

Targeting PCOS-associated Insulin Resistance: Aerobic Exercise and Hypocaloric Diet without Medications could adjust the Hyperandrogenic milieu and help Induction of Ovulation in Infertile PCOS women

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Abstract: Objectives: To evaluate the impact of weight reduction and exercise interventions on ovulatory function of infertile polycystic ovary syndrome (PCOS) women. Patients & Methods: 90 infertile PCOS women diagnosed depending on the Rotterdam criteria underwent anthropometric measurements and determination of body fat mass (FM), fat-free mass (FFM), and percent body fat (BF%) using dual-energy x-ray absorptiometry. Fasting blood glucose (FBG), plasma insulin (FPI) and serum testosterone (Test), sex hormone binding globulin (SHBG) were measured and free androgen index (FAI) was calculated. Insulin resistance (IR) was evaluated by homeostasis model assessment (HOMA) with HOMA-IR score >2 was considered insulin resistant (IR). All women performed 6-months weight-reduction dieting regimen in association with no exercise (Group A), aerobic exercise (Group B) or combined aerobic-resistance exercise (Group C). All measures were evaluated at 3 and 6-months but ovulation was monitored monthly. Results: At end of 6-months, all women showed significant change of anthropometric measures with significantly higher extent of change in groups B and C compared to group A. Also, IR was significantly modulated with significant reduction of HOMA-IR compared to pre-treatment levels; however, change was least in Group A and only 15 of 63 women were still IR. Serum testosterone and SHBG levels estimated at 6-m showed significant difference compared to baseline levels in groups B and C and all groups showed progressive decrease of FAI with significantly lower FAI level in group B compared to group A. Fifty-nine women got ovulation with ovulatory success rate of 65.6% with non-significant difference among studied groups. Conclusion: Weight reduction regimens associated with aerobic physical exercise intervention could induce weight loss and improve insulin sensitivity with subsequent amelioration of inhibitory effect of obesity and insulin resistance on the reproductive function and adjustment of the hyperandrogenic milieu.

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1. Introduction

Polycystic ovary syndrome is associated with a number of reproductive disorders and is characterized by the presence of polycystic ovaries, menstrual dysfunction, infertility or reduced fertility, and biochemical or clinical hyper androgenism. PCOS also increases the prevalence and risk of a number of cardiometabolic disturbances including insulin resistance, hypertension, dyslipidemia, and diabetes (Jeanes *et al.*, 2009).

In PCOS women, an impaired cardiopulmonary functional capacity strictly related to IR was documented. In women with proven coronary artery disease, an impaired cardiopulmonary functional capacity is associated with an increased risk of mortality for cardiovascular events (Kavanagh *et al.*, 2003). Although nowadays PCOS women do not seem to be at increased risk for cardiovascular mortality (Wild *et al.*, 2000) there are some intriguing reports showing higher CVR in PCOS even at an early age (Orio *et al.*, 2004, Ehrmann, 2005).

Although the pathogenesis of PCOS is complex and not entirely understood, obesity (particularly abdominal obesity) is mediated by the development of insulin resistance (Moran and Norman, 2004) and is closely linked to the development of this condition and its clinical features, particularly menstrual irregularities and increased serum androgens. The central role of insulin resistance in the manifestations of PCOS has led to it becoming a primary target for PCOS management (Norman *et al.*, 2006).

Weight gain and obesity worsen the features of PCOS, while weight loss improves the features of PCOS. While there are potential barriers to successful weight management in young women who do not suffer from PCOS, women with PCOS may experience additional barriers. Weight management strategies in younger women with or without PCOS should encompass both the prevention of excess weight gain and achieving and maintaining a reduced weight through multidisciplinary lifestyle management, comprising dietary, exercise and

behavioral therapy, as well as attention to psychosocial stress and practical and physiological barriers to weight management (Moran *et al.*, 2010).

In non-PCOS subjects, lifestyle modification has proved as efficacious as pharmacological intervention in reducing the risk of developing type 2 diabetes mellitus. The National Institutes of Health clinical guidelines for the long-term treatment of overweight and obesity emphasize the importance of achievable and sustainable goals, notably a combination of diet modification, physical activity, and behavior therapy (McNaughton *et al.*, 2009).

A separate line of evidence has shown that exercise training independent of weight loss in overweight and obese subjects with cardiometabolic disturbances and a wide range of insulin resistant states decreases abdominal fat and improves insulin sensitivity and an array of cardiovascular disease risk factors (Moro *et al.*, 2009). Thus, the present study was designed to evaluate the impact of weight reduction and exercise interventions on the ovulatory function and hyperandrogenemic milieu of infertile PCOS women

2. Patients and Methods

The present study was conducted at Department of Obstetrics and Gynecology, Benha University Hospital in conjunction with Medical Biochemistry Department, Faculty of Medicine, Benha University since Jan 2010 till June 2011. After obtaining written fully informed patients' consents, the study included 90 PCOS diagnosed depending on the **Rotterdam criteria (2004)**, in which at least two of the following three criteria were met: Oligomenorrhea (<8 spontaneous menstrual cycles per year for at least 3 years before enrollment) or amenorrhea, biochemical hyperandrogenemia (serum total testosterone level >0.8 ng/ml), and polycystic ovaries (>12 follicles in the 2–9 mm range and/or an ovarian volume >10 ml per ovary by vaginal ultrasound).

Patients with obesity inducing endocrinopathy, current or previous pregnancy within 1 year of enrollment or the use of hormonal contraception within the last 6 months prior to inclusion in the study were excluded.

All patients underwent transvaginal ultrasonographic (TVU) examination and anthropometric measurements including body height and weight, and BMI was calculated as weight (kg)/height (m²), (Khosla and Lowe, 1967). Fat mass (FM), fat-free mass (FFM), and percent body fat (BF%) were determined by dual-energy x-ray absorptiometry. Obesity grades were defined after the **WHO expert consultation (2004)** as BMI <24.9 as average, 25–<30 kg/m² as overweight, BMI ≥30–35 kg/m² as obese and BMI ≥35 kg/m² as morbid obese.

Fasting plasma and serum samples were collected and stored at -80°C for analysis after study completion. Testosterone and SHBG were measured by RIA using commercial enzymatic kits (Diagnostic Systems Laboratories). Free androgen index (FAI) was calculated as (testosterone/SHBG) x100. Plasma insulin concentrations were determined using a commercial ELISA kit (Mercodia ELISA; ALPCO Diagnostics, Uppsala, Sweden) and 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 (Matthews *et al.*, 1985) considering an abnormal HOMA-index >2 (Ascaso *et al.*, 2001).

Enrolled women were randomly, irrespective of their clinical data, allocated into three groups according to 6-months lifestyle interventions without medications: diet only (Group A), diet and aerobic exercise (Group B) and diet and combined aerobic-resistance exercise (Group C). Anthropometric measures, HOMA-IR and FAI were evaluated at 3-months and 6-months and were compared versus baseline measurements. For better outcome evaluation the extent of change was calculated as the 6-months value minus the baseline value and the percentage of BMI loss (%BMIL) was calculated as the difference between 6-month and baseline BMI divided by the baseline BMI multiplied by 100. Ovulation was monitored by measuring the serum concentration of progesterone on Day 21 of the menstrual cycle and serum progesterone level of ≥25 nmol/l was used to indicate ovulation that was assured using TVU for evident ovulation with a dominant follicle size >16 mm and the frequency of women got these follicles was considered as ovulation success rate.

Dieting and Exercise intervention

All subjects were prescribed the same energy-restricted, high-protein diet (5000–6000 kJ/d) for a planned weight loss of 10–15 kg over the study period. The diet provided 30% of energy as protein, 40% as carbohydrate, and 30% as fat. Group B women were assigned to undergo a walking/jogging program comprising five sessions per week. The training heart rate (HR) was based on a percentage of the maximum heart rate (MHR) achieved in the treadmill tests conducted at time of enrollment and at 3-m. Exercise intensity progressed from 30 min at 60–65% initial MHR to achieve 45 min at 75–80% MHR by study end. HR during exercise was monitored using a personal HR monitor (FS1 Polar Heart Rate Monitor; Polar Electro Oy, Kempele, Finland). Group C women performed the same aerobic exercise program as group B three times per

week, and undertook a progressive resistance training program twice per week on non-consecutive days. The resistance training program consisted of five resistance exercises: bench press, lat pulldown, leg press, knee extension, and sit-ups. The training load was set using a percentage of 1RM, which was assessed for each exercise. For the first 2 wk, the training load was 50–60% 1RM and increased to 65–75% 1RM for the following weeks. The training load was increased progressively once subjects could successfully perform three sets of 12 repetitions at that load.

Statistical analysis

Results were expressed as mean±SD, range, numbers and percentages. Intra-group data was statistically analyzed using paired t-test and inter-group analysis was examined using Wilcoxon Ranked test for related data (Z test). Statistical analysis was conducted using SPSS statistical program, (Version 10, 2002). P value <0.05 was considered statistically significant.

3. Results

Patients' characters evaluated prior to study enrollment showed non-significant difference among the three groups. The applied modalities of intervention significantly ($p<0.05$) reduced evaluated anthropometric measures at end of intervention period compared to baseline measures. The %BMIL was significantly higher in group B compared to groups A and C with significantly higher %BMIL reported in group C compared to group A (Table 1).

Table (1): Mean (±SD) BMI measures reported throughout the study period in studied groups compared to baseline measures

		Group A	Group B	Group C
BW (kg)	Baseline	101±10	104.8±9	103.9±9
	3-m	95.3±9	96.7±9.2	95.8±5.3
	6-m	91.7±9*	90.5±8*	92.6±7*
Body height (cm)		166.3±4	165.7±3	166.2±4
BMI (kg/m ²)	Baseline	36.8±3.8	38.4±3.1	37.6±2.9
	3-m	34.9±3.5	35.4±3.5*	34.6±3*
	6-m	33.6±4*	33.2±3†*	33.5±3*
	%BMIL	8.75±1	13.6±4‡#	10.9±3‡

BW: body weight

BMI: body mass index

%BMIL: percentage of BMI loss

*: significant versus baseline

†: significant versus 3-m measures

‡: significant versus group A #: significant versus group B

The %BF and WC showed significant progressive decrease with significant difference between %BF determined at 3-m and 6-m compared to baseline percentage with significant difference in favor of 6-m estimation. The extent of change of

evaluated parameters was significantly higher in groups B and C compared to group A with non-significantly higher extent of change in group B compared to group C. Only the extent of decrease of FFM was significantly higher in group A compared to groups B and C with non-significantly higher decrease of FFM in group C compared to group B (Tables 2 & 3).

Table (2): Mean (±SD) body fat measures reported throughout the study period in studied groups compared to baseline measures

		Group A	Group B	Group C
FM (kg)	Baseline	48.1±4.1	46.4±4.6	47.7±7.2
	3-m	45±5*	42.6±5.7*	43.1±6.7*
	6-m	43.2±3.8	38.2±5*†	39.2±5*†
	EC	-4.9±4.1	-8.2±4.8‡	-8.5±6.3‡
FFM (kg)	Baseline	51.3±6.1	50.7±4.9	52.4±5.1
	3-m	46±5.3*	48.1±3.2*	48.6±3.8*
	6-m	43.5±5*	46.8±3.9*	48.1±4.1*
	EC	-7.8±3.7	-3.9±4.7‡	-4.3±3.1‡
BF%	Baseline	47.1±5.1	46.9±3.2	48.1±4.1
	3-m	46.8±6*	44.1±4.1*	46.4±3.6*
	6-m	45.9±6*	42.3±3*†	44.3±3.2*†
	EC	-1.2±4.5	-4.6±3.9‡	-3.8±2.8‡

FM: Fat mass

FFM: fat-free mass

BF%: body fat percentage

*: significant versus baseline

†: significant versus 3-m measures

‡: significant versus group A

EC: Extent of change= 6-months level – baseline level

Table (3): Mean (±SD) WC (cm) measures reported throughout the study period in studied groups compared to baseline measures

	Group A	Group B	Group C
Baseline	105.9±10.9	106.3±11.2	104.7±12.1
3-m	99.2±9.1*	97.2±8.3*	97.3±10.3*
6-m	93.5±8.4*	90.7±10.2*†	91.1±9.5*†
Extent of change	-11.4±9.65	-15.6±10.7‡	-13.6±11‡

*: significant versus baseline

†: significant versus 3-m measures

‡: significant versus group A

Extent of change= 6-months level – baseline level

Insulin resistance was modulated significantly using either of the applied strategies manifested as significant ($p<0.05$) reduction of FBG, FPI and HOMA-IR at the end of intervention period compared to baseline levels. Group A patients showed the least extent of HOMA-IR change that was significantly inferior to that reported in groups B and C with non-significantly lower HOMA-IR in group C compared to group B.

Prior to starting interventions, 63 women were insulin resistant with $IR>2$, while 27 women had $IR<2$ with non-significant difference between the three groups as regards distribution of insulin resistant women. At end of interventions, only 15

women were still insulin resistant (IR>2) with successful IR reduction rate of 79.4%.

All intervention modalities significantly decreased the frequency of patients had IR compared to pre-treatment frequency and with higher frequency of insulin sensitivity in groups B and C compared to group A, but with non-significant difference between groups B and C, despite being in favor of group B, (Table 4).

Table (4): Patients' insulin resistance data recorded at end of 6-months intervention period compared versus data obtained at time of study enrollment

		Group A	Group B	Group C
FBG	Baseline	124.7±10.7	127.1±9.1	126.3±11.4
	6-m	118.3±7.6*	121.9±6.8*	122±8.7*
FPI	Baseline	5.34±1.25	5.71±1.01	5.43±1.21
	6-m	4.51±1.31*	4.23±1.19*	4.46±1.15*
HOMA-IR	Baseline	1.71±0.48	1.87±0.29	1.8±0.33
	6-m	1.42±0.32*	1.22±0.26*‡	1.23±0.22*‡
% of HOMA-IR change		-0.29±0.13	-0.65±0.18‡	-0.57±0.14‡
IR:IS ratio	Baseline	16:14	18:12	19:11
	6-m	8:22	2:28‡	3:27‡

FBG: fasting blood glucose FPI: fasting plasma insulin
 IR: insulin resistant IS: insulin sensitive
 *: significant versus baseline ‡: significant versus group A

Mean baseline levels of androgenic hormones showed non-significant (p>0.05) difference between studied patients. Three months of intervention induced non-significant (p>0.05) changes of androgenic hormones serum levels compared to their baseline levels with non-significant difference among groups despite being least in group A. On contrary, serum levels estimated at 6-m of intervention showed significant difference compared to their baseline levels in groups B and C, but the difference was non-significant in group A.

For better result adjustment, results were evaluated as the mean extent of change; the extent of decreased serum testosterone levels was non-significant (p>0.05) among studied groups despite being least in group A, while the extent of increased serum SHGB was significantly (p<0.05) higher in groups B and C compared to group A and was in favor of group B.

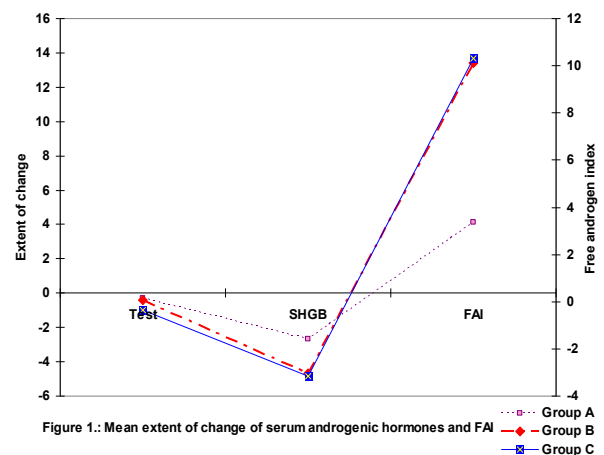
As regards FAI, all modalities of intervention showed progressive decrease of FAI that was significant at 6-m compared to baseline in the three studied groups. The extent of FAI decrease in

group B was significant (p<0.05) compared to group A, but non-significant (p>0.05) compared to group C with non-significant (p>0.05) difference in favor of group C compared to group A, (Table 5, Figure 1).

Table (5): Mean (±SD) levels of androgenic hormones estimated throughout the study period in the studied groups

		Group A	Group B	Group C
Testosterone (nmol/l)	Baseline	2.33±0.64	2.41±0.64	2.49±0.58
	3-m	2.12±0.56	2.22±0.59	2.31±0.54
	6-m	2.1±0.58	2.01±0.54*	2.04±0.56*
	EC	-0.29±0.08	-0.4±0.09	-0.37±0.11
SHGB (nmol/l)	Baseline	27.43±9.14	33.57±11.2	29.52±10.14
	3-m	30.58±10.19	39.44±13.17	33.95±11.67
	6-m	31.54±10.5	47±15.7*	39.9±13.7*
	EC	4.11±1.37	13.43±4.48‡	10.33±3.55‡
FAI	Baseline	46.6±4.24	47±4.26	47.3±4.23
	3-m	45.3±4.33	43.58±4.5	45.2±4
	6-m	43.9±4.52*	42.33±4.53*	44.15±4.1*
	EC	-2.69±1.31	-4.67±2.4‡	-3.15±1.14

SHBG: sex hormone binding globulin
 FAI: free androgen index *: significant versus baseline
 ‡: significant versus group A
 EC: Extent of change= 6-months level – baseline level



Fifty-nine women got ovulation throughout the intervention period with ovulatory success rate of 65.6%. Ovulatory success rate in group A 56.7%, 73.3% in group B and was 66.7% in group C with

non-significant difference among studied groups despite being in favor of group B, (Figure 2).

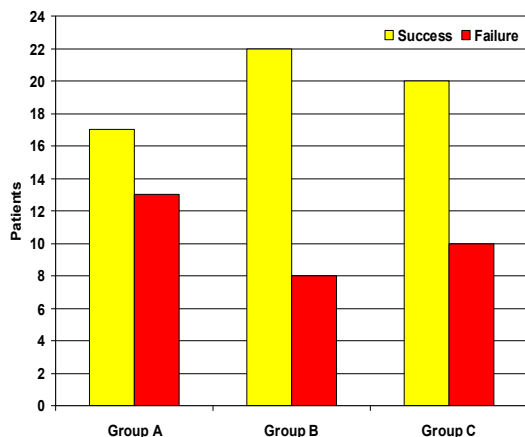


Figure 2. Patients' distribution according to successful ovulation

4. Discussion

Through the present study, the applied models of intervention significantly reduced the evaluated anthropometric measures with significantly higher extent of change in groups B and C compared to group A. These data point to the complementary role between dieting regimens and exercise to affect whole body fat and was in line with the observation of both **Ormsbee et al. (2009)** who found the effects of exercise per se on visceral adipose tissue depot are relatively limited compared with the major effects of hypocaloric diet alone and are closely associated with changes in total fat mass and **Christiansen et al. (2009)** who reported that the mechanism behind resistance exercise contributing to improved body composition may in part be due to enhanced subcutaneous abdominal adipose tissue lipolysis and improved whole body energy expenditure and fat oxidation.

However, FFM was significantly higher in group A compared to groups B and C with non-significantly higher decrease of FFM in group C compared to group B. These findings illustrate the beneficial effect of chronic weight reduction programs and exercise intervention on body constitutional parameters and fat content. However, it was evident that exercise induced more stored fat loss with preservation or minimal affection of fat free mass which was more affected by simple weight reduction program leading to muscle wasting, but extensive resistance exercise also induced more FFM loss compared to aerobic exercise without resistance training. These findings go in hand with **Chomentowski et al. (2009)** who found diet-induced weight loss significantly decreased muscle mass; however, the addition of moderate aerobic exercise

to intentional weight loss attenuated the loss of muscle mass.

Insulin resistance was modulated significantly using either of the applied strategies manifested as significant reduction of FBG, FPI and HOMA-IR at the end of intervention period despite the more superior effect of combined dieting and exercise compared to dieting alone. In line with the obtained regulations, at the end of interventions, only 15 women were still IR with successful IR reduction rate of 79.4%. Thus, either dieting regimen alone or combined with exercise induced improved insulin sensitivity with subsequent proper utilization of blood glucose so reducing their blood levels, a finding coincided with **Straznicky et al. (2009)** who found weight loss reverses blunted sympathetic responsiveness to glucose ingestion in insulin-resistant subjects with metabolic syndrome, which is relevant to postprandial energy utilization and body weight homeostasis.

In support of the beneficial effects imposed by exercise on blood glucose regulation, **Clough et al. (2009)** found decreased insulin-mediated glucose uptake in skeletal muscle is associated with impaired muscle microvascular exchange capacity that was negatively associated with a measure of glycemia and positively associated with insulin sensitivity, independently of visceral fat mass and could be improved by muscular exercise not by simple or drug induced lowering of blood lipid content. Such findings could be attributed to the facts that insulin is a regulator of muscle proteins and can stimulate the synthesis of mitochondrial proteins and IR influence the mitochondrial function and to the improved cardiopulmonary functions, which proved to be affected by IR, with chronic exercise (**Orio et al., 2006**). The impact of exercise on autonomic nervous system could be another explanation for the better control of exercise on PCOS associated metabolic disturbances and its sequale. In support of such attribution, **Giallauria et al. (2008)** found exercise training improves autonomic function and inflammatory pattern in PCOS women and **Stener-Victorin et al. (2004)** demonstrated that low-frequency electroacupuncture and physical exercise lowers high sympathetic nerve activity in women with PCOS with its subsequent hyperglycemia and cardiopulmonary effects.

Despite the non-significant differences reported between groups B and C concerning anthropometric measures and HOMA-IR score and components, these difference illustrate the impact of training characters on these parameters, this assumption support that previously reported by **Bajpeyi et al. (2009)** who found that in overweight/obese subjects a relatively chronic persistence of enhanced insulin

action may be obtained with endurance-oriented exercise training; this persistence, however, is dependent on the characteristics of the exercise training performed.

The applied models of interventions significantly improved the hyper androgenemic milieu in the studied PCOS women with ovulation induction success rate of 65.6% without use of medications. These findings were in line with that previously and recently observed in literature; **Moran et al. (2009)** reported that the emerging evidence suggests that exercise offers additional benefits to dietary energy restriction for reproductive features of PCOS and should be used as the primary therapy in overweight and obese women with PCOS for the treatment of metabolic complications and improved ovulatory function and pregnancy.

Thomson et al.(2010) reported significant reductions in waist circumference, blood pressure, fasting insulin, fasting glucose, homeostasis model assessment of insulin resistance, testosterone, free androgen index, and an increase in SHBG with improved heart rate recovery which suggests improved autonomic function and thus highlights the importance of weight loss and exercise to reduce the cardiovascular disease risk in PCOS women.

Vause et al. (2010) defined the guidelines for management of PCOS as following: weight loss, exercise, and lifestyle modifications have been proven effective in restoring ovulatory cycles and achieving pregnancy in overweight women with PCOS and should be the first-line option for these women.

In support of the applied intervention model without medications, **Karimzadah and Javedani (2010)** reported that lifestyle modification of PCOS women achieved a significant reduction in waist circumference, total androgen, and lipid profile with clinical pregnancy rate of 20% with lifestyle modification compared to 12.2% in those received clomiphene citrate alone, 14.4% with metformin alone, 14.8% with combined clomiphene citrate and metformin.

It could be concluded that in PCOS women combined weight reduction regimens associated with aerobic physical exercise intervention induce weight loss and improves insulin sensitivity with subsequent amelioration of inhibitory effect of obesity and insulin resistance on the reproductive function and adjustment of the hyper androgenic milieu.

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