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Modulation of hormonal, metabolic, inflammatory and oxidative stress biomarkers in women with polycystic ovary syndrome following combined (resistant and endurance) training: a randomized controlled trail

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Abstract

Purpose Polycystic ovary syndrome (PCOS) is a frequent disorder among women. Exercise training has been known as an effective treatment for this disorder; however, there is small amount of evidence examining the optimal exercise programs. We evaluated the function of combined (COM) training on metabolic, hormonal parameters, and biomarkers of oxidative stress and inflammation in PCOS patients.

Methods This randomized controlled clinical trial was conducted on 30 women with PCOS divided (age: 23.8 ± 5.3 years, height:162.8 ± 4.9 cm, weight: 82.4 ± 9.7 kg, body mass index: 30.3 ± 3.9 kg/m^2) into two groups to receive COM training intervention ($n = 15$) or control group ($n = 15$) for eight weeks. At the baseline and end-of-intervention, metabolic profiles including fasting plasma glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), lipid profiles, testosterone, free androgen index (FAI), sex hormone binding globulin, anti-Müllerian hormone, malondialdehyde, total antioxidant capacity, and high Sensitive-C reactive protein were evaluated.

Results After eight-week intervention in training group, insulin ($P < 0.001$), HOMA-IR ($P < 0.001$), total cholesterol ($P < 0.001$), LDL-cholesterol ($P < 0.001$), total testosterone ($P < 0.001$), AMH ($P = 0.02$),MDA ($P = 0.04$) and FAI ($P < 0.001$) were significantly decreased, while QUICKI ($P = 0.002$) was remarkably increased compared with the control group. Moreover, findings showed that there are no significant differences in other variables in the training group compared to the control group.

Conclusions We concluded that combined training is an effective training protocol (50%-70% 1RM for strength training and 60%-70 THR for endurance training) for treatment of PCOS, although further studies are needed to reach comprehensive data regarding the design of exercise protocols with different intensity and volume for PCOS patients.

Trial registration Registered retrospectively in the Iranian Registry of Clinical Trials (IRCT20130812014333N143) on March 22, 2020. Access at https://en.irct.ir/trial/46295.

Keywords Endurance training, Resistance training, PCOS, Metabolic biomarkers

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Introduction

Polycystic ovary syndrome (PCOS) is a hormonal and metabolic condition affecting women of a reproductive age with the prevalence 5–7% [1]. It was reported that PCOS increases the risk for cardio metabolic disorders, dyslipidemia, type 2 diabetes mellitus (T2DM), and hypertension. In addition, PCOS is accompanied by other issues such as more danger of little self-esteem, depression, stress, decreased quality of life, and poor body image [2]. The certain etiology of PCOS is unknown, though raised adiposity is documented to be vital. In fact, obesity is not the only factor that worsens the symptoms of this syndrome, but another important index called insulin resistance should be considered as another powerful factor. Approximately 40% of women with PCOS have a normal BMI (< 25 kg/m^2) and the prevalence of insulin resistance among lean women with PCOS is estimated to be around 75% [3].

An individual crucial etiological element causing the severity of reproductive and metabolic complications in PCOS is insulin resistance (IR). Moreover, obesity is a significant cause identified to intensify the severity of medical signs. Subsequently, impaired glucose tolerance and T2DM has two to eight times more risk of rising in women with PCOS than the women without PCOS [4]. Likewise, further severe IR has been seen in women with PCOS than weight-matched women without PCOS, though their greater predisposition to obesity may aggravate IR more and the additional metabolic and reproductive dysfunctions [5]. A delay in insulin production causes the production of internal androgens, and on the other hand, insulin resistance leads to hyperinsulinemia and a decrease in sex hormone-binding globulin (SHGB) and an increase in free testosterone (FT) in the blood circulation [6]. In addition, these patients have higher LDL-cholesterol and triglycerides levels and lower HDL-cholesterol levels. Existence evidence has revealed that increased oxidative stress and inflammatory markers such as C-reactive protein (CRP) in women with PCOS are linked with obesity and insulin resistance [7].

Therapeutic strategies are mainly aimed to improve anovulation and improving metabolic markers. Improved abdominal fat, IR, lipid profiles and hyperandrogenemia are also the main goals of the treatment. Most of the gynecologists have prescribed not only diet but also exercise as first-line treatments to recover overall health, hormonal outcomes, and quality of life in PCOS [6]. Generally, exercise is well-recognized as a treatment for inhibiting and handling chronic diseases [6] especially PCOS [8, 9]. Moran et al. (2019) in a study conducted on 221 women with PCOS, showed that weight loss of 63% of women with PCOS in the form of having a regular weight loss program was able to have many improvement effects in this disease [10]. Besides, numerous reports have shown that weight control in women with PCOS via frequent training and diet can relieve its clinical symptoms and decreases the onset of T2DM and cardiovascular disease (CVD) [9, 11, 12]. Considering the advantages of exercise involvement in other IR populations independent of weight loss, training may be extremely benefit in PCOS therapy [9]. A large amount of studies approves this claim; however, some trials have shown little or no advantages of exercises [2]. Additionally, exercise may represent advantageous impacts on body fat distribution in these individuals [9].

Human studies in PCOS have indicated that aerobic exercises or high-intensity interval training (HIIT) recommended for 12 to 24 weeks can potentially lead to significant clinical improvements, such as body fat percentage, insulin sensitivity, CRP, total cholesterol and LDL-cholesterol levels [7]. These trials have illuminated clinical practice guidelines prescribing PCOS patients to take part in more than 90 min of aerobic exercise weekly [13]. Kiel et al. (2020) conducted a clinical trial on women with PCOS in two centers (Norway and Australia) simultaneously and two protocols of high intensity and low volume interval (LV-HIT) and high intensity and high volume interval (HV-HIT) for 36 weeks were compared. The findings indicated the appropriate effect of the HV-HIT protocol on the health and fertility indicators of women in this group [3]. Additionally, CVD risk may be reduced by returning back the parameters including waist and hip (WHR) size, blood glucose, BMI, blood pressure, and lipid profiles. Combined aerobic and resistance exercise have been reported to be more beneficial than each one of them alone in ameliorating insulin sensitivity and glucose lowering as well as in decreasing abdominal fat in obese PCOS patients [14]. However, the effects of different exercise variables (intensity, volume and frequency) have not been well investigated. As decreasing weight is the primary recommendation for these patients leading to decline in androgen and insulin, as well as elevation in sex hormone binding globulin (SHBG) levels [15], providing insights into determining the best exercise intensities will advance the understanding of PCOS management [13]. In current study, we evaluated the impact of combined resistance and endurance (COM) training protocols on reproductive health, lipid profiles, insulin metabolisms, and biomarkers of inflammation and oxidative stress in PCOS patients.

Materials and methods

Study design

Current parallel randomized clinical trial was done from April to October 2020 on PCOS patients between the ages of 18 and 40 who referred to the gynecological clinic

of Imam Reza Hospital, Kermanshah, Iran. The statistical population included women with PCOS in Kermanshah city, who are selected based on the general call and completing the questionnaire and having the criteria to enter the research in an accessible and targeted manner. Inclusion criteria was performed by using Rotterdam criteria including oligo ovulation (period length more than 35 days), clinical or laboratory hyperandrogenism (clinical symptoms of hirsutism, acne and hair growth with a male pattern with increased testosterone or dehydroepiandrosterone levels), morphological appearance of PCOS in ultrasound of the ovaries [16]. Accordingly, from 36 eligible subjects who referred to the center, 6 people were excluded from the study due to not meeting the inclusion criteria (two patients due to ages more than 40 years, two patients due to very low physical fitness and two patients due to other metabolic disorders). The exclusion criteria were as follows: weight loss diet, taking oral contraceptive pills, smoking, and alcohol consumption, Having a history of hormonal and cardiometabolic diseases and hormonal and cardiometabolic drugs intake (within the last three month). Finally, 30 patients were selected to start the protocol. This study registered in the Iranian website of clinical trials with IRCT number: IRCT20130812014333N143, registration date: 2020,03,22.

We allocated 30 patients into two groups randomly for eight weeks: combined (COM) training group ($n=15$); and the control group ($n=15$) (Fig. 1). Sample size was based on the formula for calculating the sample size with a significance level less than 0.05 and statistical power above 80%. According to the previous trial [45], we used 4.4 μIU/ml as the SD and 3.5 μIU/ml as the change in mean (D) of insulin as a primary outcome. Based on the formula, we needed 12 participants in each group; after allowing for 3 dropouts in each group, the final sample size was 15 subjects in each group. Randomization was done from a computer-generated sequence, concealed in sequentially numbered, sealed, opaque envelopes, and kept by the gynecological clinic physician. At the baseline, subjects were required to have an ordinary diet throughout the project. We gave sufficient instructions to all the subjects about the positive effects of participating in the training protocol and follow-ups after ending this protocol, and we gave the necessary warnings about the lack of regular participation and the possibility of withdrawing from the research. Daily follow-ups were controlled by phone and SMS about time of gym. Paper consent was also taken from all contributors. Furthermore, N4 software modified based on the Iranian food pattern was used to obtain the nutrients intake of the patients based on the 3-day food report. In this way, the

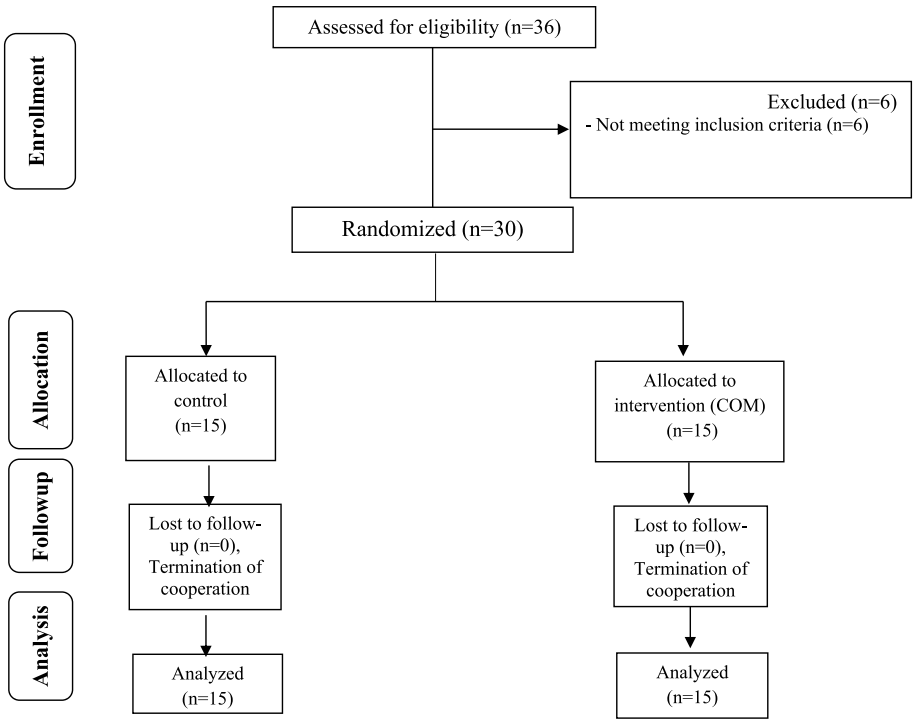

Fig. 1 Diagram of the progress through the phases of the parallel randomized trial of two groups (enrolment, allocation, follow-up, and data analysis)

aforementioned software controls the number of macronutrients (carbohydrates, protein and fat) and micronutrients (including water-soluble vitamins and fat and minerals).We used codes for each nutrient and weight of each nutrient was recorded in excel software and after collecting all data they were entered in the N4 software for final analysis. The protocol of this study was authorized by the Ethics committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (the code number: IR.kums.REC.1398.1186).

Exercise protocols

In the COM group, the resistance exercise schedule entailed 24 sessions of designated resistance trainings over eight weeks (3 times a week). The participants did eight altered exercises containing large muscle groups on the machines. These activities contain Bench press, Barbell curl, lying triceps press, lat pull down, leg press، leg extension, lying leg curl, and standing calf raise. Each training session includes a warming-up phase (5 min), a resistance training phase in the form of three sets (50–70% of one maximum repetition(1RM), 10–16 repetitions) for 30 to 40 min and lastly the cooling-down phase (5 min). Brzycki formula was used to measure 1RM as follows:

$$1\mathrm{RM} = \frac{\text{Weight of displaced}}{[1.0278 - (\text{Repeat to fatigue} * 0.278)]}$$

According to the training program shown in Table 1, the duration and intensity of training in the first week was 30 min and 50%, respectively and was added to the training time and intensity after each week until the training time reached 40 min and 70% in the eighth week. Instantly after resistance training, people were requested to do endurance training. The endurance training program was made up of 24 sessions of running on the treadmill (intensity of 60 to 70% of the target heart rate (THR). THR was calculated by means of the Carvonen formula:

$$\text{Reserve Heart Rate} = \text{Resting Heart Rate} - \text{Maximum Heart Rate}$$

$$\text{Target heart rate} = \text{Resting heart rate} + (60 - 70\%\ \text{reserve heart rate})$$

The heart rate of the subjects was checked during the training program by a Beurer pulse digital monitoring (made in Germany, model PM80). Giving the training protocol, the duration and intensity of training in the first week was 25 min and 60%, respectively and was being added to the training time and intensity after each week until the training time reached 40 min and 70% in the eighth week [11, 12, 17–20] (Table 1).

All training sessions were done in the morning between 9:30 and 11:30. The patients in the control group were also enquired to do only their normal daily accomplishments and avoid doing any sports activities throughout the program.

At the baseline and week eight, participants were tested for 1-Repetition Maximum (1RM) to determine muscle strength in the combined and the control groups. In the combined training group, the resistance training was performed with (50%–70% 1RM) and aerobic training (running, 60%–70% THR) programs were performed three times weekly for eight weeks. Multi stage fitness test (MSFT) was done to determine aerobic power on the treadmill. In this test, the speed of the subjects started from 8.5 km/h for one minute. In each stage, the patients' speed increased by 0.5 km/h. Finally, the aerobic power was calculated using the following formula:

$$\mathrm{VO_{2max}} = 6(\text{measured speed}) - 22.$$

Outcome's measurements

Insulin resistance was as the primary outcome, and other variables were as the secondary outcomes.

Table 1 Two training program (endurance and strength training) in eight weeks

Training programs	Weeks of training							
	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth
Endurance training								
Intensity (HRR), %	60	60	65	65	60	65	70	70
Duration (min)	25	30	35	30	35	40	35	40
Strength training								
Intensity (1RM), %	50	50	60	50	60	70	60	70
SET	2	3	3	3	3	3	3	3
Repetition	16	16	14	16	14	10	14	10
Rest (min)	1–3	1–3	1–3	1–3	1–3	1–3	1–3	1–3

Biochemical assessment

Blood samples after fasting were taken in the beginning and the end point followed by immediate centrifuging (Hettich D-78532, Tuttlingen, Germany, 3500 rpm, 10 min) to isolate serum. Then, the samples were kept at − 80 °C until next examinations. Enzymatic Kits (Pars Azmun, Tehran, Iran) were used to measure FPG and lipid profiles. FPG, TAC and MDA were measured in blood plasma, and other metabolic profiles were measured in blood serum. Commercial ELISA kits were applied to examine high Sensitive-C reactive protein (hs-CRP) (LDN, Germany), insulin, SHBG, and total testosterone (Monobind, California, USA). AMH concentration were measured by ELISA method and using kit (AMH-EIA; Beckman Coulter, Marseilles, France), FAI index was calculated by this formula:(TS/SHBG × 100). TAC concentrations were evaluated by using the Benzie and Strain method [21]. MDA concentrations of thiobarbituric acid–reactive substances were examined by a spectrophotometric test. HOMA-IR and QUICKI were quantified based on the standard formula [22].

Statistical analysis

The shapiro–wilk test was utilized defining the normality of data. One -way ANOVA test was used to assess treatment effects (pre-test and post-test in terms of Delta, Δ changes) on study outcomes and comparison between groups. Paired t-test tests were used to compare within groups differences. The effect size using Cohen's d used to validate our finding. Calculations were performed using SPSS software version 23 (SPSS Inc., Chicago, Illinois, USA) and the significance levels of the tests were considered as $P < 0.05$ in two-tailed test statistical analysis.

Results

As shown in the flow diagram (Fig. 1), 36 women with PCOS recruited in this study; however, 6 individuals were not eligible based on the inclusion criteria. Finally, 30 participants were allocated into 2 groups, 15 in each group. All of the patients completed the study.

Table 2 has shown general characteristics of patients. As indicated, there were no significant change between participants in terms of age ($P = 0.51$), height ($P = 0.74$), BMI ($P = 0.59$) and weight ($P = 0.34$) at study baseline.

After eight-week intervention in both training groups, insulin ($P < 0.001$), homeostatic model assessment for insulin resistance (HOMA-IR) ($P < 0.001$), total cholesterol ($P < 0.001$), LDL-cholesterol ($P < 0.001$), total testosterone ($P < 0.001$) (Fig. 2B), Anti-Müllerian Hormone (AMH) ($P = 0.02$) (Fig. 2A), Malondialdehyde(MDA) ($P = 0.04$) and free androgen index (FAI) ($P < 0.001$) (Fig. 2C) were significantly decreased, while quantitative insulin sensitivity check index (QUICKI) ($P < 0.001$) was remarkably increased compared with the control group (Table 3). Moreover, findings showed that there are no significant differences in fast blood sugar (FBS) ($P = 0.57$), Triglyceride(TG) ($P = 0.39$), High-density lipoprotein-cholesterol(HDL) ($P = 0.48$), Sex hormone binding globulin (SHBG) ($P = 0.16$) (Fig. 2), Total antioxidant capacity (TAC) ($P = 0.37$) and high sensitive-C reactive protein (HS-CRP) ($P = 0.24$) (Fig. 2D) in the training group compared to the control group. The result also showed that there are no significant differences in AMH ($P = 0.23$) and MDA ($P = 0.57$) after eight weeks of COM training in within group comparison (Table 3).

Table 2 General characteristics of the participants

Variables	Control group	Combined group	*P*value*
Age (y)	23.1±5.1	24.4±5.5	0.51
Height (cm)	162.6±5.5	163.1±4.5	0.77
Weight-baseline (kg)	84.1±6.3	80.7±12.2	0.34
BMI-baseline (kg/m2)	30.7±3.7	29.9±3.4	0.59

All values are means ± SD

BMI Body mass index

*Obtained from independent t- test

Discussion

In the current study, we assessed the influence of combined training protocol during eight weeks on insulin metabolism, lipid profiles, hormonal factors, biomarkers of oxidative stress and inflammation in women with PCOS. The current findings reveled that combined trainings significantly reduced insulin, total cholesterol, LDL-cholesterol, total testosterone levels and FAI, while significantly increased QUICKI score.

However, to our best knowledge, data on the influence of combined training protocols (strength and endurance) on metabolic profiles of women with PCOS are limited, we compared lifestyle interventions with control. These results are in accordance with prior systematic reviews which compared lifestyle interventions with control. Domecq et al. stated lifestyle modification decreased fasting blood glucose and insulin levels in subjects with PCOS [22]. Another review, Moran et al. shown that lifestyle intervention improved hyperandrogenism and insulin resistance in women with PCOS, but there was no evidence of effect for lifestyle intervention on improving lipid profiles or glucose tolerance and no literature assessing quality of life, clinical reproductive outcomes, and treatment satisfaction. While the PCOS diagnostic criteria do not presently consist of IR, it is extensively recognized that IR shows a main action in the pathophysiology of PCOS [23]. About 50–70% of women with PCOS have IR and hyperinsulinemia, while glucose intolerance

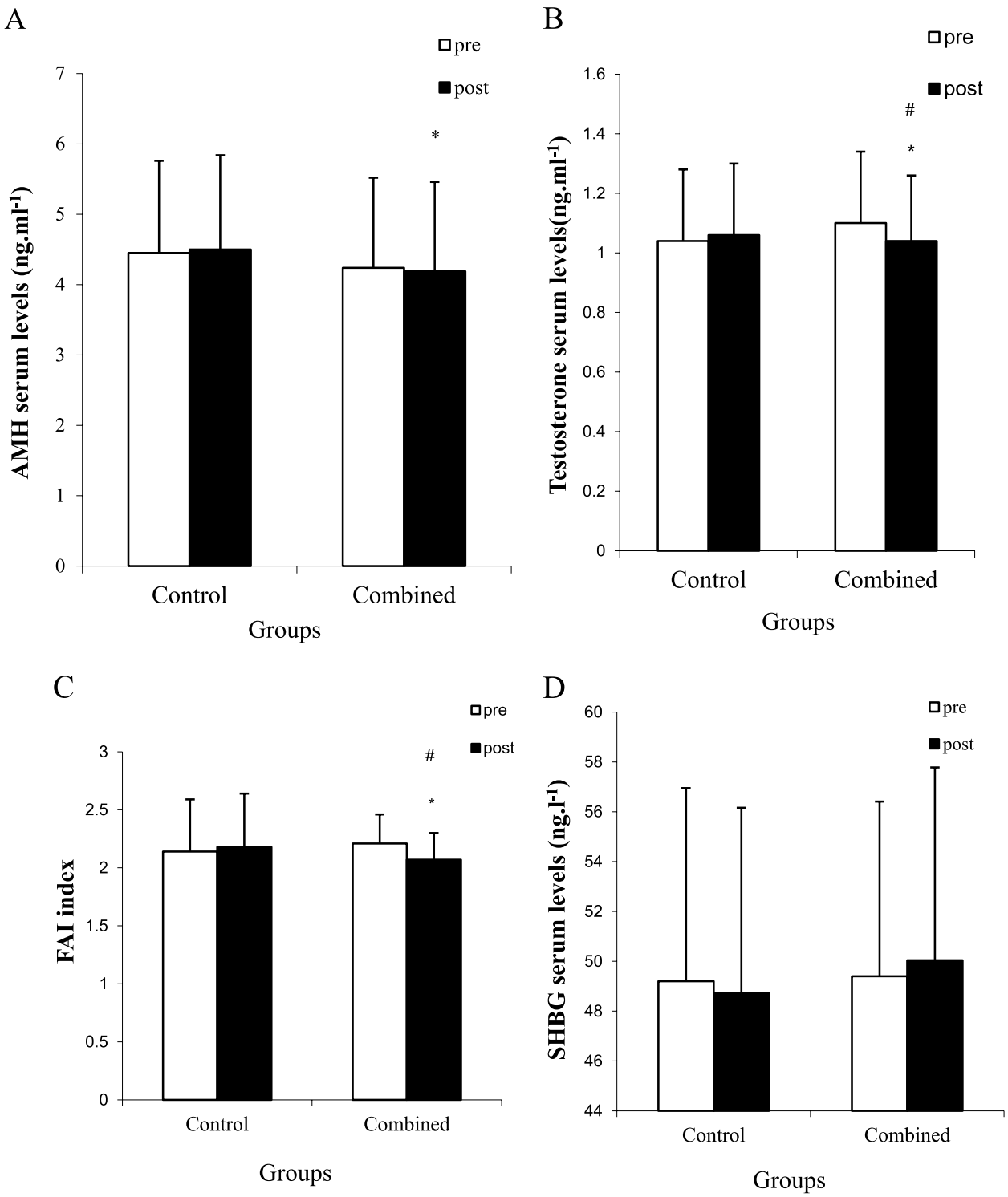

Fig. 2 Androgens and AMH profiles at baseline and after eight-week intervention in patients with PCOS. AMH, Anti-Müllerian Hormone; FAI, Free androgen index; SHBG, Sex hormone binding globulin. * Significant difference with pre-test ($p < 0.05$). # Significant difference with the changes of the control group (Δ) ($p < 0.05$)

Table 3 Metabolic profiles at baseline and after eight-week intervention in patients with PCOS

Variables	Control group				Combined training group				*P*value[b]	η
	Baseline	Week 8	Change	*P*value[a]	Baseline	Week 8	Change	*P*value[a]		
FPG (mg/dl)	98.53±4.44	98.86±4.71	0.33±1.56	0.25	97.86±4.12	97.30±4.08	0.56±2.04	0.57	0.31	0.03
Insulin (μU/ml)	11.03±1.65	11.08±1.61	0.05±0.49	0.38	11.23±1.56	10.48±1.46	−0.75±0.28	0.001	0.001	0.35
HOMA-IR	2.69+0.49	2.72±0.49	0.02±0.13	0.24	2.72±0.47	2.52±0.42	−0.19±0.08	0.001	0.001	0.35
QUICKI	0.33±0.009	0.32±0.009	−0.0003±0.004	0.25	0.32±0.008	0.33±0.008	0.002±0.004	0.006	0.002	0.29
Total-Chol (mg/dl)	170.73±12.76	171.03±12.65	0.30±1.44	0.19	171.66±13.27	162.13±13.43	−9.53±1.54	0.001	0.001	0.43
Triglyceride (mg/dl)	147.33±13.56	147.83±12.67	0.50±3.01	0.66	148.73±10.42	147.76±10.84	−0.96±4.42	0.18	0.39	0.02
LDL-C (mg/dl)	103.70±7.18	104.16±7.79	0.46±2.03	0.39	105.08±7.96	95.51±8.41	−9.57±2.23	0.001	0.001	0.68
HDL-C (mg/dl)	37.56±3.97	37.30±3.85	−0.26±1.48	0.11	36.83±5.81	37.06±5.81	0.23±1.07	0.76	0.48	0.01
AMH (ng/ml)	4.45±1.31	4.50±1.34	0.05±0.30	0.69	4.24±1.28	4.19±1.27	−0.05±0.18	0.23	0.02	0.16
Testosterone (ng/ml)	1.04±0.24	1.06±0.24	0.01±0.10	0.27	1.10±0.24	1.04±0.22	−0.06±0.05	0.001	0.001	0.47
FAI	2.14±0.45	2.18±0.46	0.04±0.24	0.29	2.21±0.25	2.07±0.23	−0.14±0.13	0.001	0.001	0.40
SHBG (nmol/l)	49.20±7.75	48.73±7.43	−0.46±1.71	0.24	49.40±7.01	50.04±7.74	0.64±2.25	0.34	0.16	0.06
MDA (μmol/l)	2.23±0.24	2.24±0.24	0.006±0.05	0.52	2.22±0.26	2.21±0.25	−0.009±0.04	0.57	0.04	0.14
TAC (mmol/l)	1.17±0.24	1.16±0.25	−0.01±0.03	0.86	1.13±0.21	1.14±0.21	0.01±0.06	0.07	0.37	0.02
hs-CRP (mg/l)	2.37±0.43	2.40±0.44	0.02±0.09	0.36	2.52±0.72	2.49±0.68	−0.03±0.13	0.42	0.24	0.04

P values calculated using two-way analysis of variance followed with Bonferroni' s post-hoc test

FPG Fasting plasma glucose, *HOMA-IR* Homeostasis model of assessment-insulin resistance, *QUICKI* Quantitative insulin sensitivity check index, *LDL-C* Low-density lipoprotein-cholesterol, *HDL-C* High-density lipoprotein-cholesterol, *AMH* Anti-Müllerian Hormone, *FAI* Free androgen index, *SHBG* Sex hormone binding globulin, *MDA* Malondialdehyde, *TAC* Total antioxidant capacity, *hs-CRP* high sensitive-C reactive protein

η Effect size of training protocol

*Obtained from ANOVA test. All values are means ± SD

[a] Significant difference with pre-test ($p < 0.05$)

[b] Significant difference with the changes of the control group (Δ) ($p < 0.05$)

has been also presented in these patients. Hyperinsulinemia in PCOS stimulates secretion of androgens from the ovarian theca cells in advance, though inhibits SHBG hepatic secretion, which in turn enhance free androgens and worsening the related symptoms [24]. Even though insulin links with IR, numerous investigations, particularly in normoglycemic people [25, 26], have revealed that HOMA-IR can be a superior evaluation of insulin sensitivity [27]. In the present study, the mean baseline HOMA-IR for intervention group' participants decreased after exercise with no sign of reduction in the control group. This recommends that exercise can have a clinically important result on IR compared with normal care. Participants were within normal FPG at starting point; thus, this joint with the influence on insulin shows that fewer insulin is required to keep normoglycemia after workout.

We observed COM training was successful in improving IR compared with control group. The enhancement in HOMA-IR after COM training was affected by reduced insulin levels, but without alteration in fasting glucose. Earlier randomized controlled trials were found no significant reduction in IR following moderate-intensity exercise for 12 weeks [28], dietary management and exercise, alone or in combination for 4 months [29], and low-frequency electro acupuncture and physical exercise for 16 weeks [30] in women with PCOS. In addition, Sprung et al. did not observe any significant change of moderate intensity exercise on IR in patients with PCOS for 16 weeks [31]. However, others have established a significant reduction in IR after the combination of moderate intensity exercise and diet interferences among subjects with PCOS for 20 weeks and 3 months, respectively [32]. Similar to our study, it has been observed in other insulin resistant cases that IR is affected more by HIIT relative to moderate intensity training [33]. It seems that intensity and volume of combined training are key factors in altering IR in these patients.

We also demonstrated that the combined training protocol significantly reduced total cholesterol and LDL-cholesterol levels, but did not affect other lipid profiles. LDL-cholesterol seems to perform a key part in atherogenesis, with increasingly growing danger of coronary heart disease (CHD) with elevated LDL-cholesterol concentrations [33]. We reported that exercise reduced triglycerides levels; however, it is not statically significant. Triglycerides are independent predictors of death-related CVD in women [34]; however, the amount of the detected exercise-induced triglycerides reduction is expected to have slight clinical significance. Prospect investigations are essential to examine the independent influence of exercise in women with hypertriglyceridemia. Generally, the important functions of physical fitness are linked to decreasing danger of cardiovascular dysfunction [35]. Hence, by exercise, PCOS patients can improve their cardiopulmonary capacity. Research of PCOS has established that lifestyle modifications should be considered in the treatment of these patients. Nevertheless, there is no agreement on the basic aspects of exercise training, containing its type, intensity, duration, frequency, and progression.

In the current study, FAI significantly reduced after COM intervention. In overweight and obese clomiphene citrate-resistant PCOS subjects, a 6-week intervention of structured exercise training and a hypocaloric diet reduced insulin sensitivity indexes and biochemical androgen [36]. However, in overweight and obese subjects with PCOS, the addition of aerobic or combined aerobic-resistance exercise to an energy-restricted diet for 20 weeks had no significant effect on hormonal, cardiometabolic, and reproductive variables relative to diet alone [32]. The current study revealed that anti-Müllerian hormone (AMH) and SHBG levels were not changed significantly after our intervention. Few prior studies have evaluated the impact of exercise training on AMH concentrations in women with PCOS. Similar to our study, Thomson et al. found no significant changes in AMH levels after a 20-week weight loss intervention in overweight/obese PCOS [36]. In contrast, Moran et al. observed a significant reduction in AMH levels following 12 weeks of exercise in PCOS women [37]. Nybacka et al. reported reduced AMH concentrations only after low-caloric diet intervention for 4 months, but not after exercise or after the combination of diet and exercise [38]. A larger cohort showed that a 16-week program with fast walking (three times a week) among patients with PCOS did not affect AMH concentrations [39]. In addition, HIIT did not improve testosterone levels in a 10-week intervention among subjects with PCOS [40]; however, in another study, a 12-week aquatic HIIT program ameliorated total testosterone, SHBG levels and FAI score [41]. Among the small number of studies investigating the effect of resistance training intervention, improvements in total testosterone levels were seen following progressive resistance training for 4 months among women with PCOS [42, 43]. Different factors, including baseline levels of AMH, SHBG, and total testosterone of study participants, study duration and ethnicity may influence the associations between training programs, and blood levels of these variables. Together, the current evidence suggests that combined resistance and endurance training may lead to improvements in testosterone levels. This proposes that exercises that improve muscle growth, mainly of glycolytic, and fast-twitch muscle fibers may increase the application of testosterone lowering its blood levels. On the other hand, aerobic training may

influence androgens. In addition, other mechanisms may account for these beneficial effects and promise future research. Furthermore, research in this area is limited, and future studies could reveal some beneficial aspects of exercise training on levels of these biochemical and hormonal status. The use of COM protocol with intensity of (50%−70% 1RM for strength training and 60%−70 THR for endurance training) for eight weeks is a strength of this study. This suggests combined training with these intensity and volume may confer advantageous therapeutic potential(improvement in insulin, total cholesterol, LDL-cholesterol, total testosterone levels, FAI, and QUICKI score) for women with PCOS that may determine clinically significant of these training protocol (combined instead of resistance and aerobic trainings alone) for these patients. The small sample size due to the lack of available subjects was one of the limitations of this study. Therefore, we suggest further similar studies with larger sample sizes. The training period was also another limitation that may have affected the results. Some other factors such as METs and energy expenditure that may have affected the body composition and lipid profiles were not controlled.

Conclusions

The results of our study indicated that combined training program with moderate intensity (50%−70% 1RM for strength training and 60%−70 THR for endurance training) is mor effective than positive effect of resistance and endurance trainings alone on insulin, total cholesterol, LDL-cholesterol, total testosterone levels, FAI, and QUICKI score. This suggests combined training with these intensity and volume may confer advantageous therapeutic potential for women with PCOS. Further research is needed in other participants including patients with metabolic syndrome and for longer periods to determine the beneficial effects of COM training. However, further studies are needed to reach a comprehensive data regarding the design of exercise protocols for PCOS patients.

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Authors' contributions
M.N., S.A.M.; Conceptualization, Methodology, Software. A.A.M.; Data curation, Writing- Original draft preparation, and Supervision. M.N., Z.A.; Visualization, Investigation. A. A.M.; Software, Validation. A.A.M.; Writing- Reviewing and Editing. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This research was approved by the Ethics Committee of Kermanshah University of Medical Sciences with the code (IR.kums.REC.1398.1186). The Iranian website of clinical trials registration approved (2020–03-22) the current study with IRCT number: IRCT20130812014333N143, URL: https://en.irct.ir/trial/46295, and this study was conducted under the Declaration of Helsinki. After being informed of the benefits and risks of research, participants signed written consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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