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Adipose Tissue Inflammation in Breast Cancer Survivors: Effects of a 16-week Combined Aerobic and Resistance Exercise Training Intervention

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Abstract

Purpose.—Obesity is a leading modifiable contributor to breast cancer mortality due to its association with increased recurrence and decreased overall survival rate. Obesity stimulates cancer progression through chronic, low-grade inflammation in white adipose tissue, leading to accumulation of adipose tissue macrophages (ATMs), in particular the pro-inflammatory Ml phenotype macrophage. Exercise has been shown to reduce M1 ATMs and increase the more anti-inflammatory M2 ATMs in obese adults. The purpose of this study was to determine whether a 16-week exercise intervention would positively alter ATM phenotype in obese postmenopausal breast cancer survivors.

Methods.—Twenty obese postmenopausal breast cancer survivors were randomized to a 16-week aerobic and resistance exercise (EX) intervention or delayed intervention control (CON). The EX group participated in 16 weeks of supervised exercise sessions 3 times/week. Participants provided fasting blood, dual-energy X-ray absorptiometry (DXA), and superficial subcutaneous abdominal adipose tissue biopsies at baseline and following the 16-week study period.

Results.—EX participants experienced significant improvements in body composition, cardiometabolic biomarkers, and systemic inflammation (all p<0.03 vs CON). Adipose tissue from

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EX participants showed a significant decrease in ATM M1 ($p<0.001$), an increase in ATM M2 ($p<0.001$), increased adipose tissue secretion of anti-inflammatory cytokines such as adiponectin, and decreased secretion of the pro-inflammatory cytokines IL-6 and TNF- α (all $p<0.055$).

Conclusions—A 16-week aerobic and resistance exercise intervention attenuates adipose tissue inflammation in obese postmenopausal breast cancer survivors. Future large randomized trials are warranted to investigate the impact of exercise-induced reductions in adipose tissue inflammation and breast cancer recurrence.

Keywords

adipose tissue; macrophages; obesity; body composition

Introduction

Approximately 40,000 women in the United States die from breast cancer each year, a statistic largely influenced by obesity and its physiologic consequences (1). In fact, obese breast cancer patients have twice the mortality of non-obese breast cancer patients (2). Various biologic mechanisms linking obesity and cancer prognosis have been proposed to explain this association. One such hypothesis suggests that excess adipose tissue, specifically visceral, may promote neoplasia and tumor progression via adipose tissue inflammation (3).

Adipose inflammation could potentially influence breast cancer cells systemically, via circulating cytokines such as tumor necrosis factor (TNF)-αand interleukin (IL)-6. However, because breast cancer resides in an adipose-rich environment, studies have more recently focused on local effects of inflamed adipose tissue, measuring the levels of these cytokines within adipose tissue itself (4,5). To date, however, no investigations to our knowledge have examined adipose tissue inflammation in cancer survivors. Because macrophages are key contributors to adipose tissue inflammation in obesity, some have proposed that adipose tissue macrophages (ATMs) may mediate the association between obesity with poorer cancer outcomes. Obesity induces a phenotypic change in ATM "polarization", from a predominance of M2, "alternatively activated" ATMs, which act in a primarily anti-inflammatory manner, to an increase in the prevalence of M1, "classically activated" ATMs, which are described as pro-inflammatory (6,7). M1 ATMs are of particular concern as they produce TNF-α and IL-6, which not only contribute to insulin resistance but are linked to cancer recurrence (3,8). M1 ATMs also produce paracrine and angiogenic factors that can promote survival of damaged cells and actively participate in the promotion of tumor growth (9). In this respect, M1 ATM's share similar gene expression profiles to tumor-associated macrophages (TAM)(10), which themselves have been shown to promote cancer progression and metastasis through stimulation of angiogenesis (11). Thus, it is plausible that obesity-related induction of M1 ATMs could stimulate breast cancer development and/or progression.

Exercise, accompanied by weight loss, reduces adipose tissue inflammation in younger (20-40 years of age), overweight (BMI 25-30 kg/m^2) men (12,13); yet, no randomized controlled trials have been conducted to test whether this non-pharmacologic intervention is

effective at modifying adipose tissue inflammation in breast cancer survivors. Further, exercise has been shown to improve circulating levels of pro- and anti-inflammatory cytokines, but this has not been assessed in the adipose tissue in breast cancer survivors (14,15). Indeed, only one study, in younger, overweight men, has investigated whether exercise training can alter adipose tissue macrophage polarization in humans (12).

Given the links between obesity, adipose tissue inflammation, and breast cancer recurrence, and the known benefits and minimal down-side of exercise, we conducted a randomized pilot trial to assess whether exercise can attenuate adipose tissue inflammation. We hypothesized that a 16-week traditional aerobic and resistance exercise intervention would reduce adipose tissue inflammation, measured by ATM phenotypes and cytokine secretion, in obese postmenopausal breast cancer survivors.

Methods

Study design

This pilot study targeted obese (BMI 30 kg/m^2) women with stage I-III breast cancer who had completed radiation and/or chemotherapy treatments.

Participants were randomized to a supervised aerobic and resistance exercise intervention (EX Group) or delayed intervention control (CON Group). Endpoints were assessed at baseline and after the end of the 16-week intervention. Participants in the CON group were offered the exercise program following the study period. Participants in the EX group were supervised by a certified exercise specialist who adhered to and delivered the same prescribed exercise program, outlined in the Standard Operating Procedures trial manual, to ensure treatment fidelity. This study was approved by the Institutional Review Board of the University of Southern California (HS-12-00141).

Recruitment and randomization

Inclusion and exclusion criteria are provided in Table 1. All eligible breast cancer patients scheduled for chemotherapy and/or radiation at the USC Norris Comprehensive Cancer Center (NCCC) or Los Angeles County Hospital were briefly informed about the trial during their medical oncology or surgical oncology appointments. If interested, patients were then informed in detail about the trial by the study principal investigator and inclusion/exclusion criteria were verified. The participants were randomly assigned to either the EX or CON group, and scheduled for the baseline visit. Randomization was performed by the Clinical Investigation Support Office (CISO) at the USC NCCC. To prevent possible bias, study personnel involved in the recruitment did not have access to the randomization lists; the biostatistician who developed the randomization list did not have any patient contacts to influence the recruitment procedure.

Physical fitness tests

A single-stage submaximal treadmill test was used to estimate maximal oxygen uptake.(16) Participants first performed a 4-minute warm up by walking on a treadmill (Desmo Woodway, Waukesha, WI) at a speed (2.0, 3.0, 4.0, or 4.5 mph) that increased their heart

rate (HR) between 50-70% HR maximum. This was followed by the 4-minute test at the same speed with a 5% grade; heart rate was measured during the final 30 seconds of the test. Maximal oxygen uptake was calculated using the test-specific formula. Maximal voluntary strength was evaluated by the 10-repetition maximum (10-RM) method for the following exercises: chest press, latissimus pulldown, knee extension, knee flexion, (Tuff Stuff, Pomona, CA). Ten-RM values were used to calculate 1-RM (maximum strength).(17) Physical fitness test results were used to assess baseline fitness and to prescribe the relative exercise intensity for the intervention.

Aerobic and Resistance Exercise (EX) Intervention

The progressive, combined aerobic and resistance exercise program was designed to comply with American College of Sports Medicine/American Cancer Society (ACSM/ACS) exercise guidelines for cancer survivors, which includes 150 minutes of moderate-vigorous aerobic exercise and 2-3 days of resistance exercise training/week.(18,19) During the intervention, participants received 3 supervised one-on-one exercise sessions per week at the Integrative Center for Oncology Research in Exercise (ICORE) in the Division of Biokinesiology and Physical Therapy at USC. Days 1 and 3 were comprised of resistance and aerobic exercise of approximately 80 minutes and Day 2 included only aerobic exercise and lasted approximately 50 minutes. All sessions were led by a certified ACSM/ACS Cancer Exercise Trainer. Participants were required to wear a Polar® heart monitor (Lake Success, NY) during each exercise session.

Each session began with a 5-minute aerobic exercise warm up at 40-50% estimated VO_2max. This was then followed by a bout of resistance exercise including leg press (LP), lunges (LUN), leg extension (LE), leg flexion (LF), chest press (CP), seated row (SR), triceps extension (TE), and biceps curl (BC). Resistance exercise was performed in a circuit training fashion where by no formal rest period was assigned between each exercise and rather a muscle group rested while another muscle group was active. The circuit was performed as follows: LP CP LUN SR LE TE LF BC; where indicates the 2 exercises that alternated until all sets were completed then the following pair of exercises was performed. Initial resistance was set at 80% of the estimated 1-RM for lower body exercises and 60% estimated 1-RM for upper body exercises. When participants were able to complete 3 sets of 10 repetitions at the set weight in 2 consecutive sessions then the weight was increased by 10%. Repetitions increased from 10 (week 4) to 12 (week 8) to 15 (week 12) every 4 weeks to safely build muscular endurance. Participants with a compression garment were required to wear the garment during the exercise sessions.

Following the resistance exercise bout, the participants initiated the aerobic exercise session by self-selecting their preferred mode of exercise including treadmill walking/running, rowing machine, or stationary bicycle. HR was monitored throughout the aerobic exercise sessions to maintain an exercise HR at 65-80% of maximum HR. Duration of the aerobic exercise sessions was increased from 30 minutes (week 1) to 50 minutes (week 16) as cardiorespiratory fitness increased. Participants ended each session with a 5-minute aerobic exercise cool down at 40-50% estimated VO_2max.

Outcome measures

Body composition—A tape measure was used to obtain waist circumference measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured, around the widest portion of the buttocks, with the tape parallel to the floor, to determine waist-hip ratio. BMI in kg/m^2 was calculated from height and weight measurements obtained using a medical scale (Detecto® 437, Webb City, MO). Total lean mass, fat mass, and percent body fat were measured from a whole-body scan using Dual-Energy X-ray Absorptiometry (DXA, GE iDXA, Fairfield, Connecticut).

Systemic inflammation—Blood (~30 cc) was drawn from the antecubital vein by trained phlebotomists after a 12 hour fast. Plasma was derived from whole peripheral blood samples, immediately processed within taking the blood sample, transported on ice (for ~5minutes) to freezer storage at −80 for analyses of biomarkers after completion of last study participant. Plasma levels of high sensitivity C-reactive protein (CRP), glycosylated hemoglobin (HbA1c), leptin, adiponectin, IL-6, and IL-8, fasting blood glucose, insulin, HDL-cholesterol, and triglycerides were measured at the Clinical Reference Laboratory on the Vitros 4600 Analyzer (Ortho Clinical Diagnostics, Rochester, NY) and microslide technology.

Adipose tissue biopsy and tissue biomarkers—Participants fasted (12 hours) and refrained from consumption of any form of anti-inflammatory pharmaceutical for 3-5 days prior to the biopsy. After anesthetizing the skin at the biopsy site (right anterior axillary line, level of the umbilicus) with 1% lidocaine injection, a 6 mm Bergstrom biopsy needle was introduced through a 6-7 mm incision in the abdominal skin. Manual suction from a 60cc syringe attached via tubing to the inner bore of the biopsy needle was applied to pull tissue into the side cutting window which was then sheared with the inner trochar (20). Adipose tissue was rapidly irrigated with iced saline and immediately transported to the laboratory, where it was sectioned and processed for further analysis.

To quantify macrophage subtypes in adipose tissue we used flow cytometry. Briefly, adipose tissue was digested with Liberase (Roche, Indianapolis, IN) and stromal vascular fraction was separated from adipocytes by centrifugation. Macrophages were purified with CD14 microbeads (Miltenyi Biotec, San Diego, CA) and incubated with CD45, CD14, CD40 and CD206 antibodies or their respective isotype controls (Biolegends, San Diego, CA). The samples were run at the Fluorescence Activated Cell Sorting Core at CHLA on LSR II Analyzer from Becton Dickinson (BD). Samples were gated for live cells (DAPI⁻), leukocytes (CD45⁺), monocytes and macrophages (CD45⁺/CD14⁺), M1 pro-inflammatory (CD45+/CD14+/CD40+) or M2 anti-inflammatory (CD45+/CD14+/CD206+) macrophages. The percent of monocytes and macrophages subtypes: M1, M2, and M1/M2 (i.e. CD40 and CD206+) was calculated as the difference between the percent of CD40+ or CD206+ cells and of isotype control cells.

For quantitation of adipose tissue secreted cytokines, 100 mg of pieces of adipose tissue explant were incubated in 1 mL of complete media (DMEM+10%FBS) in a 5% CO_2 humidified incubator and after 24 hours conditioned media was stored at −80 C for further

analysis. Level of 40 cytokines and adipokines were measured on 100 uL of conditioned media using Quantibody Human Obesity Array Q3 (Raybiotech, Norcross, GA).

Participant-reported outcomes—Throughout the duration of the study period, weekly 7-day physical activity logs were completed by all participants and returned to the PI by mail for the Control group. Three-day dietary records were completed at baseline and at the completion of the study period to assess recent dietary patterns.

Data analysis—Trial outcomes analyzed were changes (from pre-intervention baseline to 16-week completion) in adipose tissue and systemic inflammation and body composition measures. Because many trial measures were not normally distributed, Wilcoxon rank sum tests were used to compare the two study groups at baseline and on changes in trial outcomes. Within each study group, non-parametric Wilcoxon signed rank tests were used to compare differences in baseline versus 16-week measures. The 16-week changes in adipose M1 and M2 were correlated with changes in body composition, cardiometabolic and inflammation measures using Spearman correlations.

Results

Twenty of the 21 participants randomized to this pilot trial completed the study and provided a baseline and post-study period biopsy (Figure 1). No adverse events were reported, although 1 patient elected not to undergo the post-intervention biopsy. Table 2 displays the participant characteristics for the sample. Overall, our sample included 50% non-Hispanic white women, with the majority having undergone mastectomy surgery (75%) and chemotherapy treatment (75%). The two study groups were comparable at baseline on age and body composition (all p>0.6), as well as cancer stage and treatment characteristics.

The exercise intervention was well tolerated, without significant adverse events. The EX participants were highly compliant (97%) and completed on average 46 of the 48 exercise intervention sessions. Total caloric intake (1867 493 kcal) did not differ among groups at baseline and post-intervention (p>0.5).

Exercise-induced Changes in Body Composition (Table 3) and Cardiometabolic Profile (Table 4).

Compared to CON, the 16-week EX intervention resulted in significant improvements in body composition, including decreases in body weight, fat mass, percent body fat, waist circumference, hip circumference and an increase in lean mass (all p<0.03; Table 3). When compared to baseline, all body composition measures significantly improved for the EX group (all p<0.05), while percent body fat significantly increased from baseline in the CON group (p=0.008). Notably, the EX group experienced an approximate 4kg decrease in fat mass, in the absence of dietary modifications.

Cardiometabolic profile also improved with the EX intervention; EX participants experienced decreases in fasting blood glucose, insulin, HOMA-IR, total cholesterol, LDL, triglycerides, HgA1c, and increased HDL-C, when compared to baseline (all p<0.02) and to

the CON group (all p<0.01; Table 4). Insulin, HOMA-IR, total cholesterol, LDL, and HbA1c significantly increased in the CON group (all p<0.02).

Exercise-induced Changes in Systemic Inflammation (Table 5).

Following the 16-week intervention, the EX group experienced significant reductions in plasma CRP, leptin, IL-6, IL-8 and increases in adiponectin, when compared to the CON group (all p<0.001) and to baseline (all p<0.008). The CON group experienced significant increases in leptin, IL-6, and IL-8 (all p<0.02).

Exercise-induced Changes in Adipose Tissue Inflammation (Table 5).

Of note, 20 of 21 participants agreed to undergo a second biopsy after the intervention. Following the 16-week intervention, adipose tissue from the EX participants showed statistically significant reductions in the percent of M1 and increases in the percent of M2, when compared to the CON group (p<0.001) and to baseline (p=0.002). The EX intervention resulted in significant reductions in *ex vivo* adipose tissue secretion of pro-inflammatory cytokines (IL-6 and TNF-α) and increased secretion of anti-inflammatory mediators (adiponectin and IL-12), compared to the CON group (p 0.05). The EX group experienced a significant increase in adipose tissue secretion of adiponectin and reduction in IL-6 when compared to baseline (p=0.03).

The Cohen's effect size values for changes in body composition (d>0.90), cardiometabolic biomarkers (d>1.10), systemic inflammation (d>1.50), macrophage phenotype (d>1.70) and adipose tissue cytokine secretion (d>1.10) suggest not only a high statistical significance but also clinical relevance.

We further examined whether changes in macrophage phenotype were correlated with changes in body composition, cardiometabolic biomarkers, or systemic inflammation (Table 6). Change in M2 was inversely correlated with changes in body weight, fat mass, waist and hip circumference, cardiometabolic biomarkers, and systemic inflammation, and were positively correlated with changes in HDL cholesterol and adiponectin (all p values <0.01).

Discussion

Our results demonstrate for the first time that an exercise intervention can alter adipose tissue macrophage profile and release of inflammatory cytokines in superficial abdominal adipose tissue in cancer survivors. Our 16-week intervention was well-tolerated, engendered high compliance, and yielded improvements in body composition and glucose metabolism. In addition, the intervention reduced systemic and adipose tissue pro-inflammatory mediators, and decreased the ratio of M1 to M2 ATMs. Importantly, alterations in M1 and M2 were associated with body composition, cardiometabolic biomarkers, and systemic inflammation.

Our exercise outcomes were comparable to those reported by Auerbach et al. (2013) (12), who investigated the effects of a 12-week exercise intervention in 20-40 year-old overweight men. Using daily moderate to high-intensity aerobic training along with reduced caloric intake, the authors reported an increase in anti-inflammatory macrophages in subcutaneous

adipose tissue to a similar degree as we observed. Our intervention differed in that it was four weeks longer, and was not daily (three days of moderate intensity aerobic training and two days of total- body resistance exercise sessions per week). Thus, our incorporation of resistance training and reducing aerobic intensity did not seem to diminish the effect on adipose tissue inflammation.

Our exercise approach could yield additional benefits to cancer survivors, including improved compliance and long-term feasibility, as well as potential improvements in muscle strength, balance, and bone health, all of which could improve long-term morbidity/ mortality. Preclinical evidence in animal models further support aerobic exercise-induced improvements in ATM polarization following an acute bout of swimming in rats fed a high-fat diet (21), and chronically after 8-16 weeks of treadmill running in mice (22,23). Thus, larger RCTs are needed to evaluate which exercise approaches yield the most improvement in ATM inflammation and overall prognosis for breast cancer survivors.

In conjunction with the attenuation of adipose tissue inflammation, our intervention resulted in reductions in systemic pro-inflammatory and improvements in cardiometabolic biomarkers. These effects are consistent with the wide body of literature on exercise intervention in breast cancer survivors, which has been recently summarized by two systematic reviews with meta-analysis (14,15). These meta-analyses found that exercise improved serum concentrations of IL-6, TNF-a, and IL-2 (15). While four of those trials included a combined aerobic and resistance exercise approach (24-27) similar to the present study, ours was the only one to use resistance exercise machines and free weights for the resistance portion, which would theoretically elicit a greater metabolic demand in skeletal muscle to impact systemic inflammatory markers. For example, our intervention resulted in superior changes in IL-6 with a mean change of -1.02 ng/mL vs the -0.55 noted from the meta-analysis. Further, our intervention used a systematic progressive approach to the exercise program which allowed for the exercise intensity to be increased as the participants became more physically fit. These differences may also have contributed to the substantial positive changes in body composition we observed and therefore the significant improvements in systemic and adipose tissue inflammation.

Hyperinsulinemia caused by insulin resistance is known to be associated with increased cancer recurrence and mortality (28,29) presumably by promoting the survival and growth of residual cancer cells. Thus, the decreases in circulating insulin and HOMA-IR with exercise that were observed in the present study represent an additional mechanism which could potentially translate into survival benefits. While a variety of exercise approaches have been shown to reduce insulin levels in cancer survivors (14), it is not clear which exercise methodology will provide the optimal results. Studies evaluating exercise type, setting (clinic, home-based, with or without supervision), frequency, intensity, time and intervention period on insulin sensitivity are needed to best advise clinicians and patients.

Limitations of our pilot study include a small sample size, albeit appropriate for a pilot study. Further, we examined one exercise program and thus the question remains as to which combination of aerobic and resistance exercise may exert the greatest benefit on adipose tissue inflammation. Indeed, aerobic exercise alone, resistance exercise alone, and a

combined exercise approach have all been shown to improve systemic inflammation, though it is not clear which might have the best effect in cancer survivors or in other populations. Additionally, while our intervention was designed to be weight-neutral, participants in the EX group experienced a mild (~4%) weight loss, despite reporting no change in caloric intake on 3-day diet recalls. This occurred even though the volume of exercise prescribed did not meet the exercise guidelines (150-250 minutes/week of moderate-intensity exercise) for weight loss set forth by the ACSM (30). Thus, we cannot rule out an effect of weight loss to induce the observed changes in adipose tissue inflammation. Interestingly, participants in the exercise only group of the Auerbach study also reported an average of ~6% weight loss; thus, to our knowledge, there are no clinical studies to date that evaluate the effects of exercise in the absence of weight loss on adipose tissue inflammation.

A major strength of this study is the randomized controlled design to examine the effects of a supervised clinical exercise intervention when compared to a control group. Further, our study supports the feasibility of obtaining subcutaneous abdominal adipose tissue samples from breast cancer survivors who have recently (within the last 6 months) completed treatment. Additional strengths of the study include high volume of adipose tissue extracted per procedure (generally > 1g), high compliance with the post-biopsy procedure (100%) and participation in exercise sessions (97%).

In summary, our study demonstrates that moderate-to-vigorous intensity resistance and aerobic exercise can attenuate adipose tissue inflammation in obese breast cancer survivors, measured by changes in ATM polarization and improvements in cytokine profiles at both the systemic and adipose tissue level. While the long-term benefit of this type of intervention on cancer prognosis requires further study, the short-term impact on these important physiological biomarkers is promising.

Acknowledgements

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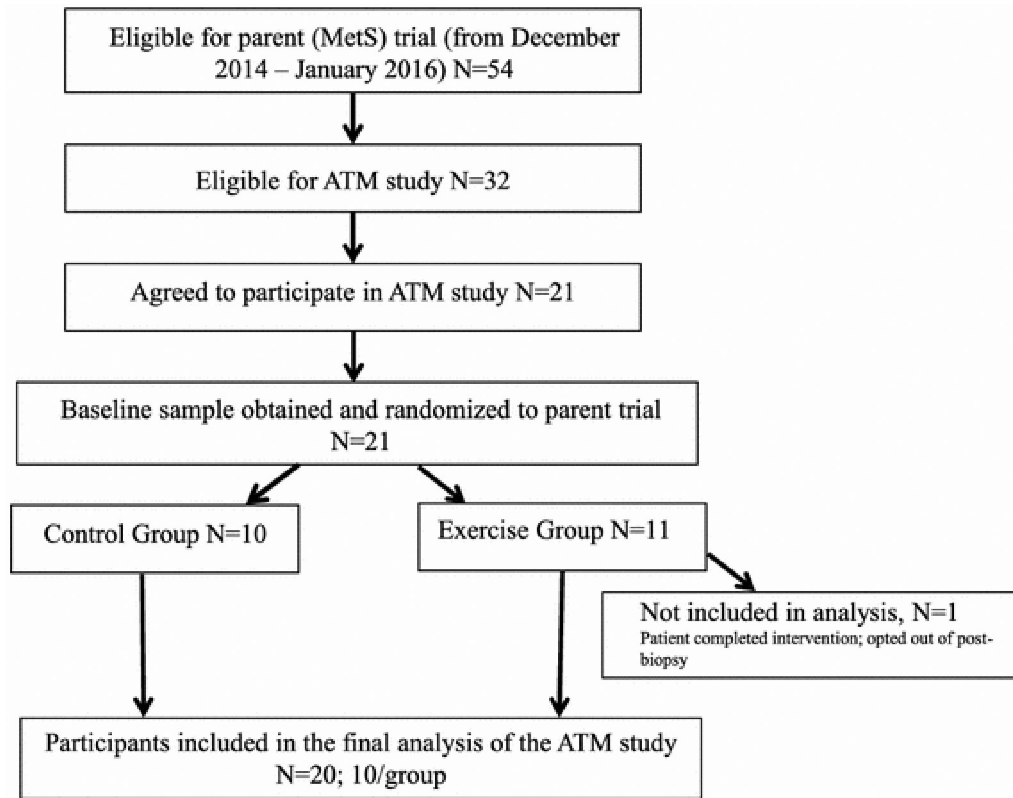
Fig. 1.
Study schema

Table 1.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Women with primary breast cancer, stage I-III	• History of chronic disease (i.e, diabetes, uncontrolled hypertension, thyroid disease)
• 18 years of age	• Weight reduction > 10% within past 6 months
• Have undergone lumpectomy or mastectomy	• Metastatic disease
• Have completed neoadjuvant/adjuvant chemotherapy and/or radiation therapy	• Planned reconstructive surgery with flap repair during trial or follow-up period
• Able to initiate exercise program (if randomized to that arm) within 24 weeks of therapy completion	• Cardiovascular, respiratory, or musculoskeletal or joint problems that preclude moderate physical activity
• BMI 30 kg/m^2*	
• Currently participates in < 60 minutes of physical activity per week	
• May use adjuvant endocrine therapy if use will be continued for duration of study period	
• Does not currently smoke (No smoking during previous 12 months)	
• Willing to travel to USC	
• Able to provide physician clearance to participate in exercise program	
• Women of all racial and ethnic backgrounds will be included in the study enrollment process	

Table 2.

Baseline Participant Characteristics

	EX group N=10	CON group N=10	p-value
Age, y	53.0 ± 10.0	55.0 ± 4.5	0.82
Weight, kg	85.0 ± 10.5	84.5 ± 10.5	0.62
BMI, kg/m^2	33.5 ± 5.7	33.3 ± 8.7	0.60
Body fat, %	36.8 ± 4.7	36.4 ± 5.7	0.73
Waist, cm	100.3 ± 10.4	100.8 ± 9.4	0.85
Race/ethnicity[a]			
Non-Hispanic White	6 (60)	4 (40)	
Hispanic	4 (40)	6 (60)	0.66
Cancer stage[a]			
I	3 (30)	3 (30)	
II	4 (40)	4 (40)	
III	3 (30)	3 (30)	1.00
Treatment history[a]			
Previous chemotherapy	8 (80)	7 (70)	
Previous radiation	5 (50)	6 (60)	1.00
Surgical history[a]			
Lumpectomy	3 (30)	2 (20)	
Mastectomy	7 (70)	8 (80)	1.00

[a]Data expressed as frequency (%); Fisher's exact test

Table 3.

Effects of Exercise on Body Composition

	EX group N=10	CON group N=10	p-value[a]	Effect Size[b]
Weight, kg				
PRE	84.99 ± 10.53	84.53 ± 10.54	0.62	
CHANGE	−3.69 ± 2.12	0.47 ± 0.67	0.0002	1.58
Within group p-value[c]	0.002	0.062		
Lean mass, kg				
PRE	53.78 ± 7.90	53.69 ± 8.37	0.85	
CHANGE	1.80 ± 2.30	−0.71 ± 2.30	0.03	0.97
Within group p-value[c]	0.049	0.065		
Fat mass, kg				
PRE	31.21 ± 5.40	30.84 ± 6.11	0.79	
CHANGE	−5.49 ± 1.93	1.18 ± 2.30	0.0004	1.66
Within group p-value[c]	0.002	0.065		
Body fat, %				
PRE	36.75 ± 4.74	36.44 ± 5.72	0.73	
CHANGE	−2.75 ± 1.40	1.16 ± 0.79	0.0002	1.71
Within group p-value[c]	0.002	0.008		
Waist circumference, cm				
PRE	39.5 ± 4.1	39.7 ± 3.7	0.85	
CHANGE	−2.1 ± 0.7	0.5 ± 1.0	0.0003	1.60
Within group p-value[c]	0.002	0.15		
Hip circumference, cm				
PRE	41.9 ± 5.5	42.7 ± 3.9	0.73	
CHANGE	−2.7 ± 1.2	0.9 ± 1.5	0.0001	1.59
Within group p-value[c]	0.002	0.062		

[a]Wilcoxon rank sum test

[b]Effect size: difference between groups divided by SD

[c]Wilcoxon signed rank test

Table 4.

Effects of Exercise on Cardiometabolic Profile

	EX group N=10	CON group N=10	p-value[a]	Effect Size[b]
Glucose, mg/dL				
PRE	109.6 ± 17.6	94.7 ± 14.0	0.06	
CHANGE	−12.0 ± 16.0	4.1 ± 6.6	0.0012	1.11
Within group p-value[c]	0.016	0.12		
Insulin, uIU/mL				
PRE	35.0 ± 22.2	31.9 ± 5.7	0.50	
CHANGE	−13.5 ± 13.8	7.6 ± 4.2	0.0001	1.44
Within group p-value[c]	0.002	0.004		
HOMA-IR				
PRE	10.04 ± 8.80	7.50 ± 2.09	0.79	
CHANGE	−4.91 ± 6.93	2.20 ± 0.99	0.0002	1.18
Within group p-value[c]	0.002	0.004		
Total Cholesterol, mg/dL				
PRE	190.5 ± 50.40	189.4 ± 18.9	0.91	1.47
CHANGE	−39.5 ± 32.7	16.4 ± 16.0	0.0002	
Within group p-value[c]	0.004	0.004		
LDL, mg/dL				
PRE	102.9 ± 34.4	89.2 ± 18.8	0.38	1.43
CHANGE	−25.0 ± 23.2	25.6 ± 25.9	0.0003	
Within group p-value[c]	0.008	0.008		
HDL, mg/dL				
PRE	43.2 ± 6.6	41.0 ± 4.3	0.54	1.67
CHANGE	20.2 ± 8.2	1.1 ± 2.1	0.0001	
Within group p-value[c]	0.002	0.25		
Triglycerides, mg/dL				
PRE	242.6 ± 26.8	229.7 ± 24.6	0.34	1.83
CHANGE	−97.7 ± 27.2	1.0 ± 3.2	<0.0001	
Within group p-value[c]	0.002	1.0		
HbA1c (%)[d]				
PRE	5.48 ± 0.44	5.30 ± 0.48	0.40	1.71
CHANGE	−1.74 ± 0.72	0.72 ± 0.70	0.0002	
Within group p-value[c]	0.002	0.016		

[a] Wilcoxon rank sum test

[b] Effect size: difference between groups divided by SD

[c] Wilcoxon signed rank test

d Absolute change in %

Abbreviations: HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin

Table 5.

Effects of Exercise on Systemic and Adipose Tissue Inflammation

	EX group N=10	CON group N=10	p-value[a]	Effect Size[b]
CRP, mg/dL				
PRE	3.20 ± 0.64	4.01 ± 0.25	0.005	
CHANGE	−0.92 ± 0.72	0.40 ± 0.84	0.0008	1.29
Within group p-value[c]	0.008	0.50		
Leptin, ng/mL				
PRE	12.2 ± 2.0	12.5 ± 2.0	0.91	
CHANGE	−3.0 ± 1.9	1.9 ± 1.6	0.0004	1.60
Within group p-value[c]	0.008	0.016		
Adiponectin, ng/mL				
PRE	13.2 ± 1.7	13.0 ± 1.8	0.62	
CHANGE	8.7 ± 2.1	−1.6 ± 2.8	0.0001	1.78
Within group p-value[c]	0.002	0.13		
IL-6, ng/dL				
PRE	3.15 ± 0.49	3.23 ± 0.51	0.68	
CHANGE	−1.02 ± 0.53	0.42 ± 0.35	0.0002	1.67
Within group p-value[c]	0.002	0.004		
IL-8, ng/dL				
PRE	5.53 ± 1.00	5.46 ± 0.62	0.91	
CHANGE	−1.28 ± 0.80	0.48 ± 0.56	0.0002	1.57
Within group p-value[c]	0.002	0.016		
M1, %				
PRE	24.0 ± 6.2	26.3 ± 7.9	0.65	
CHANGE	−17.4 ± 7.1	3.0 ± 4.8	0.0001	1.70
Within group p-value[c]	0.002	0.13		
M2, %				
PRE	4.0 ± 1.3	4.3 ± 1.1	0.76	
CHANGE	9.0 ± 1.6	−0.4 ± 1.0	0.0002	1.88
Within group p-value[c]	0.002	0.31		
Adiponectin, ng/mL[d]				
PRE	91.68 ± 21.05	88.58 ± 37.81	0.65	
CHANGE	46.61 ± 25.19	−13.83 ± 26.03	0.008	1.52
Within group p-value[c]	0.03	0.31		
IL-12 p40, pg/mL[d]				
PRE	8.83 ± 13.13	11.48 ± 19.45	1.00	
CHANGE	1.93 ± 20.18	50.36 ± 44.57	0.055	1.20

	EX group N=10	CON group N=10	p-value[a]	Effect Size[b]
Within group p-value[c]	0.75	0.13		
IL-12 p70, pg/mL[d]				
PRE	2.53 ± 1.06	1.70 ± 1.32	0.46	
CHANGE	−1.02 ± 2.12	1.56 ± 1.62	0.08	1.14
Within group p-value[c]	0.28	0.063		

[a]Wilcoxon rank sum test

[b]Effect size: difference between groups divided by SD

[c]Wilcoxon signed rank test

[d]Adipose tissue cytokine secretions

Abbreviations: CRP, C-reactive protein; IL-6,8,12 Interleukin-6,8,12, TNF- α, tumor necrosis factor- α

Table 6.

Correlations of biomarker changes with change in macrophage phenotype 1 and macrophage phenotype 2 composition

	M1[a]	M2[a]
Weight, kg	0.71 (0.0005)	−0.80 (<0.0001)
Lean mass, kg	−0.65 (0.002)	0.32 (0.17)
Fat mass, kg	0.81 (<0.0001)	−0.68 (0.0009)
Body fat, %	0.71 (0.0004)	−0.88 (<0.0001)
Waist circumference, cm	0.79 (<0.0001)	−0.63 (0.0028)
Hip circumference, cm	0.75 (0.0001)	−0.79 (<0.0001)
Glucose, mg/dL	0.77 (<0.0001)	−0.65 (0.002)
Insulin, uIU/mL	0.78 (<0.0001)	−0.67 (0.002)
HOMA-IR	0.76 (0.0001)	−0.66 (0.002)
Total Cholesterol, mg/dL	0.74 (0.0002)	−0.67 (0.0012)
LDL, mg/dL	0.68 (0.001)	−0.72 (0.0003)
HDL, mg/dL	−0.83 (<0.0001)	0.78 (<0.0001)
Triglycerides, mg/dL	0.86 (<0.0001)	−0.75 (0.0001)
HgA1c (%)	0.89 (<0.0001)	−0.73 (0.0002)
CRP, mg/dL	0.60 (0.0061)	−0.59 (0.006)
Leptin, ng/mL	0.75 (0.0001)	−0.60 (0.005)
Adiponectin, ng/mL	−0.70 (0.0006)	0.66 (0.002)
IL-6, ng/dL	0.78 (<0.0001)	−0.78 (<0.0001)
IL-8, ng/dL	0.80 (<0.0001)	−0.83 (<0.0001)

[a]Spearman correlation (p-value)