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Effects of Exercise on Lipoprotein Particles in Women with Polycystic Ovary Syndrome

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Abstract

Purpose—Women with polycystic ovary syndrome (PCOS) commonly have insulin resistance. Insulin resistance is associated with marked abnormalities of lipoprotein size and subclass particle concentration. The purpose of this study was to examine the effects of a moderate-intensity exercise program without weight loss on lipoprotein profiles in women with PCOS.

Methods—Thirty-seven sedentary PCOS women were randomized to either an 8–12-week ramp-up followed by a12-week moderate-intensity exercise program (16–24 weeks total, ~228 min/wk at 40–60% peak VO2, n=21) or control (no change in lifestyle, n=16). PCOS was defined as < 8 menses per year and hyperandrogenism (biochemical or clinical with Ferriman-Gallwey score >8). Fasting lipoprotein profiles were obtained before and after the intervention. Nuclear magnetic resonance spectroscopy (NMR) was used to quantify the following: average particle size, total and subclass concentrations of HDL, LDL and VLDL particles, and calculated HDL cholesterol, triglycerides, and VLDL triglycerides. Wilcoxon exact rank sums tests were used to compare changes in these parameters in the exercise group relative to controls.

Results—Twenty women (8 exercisers, 12 controls) completed the study. Comparing exercisers to controls, significant changes were seen in concentrations of the following lipoprotein parameters which are associated with decreased insulin resistance: decreased large VLDL (p=0.007), calculated triglycerides (p=0.003), VLDL triglycerides (p=0.003), and medium/small HDL (p=0.031); and increased large HDL (p=0.002) and average HDL size (p=0.001).

Conclusions—In this trial, moderate-intensity exercise without significant weight loss improved several components of the lipoprotein profiles of women with PCOS. These findings support the beneficial role of moderate exercise in this high-risk population.

Keywords

PCOS; cholesterol; lipids; nuclear magnetic resonance spectroscopy

Introduction

Polycystic ovary syndrome (PCOS) is associated with an increased risk of several metabolic complications including insulin resistance (6), type 2 diabetes (7,21), dyslipidemia (25–278,

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and possibly cardiovascular disease (3,27). Hypertriglyceridemia and decreased high-density lipoprotein (HDL) are frequently found in affected women (1). Though detailed analyses of lipoprotein size and subclass concentrations by nuclear magnetic resonance spectroscopy (NMR) have not been reported in this population, women with PCOS are known to have small, dense low-density lipoprotein (LDL) compared to age- and body mass index (BMI)-matched controls (2,5). In other populations, cardiovascular disease and insulin resistance are associated with similar abnormalities of lipoprotein size and subclass concentrations (9,11,23). Specifically, studies utilizing NMR have shown that insulin resistance is associated with increased concentrations of large VLDL and small LDL particles, and decreased numbers of large HDL particles (11,12). Larger VLDL size and smaller HDL size were also shown to be strongly associated with the development of type 2 diabetes (9). Thus, abnormalities in lipoprotein size and subclass concentrations may have important associations with two major potential complications of PCOS: diabetes and cardiovascular disease. Characterization of the lipoprotein profiles of women with PCOS and possible interventions to modify these profiles is warranted.

Previously, results from exercise trials in other populations did not demonstrate dramatic improvements in conventional measures of lipids. However, the STRRIDE study (Studies of Targeted Risk Reduction Interventions through Defined Exercise) recently reported improvement in several lipoprotein variables, as measured by NMR, following moderate- and high-intensity exercise regimens (18). This suggests that the analyses provided by NMR may be more sensitive indicators of the effects of exercise on lipoproteins than conventional lipid panels. In addition, the STRRIDE exercise regimens resulted in improved insulin sensitivity among participants, as measured by the intravenous glucose tolerance test (IVGTT). The purpose of our study was to evaluate whether a moderate-intensity exercise regimen similar to one of the regimens used in the STRRIDE study had beneficial effects on the cardiometabolic risk profiles of young women with PCOS. Therefore, we examined the effects of monitored exercise consisting of an 8–12-week ramp-up period followed by 12 weeks of moderate-intensity exercise (caloric equivalent to walking 12 miles per week) without weight loss on lipoprotein subclass profiles and insulin sensitivity in women with PCOS.

Methods

Study Design

This study was approved by the Duke Institutional Review Board, and informed consent was obtained from all participants. Participants were evaluated at the Duke General Clinical Research Center (GCRC) and at the Duke Center for Living. Following a baseline assessment, participants were randomized to either moderate-intensity exercise training (8–12-week ramp-up period followed by 12-weeks of monitored exercise) or a non-exercising control group. Randomization was accomplished by generating a random sequence of two variables (for instance, As and Bs, representing the two treatment groups) using the online program at http://graphpad.com/quickcalcs/randomize2.cfm. Each group assignment was placed in its own sequentially numbered envelope by an individual not involved in the study. Participants were assigned to a group based on these envelopes, and each participant had an equal chance of being randomized to either group. Control group participants were not contacted during the 12 weeks of their enrollment in the study. Following completion of the study protocol, they were offered optional exercise training.

Subjects

Pre-menopausal women with PCOS were recruited for participation in this clinical trial between April 2003 and April 2005. Utilizing conventional recruitment strategies, as well as those recommended by a community advisory board formed for the study, participants were

recruited through posters in the community, newspaper advertisements, community speaking engagements, information on the web, letters to referring providers, and letters to the principal investigator's clinic patients with PCOS, seen at Duke University Endocrine Clinic.

Women aged 18 to 50 years were eligible if they reported eight or fewer menses per year and had either clinical or biochemical evidence of hyperandrogenism (hirsutism with Ferriman-Gallwey score ≥ 8 or bio-available testosterone > 8.4 ng/dl (291.2 pmol/l, a value two standard deviations above the mean for the performing lab). Diagnosis of PCOS was confirmed by history, physical exam and lab testing performed as part of the study. All exams and Ferriman-Gallwey scoring were performed by a single trained examiner. Other eligibility requirements included sedentary lifestyle (defined as no regular exercise during a usual week), ability to come to the study exercise facility for monitored exercise, and agreement to maintain their current weight and dietary patterns for the study period. Exclusion criteria included menopause, hormonal contraceptive use, anti-androgen therapy, pregnancy (current or planned during the study period), recent breastfeeding, congenital adrenal hyperplasia, uncontrolled thyroid disease, hyperprolactinemia, or fasting hyperglycemia [>125 mg/dl (6.9 mmol/l)]. Participants who had taken therapy known to affect carbohydrate metabolism (metformin, thiazolidinediones) within the past 90 days were excluded. Potential participants were also excluded if they had unresolved medical conditions, a history of malignancy other than non-melanoma skin cancer in the past five years, or had participated in another study within the past 30 days.

Exercise Protocol and Cardiorespiratory Fitness

Our exercise protocol was adapted from the STRRIDE study (18). Individual exercise prescriptions were determined by the study exercise physiologist as described by Kraus et al (17.) An exercise dose of 14 kcal/kg/week (caloric equivalent of walking approximately 12 miles per week at 40–60% peak oxygen consumption) was chosen because it produced the greatest improvement in insulin sensitivity in the STRRIDE study (13). In addition, this intensity with similar and lower volumes, has been shown to improve cardio-respiratory fitness in other populations of women (4). Multiplying each participant's weight by the target exercise dose determined the target energy expenditure (kcal/kg/week X kg = kcal/week). Exercise duration was then determined as follows. Peak V02 (liters of 02 consumption per min) was determined by maximum exercise tolerance testing (treadmill) with expired gas analysis using a ParvoMedics TrueMax 2400 oxygen consumption metabolic cart. This value (L/min) was multiplied by 50% (mid-point between 40 and 60%) to determine target 02 consumption. Using this value (L/min), and the assumption of 5 kcal of energy expended per liter of oxygen consumed, kcal/min could be derived (L/min X 5 kcal/L = kcal/min). From this, and the target energy expenditure per week, the target number of minutes of exercise per week was determined (kcal/week X min/kcal = min/week). This calculation provided the weekly exercise duration. Each exercise session was limited to 60 minutes in any 24 hour period. At the midpoint of the exercise training period a repeat submaximal exercise test with gas exchange was performed and training minutes adjusted at the new 50% peak VO2 level to maintain energy expenditure per week at 14 kcal/kg/wk.

Intensity was determined with a submaximal test. Based on this test, each patient was prescribed a treadmill speed and incline to achieve 50% peak V02. After working at that speed and incline for 2 weeks a target heart rate range was developed based on the heart rate files from those workouts. Participants were then asked to stay within that heart rate range as they exercised for their specified number of minutes. Heart rate monitors (Polar Electro, Inc; Woodbury, NY) were worn by each participant during each exercise session. Participants could elect to use a treadmill, elliptical machine or stationary cycle to complete their exercise, and were instructed to reach their target heart rate regardless of the exercise mode used. Heart rate

monitor data were downloaded weekly and reviewed by the study exercise physiologist. Exercise sessions were completed at the Duke Center for Living. However, if the participant could not come to the study exercise facility, they were allowed to exercise at a site of their choosing, as long as they wore a heart rate monitor.

To minimize risk of injury, exercisers completed an initial 8 to 12 week ramp period in which the exercise duration and intensity gradually increased until the full exercise prescription was reached. After completing the ramp phase, exercisers completed an additional 12 weeks of exercise at their full individual exercise prescription. Thus, the total duration of the study period was 20 to 24 weeks for exercisers (ramp + exercise), and 12 weeks for controls. For exercisers, peak VO_2 was determined at baseline, mid-way through the 12-week exercise period, and upon completion of the program. Controls were assessed at baseline and at study completion.

Exercise adherence (duration, time at goal heart rate, and frequency) was monitored through direct supervision and through data recorded by a heart rate monitor worn during all exercise sessions. Data from the heart rate monitors were reviewed weekly. If exercise adherence declined, exercisers were contacted by the exercise physiologist to encourage adherence. Body mass and dietary patterns were monitored regularly. If monthly three-day diet records, reviewed by the study nutritionist, indicated a change in dietary pattern, or if weight changed by >3%, the study nutritionist counseled participants regarding weight and diet stability. Weight maintenance was chosen as the goal because we wished to separate the effects of exercise from weight loss on metabolic parameters.

Lipoprotein Analysis

Before and after the exercise intervention, blood samples were drawn after a twelve hour overnight fast into tubes containing EDTA for NMR lipoprotein analysis. Samples were centrifuged for 15 minutes at 3000 rpm. Plasma was subsequently transferred to cryovials and stored at −80°C. All NMR measurements were performed at one time on specimens thawed immediately prior to analysis. Analysis was performed at LipoScience Inc. (Raleigh, NC) as previously described in detail (14). The particle concentrations of the following 8 subclass categories were investigated: large VLDL (including chylomicrons, if present) (>60 nm), medium VLDL (35 to 60 nm), small VLDL (27 to 35 nm), IDL (23 to 27 nm), large LDL (21.2 to 23 nm), small LDL (18 to 21.2 nm), large HDL (8.8 to 13 nm), medium/small HDL (sum of medium + small HDL; 7.2 to 8.8 nm). The medium and small HDL subclasses were combined for simplification, owing to their similar relations with insulin resistance (12) and atherosclerosis (19). Summation of the lipoprotein subclass levels provides total VLDL, LDL (including IDL), and HDL particle concentrations. Weighted-average VLDL, LDL, and HDL particle sizes (in nanometer diameter units) were also computed. Estimates of total triglycerides and HDL cholesterol were obtained by converting the subclass particle concentrations to lipid mass concentration units using conversion factors that assume each subclass has a normal lipid content. NMR-calculated triglyceride and HDL cholesterol levels are highly correlated ($r>0.95$) with chemically measured values (14). Inter-assay reproducibility, determined from replicate analyses of plasma pools, is indicated by the following coefficients of variation: lipoprotein subclasses <10%; VLDL size <2%; LDL and HDL size <0.5%; total VLDL, LDL, and HDL particles <5%; triglycerides and HDL cholesterol <3%.

Conventional lipid analysis (total cholesterol, direct LDL and HDL cholesterol, triglycerides) was also performed before and after the intervention. For these analyses, fasting blood samples were drawn into serum separator tubes, allowed to clot for 30 minutes, and centrifuged for 15 minutes at 3000 rpm. Analyses were performed within 2 days of the blood draw at LabCorp Inc. (Burlington, NC) using standardized automated methods.

Screening labs included prolactin, morning 17-alpha-hydroxyprogesterone (17-OHP), bio-available testosterone (Mayo Labs), thyroid stimulating hormone, serum pregnancy test, glucose, blood urea nitrogen, creatinine, electrolytes, total protein, albumin, a complete blood count with differential and liver function tests.

Insulin sensitivity was assessed before and after the intervention using the modified frequently sampled IVGTT with minimal model analysis. Additional pre- and post-intervention labs included a 75-g oral glucose tolerance test (OGTT) and bio-available testosterone.

Statistical Analysis

Sample size calculations for this study were based on changes in insulin sensitivity seen in the STRRIDE study. Due to the small sample size of our ultimate study population and skewness of the data, Wilcoxon exact rank sum tests were used to identify the effects of the exercise intervention. Statistical significance was set at a two-sided $p < 0.05$. Data are reported as median values for baseline characteristics and as median absolute change scores for intervention effects. Because we were unable to obtain end-of-study testing for participants who dropped out (44%) and because imputation was considered inappropriate in this setting, their data were excluded from the analyses.

Results

Participant recruitment, enrollment and study completion

Six hundred twenty two (622) individuals completed a phone screen, 187 of whom met screening criteria by phone. Seventy two (72) of these then completed the screening visit and thirty-seven (37) were randomized. Following randomization, sixteen women dropped out of the study (3 control, 13 exercise). In the exercise group, 5 dropped out immediately following randomization and prior to ramp-up, 4 dropped out during the ramp-up phase, and 2 dropped out during the first week of training (following ramp-up), and 2 dropped out mid-way through the exercise program. Reasons given for dropping out of the exercise group included time constraints, injuries unrelated to exercise, and one pregnancy. One participant was excluded after randomization due to a cholecystectomy with a subsequent major change in diet. The final group completing the study included 20 participants (12 control, 8 exercise).

Baseline Characteristics (Table 1 and Table 2)

Baseline characteristics are listed in table 1 (endocrine and anthropometric characteristics) and table 2 (lipoprotein measures). Among those who completed the study, exercisers were older than controls (36.5 vs. 28.0 years, p=0.049). The exercisers had significantly higher particle concentrations of large VLDL/chylomicrons (4.5 vs. 0.7 nmol/L, p=0.025), total HDL (33.9 vs. 29.0 umol/l, p=0.031), and calculated triglycerides (142.6 vs. 81.0 mg/dl, p=0.031). Although not statistically significant, exercisers tended to be heavier (BMI 37.9 vs. 31.3 kg/m^2), less hyperandrogenemic (bio-available testosterone 319.0 vs. 450.7 pmol/l), less hirsute (Ferriman-Gallwey score 9.0 vs. 15.0) less fit (peak VO2 22.5 vs. 27.0 ml/kg/min), and more insulin resistant (Si=1.2 vs. 2.5) than controls. Twenty-five percent (25%) of both groups were minorities.

Of note, when we compared our study dropouts with study completers, subjects who were randomized to exercise and subsequently dropped out of the study were younger (median age 33.0 vs. 36.5 years, p=0.016) and more hirsute (Ferriman-Gallwey score 17 vs. 9, p=ns). In addition, more minority women dropped out of the exercise intervention than majority women (9 minority vs. 3 Caucasian women).

Exercise Prescription and Adherence

The average exercise duration and frequency prescribed to the exercise group was 228 minutes weekly, performed during an average of 4.4 sessions per week. Participants completed an average of 3.6 exercise sessions and 204 minutes of exercise per week, yielding a mean adherence rate (minutes of exercise at prescribed heart rate completed divided by minutes prescribed) of 89.8%.

Effects of Exercise Training (Table 3)

Peak VO_2 increased in the exercise group compared to controls (+1.0 vs. 0.0 ml/kg/min, p=0.033). No other outcomes changed significantly after the exercise training, including insulin sensitivity as measured by the IVGTT with minimal model analysis. However, there was a trend toward improvement in insulin resistance in exercisers vs. controls, as measured by area under the curve (AUC) insulin (−4930.7 vs. +476.5, p=0.083). In addition, conventional lipid panels measured via spectrophotometric assays demonstrated a trend toward improvement in triglycerides among exercisers compared to controls (−41.5 vs. +6.5mg/dl, p=0.083). There were no other trends in the conventional lipid panel between exercisers and controls (total cholesterol −2.5 vs. −6.0 mg/dl, p=0.640; HDL cholesterol +0.5 vs. −2.0 mg/dl, p=0.196; LDL cholesterol +5.0 vs. −3.0 mg/dl, p=0.405).

There were several significant lipoprotein particle changes among participants in the exercise group compared to controls (Table 4). The concentration of large VLDL/chylomicrons was reduced in the exercise group compared to controls (−1.7 vs. +1.1 nmol/L, p=0.007). There was an increase in the concentration of large HDL (+1.3 vs. −0.8 umol/L, p=0.002) accompanied by a decrease in medium/small HDL subclass concentration (−1.9 vs. +1.0 umol/L, p=0.031) and an increase in the average HDL size in the exercisers compared to controls (+0.1 vs. −0.1 nm, p=0.001). Exercisers had reductions in both the calculated triglycerides (−44.3 vs. +10.6 mg/dl, p=0.003) and VLDL-triglycerides (−41.6 vs. +11.6 mg/dl, p=0.003), compared to controls. There were trends toward improved concentrations of IDL particles (−12.9 vs. +11.4 nmol/L, p=0.057) and calculated HDL cholesterol (+2.2 vs. −1.9 mg/dl, p=0.069). There were no significant changes in total or subclass LDL particle concentrations or LDL size.

Discussion

This randomized controlled trial in women with PCOS demonstrated that exercise without weight loss can significantly improve lipoprotein particle parameters that are associated with insulin resistance and cardiovascular disease risk. There were significant reductions in the concentration of large VLDL/chylomicrons and medium/small HDL, and increased large HDL and average HDL size in the exercise group compared to controls. Further, there were reductions in calculated triglycerides and VLDL-triglycerides in the exercise group compared to controls. Finally, there were trends toward improved concentrations of IDL particles and NMR-calculated HDL cholesterol. These changes occurred in the absence of significant weight loss, and are consistent with those expected with improved insulin sensitivity. Although insulin sensitivity did not show significant improvement by IVGTT with minimal model analysis, there was a positive trend in insulin resistance as measured by the AUC for insulin. The average amount of exercise performed by study participants to obtain these beneficial changes in lipoprotein profiles was 3 hours and 24 minutes of moderate-intensity exercise per week (the caloric equivalent to walking approximately 12 miles per week). These findings support the recommendation to increase physical activity in women with PCOS to obtain improvements in metabolic health.

Conventional lipid measurements quantify lipoproteins on the basis of the amount of cholesterol and triglycerides they carry, rather than quantifying the particles themselves. In conventional lipid panels, levels of LDL cholesterol, HDL cholesterol, and triglycerides serve as surrogate markers for LDL, HDL and VLDL particles, respectively. NMR spectroscopy provides direct measurement of lipoprotein particles of varying diameter based on characteristic signals emitted by each lipoprotein subclass (14). For NMR testing, an untreated plasma sample (approximately 200 microliters) is injected into a 400 MHz magnet and subjected to a short radio-frequency pulse. In response to this pulse of energy, the methyl protons from the various lipid molecules carried within lipoprotein particles emit signals which are slightly, but reproducibly, different depending on the diameter of the particle. The amplitudes of these characteristic lipoprotein subclass signals, obtained by computer deconvolution of the measured plasma methyl signal envelope, are directly proportional to the subclass particle concentrations. From the concentrations and known diameters of the measured lipoprotein subclasses, average VLDL, LDL, and HDL particle sizes are calculated. The entire automated measurement process requires about 1 minute and produces highly reproducible results.

Studies have suggested that direct measurement of lipoprotein subclasses and particle sizes by NMR may be a better predictor of cardiovascular risk than traditional lipid panels (23,24). Previously, the focus has been on particle size as a risk factor. For instance, small LDL (16, 20), small HDL (23), and large VLDL (10) have been strongly associated with increased cardiovascular risk in men, whereas large HDL has been associated with cardioprotective properties (15,19). More recently, it has been suggested that the number of particles may actually be more important than the size of the particles. A large cross-sectional study has shown that after adjusting for confounders, both large and small LDL particle number are associated with atherosclerosis (22). Thus, the previous associations between atherosclerosis and small LDL may not be because small LDL is more atherogenic, but because individuals with small LDL generally have elevated numbers of LDL particles.

Studies have also demonstrated that insulin resistance is associated with several characteristics of the lipoprotein particle profile. Garvey et al. (11) evaluated the association of insulin resistance and lipoprotein profiles in 56 insulin sensitive subjects, 46 insulin resistant subjects without diabetes, and 46 untreated subjects with type 2 diabetes. They measured insulin sensitivity by the euglycemic-hyperinsulinemic glucose clamp method and lipoprotein profiles by NMR. Their results demonstrated that insulin resistance is associated with altered lipoprotein profiles. Specifically, insulin resistant participants had larger VLDL, and higher concentrations of large VLDL particles (see table 5). They had higher concentrations of LDL particles overall, higher concentrations of small LDL, and lower concentrations of large LDL. In addition, insulin resistant participants had lower concentrations of HDL particles secondary to a decrease in the number of large HDL and a minor increase in small HDL. The Insulin Resistance Atherosclerosis Study (IRAS) demonstrated that several of these lipid characteristics were also associated with the development of type 2 diabetes (9). Thus, NMR may provide valuable insight into the proatherogenic state of individuals at high risk of developing diabetes. Similarly, lipoprotein changes, such as those seen in our study, may indicate a related change in risk for complications associated with the dyslipidemia of pre-diabetes and diabetes.

The usefulness of NMR spectroscopy in determining the beneficial effects of exercise was first demonstrated by the STRRIDE study (17). Prior to the STRRIDE study, exercise studies using conventional lipid panels concluded that moderate exercise had limited effects on lipids. The STRRIDE study challenged this conclusion by demonstrating that middle-aged men and women randomized to a moderate-intensity exercise regimen (caloric equivalent of walking 12 miles per week) had improvements in triglyceride concentration, and VLDL particle size

and concentration. Further, participants randomized to a higher-intensity exercise regimen (caloric equivalent of jogging 17 to 18 miles per week) also had significant improvement in particle size and concentration of LDL and HDL particles (17).

The protocol for our study was adapted from the moderate-intensity protocol of the STRRIDE study (caloric equivalent of walking 12 miles per week). We believed that the low-amount, moderate-intensity protocol was the safest and most feasible protocol for our group of participants that were quite obese and sedentary. In addition, the results of the STRRIDE study indicated that this exercise protocol produced the greatest change in insulin sensitivity, compared to the higher intensity and higher amount groups (13). Participants that completed the study adhered closely to the protocol, with 89.8% of all prescribed exercise minutes completed. Their adherence to the protocol was reflected by a significant improvement in fitness, measured as peak $V0_2$. No exercisers experienced injury related to the protocol, suggesting that the protocol is a safe intervention that can improve fitness in this population.

Study Limitations

The largest limitation to our study is the high drop out rate. We planned for a drop out rate of 30% based on the experience of the STRRIDE study. Although we used the same personnel, protocol, and exercise facility as that of the STRRIDE study, our dropout rate was higher overall (44%) and higher in the exercise group (62% vs. 32%). We hypothesize that our higher dropout rate was due in part to the young age of our participants (median age was 33 vs. 52 years for STRRIDE), with the possible accompanying responsibilities for small children, school and work. However, the overall attrition rate of 44% (exercisers and controls) was also higher than that found in other exercise studies of young women with PCOS (25–28%). Our requirements to maintain a stable weight and to perform exercise sessions at the study exercise facility may have contributed to our high drop out rate. We speculate that changes to the exercise interventions could enhance retention. For instance, allowing more flexibility in location of exercise, using a “buddy” system to strengthen accountability, or providing for group work-outs, might improve adherence for this group. However, for those who did not drop out, adherence was outstanding, suggesting that the essential protocol can be maintained, but perhaps be made more flexible.

Attrition of minority women was especially high (13 out of 18 randomized participants). The reasons for this are not clear and require further investigation.

The high drop out rate led to differences in baseline characteristics between exercisers and controls, and these differences may well have affected study results. Exercisers were more insulin resistant, older, heavier and less fit at baseline compared with controls. A post hoc analysis of STRRIDE data (personal communication, C Slentz PhD) suggests that participants in that study who were more insulin resistant (Si < 3.0), older (Age >53.3) and less fit (peak V02 <23) responded robustly with improved Si to the exercise intervention we used in this study. However, those who were heavier (BMI >30) appeared to show an attenuated response to exercise. Based on this observation, it is possible to speculate that the greater BMI in our exercise group might help explain the lack of measurable change in Si.

Had our groups been more closely matched, we might anticipate results similar to the STRRIDE study. In that study, the same exercise regimen led to a change in Si from 2.6 +/− 0.3 to 4.3 +/− 0.6 (12). While we did not see a similar change in Si in our study, we did see a trend toward improved insulin sensitivity measured by AUC insulin, and changes in plasma lipoproteins similar to those in STRRIDE. Exercisers in both the STRRIDE study and ours showed decreased triglycerides (calculated from NMR), and decreased concentration of large VLDL particles (17), changes expected with improved insulin sensitivity. We speculate that these

lipid changes, and changes in insulin sensitivity, would have been more pronounced, had our groups been better matched.

Since we were unable to obtain end-of-study testing for participants who dropped out, we could not perform an intention-to-treat analysis.

Conclusions

Women with PCOS are at an increased risk of type 2 diabetes, dyslipidemia, and possibly cardiovascular disease. Lifestyle interventions play an important role in the prevention of metabolic complications. The individual roles of different lifestyle components such as diet and exercise are not well understood. This study demonstrates that moderate-intensity exercise (caloric equivalent of walking 12 miles per week), without significant weight loss, can significantly improve several components of lipoprotein profiles. While the clinical significance of some of these changes is based on their association with cardiovascular disease and insulin resistance, our results support the role of exercise in women with PCOS. Further, they lay the ground work for future intervention studies involving lipoprotein profiles in women with PCOS.

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Abbreviations

PCOS
: polycystic ovary syndrome

LDL
: low-density lipoprotein

VLDL
: very low-density lipoprotein

IDL
: intermediate-density lipoprotein

HDL
: high-density lipoprotein

NMR
: nuclear magnetic resonance

BMI
: body mass index

IVGTT
: intravenous glucose tolerance test

OGTT
: oral glucose tolerance test

AUC

area under the curve

IRAS

insulin resistance atherosclerosis study

STRRIDE

studies of targeted risk reduction interventions through defined exercise

References

1. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1929–1935. [PubMed: 15623819]
2. Berneis K, Rizzo M, Lazzaroni V, Fruzetti F, Carmina E. Atherogenic lipoprotein phenotype and low-density lipoproteins size and subclass in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2007;92:186–189. [PubMed: 17062762]
3. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:2562–2568. [PubMed: 12788855]
4. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA 2007;297:2081–91. [PubMed: 17507344]
5. Dejager S, Pichard C, Giral P, Bruckert GE, Federspield MC, Beucler I, Turpin G. Smaller LDL particle size in women with polycystic ovary syndrome compared to controls. Clin Endocrinol 2001;54:455–462.
6. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity in polycystic ovary syndrome. Diabetes 1989;38:1165–1174. [PubMed: 2670645]
7. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141–146. [PubMed: 10333916]
8. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. PCOS/Troglitazone study group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:48–53. [PubMed: 16249284]
9. Festa A, Williams K, Hanley AJG, Otvos JD, Goff DC, Wagenknecht LE, Haffner SM. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the insulin resistance atherosclerosis study. Circulation 2005;111:3465–3472. [PubMed: 15983261]
10. Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ, Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. Arterioscler Thromb Vasc Biol 1998;18:1046–1053. [PubMed: 9672064]
11. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, Pugh K, Jenkins AJ, Klein RL, Liao Y. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. Diabetes 2003;52:453–462. [PubMed: 12540621]
12. Goff DC, D'Agostino RB Jr, Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the Insulin Resistance Atherosclerosis Study. Metabolism 2005;54:264–270. [PubMed: 15690322]
13. Houmard JA, Tanner CJ, Slentz CA, Buscha BD, McCartney JS, Kraus WE. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004;96:101–106. [PubMed: 12972442]
14. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. Clin Lab Med 2006;26:847–70. [PubMed: 17110242]
15. Johansson J, Carlson LA, Landou C, Hamsten A. High density lipoproteins and coronary atherosclerosis: A strong inverse relation with the largest particles is confined to normotriglyceridemic patients. Arterioscler Thromb 1991;11:174–182. [PubMed: 1987996]

16. Kamigaki AS, Siscovick DS, Schwartz S, Psaty BM, Edwards KL, Raghunathan TE, Austin MA. Low density lipoprotein particle size and risk of early-onset myocardial infarction in women. Am J Epidemiol 2001;153:939–945. [PubMed: 11384949]

17. Kraus WE, Torgan CE, Duscha BD, Norris J, Brown SA, Cobb FR, Bales CW, Annex BH, Samsa GP, Houmard JJA, Slentz C. Studies of a targeted risk reduction intervention through difined exercise (STRRIDE). Med Sci Sports Exerc 2001;33:1774–1784. [PubMed: 11581566]

18. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002;347:1483–1492. [PubMed: 12421890]

19. Lamarche B, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Associations of HDL2 and HDL3 subfractions with ischemic heart disease in men. Arterioscler Thromb Vasc Biol 1997;17:1098–1105. [PubMed: 9194760]

20. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. Circulation 1997;95:69–75. [PubMed: 8994419]

21. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–169. [PubMed: 9920077]

22. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the multi-ethnic study of atherosclerosis (MESA). Atherosclerosis 2007;192(1):211–7. [PubMed: 16765964]

23. Otvos JD, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, Bloomfield HE, Robins SJ. LDL and HDL particle subclasses predict coronary events and are changed favorably by gemfibrozil therapy in the Veterans Affairs HDL Intervention Trial (VA-HIT). Circulation 2006;113:1556–63. [PubMed: 16534013]

24. Cromwell WC, Otvos JD. Low-density lipoprotein particle number and risk for cardiovascular disease. Curr Atheroscler Rep 2004;6:381–7. [PubMed: 15296705]

25. Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, Kuller L. Coronary heart disease risk factors in women with polycystic ovary syndrome. Arterioscler Thromb Vasc Biol 1995;15:821–826. [PubMed: 7600112]

26. Talbott EO, Zborwski JV, Rager JR, Boudreaux MY, Edmndowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Enodcrinol Metab 2004;89:5454–5461.

27. Wild RA, Painter PC, Coulson PB, Carruth KB, Ranney GB. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1985;61:946–951. [PubMed: 4044782]

28. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: A retrospective cohort study. Clin Endocrinol 2000;52:595–600.

Table 1

Baseline characteristics of study completers

	Exercise (n=8)		Control (n=12)	
Variable	**Median**	**IQR**	**Median**	**IQR**
Age (years)*	36.5	5.0	28.0	11.0
Weight (kg)	89.1	31.5	87.3	40.8
BMI (kg/m^2)	37.9	9.4	31.3	14.9
Systolic BP (mmHg)	122.0	18.5	104.0	20.0
Diastolic BP (mmHg)	70.5	18.0	59.0	10.0
Ferriman-Gallwey	9.0	16.0	15.0	8.0
Bioavailable testosterone (pmol/l)	319.0	589.4	450.7	329.4
Waist circumference (cm)	98.0	20.5	97.0	39.0
Hip circumference (cm)	122.0	29.5	119.5	26.0
Peak VO_2 (ml/kg/min)	22.5	6.0	27.0	13.0
HOMA-IR	3.8	5.9	4.5	4.5
Fasting Glucose (mmol/l)	4.8	0.3	4.8	0.4
2hr Glucose (mmol/l)	6.7	1.2	6.8	2.3
AUC Glucose	895.9	236.9	846.0	280.6
Fasting Insulin (pmol/l)	141.7	173.6	139.6	148.6
2hr Insulin (pmol/l)	791.0	853.5	557.7	645.2
AUC Insulin	106582.1	43281.9	74822.7	95807.0
Insulin Sensitivity (Si)	1.2	1.4	2.5	2.9
HbA1c	5.5	0.4	5.3	0.4

Values are expressed as medians (interquartile range; IQR) or n (%).

*$p<0.05$, all other differences between groups were not significant

Table 2

Baseline Lipoprotein Measures

	Exercise Group (n=8)		Control Group (n=12)	
	Median	**IQR**	**Median**	**IQR**
Lipoprotein Particle Concentrations				
VLDL particles (nmol/L)				
Total	60.6	23.3	45.9	31.5
Large VLDL/chylomicrons	4.52	9.48	0.74	3.43
Medium VLDL	22.8	17.9	20.3	17.2
Small VLDL	31.0	15.2	29.5	9.0
LDL particles (nmol/L)				
Total	1124.6	437.9	1028.6	353.0
IDL	33.5	55.2	23.5	26.2
Large LDL	399.9	184.7	365.6	244.1
Small LDL	697.9	390.3	535.6	375.7
HDL particles (umol/L)				
Total	33.9	3.9	29.0	7.2
Large HDL	8.1	3.4	6.6	4.1
Medium/Small HDL	26.5	3.3	21.6	7.7
Mean Particle Sizes (nm)				
VLDL	54.7	22.2	48.4	10.3
LDL	21.1	0.8	21.3	0.9
HDL	9.0	0.3	9.0	0.5
Calculated Lipids (mg/dl)				
Triglycerides	142.6	132.4	81.0	49.2
VLDL-triglycerides	108.2	132.0	50.7	46.1
HDL cholesterol	54.3	12.2	47.4	15.6

Table 3

Effect of exercise intervention on outcome measures.

	Exercise Group(n=8)		Control Group(n=12)	
	Median % change	**IQR**	**Median % change**	**IQR**
Weight (kg)	−1.29	4.2	0.45	3.5
BMI (kg/m^2)	−1.28	4.2	0.46	3.5
SBP (mmHg)	−0.42	10.9	−1.83	15.0
DBP (mmHg)	4.98	16.1	3.19	20.4
Ferriman-Gallwey	0.00	4.00	0.00	19.2
Bioavailable testosterone	−15.19	49.1	0.00	58.1
Waist circumference (cm)	−1.08	7.4	0.43	5.3
Hip circumference (cm)	−0.94	2.28	−1.00	5.1
Peak VO_2	5.28	8.25	0.00	6.1
HOMA*	−8.56	19.77	11.18	94.4
Fasting glucose	4.57	21.2	−0.54	9.6
2-hour glucose	1.32	6.1	−3.54	53.6
AUC glucose	5.47	25.2	2.95	28.1
Fasting insulin	−4.88	18.6	7.79	77.7
2-hour insulin	−7.77	45.54	2.60	39.5
AUC insulin**	−26.0	36.6	2.11	40.1
Insulin Sensitivity (S_i)	−2.77	35.94	−5.96	44.4

Values are expressed as median percent change. IQR=inter-quartile range. All differences are non-significant

* HOMA [Fasting Glucose × .055] × [Fasting Insulin] ÷ 22.5

** p=0.098 for AUC insulin

Table 4

Effect of exercise intervention on lipoprotein particles.

	Control (n=12)	Exercise (n-8)	
Variable	**Median Absolute Change (pre-post) (25%,75%)**	**Median Absolute Change (pre-post) (25%,75%)**	**P value***
Lipoprotein Particle Concentrations			
Total VLDL particles (nmol/L)	−3.3 (−10.6, 5.5)	−9.6 (−17.5, 2.4)	0.571
Large VLDL/chylomicrons	1.1(0.2, 4.2)	−1.7(−3.4, 0.4)	**0.007**
Medium VLDL	1.0(−4.3, 8.2)	−4.8(−10.4, 7.1)	0.343
Small VLDL	−3.5(−10.8, 0.8)	−5.4(−11.7, 8.0)	0.851
Total LDL particles (nmol/L)	57.9(−67.0, 139.7)	−18.4 (−167.8, 78.4)	0.208
IDL	11.4(−8.3, 33.1)	−12.9(−30.3, 5.3)	0.057
Large LDL	−24.5(−137.2, 20.8)	−19.5(−69.2, 151.8)	0.305
Small LDL	55.2(−107.2, 191.7)	−0.7(−232.0, 115.8)	0.270
Total HDL particles (umol/L)	−0.5(−2.9, 1.9)	−0.6(−2.6, 0.7)	0.678
Large HDL	−0.8(−2.2, −0.4)	1.3(0.5, 1.5)	**0.002**
Medium/Small HDL	1.0(−1.2, 1.9)	−1.9(−4.1, −0.5)	**0.031**
Mean Particle Sizes (nm)			
VLDL	1.2 (−2.0, 7.2)	−2.2 (−7.9, 3.1)	0.181
LDL	−0.1(−0.6, 0.2)	−0.1(−0.2, 0.6)	0.208
HDL	−0.1(−0.2, −0.1)	0.1(0.1, 0.2)	**0.001**
NMR Calculated Lipids (mg/dl)			
Triglycerides	10.6(−6.5, 45.7)	−44.3(−53.7, −17.9)	**0.003**
VLDL-triglycerides	11.6(−8.7, 42.5)	−41.6(−53.4, −16.4)	**0.003**
HDL cholesterol	−1.9(−6.1, 0.7)	2.2(0.2, 3.0)	0.069

Expressed as median absolute change, with interquartile range

* Two sided p values calculated from Wilcoxon exact rank sum test

Table 5

NMR lipid characteristics associated with insulin resistance

		Insulin Resistance (without diabetes)*	Change in PCOS study
Particle Size			
VLDL		↑	-
LDL		↓	-
HDL		↓	↑
Particle Concentration			
VLDL	Total	-	-
	Large	↑	↓
	Intermediate	-	-
	Small	-	-
IDL		-	-
LDL	Total	↑	-
	Large	↓	-
	Small	↑	-
HDL	Total	-	-
	Large	↓	↑
	Intermediate	-	↓**
	Small	-	

*Garvey 2003. ↑= increase, ↓= decrease, - = no change

**Intermediate and Small combined