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Effect of aerobic exercise on inflammation and sex hormones in obese polycystic ovarian syndrome women: A randomized controlled study

Wpływ ćwiczeń aerobowych na stan zapalny i hormony płciowe u otyłych kobiet z zespołem policystycznych jajników: randomizowane badanie kontrolowane

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Abstract

Purpose. This study aimed to investigate the effect of aerobic exercise on inflammation and female sex hormones in obese PCOS women. **Materials and methods.** Forty volunteer obese PCOS women were participated in this study, their ages ranged from 20 to 35 years and body mass index (BMI) ranged from 30 to 34.9 kg/m², they randomly divided into two equal groups in numbers; group A, followed diet control therapy and group B, participated in an aerobic exercise three times per week and followed the same diet control therapy as group A. Both groups were evaluated before and after therapy (12weeks) through measuring their BMI, C-reactive protein (CRP), luteinizing hormone (LH), follicular stimulating hormone (FSH), LH/FSH ratio and modified Ferryman–Gallwey (mFG) scoring system for hirsutism. **Results.** showed that there was a statistically significant difference ($P < 0.05$) in both groups (A&B) in BMI, LH, FSH, LH/FSH ratio, CRP and mFG in favor to group (B) after therapy (12 weeks). **Conclusions.** revealed that aerobic exercises are effective in decreasing weight and inflammation which lead to improve fertility by improving female sex hormonal variables.

Key words:

Polycystic ovarian syndrome, Aerobic exercise, Follicular stimulating hormone, luteinizing hormone, C-reactive protein

Streszczenie

Cel. Badanie miało na celu sprawdzenie wpływu ćwiczeń aerobowych na stany zapalne i żeńskie hormony płciowe u otyłych kobiet z zespołem policystycznych jajników. **Materiały i metody.** W badaniu wzięło udział czterdzieści otyłych ochotniczek z zespołem policystycznych jajników, ich wiek wahał się od 20 do 35 lat, a wskaźnik masy ciała (BMI) wahał się od 30 do 34,9 kg/m². Uczestniczki podzielono losowo na dwie równe grupy; grupa A stosowała dietę i terapię kontrolną, a grupa B uczestniczyła w ćwiczeniach aerobowych trzy razy w tygodniu i stosowała taką samą terapię kontrolną i dietę jak grupa A. Obie grupy były oceniane przed i po zastosowaniu leczenia (12 tygodni) poprzez pomiar BMI, poziomu C-reaktywnego białka (CRP), hormonu luteinizującego (LH), hormonu folikulotropowego (FSH), stosunku LH/FSH oraz zmodyfikowanego systemu punktacji Ferryman-Gallwey (mFG) dla hirsutyzmu. **Wyniki.** Wykazano istotną statystycznie różnicę ($P < 0,05$) w obu grupach (A&B) pod względem BMI, LH, FSH, LH/FSH, CRP i mFG na korzyść grupy (B) po terapii (12 tygodni). **Wnioski.** Wykazano, że ćwiczenia aerobowe skutecznie zmniejszają wagę i stany zapalne, co prowadzi do poprawy płodności poprzez poprawę zmiennych hormonalnych płci żeńskiej.

Słowa kluczowe

Zespół policystycznych jajników, ćwiczenia aerobowe, hormon folikulotropowy, hormon luteinizujący, białko C-reaktywne

Introduction

Polycystic ovary syndrome (PCOS) is the most common complex endocrine disorder affecting approximately 10–15% of reproductive aged females [1]. The incidence of overweight and obesity in PCOS women ranged between 50 and 60% [2, 3]. Menstrual cycles are dependent on BMI, so ovulation can be highly affected by the increased weight [4].

PCOS Women have hyperandrogenism and insulin resistance (IR), which are associated with reproductive, metabolic, and psychological disorders. Also, the severity of PCOS is more likely experienced with obesity and central obesity compared with healthy women [5].

Also, PCOS is characterized by chronic low-grade inflammation and hyperandrogenemia that lead to metabolic and ovarian dysfunction [6]. The low grade of chronic inflammation, reflected in increasing levels of serum C-reactive protein (CRP), which has recently been linked to obesity, IR, and PCOS [7]. The underlying pathophysiology of PCOS is not fully determined, so, treatment is currently managed according to symptoms rather than targeting a special causal pathway [8].

PCOS is considered a proinflammatory state, and data suggests that chronic low-grade inflammation causes the development of metabolic aberration and ovarian dysfunction in the disorder [9–10]. So, inflammation directly stimulates excess ovarian androgen production. Increased abdominal adiposity leading to the inflammatory load in PCOS, and its development may be controlled by the severity of hyperandrogenism [11].

Exercise and diet, is the first-line of therapeutic approach in improving health outcomes in PCOS as regular, moderate-intensity aerobic exercise over a short period improves reproductive outcomes including ovulation and menstrual cycle regulation in addition to reducing weight and IR [12–14].

Hence, there is increasing interest in the use of aerobic exercise as a noninvasive, cost-effective and safe than drugs and surgical procedures for reduction of inflammation as exercise has important effect in lowering interleukin-6 and tumor necrosis factor alpha (TNF α), as well as CRP, which seen in different disease states and populations. Thus, exercise has an effect on adiposity which correlates strongly with the circulating inflammatory biomarkers. Consequently, it is feasible that inflammation is lower in physically active individuals primarily because of lower absolute amount of total and visceral body fat. Exercise regulates interleukins and related cytokines, including interleukin-6 and TNF- α , both of which are released by adipose tissue (as well as by peripheral blood mononuclear cells) and the former stimulates hepatic release of CRP [15].

But, no proved study was conducted to reveal the effect of exercise on inflammation in obese PCOS women, so this study was conducted hoping to reduce inflammation which accompanied with obese PCOS women, thus improving female sex hormones and also to provide an effective data for the field of physical therapy.

Material and Methods

Design of the study

The study was designed as a prospective, randomized, double blind, pre- post-test, controlled trial.

Participants

A convenient sample of forty obese PCOS female were recruited by a physician and referred to the physical therapy outpatient clinic, Abassya chest Hospital. They were enrolled and assessed for their eligibility to participate in this study. Their age ranged from 20 to 35 years and their body mass index (BMI) range from 30 to 34.9 kg/m². Subjects were excluded if they had hyperprolactinemia, Cushing's syndrome, thyroid dysfunction, malignancy and using hormonal therapy, anti-inflammatory, and weight reduction drugs. PCOS cases criteria done following Rotterdam Consensus Workshop, in which PCOS can be diagnosed when 2 of the following 3 features are present: *Oligo- or anovulation, *Clinical and/or biochemical signs of hyperandrogenism (i.e, hirsutism, acne, male pattern balding and elevated serum androgens), and *Polycystic ovaries by ultrasonographic examination [16, 17]. Written informed consent was obtained from each participant.

Randomization

A computer-generated randomized table was the method used to implement the randomization using the SPSS program (version 26 for Windows). Each participant had an identification number. These numbers were assigned into two groups equal in number. Sequentially numbered index cards were secured in opaque envelopes [18]. A blinded researcher opened the sealed envelope and allocated the patients according to their groups (figure 1).

Outcomes measurements

Prior to enter the study, each woman in both groups (A & B) made an ultrasonographic examination by LOGIC P 3 Ultrasound Machine with model number 2401359 and serial number 302179 wx7, to confirm the diagnosis of PCOS. Then, they underwent the following assessments before starting and after the end of the study (3 months):

- Weight and height were measured while the woman wore light clothes and bare feet, and BMI was calculating using this equation $\text{weight [kg]} / \text{height}^2 [\text{m}^2]$.
- Two blood samples were collected at the second day of menstruation, to measure the levels of the circulating LH and FSH by using Monoclonal antibodies and immunometric assay Immulite 1000, DPC® made in Germany by Siemens with technical specification of random access immunoassay and NycoCard reader II®, with model number 1113117, made in Sweden by Axis-shield Poc, used to measure CRP ratio.
- Modified Ferryman–Gallwey (mFG) scoring system in which 9 androgen-sensitive areas of the body tested to measure hirsutism. The score of each area from 0 to 4. A score of ≥ 8 shows the presence of hirsutism. the lip, chin, chest, upper abdomen, lower abdomen, upper arm, thigh, upper back, and lower back were the checked 9 body areas [19, 20].

Intervention

Group (A) received diet control therapy. Group (B) received aerobic exercises and prescribed diet as in group (A). All groups received the treatment three sessions per week for 12 weeks.

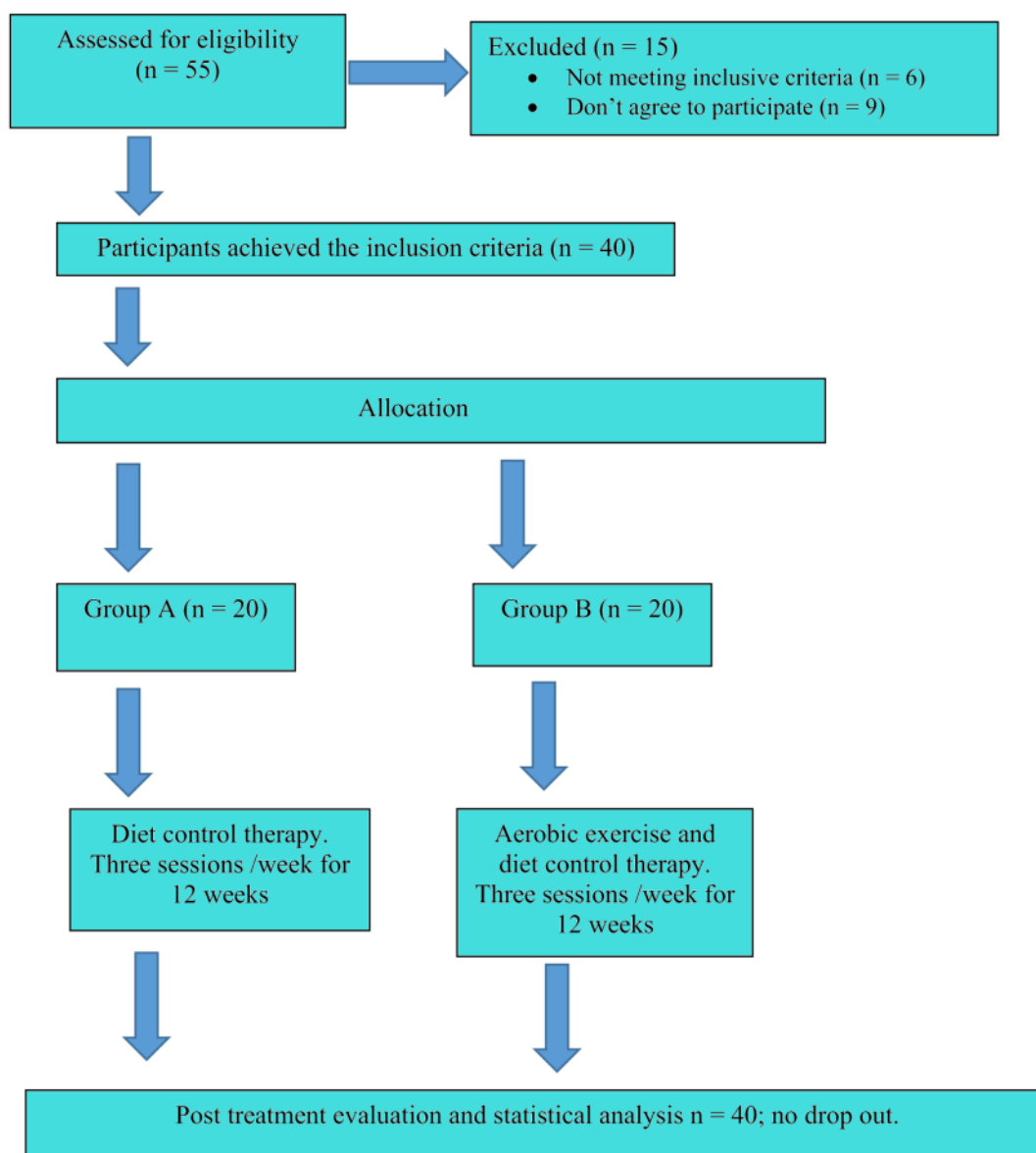


Figure 1. Flow chart of the study

Diet control therapy

Women in (A&B) group followed high-carbohydrate (55% calories) and low fat (30% of calories) with average protein (15%) diet (Hypocaloric diets) during the study period for 12 weeks [21], to permit the daily caloric requirement according to Harris-Benedict formula; (for women: $BMR = 655 + (9.6 \times \text{weight in kg}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$), then multiply the result by the activity multiplier $BMR \times 1.2, 1.375, 1.55, 1.725$ and 1.9 for sedentary, lightly active, moderately active, very active and extremely active; respectively [22]. After calculating the daily caloric requirement for each woman in the study, 500kcal/day was lowered in the 1st 6 weeks of the study and raised to 1000 kcal/day in the next 6 weeks, and the previous procedure was repeated in the beginning of each week according to current weight of each woman to determine her allowed caloric intake.

Aerobic exercises

Each woman in group (B) was instructed prior to each exercise session to evacuate her bladder to make sure that she was comfortable and relaxed throughout the session, wearing comfortable outfit and flexible shoes. Before starting the session, the therapist explained to them the sequence of the session. Exercise was applied on the treadmill and each session was divided into 3 stages; 1st stage (Warming up) of walking for 5 minutes at slow speed with zero inclination on the treadmill in the form of slow progressive exercise, 2nd stage (Active phase) of walking for 20 minutes with 15° inclination of the treadmill to achieve 70% of maximum heart rate (HR max) for each woman and 3rd stage (Cooling down or Recovery Period) at the same speed, time and inclination as 1st stage to reach resting level for heart rate.

Statistical analysis

The statistical Package for Social Studies (SPSS) version 26 for windows for data analysis performed for all measures. P-value ≤ 0.05 was considered significant. Paired t-test was carried out for comparison of mean values of variables before and after interventions in each group. Independent t-test was conducted to compare the mean values of variables between the two groups at the baseline

and post interventions. Results are expressed as mean \pm standard deviation.

Results

Statistical tests revealed no violations of the assumptions of normality and homogeneity of variance for any of the dependent variables. Results revealed non-significant differences ($P > 0.05$) between the two groups regarding to demographic characteristics as shown in Table 1.

Table 1. Demographic data of participants in all groups

Variables	Group A (N = 20)	Group B (N = 20)	T-value	P-value
Age [year]	28.6 \pm 2.4	28.23 \pm 1.98	0.141	0.888 ^{NS}
Height [cm]	160.24 \pm 12.14	167.23 \pm 11	0.777	0.442 ^{NS}

Data are represented as (Mean \pm SD); Level of significance at $P \leq 0.05$; NS - non significant

Within groups; there was a statistically significant differentiation in group (A & B) ($p < 0.01$) between the mean value of all measurements between pre and post treatment levels. Weight, BMI, LH, FSH, LH/FSH ratio, CRP and mFG scores was improved by percentage of 2.177%, 8.16%, 2.17%, 8.24%, 0.26%, 35.07% and 4.76% in group (A) while

24.78%, 5.036%, 12.34%, 6%, 33.39%, 6.06% and 22.11% in group (B) respectively. Between groups; At pre-treatment, there is a statistically no significant differentiation ($p > 0.05$), while at post-treatment, there was statistically significant difference ($P < 0.05$) in the values of all measurements between both groups (A&B) with favor of group (B).

Table 2. Mean values of the selected measures in both groups at pre and post treatment

Dependent variables		Group (A) (n = 20)	Group (B) (n = 20)	t-value	P-value*
Weight [kg]	Pre-treatment	80.4 \pm 1.649	87 \pm 1.62	1.334	0.190 ^{NS}
	Post-treatment	78.65 \pm 1.649	79.9 \pm 1.62	2.292*	0.0275 ^S
	p-value**	0.046 ^S	0.006 ^S		
	t-value	2.021*	3.129*		
BMI [kg/m ²]	Pre-treatment	32.2 \pm 0.606	32.22 \pm 0.606	1.666	0.104 ^{NS}
	Post-treatment	31.5 \pm 0.619	29.564 \pm 0.619	3.225	0.003 ^S
	p-value**	0.047 ^S	0.003 ^S		
	t-value	2.049	3.334		
LH [mIU/mL]	Pre-treatment	11.49 \pm 0.517	10.52 \pm 0.517	1.065	0.293 ^{NS}
	Post-treatment	11.46 \pm 0.429	6.83 \pm 0.429	3.791	0.000 ^S
	p-value**	0.902 ^{NS}	0.002 ^S		
	t-value	0.125	3.588		
FSH [mIU/mL]	Pre-treatment	6.92 \pm 0.413	6.022 \pm 0.413	1.019	0.315 ^{NS}
	Post-treatment	6.59 \pm 2.61	4.530 \pm 2.61	2.879	0.007 ^S
	p-value**	0.853 ^{NS}	0.001 ^S		
	t-value	0.187	3.701		
LH/FSH ratio	Pre-treatment	1.76 \pm 0.10	1.63 \pm 0.10	1.271	0.211 ^{NS}
	Post-treatment	1.85 \pm 0.10	1.43 \pm 0.10	3.239	0.002 ^S
	p-value**	0.845 ^{NS}	0.014 ^S		
	t-value	0.198	2.701		
CRP [mg/L]	Pre-treatment	9.82 \pm 0.64	10.45 \pm 0.64	1.211	0.233 ^{NS}
	Post-treatment	9.23 \pm 0.66	6.96 \pm 0.66	3.298	0.002 ^S
	p-value**	0.296 ^{NS}	0.014 ^S		
	t-value	1.075	2.702		
mFG scores	Pre-treatment	9.9 \pm 0.34	10.4 \pm 0.344	1.056	0.297 ^{NS}
	Post-treatment	9.3 \pm 0.276	8.1 \pm 0.276	3.31	0.002 ^S
	p-value**	0.104 ^{NS}	0.002 ^S		
	t-value	1.721	2.557		

Data are expressed as Means \pm SD. * Inter-group comparison; ** intra-group comparison of the results at the baseline and post treatment. NS $P > 0.05$ = non-significant, S $P < 0.05$ = significant, P = Probability.

Discussion

This study aimed express the effect of aerobic exercises on inflammation and sex hormones in obese women with PCOS. By assessing weight, BMI, LH, FSH, LH/FSH ratio, CRP and mFG for both groups (A&B) after 12 weeks of treatment. The net results of this study confirmed that there was significant differentiate in all measured parameters within the groups (pre vs. post- treatment), and also post- treatment there is a statistically significant differentiate between both groups (A&B) in favor of group (B).

In this study, patients follow the weight-loss diets for obese PCOS patients include highcarbohydrate (55% calories) and low fat (30% of calories) with average protein (15%). There was significant lower in weight in both groups (A&B) comparing pre and post- treatment data in the present study, approved that this type of diet control is usefull for PCOS patients with high BMI and this come in acceptance of Moran et al [21]. Before starting fertility treatment, lower weight through lifestyle modification is described as the first step for overweight/obese PCOS women [23].

BMI reduction after training program was statistically significant, this resulting is similar to the finding of Vigorito et al, Orio et al and Palomba et al. [24, 25, 26]

Positive effects of lowering the weight of PCOS patients by 5 to 10 percent from her initial weight on improving her hormonal profile and androgen levels explained by a lot of studies [27,28] which confirm the net results of this approach.

Through the present approach, the application of aerobic training for the study group expressed improvement in all measured parameter of weight, BMI, LH, FSH, LH/FSH ratio, CRP and mFG. This appear through the strong anti-inflammatory effect of aerobic exercise which decreases the CRP and BMI; which lead to improves the hormones of obese PCOS patients as LH/FSH ratio and level of androgens which decreases the hirsutism. This come with acceptance of Kelley et al. [29] evaluated the effects of training on mares through ovarian folliculogenesis and related hormones, which expressed that moderate training significantly stimulated stress response in mares and decreased levels of LH. Also Atuegbu et al [30] report that Physical exercise specifically causes suppression of hypothalamic pulsatile release of GnRH, limits release of (LH) and (FSH) which, in turn, limits ovarian stimulation and estradiol production.

Regarding the decrease on LH/ FSH ratio, in a study which conducted 8 weeks of combined diet and aerobic exercise, the

results showed acceptance with the results of the current study as there was weight loss ($p < 0.05$), body fat decreased ($p < 0.05$), and increased IR (32% increase, $p < 0.05$) and improvement in estradiol and LH: FSH ratio [31]. It was also found that moderate exercise may increase the sensitivity and responsiveness of the follicles to FSH and LH with an increase in the ovulatory status [32]. According to the present result, there were significantly lowered in the levels of CRP concentration in study group (B) which receive aerobic training and diet control therapy compared to the control group which receive diet only. And these findings the same of the findings of Koichi Okita et al. [33] and Thompson [34]. Also the finding of Michael et al [35] came in acceptance with the present study who suggested decrease in CRP levels regardless of the age or sex of the individual when engaged in exercise training; however, greater improvements in CRP level occur with a decrease in.

The study of Lakka et al [36] reported that Reduction in plasma C-reactive protein levels appear in response to exercise training in sedentary healthy adults with high initial C-reactive protein levels, who are known to have Type 2 diabetes and an increased risk of cardiovascular diseases. However, it is not same with the findings of Arsenault et al., [37] as they reported that exercise training did not reduce CRP. The effectiveness of exercise training to reduce CRP concentrations remains an unresolved issue.

There are some limitations in the current study that include a short treatment period and lack of long-term follows up for patients after treatment.

Conclusion

It was concluded that aerobic training therapy is an effective modality which can be added in the protocols of treating PCOS patients with high BMI; as it helps in lowering the inflammation noticed in PCOS patients; leading to lowering weight and CRP which help in normalizing the hypothalamic pituitary ovarian axe leading to lowering LH/FSH ratio and lower androgen secretion which in turn lower hirsutism.

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