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Effect Of Physical Activity On Lipid Markers In Breast Cancer Survivors Taking Aromatase Inhibitors: The Hormones And Physical Exercise Study

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ABSTRACT

The use of aromatase inhibitors (AIs) has been associated with increased risk of cardiovascular disease and unfavorable changes in lipid profile in postmenopausal breast cancer survivors. In other populations, physical activity has been shown to successfully reduce CVD risk and improve lipid parameters. The Hormones and Physical Exercise (HOPE) study was a yearlong randomized trial examining the impact of exercise vs. usual care on AI-associated side effects. This analysis examined the effect of exercise on lipid profiles among HOPE participants.

We enrolled 121 physically inactive (<90 min/wk of aerobic activity and no strength training) postmenopausal breast cancer survivors receiving an AI for at least 6 months. Participants were randomly assigned to exercise (150 min/wk of aerobic exercise and supervised strength training 2x/wk) or to usual care. Fasting blood samples (>12 hours) were collected at the baseline, 6- and 12-month clinic visits. Intervention effects were evaluated using generalized linear models, with change from baseline to 6 months and 12 months as the primary end points.

Over 12 months, women randomized to exercise increased their exercise by 159 (SD 136) minutes per week and decreased their body weight by 2.4% (SD 5.4%). LDL/HDL ratio increased by 3% at 6 months among women randomized to exercise versus a 6% decrease among those in the attention control group ($p = 0.036$). Likewise, TC/HDL ratio increased by 2% at 6 months among women randomized to exercise versus a 5% decrease among those in the attention control group ($p = 0.038$). A dose-response inverse relation between attendance to supervised exercise sessions and triglycerides was also observed ($p = 0.047$).

We observed an unfavorable effect of exercise on the lipid ratios. Further research is needed to examine the impact of exercise on lipid levels and CVD risk in breast cancer survivors initiating AI use.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related death among American women.[1] In 2014, there were an estimated 232,670 incident cases of breast cancer and 40,000 deaths due to breast cancer.[2] Globally, breast cancer incidence increased by more than 20% between 2008 and 2012, with 1.67 million women diagnosed with breast cancer worldwide in 2012.[3] More than half of breast cancer cases (52.8%) and deaths (62.1%) occurred in less developed countries, reflecting the shifting lifestyles in these regions, as well as lack of early detection leading to poorer survival.[4]

Due to improved survival resulting from earlier detection and treatment advances, there are an estimated 3.1 million breast cancer survivors in the U.S.[5] More than two thirds of breast cancer cases are hormone receptor-positive and responsive to adjuvant endocrine therapy.[6] Tamoxifen has historically been the standard hormonal treatment for both pre- and postmenopausal women. However, third-generation aromatase inhibitors (AIs) - including exemestane, letrozole, and anastrozole - have increasingly been viewed as the standard of care for postmenopausal women, with several randomized trials demonstrating reduced recurrence rates and improved disease-free survival for AIs compared to 5 years of tamoxifen.[7-11] Current guidelines recommend that postmenopausal women with hormone receptor-positive breast cancer receive an AI, either as primary therapy or following 2-5 years of tamoxifen.[12]

Two recent meta-analyses indicate that, compared with tamoxifen, the use of AIs in postmenopausal women is associated with a small increase in risk of developing cardiovascular disease (CVD).[13,14] However, another recent review of AI trials showed no significantly increased risk of CVD events compared to placebo, indicating that increases in CVD risk with AIs compared to tamoxifen may have been confounded by the use of tamoxifen as a comparator,

due to the known cardioprotective effects of tamoxifen.[15] The evidence on the effect of AIs on lipid profile is similarly mixed. Two recent randomized trials found overall unfavorable effects of AIs on lipid profile, although these findings may be explained in part by the withdrawal effect of tamoxifen. The MA-17L sub-study observed significant increases in total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol among postmenopausal women on letrozole after 5 years of tamoxifen.[16] The ELPh trial compared treatment with exemestane (steroidal AI) to letrozole (non-steroidal AI), finding significant decreases in total cholesterol and HDL in the exemestane group and significant increases in total cholesterol and LDL in the letrozole group, as well as a significant increase in LDL/HDL ratio in the entire cohort.[17] Given that CVD is the leading cause of death for breast cancer survivors and postmenopausal women are at an increased risk for CVD, these findings have important implications on the risk-benefit ratio of adjuvant treatment choice.[18]

Effective interventions are therefore needed to reduce cardiovascular disease risk in breast cancer survivors. Physical activity may be an effective intervention for inducing favorable changes in lipid profile and reducing risk for CVD. Physical activity is associated with reduced CVD risk in the general population.[19] Physical activity has also been shown to produce favorable modifications to lipid profile in the general population, increasing HDL and decreasing total cholesterol, LDL, and trigylcerides.[20-22] In women, a large meta-analysis has shown that aerobic exercise significantly reduces total cholesterol, LDL cholesterol and triglycerides, and significantly increases HDL cholesterol.[23] Fewer studies have been conducted in postmenopausal women. Although many studies in postmenopausal women have failed to find a significant effect of physical activity on lipid profile, the EFOPS trial found that participants randomized to exercise significantly reduced total cholesterol and triglyceride levels over 2 years.[24,25] Among

breast cancer survivors, a 2010 systematic review found that exercise interventions significantly decreased serum triglycerides, but had no significant effect on total cholesterol, HDL, or LDL.[26] To our knowledge, no studies have examined the effect of exercise on lipid profile in breast cancer survivors taking AIs.

Given the lack of existing literature, the purpose of this analysis was to examine the effect of exercise versus usual care on lipid profile in sedentary postmenopausal breast cancer survivors taking AIs in the Hormones and Physical Exercise (HOPE) study. We hypothesized that exercise would improve lipid profiles, increasing HDL cholesterol and decreasing total cholesterol (TC), LDL cholesterol, triglycerides, LDL/HDL ratio and TC/HDL ratio.

METHODS

Study Population

The 121 postmenopausal breast cancer survivors who were enrolled in the Hormones and Physical Exercise (HOPE) study are included in this report. Eligible women were English speaking, physically inactive (< 90 minutes per week of aerobic activity in past 6 months and no strength training in past year), had been diagnosed with hormone receptor-positive stage 0-III breast cancer 0.5 to 4 years before enrollment, and had physician consent to exercise. Participants must also have been taking an AI for at least 6 months and experiencing mild or greater severity arthralgia (score ≥ 3 for worst pain item on modified Brief Pain Inventory) associated with AI use at time of enrollment.[27] Exclusion criteria included being over 75 years of age.

Recruitment

Potentially eligible women were identified at five hospitals in Connecticut through the Rapid Case Ascertainment Shared Resource Center of the Yale Cancer Center (RCA) between

June 1, 2010, and December 30, 2012. Study staff contacted patients' physicians for permission to contact the participants and approval for the patient to exercise. Following receipt of physician consent, an invitation letter was mailed to the participant. Within two weeks of mailing, participants were contacted by telephone to gauge interest and determine eligibility through a screening questionnaire. Women who were interested and considered to be eligible were scheduled for a baseline interview, where signed consent was obtained and several study questionnaires were completed. Final study eligibility was determined at the baseline clinic visit. At the conclusion of the baseline clinic visit, women were randomized to the exercise intervention program (N = 61) or to an attention control (health education) program (N = 60).

All procedures, including written informed consent, were approved by the Yale School of Medicine Human Investigation Committee and Connecticut Department of Public Health Human Investigation Committee.

Procedures and Measures

At each of the baseline, 6- and 12-month clinic visits, standard questionnaires were used to collect information on demographics, anthropometrics, medical history and health habits. Self-reported demographic variables collected at baseline included current age, race/ethnicity, education level, and marital status. Interviewer-administered questionnaires were used to determine time since diagnosis, time since initiating AI therapy, disease stage, use of cholesterol-lowering medication, and history of physician-diagnosed high cholesterol. Height and weight measures were performed with participants in light clothing and without shoes. All measures were performed and recorded twice in succession, with weight (digital scale) rounded up to the nearest 0.1 kg and height (stadiometer) rounded up to the nearest 0.1 cm.

Cardiorespiratory fitness was measured with a maximal oxygen consumption (VO_2 max) treadmill test at baseline and 12 months.[28] Physical activity was assessed using a physical activity questionnaire (PAQ) that all participants completed at baseline and at 6 and 12 months, measuring the past 6 months of activity, including the type, frequency, and duration of 20 activities.[29]

Blood samples were collected at each of the baseline, 6-month and 12-month clinic visits by a trained phlebotomist. Participants were instructed to fast for a minimum of 12 hours prior to the blood draw and the time last ate was recorded. Participants were also questioned about alcohol consumption within the past 48 hours. Plasma samples were centrifuged at 2,500 rpm for 10 minutes at 4° C, then were stored at -80° C until assayed. Plasma total cholesterol, HDL, and triglycerides were enzymatically measured on an Alfa Wassermann ACE Alera Chemistry Analyzer (Alfa Wassermann, West Caldwell, NJ).

Intervention

Women in the exercise intervention group were counseled to increase their physical activity to include twice-weekly strength training sessions and 150 minutes per week of walking during the 12-month intervention, based on current recommendations for cancer survivors.[30] Participants were provided with a 12-month membership to a local gym and met twice weekly with an American College of Sports Medicine-certified cancer exercise trainer. Supervised strength training sessions consisted of six common strength-training exercises, using the protocol developed by Schmitz et al.[31] The aerobic exercise intervention consisted primarily of brisk walking, and could be completed at the gym or at home. Exercise started at 50% of maximal heart rate (determined from VO_2 max testing) and increased to 60% to 80% of maximal heart rate over the course of the study.

Women in the health education group were instructed to continue with their usual activities. They were provided written information emphasizing the importance of a healthy lifestyle and were encouraged to follow the NCI and ACS physical activity guidelines (150 minutes per week of moderate-intensity physical activity for women diagnosed with breast cancer).[30] Health education participants each received a one-on-one session with an exercise trainer and a personalized exercise prescription upon completion of the study.

All participants received an educational booklet prepared for the HOPE study with breast cancer topics of interest that were discussed monthly over the telephone (health education) or at an exercise session (exercise). Upon completion of the intervention, all participants were also given information on survivorship resources in Connecticut.

Statistical Analyses

Data were analyzed according to the intention-to-treat principle. Descriptive statistics - Student t-test, chi-square test, and Fisher's exact test – were used to compare the intervention groups at baseline. We used generalized linear models (GLM) controlling for baseline scores of the relevant component of the lipid profile and lipid-lowering medication use to compare the mean changes over time (baseline to 6-month and baseline to 12-month time points) between the intervention and health education group for each component of the lipid profile. Other potential covariates included age, race/ethnicity, BMI, cancer stage, time on AI, fasting status, and alcohol use. Covariates were selected for inclusion in the final models using a step-down approach, with a covariate retained across all of the models for each component of the lipid profile if it was a significant predictor ($p < 0.05$) of at least one component. Our primary time points were baseline, 6 months, and 12 months. For women who did not have a follow-up blood drawn at the 6- or 12-

month clinic visits, a conservative last observation carried forward imputation approach was used.

To evaluate the presence of a dose-response effect of the intervention, several sub-group analyses were performed among women in the intervention group. We examined the impact of attendance at the supervised sessions on lipid profile by comparing women who attended at least 80% of sessions to those who did not. Likewise, we examined the impact of aerobic exercise dose on lipid profile by comparing women who participated in at least 120 minutes per week (i.e., 80% of the 150 minutes per week goal) of moderate-intensity aerobic exercise to those who did not. Finally, we performed stratified analyses by cholesterol-lowering medication status at baseline and baseline lipid status (above/below recommended value) to assess the presence of effect modification. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC), with two-sided statistical significance set at $p < 0.05$.

RESULTS

A total of 1,537 estrogen receptor-positive breast cancer survivors were identified through the RCA. Screening telephone calls were completed with 1,016 women (66%). Of these women, 253 were not taking an AI, 407 were ineligible for other reasons, and 235 were not interested. The remaining 121 women were randomly assigned to the exercise intervention (N = 61) or to the attention control (N = 60). The last 25 women recruited were enrolled into a 6-month trial rather than the full 12-month trial, due to funding cuts. The flow of patients through the HOPE study has been described in more detail previously.[32]

Demographic and clinical characteristics at baseline are shown in Table 1. There were no significant differences between the two study arms at baseline. The average age of study participants was 61 years, while the average BMI was 29.3 kg/m^2. The average time between

diagnosis of breast cancer and enrollment was 3.0 years and participants had been taking AIs for 1.8 years on average. A majority of the women were non-Hispanic white (86%), were presently married (53%), had completed some additional schooling after high school (37%), and were diagnosed with stage I disease (60%). A physician diagnosis of high cholesterol was reported by 49 women (44%), while 43 women (36%) reported taking lipid-lowering medication. At baseline, the participants had a mean total cholesterol level of 198.2 mg/dL (SD 35.9), HDL level of 59.1 mg/dL (SD 14.3), LDL level of 115.7 mg/dL (SD 31.9), triglyceride level of 117.6 mg/dL (SD 50.4), LDL/HDL ratio of 2.1 (SD 0.7) and TC/HDL ratio of 3.5 (SD 0.9).

As assessed via the physical activity questionnaire, women randomized to exercise increased their physical activity by 159 minutes per week from baseline to 12 months, while women in the attention control group increased their physical activity by 49 minutes per week ($p < 0.001$). Exercisers significantly ($p < 0.001$) improved their cardiorespiratory fitness from baseline to end-of-study compared to the control group, with a 6.5% increase versus a 1.8% decrease, respectively. Exercisers also reduced their body weight by 2.1 kg (2.4%) from baseline to 12 months, compared to a 0.1 kg (0.0%) increase in the control group ($p = 0.04$).

Table 3 presents the mean baseline and adjusted 6- and 12-month change from baseline values by intervention group for the lipid parameters. There were no statistically significant differences between groups in baseline total cholesterol ($p = 0.71$), HDL cholesterol ($p = 0.93$), LDL cholesterol ($p = 0.77$), triglycerides ($p = 0.83$), LDL/HDL ratio ($p = 0.87$), or TC/HDL ratio ($p = 0.80$). LDL/HDL ratio significantly increased from baseline to 6 months in the exercise group compared to the attention control group (0.07 ± 0.06 vs. -0.13 ± 0.06, $p = 0.036$). Similarly, TC/HDL ratio significantly increased from baseline to 6 months in the exercise group compared to the attention control group (0.06 ± 0.07 vs. -0.17 ± 0.07, $p = 0.038$). Both ratios also

increased from baseline to 12 months in the exercise group compared to the attention control group, but these differences were not significant ($p = 0.17$). There were no significant differences between groups for 6- and 12-month change in total cholesterol, HDL, LDL and triglycerides.

Stratifying by lipid-lowering medication status at baseline, by baseline lipid status (above/below recommended value), or by AI type (steroidal/non-steroidal) resulted in no significant findings (data not shown). Table 4 shows the dose-response effect of attendance to supervised sessions on adjusted changes in lipid profile at 6 and 12 months among exercisers. Greater attendance to sessions was associated with decreases in triglycerides from baseline to 6 months (-11.6 ± 11.3, $p = 0.31$) and from baseline to 12 months (-28.7 ± 13.9, $p = 0.047$). More minutes per week of aerobic exercise was not significantly associated with any changes in lipid profile (data not shown).

DISCUSSION

We investigated whether a 12-month exercise intervention would have a positive effect on lipid levels in a population of sedentary postmenopausal breast cancer survivors taking AIs. We found that the atherogenic risk ratios increased from baseline to 6 months in women randomized to exercise, whereas these ratios decreased in women randomized to the health education group. A trend toward significance was observed for HDL cholesterol and triglycerides, with decreased levels of each lipid parameter in the exercise group compared to the control group at both 6 and 12 months. A dose-response inverse relationship between attendance at supervised sessions and triglyceride level was also observed, with increased attendance ($\geq$ 80% of sessions) associated with a decrease in triglycerides. A decrease in triglycerides due to exercise is consistent with the prior literature in postmenopausal women and breast cancer survivors.

Increases in the atherogenic risk ratios are not desirable, as these ratios are positively associated with CVD risk, and have greater predictive value than isolated lipid parameters.[33] One mechanism by which exercise could affect lipid concentrations in this way is through a negative effect on body fat, and ultimately circulating estrogen levels. A previous randomized trial showed that exercise can lower levels of circulating estrogens in a clinically significant way in a population of previously sedentary, overweight/obese postmenopausal women.[34] As inhibition of estrogen synthesis is a primary goal of treatment of hormone receptor-positive breast cancer, patients treated with AIs experience a high level of estrogen deprivation.[35] It is possible that exercise exacerbates this decrease in estrogen levels through its effect in decreasing body fat, thus further increasing the risk of altered lipid profiles. This is supported by the fact that participants randomly assigned to exercise reduced their body weight by 2.1 kg on average, and that, after controlling for change in BMI, there were no longer significant differences in LDL/HDL ratio and TC/HDL ratio between groups.

Caution should be used in interpreting these data, as alteration of lipid levels is only one way in which exercise may impact cardiovascular risk. Results from large epidemiological studies have repeatedly shown that exercise reduces the risk for CVD independent of changes in cardiovascular risk markers, including BMI and lipids.[36]

Prior tamoxifen use, type of AI used, and inclusion of patients on lipid-lowering medications may have impacted the results. Use of tamoxifen reduces LDL cholesterol and previous studies have reported a washout effect for tamoxifen on lipid levels, with Bell et al. finding that prior use of tamoxifen was a significant independent predictor of increased LDL cholesterol.[16,17] It is unclear if we should expect a similar washout effect in the current study, given that all study participants had been taking AIs for at least 8 months at time of enrollment.

By contrast, participants with prior tamoxifen use in the Bell et al. and Wasan et al. studies were withdrawn from adjuvant tamoxifen just before entry into the two trials. Significant increases in LDL cholesterol were seen at 3 and 6 months, respectively. We did not collect information on participants' prior tamoxifen use. The type of AI – steroidal (exemestane) or non-steroidal (letrozole or anastrozole) – was an independent predictor of change in HDL, LDL/HDL ratio and TC/HDL ratio in our study, with use of a steroidal AI significantly associated with decreased HDL, increased LDL/HDL ratio and increased TC/HDL ratio across both groups. Similarly, use of lipid-lowering medications was significantly associated with a decrease in LDL and a decrease in LDL/HDL ratio. Stratifying by type of AI used or use of lipid-lowering medications did not result in any significant findings for the effect of exercise, although this may indicate that the study was not powered for stratified analyses.

Baseline lipid parameters tended to be lower than values reported in previous studies of postmenopausal breast cancer patients, with lower decreased average total cholesterol, HDL and LDL and higher average triglycerides in our study.[16,17] This may reflect the higher usage of lipid-lowering medication in this population. In our sample, 17.2% of women aged 40-59, 50.8% of women aged 60-74, and 100% of women aged 75 and over used a prescription lipid-lowering medication. This usage is higher than that of women in the general population within each age stratum.[37]

To our knowledge, this is the first study to examine the effect of exercise on lipid parameters in a sample of postmenopausal breast cancer survivors exclusively taking AIs. A major strength of our study is the strong methodological design, including randomization with an attention control group, a population with variable BMI, large sample size, population-based recruitment, and 12-month follow-up period. An additional strength is the high adherence to the

exercise intervention. Our study had several limitations, however. We lacked information about other risk factors associated with changes in lipid profile, most notably prior tamoxifen use. Women in the HOPE study had been taking AIs for 8 months to 4 years at time of enrollment, and this variability may have had an effect on lipid profile independent from exercise, although the amount of time on AIs was not a significant predictor of change in any of the lipid parameters. If we had enrolled women prior to initiation of AIs, and measured change in lipids with exercise during the first year of AI use, we may have observed different effects of exercise. Finally, the statistical power for stratified analyses was likely limited by the sample size of the study.

In conclusion, we observed no effect of exercise on the lipid profile of postmenopausal women with breast cancer taking aromatase inhibitors, and an unfavorable effect of exercise on the lipid ratios; however this effect become non-significant after adjusting for change in BMI. Further research is needed to examine the impact of exercise on lipid levels and CVD risk in breast cancer survivors initiating AI use.

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Table 1. Baseline Characteristics of Randomly Assigned Participants in HOPE Study[a]

Characteristic	Exercise Intervention (N=61)[b]	Attention Control (N=60)[b]	P[c]
Age (years)	62.0 ± 7.0	60.5 ± 7.0	0.25
Race/ethnicity			0.67
Non-Hispanic white	53 (86.9)	51 (85.0)	
Non-Hispanic black	6 (9.8)	4 (6.7)	
Hispanic	1 (1.6)	3 (5.0)	
Other	1 (1.6)	2 (3.3)	
Education			0.46
≤ High school graduate	6 (9.8)	9 (15.0)	
Some school after high school	20 (32.8)	25 (41.7)	
College graduate	15 (24.6)	10 (16.7)	
≥ Some graduate school	20 (32.8)	16 (26.7)	
Marital status			0.79
Never Married/Divorced/Widowed	28 (45.9)	29 (48.3)	
Presently married	33 (54.1)	31 (51.7)	
Time since diagnosis (years)	2.7 ± 3.1	3.3 ± 3.9	0.38
Time since initiating AI therapy (years)	1.9 ± 1.9	1.8 ± 1.3	0.89
AI type			1.00
Anastrozole	30 (49.2)	30 (50.0)	
Letrozole	26 (42.6)	26 (43.3)	
Exemestane	5 (8.2)	4 (6.7)	
Disease stage			0.87
0	1 (1.6)	0 (0.0)	
I	36 (59.0)	37 (61.7)	
II	18 (29.5)	19 (31.7)	
III	6 (9.8)	4 (6.7)	
Body mass index (kg/m^2)	30.0 ± 6.8	28.7 ± 5.5	0.27
Taking lipid-lowering medication			0.80
Yes	21 (34.4)	22 (36.7)	
No	40 (65.6)	38 (63.3)	
Physician-diagnosed high cholesterol			0.92
Yes	25 (44.6)	24 (43.6)	
No	31 (55.4)	31 (56.4)	

[a] Table values are mean ± SD for continuous variables and n (column %) for categorical variables

[b] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding

[c] P-value is for t-test (continuous variables), χ^2 test (other categorical variables), or Fisher's exact test (cell counts < 5)

Table 2. Physical Activity, Cardiorespiratory Fitness, and Body Weight Changes in HOPE Study[a]

Measure	Exercise Intervention (N=61)	Attention Control (N=60)	P
Physical activity questionnaire, minutes per week			
Baseline	54.8 ± 93.0	60.7 ± 99.0	0.74
12 months	222.1 ± 118.6	103.6 ± 104.7	< 0.001*
Change	159 ± 136	49 ± 86	< 0.001*
Percent reporting ≥ 150	70	6	
VO_2 max, ml/kg per minute			
Baseline	23.0 ± 5.3	23.1 ± 3.5	0.88
12 months	24.6 ± 5.5	23.0 ± 4.7	0.17
Change	1.5 ± 2.1	-0.4 ± 2.7	< 0.001*
Percent change	6.5 ± 3.7	-1.8 ± 11.2	0.001*
Body weight, kg			
Baseline	78.5 ± 18.1	75.5 ± 14.5	0.32
Change	-2.1 ± 4.3	0.1 ± 3.6	0.014*
Percent change	-2.4 ± 5.4	0.0 ± 4.8	0.37

[a] Table values are mean ± SD

Table 3. Effect of Exercise Versus Usual Care on Lipids at Baseline and Changes at 6 and 12 Months (Adjusted for baseline value, lipid-lowering medication use, AI type, race, BMI, disease stage, and alcohol use)[a,b]

Outcome	Exercise Intervention (N=61)[c]	Attention Control (N=60)[d]	Treatment Effect (exercise minus control)	P
Total Cholesterol				
Baseline	197.0 ± 4.6	199.5 ± 4.7	-2.5 ± 6.5	0.71
6-month change	3.8 ± 2.9	1.6 ± 2.9	2.2 ± 4.2	0.60
12-month change	1.3 ± 3.4	3.8 ± 3.4	-2.5 ± 5.0	0.61
HDL Cholesterol				
Baseline	59.0 ± 1.8	59.2 ± 1.9	-0.2 ± 2.6	0.93
6-month change	0.7 ± 1.3	2.2 ± 1.3	-1.5 ± 2.0	0.45
12-month change	-0.6 ± 1.5	1.6 ± 1.5	-2.2 ± 2.3	0.35
LDL Cholesterol				
Baseline	114.8 ± 4.0	116.5 ± 4.2	-1.7 ± 5.8	0.77
6-month change	3.6 ± 2.5	-0.3 ± 2.5	4.0 ± 3.7	0.28
12-month change	2.6 ± 3.4	0.9 ± 3.4	1.7 ± 5.0	0.74
Triglycerides				
Baseline	116.7 ± 6.6	118.6 ± 6.4	-1.9 ± 9.2	0.83
6-month change	-2.7 ± 4.3	-2.5 ± 4.4	-0.2 ± 6.4	0.98
12-month change	-0.3 ± 5.9	3.7 ± 5.9	-4.0 ± 8.7	0.64
LDL/HDL Ratio				
Baseline	2.05 ± 0.09	2.07 ± 0.09	-0.02 ± 0.13	0.87
6-month change	0.07 ± 0.06	-0.13 ± 0.06	0.19 ± 0.09	0.036*
12-month change	0.09 ± 0.10	-0.11 ± 0.10	0.20 ± 0.14	0.17
TC/HDL Ratio				
Baseline	3.48 ± 0.11	3.52 ± 0.11	-0.04 ± 0.16	0.80
6-month change	0.06 ± 0.07	-0.17 ± 0.07	0.22 ± 0.10	0.038*
12-month change	0.11 ± 0.11	-0.12 ± 0.11	0.23 ± 0.16	0.17

[a] Table values are mean ± SE

[b] 6- and 12-month values are change from baseline

[c] N=48 at 12 months

[d] N=48 at 12 months

Table 4. Effect of Attendance to Supervised Sessions on Lipids at Baseline and Changes at 6 and 12 Months (Adjusted for baseline value, lipid-lowering medication use, disease stage, and alcohol use)[a,b]

Outcome	High Attendance (≥80%) [N=34][c]	Low Attendance (<80%) [N=27][d]	Treatment Effect (high minus low)	P
Total Cholesterol				
Baseline	198.8 ± 6.3	194.8 ± 6.7	4.0 ± 9.2	0.66
6-month change	4.1 ± 4.2	1.8 ± 4.7	2.3 ± 6.6	0.73
12-month change	2.0 ± 5.5	3.2 ± 5.7	-1.2 ± 8.3	0.89
HDL Cholesterol				
Baseline	61.5 ± 2.5	55.7 ± 2.5	5.8 ± 3.6	0.11
6-month change	1.0 ± 2.1	0.0 ± 2.4	0.9 ± 3.3	0.78
12-month change	-0.7 ± 2.6	-0.4 ± 2.7	-0.3 ± 3.9	0.95
LDL Cholesterol				
Baseline	114.1 ± 5.9	115.7 ± 5.4	-1.5 ± 8.2	0.85
6-month change	4.8 ± 3.6	1.2 ± 4.1	3.6 ± 5.7	0.53
12-month change	5.9 ± 5.5	1.2 ± 5.8	4.7 ± 8.4	0.58
Triglycerides				
Baseline	116.3 ± 9.0	117.1 ± 9.9	-0.9 ± 13.5	0.95
6-month change	-8.9 ± 7.1	2.7 ± 8.1	-11.6 ± 11.3	0.31
12-month change	-16.7 ± 9.2	12.0 ± 9.6	-28.7 ± 13.9	0.047*
LDL/HDL Ratio				
Baseline	1.97 ± 0.14	2.16 ± 0.13	-0.19 ± 0.19	0.31
6-month change	0.09 ± 0.09	0.01 ± 0.10	0.08 ± 0.14	0.59
12-month change	0.12 ± 0.16	0.08 ± 0.17	0.04 ± 0.24	0.88
TC/HDL Ratio				
Baseline	3.38 ± 0.16	3.60 ± 0.16	-0.22 ± 0.23	0.32
6-month change	0.07 ± 0.10	0.01 ± 0.12	0.05 ± 0.17	0.75
12-month change	0.06 ± 0.18	0.14 ± 0.18	-0.08 ± 0.27	0.76

[a] Table values are mean ± SE

[b] 6- and 12-month values are change from baseline

[c] N=25 at 12 months

[d] N=23 at 12 months