Published in final edited form as:
Fertil Steril. 2011 June 30; 95(8): 2696–2699. doi:10.1016/j.fertnstert.2011.01.137.

AEROBIC EXERCISE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME IMPROVES OVARIAN MORPHOLOGY INDEPENDENT OF CHANGES IN BODY COMPOSITION

Leanne M. Redman, Ph.D.[1], **Karen Elkind-Hirsch, Ph.D.**[2], and **Eric Ravussin, Ph.D.**[1]
[1]Pennington Biomedical Research Center, Baton Rouge, LA 70808, USA
[2]Womans Health Research Institute, Womans Hospital, Baton Rouge, LA 70815, USA

Abstract

In a prospective study, 8 women with polycystic ovary syndrome completed 16 weeks of individualized aerobic exercise training. Independent of changes in body weight and adiposity there was a significant increase in aerobic fitness and insulin sensitivity and a significant decrease in the total number of follicles measured by magnetic resonance imaging.

Recently and based initially on studies in obesity and type 2 diabetes, lifestyle modification has been adopted as the first line of treatment to manage both the reproductive and metabolic dysfunctions in overweight and obese women with PCOS (1–3). As a result a surge in clinical studies involving dietary restriction alone (4–7) or in combination with physical activity programs have been conducted (8,9). Collectively these studies indicate that a reduction in body weight of at least 5% leads to significant improvements in menstrual cyclicity, ovulation and biochemical hyperandrogenism in terms of the reproductive complaints (4,6–9) and improved glucose tolerance and reduced risk for cardiovascular disease (4,8). One intriguing finding was that in comparison to dietary restriction (800 kcal/d), aerobic exercise led to a 40% higher rate of ovulation (25% versus 65%, respectively) and greater improvements in SHBG and testosterone despite less weight loss (10). Aerobic exercise resulted in a greater reduction in fasting insulin and insulin resistance (HOMA-IR) suggesting a possible mechanistic link. Exercise-induced changes in visceral fat and ectopic lipid in non-fatty tissues are probably important components however to our knowledge only one recent study using single slice computed tomography measured changes in visceral fat with exercise training in PCOS (11). Studies using magnetic resonance imaging or spectroscopy are seldom no studies have yet quantified the effects of exercise on the polycystic ovarian morphology.

As detailed previously (13), eight young (18–30 years), overweight/obese (BMI ≥25 kg/m^2) women with PCOS completed a 16-week study of aerobic exercise. Seven normally cycling controls (BMI ≥25 kg/m^2) were also enrolled to complete baseline testing only. The

Corresponding author/address for reprints: Leanne M. Redman, PhD Assistant Professor | Pennington Biomedical Research Center, 6400 Perkins Rd, Baton Rouge, LA 70808, USA; Phone: (225) 763 0947; Fax: (225) 763 3030; leanne.redman@pbrc.edu.

Disclosure statement: The authors have nothing to disclose

Clinical Trial Registration Number: POLY, NCT01150539 (www.clinicaltrials.gov)

protocol was approved by the PBRC IRB, and volunteers provided informed consent. Following screening, all subjects were examined at baseline (before training, Week 0) and after 16 weeks of aerobic exercise training (Week 16). Testing was conducted over 3 days to measure body composition (by dual X-ray absorptiometry, Hologics QDR 4500A, Bedford, MA), abdominal adiposity and ovarian morphology (by 3.0T magnetic resonance imaging; General Electric, Signa Excite HD System, Milwaukee, WI), ectopic lipid in the soleus muscle and liver (by magnetic resonance spectroscopy; General Electric, Signa Excite HD System, Milwaukee, WI), VO_2max (graded treadmill test; Parvomedics True Max 2400, Salt Lake City, UT), insulin sensitivity/ glucose disposal rate (by 120 minute 80mU/min/m^2 euglycemic hyperinsulinemic clamp) and concentrations of insulin (Linco Research Inc., St. Charles, MO), free fatty acids (Wako Chemicals ISA, Richmond, VA), total testosterone and sex hormone binding globulin (Immulite 2000; Siemens Healthcare Diagnostics, Deerfield, IL). Body weight was measured weekly and participants completed a menstrual cycle diary prior to each exercise session.

All exercise training was performed under supervision at the PBRC Fitness Center five times per week. Exercise was prescribed on an individual basis with the objective to achieve specified exercise energy expenditure (ExEE) per day as previously described (13). Diet was not controlled throughout the exercise intervention however a standardized eucaloric diet (35% fat, 15% protein, 50% carbohydrate) was provided 2 days prior to the inpatient procedures.

Using the mean and standard deviation of glucose disposal rate normalized for fat-free mass; we estimated the sample sizes required to measure a 10–40% change in glucose disposal rate (mg/kgFFM/min) from baseline. Using our prospective study design (paired) with a target power of 80% and the significance level set at α=0.05, we can conclude that 6 subjects are needed to detect a 20% change in GDR from baseline. The percent change from baseline was computed as mean±SEM. Non-parametric statistics were used to test for the effect of exercise and the level of significance for all statistical tests was set at p<0.05.

In comparison to the normal cycling obese controls, the women with PCOS were similar in body weight and body composition (Table 1). Women with PCOS had increased concentrations of testosterone and a higher free androgen index (Table 1). Ovarian volume as well follicle number was increased in women with PCOS (Table 1). There was no difference in the mean follicle size (data not shown).

All 8 subjects were at least 98% compliant to the exercise program. After the 16 week exercise program body weight was unchanged (−1±1.7%). While there was a tendency for fat mass to be reduced by exercise training (−4.6±4.1%). Visceral fat measured by multi-slice MRI was reduced by −11.6±9.0% and subcutaneous fat by −8.1±5.6%. Intramyocellular lipid measured in the soleus and tibialis anterior muscles (adjusted for water peak) was significantly increased from baseline (Table 1).

Resting metabolic rate was similar before and after the training program (Week 0: 1589±88 vs. Week 16: 1593±90, kcal/d) so to was metabolic flexibility or the switch in substrate oxidation from the fasted to insulin stimulated state. Maximal aerobic uptake was significantly increased with training by 12±2% (p<0.01). Insulin sensitivity was significantly increased from baseline by 34±6% (p<0.001) due to an increase in non-oxidative glucose disposal. Concentrations of free fatty acids were reduced by exercise training (135±41%, p<0.001).

All subjects had oligo- or amenorrhea at enrollment to the study. Exercise training did not change total testosterone or sex hormone binding globulin (Table 1). During the 16 week intervention, 7 out of the 8 subjects (88%) reported at least 2 episodes of normal menstrual

bleeding. The first reported cycle had a mean length of 41.6±15.4 days and the second reported cycle 28.8±7 days. There was a significant decrease in the total number of follicles and the number of follicles measuring between 2–9mm, the criteria for a polycystic phenotype.

There is a growing consensus that exercise can restore menses and improve insulin sensitivity without decreasing body weight (11). In support of this, aerobic training in this study did not result in a significant change in body mass or body composition however despite exercise compliance and supervised training, there was considerable variability among the subjects with weight change from +4kg to −6 kg. Intra-individual variability in weight change is commonly observed in exercise only interventions (14–16). It is postulated that aerobic training induces metabolic and/or behavioral compensations which attenuate weight loss in compliant subjects (14–16).

A lowering of metabolic rate and reduction in energy expenditure from non-exercise activities are primary candidates of metabolic compensation whereas compliance to the intervention and an increase in dietary intake are examples of behavioral compensation. In our study compliance was excellent and the change in resting metabolic rate was not different between those subjects who lost weight and those who did not. We did not impose a dietary intervention and of course an increase in dietary intake the most likely candidate for the increase in body weight. Studies in overweight/obese women support an increase in energy intake with exercise however the extra calories consumed do not equal or exceed the energy expenditure in exercise (17,18). A major challenge for studies implementing exercise only interventions in PCOS women is how to handle dietary intake; perhaps dietary counseling should be provided to maintain dietary intake.

The current study corroborates that improvement in reproductive function in overweight/obese women with PCOS occurs in parallel with an increase in insulin sensitivity and is not dependent on a loss of body weight (10,24). We hypothesized that a key player in the mechanism would be a reduction in visceral fat since using waist circumference, previous exercise studies point to a possible association between reduced abdominal adiposity and improved reproductive function (10,24) and central obesity is a hallmark feature of PCOS in patients (25). However using multislice MRI, while we saw a more than 10% reduction in visceral fat this was not statistically significant. Although in those subjects who lost weight, the reduction in visceral fat was 35%. A recent study in 20 young women with PCOS using a single slice multislice CT scan also observed a 10% reduction in visceral fat after 3 months of aerobic training (12) indicating that lack of significance in the current report is likely due to our small sample size. Future studies should explore further the importance of visceral fat in reproductive function in PCOS.

A novel contribution of this study was the measurement of ectopic fat in the liver and skeletal muscle by MRS and ovarian morphology by MRI. Aerobic training did not induce changes in intrahepatic lipid however intramyocellular lipid in the skeletal muscle was increased. Intramyocellular lipid is increased in obesity (19) and type 2 diabetes (20) and is related to insulin resistance. However a paradox exists such that highly insulin sensitive endurance trained athletes have comparable IMCL content to obese and type 2 diabetic subjects (21). Our study supports the observation that exercise training increases IMCL content in parallel with insulin sensitivity supporting the notion that the deleterious characteristic of skeletal muscle metabolism attributed to inactivity in obesity can be overturned with moderate exercise training (22). For the first time we show that exercise training reduces follicle number. Without changes in body composition or sex steroids, the change in insulin sensitivity may explain this finding. An improvement in insulin sensitivity

with 6 months of metformin treatment in women with PCOS reduced ovarian volume by ~30% and stromal/total area ratio by ~25% as determined by ultrasound (23).

The present study strengthens the recommendation for adopting regular physical activity in the treatment of metabolic and reproductive function in women with PCOS. Importantly regular exercise in women with PCOS has benefits that exceed weight loss with improvement management of the metabolic and reproductive derangements. Exercise studies of longer duration are needed to carefully characterize the mechanisms between changes in insulin sensitivity and ovarian morphology, sex steroid concentration and reproductive function.

CAPSULE

Aerobic exercise without weight loss improves insulin sensitivity and ovarian morphology in women with PCOS.

Acknowledgments

This paper was presented in part at the 63rd Annual Meeting of the American Society for Reproductive Medicine (2007 Washington DC) and the abstract published in *Fertil Steril* 88 (1): S76. Thanks to Mandy Shipp, Laura Daray, Stacy Carling and the nursing staff of the PBRC Inpatient Unit. A special thank you goes to the study participants without whom this study could not have been conducted.

Financial Support. This study was funded by a grant from the Health and Performance Enhancement Division of PBRC (LR), a NORC Center Grant 1P30 DK072476 (ER) and Dr. Redman is supported by K99HD060762.

REFERENCES

1. Rotterdam ESHRE/ASRM-Sponsored Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod. 2008; 23:462–77. [PubMed: 18308833]
2. Rotterdam ESHRE/ASRM-Sponsored Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008; 89:505–22. [PubMed: 18243179]
3. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril. 2009; 92:1966–82. [PubMed: 19062007]
4. Moran LJ, Noakes M, Clifton PM, Wittert GA, Belobrajdic DP, Norman RJ. C-reactive protein before and after weight loss in overweight women with and without polycystic ovary syndrome. J Clin Endocrinol Metab. 2007; 92:2944–51. [PubMed: 17504892]
5. Tolino A, Gambardella V, Caccavale C, D'Ettore A, Giannotti F, D'Anto V, et al. Evaluation of ovarian functionality after a dietary treatment in obese women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2005; 119:87–93. [PubMed: 15734091]
6. van Dam EW, Roelfsema F, Veldhuis JD, Hogendoorn S, Westenberg J, Helmerhorst FM, et al. Retention of estradiol negative feedback relationship to LH predicts ovulation in response to caloric restriction and weight loss in obese patients with polycystic ovary syndrome. Am J Physiol Endocrinol Metab. 2004; 286:E615–20. [PubMed: 14678951]
7. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril. 2004; 81:630–7. [PubMed: 15037413]
8. Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008; 93:3373–80. [PubMed: 18583464]

9. Bruner B, Chad K, Chizen D. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Appl Physiol Nutr Metab. 2006; 31:384–91. [PubMed: 16900227]
10. Palomba S, Giallauria F, Falbo A, Russo T, Oppedisano R, Tolino A, et al. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. Hum Reprod. 2008; 23:642–50. [PubMed: 18158291]
11. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2010
12. Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Strauss BJ, Teede HJ. Effects of Exercise on Insulin Resistance and Body Composition in Overweight and Obese Women with and without Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2010
13. Moro C, Pasarica M, Elkind-Hirsch K, Redman LM. Aerobic exercise training improves atrial natriuretic peptide and catecholamine-mediated lipolysis in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009; 94:2579–86. [PubMed: 19366845]
14. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. PLoS ONE. 2009; 4:e4515. [PubMed: 19223984]
15. Donnelly JE, Hill JO, Jacobsen DJ, Potteiger J, Sullivan DK, Johnson SL, et al. Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: the Midwest Exercise Trial. Arch Intern Med. 2003; 163:1343–50. [PubMed: 12796071]
16. King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. Int J Obes (Lond). 2008; 32:177–84. [PubMed: 17848941]
17. Stubbs RJ, Hughes DA, Johnstone AM, Whybrow S, Horgan GW, King N, et al. Rate and extent of compensatory changes in energy intake and expenditure in response to altered exercise and diet composition in humans. Am J Physiol Regul Integr Comp Physiol. 2004; 286:R350–8. [PubMed: 14707013]
18. Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, King N, Horgan G, et al. The effect of graded levels of exercise on energy intake and balance in free-living women. Int J Obes Relat Metab Disord. 2002; 26:866–9. [PubMed: 12037658]
19. Pan DA, Lillioja S, Kriketos AD, Milner MR, Baur LA, Bogardus C, et al. Skeletal muscle triglyceride levels are inversely related to insulin action. Diabetes. 1997; 46:983–8. [PubMed: 9166669]
20. Kim JY, Hickner RC, Cortright RL, Dohm GL, Houmard JA. Lipid oxidation is reduced in obese human skeletal muscle. Am J Physiol Endocrinol Metab. 2000; 279:E1039–44. [PubMed: 11052958]
21. Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab. 2001; 86:5755–61. [PubMed: 11739435]
22. Dube JJ, Amati F, Stefanovic-Racic M, Toledo FG, Sauers SE, Goodpaster BH. Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete's paradox revisited. Am J Physiol Endocrinol Metab. 2008; 294:E882–8. [PubMed: 18319352]
23. Romualdi D, Giuliani M, Cristello F, Fulghesu AM, Selvaggi L, Lanzone A, et al. Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertil Steril. 2010; 93:2303–10. [PubMed: 19268929]
24. Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2007; 92:1379–84. [PubMed: 17264174]
25. Lord J. The central issue? Visceral fat mass is a good marker of insulin resistance and metabolic disturbance in women with polycystic ovary syndrome. BJOG. 2006:1–7.

Table 1

Clinical characteristics of the obese control and PCOS women at baseline and after 16-weeks of aerobic training in PCOS women.

	Obese Controls (n=7)	PCOS - Before and After Exercise (n=8)			
		Week 0	Week 16	%Change	P
Body Composition					
Weight (kg)	86.7 (82.3, 90.9)	84.2 (68.6, 95.5)	86.0 (66.8, 94.7)	−1±2	0.84
Fat mass (kg)	24.2 (29.5, 37.0)	29.5 (24.9, 29.5)	30.2 (22.0, 40.6)	−5±4	0.38
Fat-free mass (kg)	53.2 (53.2, 54.7)	53.3 (45.4, 55.5)	54.1 (45.7, 55.8)	1±1	0.15
Abdominal Adiposity					
Visceral fat (kg)	1.3 (0.9, 1.4)	1.2 (0.9, 1.9)	1.3 (0.7, 1.7)	−12±9	0.31
Subcutaneous fat (kg)	11.0 (8.7, 12.9)	11.0 (7.5, 12.6)	10.7 (6.9, 12.3)	−8±6	0.38
Ectopic Lipid					
Intrahepatic lipid (AU)	0.009 (0.006, 0.013)	0.019 (0.005, 0.039)	0.022 (0.005, 0.063)	20±22	0.81
IMCL soleus (AU)	0.005 (0.004, 0.009)	0.004 (0.002, 0.007)	0.008 (0.006, 0.010)	103±44	0.03
IMCL tibialis anterior (AU)	0.002 (0.001, 0.002)	0.002 (0.002, 0.003)	0.004 (0.003, 0.005)	78±21	<0.01
Insulin Sensitivity					
Glucose disposal rate (mg/kg/min)	3.8 (3.4, 4.3)	3.9 (3.0, 6.2)	5.2 (4.2, 7.7)	34±6	<0.01
Fasting insulin (μIU/mL)	11.8 (10.1, 12.7)	13.1 (9.7, 25.4)	13.0 (10.9, 22.2)	−18±10	0.47
Fasting free fatty acids (mmol/L)	0.42 (0.32, 0.43)	0.63 (0.39, 0.89)	0.31 (0.24, 0.35)	−135±41	<0.03
Energy Metabolism					
RMR (kcal/d)	1594 (1509, 2088)	1666 (1361, 1787)	1597 (1411, 1760)	1±3	1.00
Basal CHO oxidation rate (mg/min)	76.9 (40.7, 148.5)	79.1 (73.6, 101.0)	73.6 (57.5, 97.2)	−13±12	0.54
Basal fat oxidation rate (mg/min)	65.8 (63.4, 77.9)	50.6 (45.6, 75.3)	54.8 (53.5, 77.2)	14±11	0.46
Aerobic Capacity					
VO_2max (mL/kg/min)	21.8 (19.6, 24.3)	27.2 (25.5, 29.2)	29.5 (28.0, 35.3)	12±3	<0.01
Reproductive Hormones					
Total testosterone (ng/dL)	35.0 (28.0, 46.0)	86.5 (66.5, 107.5)*	73.5 (51.0, 111.5)	−7±10	0.74
Sex hormone binding globulin (nmol/L)	21.7 (19.6, 24.3)	22.5 (15.8, 29.0)*	23.8 (18.1, 42.7)	14±12	0.40
Free androgen index	5.7 (4.3, 7.0)	13.4 (8.4, 32.0)*	11.2 (4.5, 29.7)	−14±9	0.46
Ovarian Morphology [a]					
Ovarian volume (cm^3)	9.5 (6.1, 10.9)	13.6 (11.9, 20.4)*	13.5 (11.0, 18.3)	−6±4	0.25

	Obese Controls (n=7)	PCOS - Before and After Exercise (n=8)			
		Week 0	Week 16	%Change	P
Number of follicles	32.0 (24.0, 62.0)	136 (103, 147)*	104 (83, 134)	−15±5	<0.05
Number of PCO follicles [b]	27 (0.0, 60.0)	135 (98, 145)*	100 (78, 133)	−15±6	<0.05

Data are expressed as median (25^{th}, 75^{th} percentile). *P* values are for Wilcoxon Signed-Rank test conducted by the value of W18 - W2 for each measurement. The percent change from baseline (week 0) is shown as the mean±sem.

IMCL: intramyocellular lipid; RMR: resting metabolic rate; CHO: carbohydrate; RQ: respiratory quotient; VO_2max: maximal aerobic capacity. For conversion to SI units, multiply insulin by 6.945 (pmol/L) and total testosterone by 0.0347 (nmol/L).

*control group significantly different from PCOS at baseline (Wilcoxon Two-Sample Test).

[a]Ovarian morphology was acquired in 13 control subjects;

[b]PCO follicles were defined as the number of follicles measuring 2–9mm in diameter as defined by the Rotterdam adopted criteria for defining a polycystic ovary phenotype with ultrasound.