IL-6, and C-reactive protein levels in the blood have been found to be elevated in obese PCOS patients[21, 22], indicating a low-grade inflammatory pattern[13].

Inflammatory markers are elevated in both lean and obese PCOS patients, indicating that the inflammation seen in PCOS might be linked to the presence of the disorder rather than obesity[23]. In people with PCOS, inflammation may be caused by both obesity and high levels of androgens[24]. Furthermore, our study is the first to demonstrate the effect of aerobic exercise on inflammatory markers in PCOS patients with normal body mass index.

The results of this study showed a significant decline in IL6, CRP, and TNF- in the AEM group who received supervised aerobic exercise training in addition to metformin. This was supported by Covington et al[25], who showed that 16 weeks of aerobic exercise reduced circulating leukocyte inflammation and improved insulin sensitivity in women with PCOS. It is known that exercise training favorably modulates CRP levels in PCOS women. Benham et al[26] observed

Table IV. Mean values of total CRP (mg/L) for AEM and M groups before and after intervention.

	Group (AEM) (n = 20)	Group (M) (n = 20)	*t*-value	*p*-value
Before treatment	10.14 ± 2.39	9.76 ± 1.93	0.06	0.63^{NS}
After treatment	6.68 ± 1.77	8.28 ± 2	1.67	0.001^{S}
t--value	10.48	7.32		
p-value	0.001^{s}	0.01s		
d-value	0.640	0.542		

Note: Data are expressed as mean ± SD; *t*-value: unpaired *t*-test; *t*--value: paired *t*-test; s: significant; NS: non-significant.

a favorable statistical effect of exercise on CRP versus control (p=0.001). This finding is in agreement with another review[27] that found favorable effects of exercise on CRP (p=0.004). Palmefors et al[28] showed that there is sufficient evidence on aerobic exercise decreasing cytokines, particularly TNF-, and to some extent IL-6. The results of the present study are consistent with the findings of Giallauria et al[29], who indicated that exercise-induced improvement in both autonomic and cardiopulmonary functions negatively correlated with inflammatory markers, i.e., C-reactive protein levels and WBC count, strengthening the role of exercise in improving the cardiovascular risk profile and a decrease in CRP levels in PCOS women. Jafari and Taghian[30] added that aerobic exercise is useful in the management of PCOS. As a result, aerobic exercise is advised as an effective strategy for controlling PCOS and reducing its inflammatory and biochemical adverse effects. Exercise can help to reduce the inflammatory condition in women with PCOS. The anti-inflammatory role of exercise could explain its cardiometabolic protection in PCOS[31].

Some of aerobic exercises' anti-inflammatory properties could be linked to the regulation of cytokines released by adipose tissue, muscles, and mononuclear cells. TNF, IL-1, and Interferon Gamma (INFG) production by mononuclear cells may be reduced by intensive interval training, while anti-atherogenic cytokines (IL-10, IL-4, and TGF--11) production may be increased[32]. Although aerobic exercise causes an increase in oxidative stress, it improves the body's antioxidant defense in the long run by increasing antioxidant enzymes. These antioxidant properties help to keep high density lipoprotein cholesterol from oxidizing, which can lead to endothelial damage and inflammation[33]. In addition, a recent pilot study[34] has found that low-intensity aerobic exercise could improve ventilatory markers in elderly heart failure patients.

The results of our study revealed a significant decrease in IL-6, CRP and tumor necrosis factor in the M group who received metformin. Similar to our findings, decreased levels of CRP have been observed in women with PCOS who were receiving 1,000 to 2,000 mg of metformin daily[35]. Abdelbasset[36] has found that aerobic or resistance exercises combined with metformin could improve insulin sensitivity and maximal oxygen uptake in diabetic patients. Lin et al[37] observed a significant decrease in IL-6 levels after metformin treatment in PCOS women (IL-6 levels decreased from 28.05±3.26 to 22.04±2.76 pg/mL after metformin treatment in PCOS women, p=0.0342). Escobar-Morreale[l] confirmed that metformin may have beneficial effects on the inflammatory background associated with PCOS.

Limitations

This study had certain limitations, such as small sample sizes. The authors were not able to include other methods of physical exercise to compare different exercise programs (resistance training, mixed aerobic and resistance exercise).

Conclusions

The obtained results of the present study showed that women with PCOS benefit from performing aerobic exercise to reduce interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP). According to the findings of this study, aerobic exercise is beneficial in the management of PCOS and is indicated as an effective modality to control PCOS. Further clinical trials are recommended to assess the potential effects of aerobic exercise on PCOS-associated risk factors.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Approval

The Ethics Committee of the Faculty of Physical Therapy, Cairo University, approved this study (No. P.T.Rec/015/002014) and the study has been registered with ClinicalTrials.gov, ID: NCT05233514.

Informed Consent

All volunteers sign a written informed consent before participation.

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