


Exercise in Patients With Breast Cancer and Healthy Controls: Energy Substrate Oxidation and Blood Lactate Responses

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Abstract

The aim of this study was to compare select aspects of exercise energy metabolism in patients with breast cancer with that of healthy controls across a variety of exercise intensities. Posttreated patients with breast cancer were matched with healthy women based on age, physical fitness level, and menopausal status. Subjects participated in low-, moderate-, and high-intensity submaximal exercise sessions that corresponded with 40% of maximal oxygen consumption (VO_{2max}), 60% VO_{2max} , and 70% VO_{2max} . Oxygen consumption and respiratory exchange ratio were taken during submaximal exercise sessions to determine substrate oxidation rates for carbohydrate (CHO) and fat. Blood lactate and blood glucose were also measured before and after each of the submaximal exercise sessions as indices of CHO metabolism. Results indicate that the patients with breast cancer had a significantly ($P \leq .05$) lower CHO oxidation rate and higher fat oxidation rate at all exercise intensities compared with healthy women. The patients with breast cancer had a significantly ($P \leq .05$) lower blood lactate response to exercise across all intensities compared with the healthy women. Glucose responses tended ($P < .08$) to be more elevated in patients with cancer both before and after the exercise sessions. The findings indicate that posttreated patients with breast cancer have augmented fat metabolism and a reduced CHO-based energy metabolism during submaximal exercise. It is unclear whether these changes are the result of the patient's cancer or their treatment regimen for the cancer.

Keywords

energy metabolism, physical activity, carbohydrate, breast cancer, aerobic exercise

Introduction

Over the past 35 years, breast cancer has been the most prevalent type of cancer diagnosed in women in the United States.¹ Although this disease is increasingly common, the mortality rate is currently decreasing and the survival rate is increasing.¹ The decreased mortality rate can be attributed to earlier detection and more aggressive treatments.²⁻⁵ These efforts have resulted in there being more than 2.4 million breast cancer survivors in the United States in 2009.⁶

Treatment of breast cancer is multifaceted and varies individually based on the type of tumor and individual risk factors.⁶ Treatment typically consists of removal of a tumor and adjuvant therapies such as radiation, chemotherapy, hormonal therapy, or any combination of these.⁷ Adjuvant treatments for breast cancer can have many acute and long-term debilitating side effects, including but not limited to a decrease in energy expenditure, weight gain, fatigue,

increased risk of cardiovascular disease, decreased cardiopulmonary function, and decreased quality of life.^{5,7,8}

Recent studies demonstrate positive benefits of exercise training within breast cancer survivors.^{5,7-10} A review of studies by Kim et al⁵ showed that aerobic exercise training in patients with breast cancer during and after adjuvant therapies significantly improved aerobic capacity and body composition. A study of postmenopausal breast cancer survivors involved in an exercise program saw a significant increase in quality of life compared with nonexercising patients in a control group.⁹ Furthermore, Sternfeld et al¹⁰ found

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increased amounts of physical activity, including exercise training, in breast cancer survivors decreased the total occurrence of mortality due to all causes, including cancer recurrence (the form of exercise training was not specified in this study). These positive outcomes have led exercise researchers to pursue further studies on the physiological responses to exercise and exercise training in cancer patients, where there is currently only paltry information.

During the past several decades, researchers have extensively explored aspects of energy metabolism in normal healthy individuals at rest and in response to exercising at varying intensities. Characteristics of energy metabolism such as energy substrate usage (eg, glucose vs triglyceride), energy pathway activation (eg, glycolysis vs Krebs cycle), endocrine factor regulation, and energy production rates are well quantified and understood.¹¹ However, there have been only a few studies looking at such energy metabolism issues in patients with cancer. Studies have shown that glucose intolerance was present and more frequent in cancer populations when compared with healthy controls.^{12,13} Larsson et al¹⁴ found that insulin resistance and greater levels of fasting insulin are also associated with breast cancer. These studies suggest that there seems to be some association between altered carbohydrate metabolism and breast cancer disease. Furthermore, Evans and associates¹⁵ indirectly examined carbohydrate metabolism during exercise by measuring blood lactate responses. They found that posttreated patients with breast cancer had significantly lower lactate levels following high intensity (70% maximal oxygen consumption [$\dot{V}O_{2max}$]) exercise when compared with age-matched healthy controls. When exercising at a higher intensity, there is a greater reliance on carbohydrate as an energy substrate and therefore more lactate is produced through glycolytic mechanisms.^{11,16,17} The lower blood lactate during high-intensity exercise in breast cancer patients reported by Evans et al¹⁵ led us to speculate that perhaps less carbohydrate was being metabolized as an energy substrate during exercise.

The results of the study performed by Evans and associates¹⁵ and the general lack of substantial work on energy metabolism during exercise in patients with cancer led us to pursue the current study. The purpose of this study was to compare substrate usage (ie, oxidation rates) and blood lactate responses to low-intensity (40% $\dot{V}O_{2max}$), moderate-intensity (60% $\dot{V}O_{2max}$), and high-intensity (70% $\dot{V}O_{2max}$) exercise bouts in posttreated patients with breast cancer versus age-matched, sedentary, healthy controls.

Methodology

Subjects

Subjects in this study were recruited into 2 groups: a treatment group and a control group. The treatment group consisted of posttreated patients with breast cancer who were

newly enrolled in the *Get REAL and HEEL Breast Cancer* Program at the University of North Carolina–Chapel Hill. The criteria for participation in the treatment group included the following: women with confirmed diagnosis of stage I-III invasive breast cancer, within 6 months of completion of all major cancer treatments, ages ranging from 25 to 75 years (actual age range = 39-64 years), no presence of metastatic disease, and no presence of immune system deficiency that would compromise a subject's ability to participate in regular exercise. Patients receiving adjuvant hormonal therapy or adjuvant trastuzumab were eligible to participate in the treatment group. The control group consisted of women who were recruited from the Chapel Hill town area, who had not been participating in regular exercise for at least 1 year, and were healthy enough to participate in aerobic exercise (age range = 38-66 years). Subjects in the control group were matched to subjects in the treatment group based on age, physical activity level, and menopausal status.

This human subjects study was reviewed and approved by the Institutional Review Board at University of North Carolina–Chapel Hill. Before agreeing to the study, all subjects met with the primary investigator to go over the experimental protocol. Subjects were informed of all risks associated with the study and then were allowed to read and sign the informed consent form. They were also given a physical activity questionnaire (PAQ; modeled after the modifiable activity questionnaire) assessing activity levels over the past year.¹⁸ Subjects completed the PAQ at the first meeting and scores from the questionnaire were used in matching the patients with breast cancer with healthy controls. All patients with breast cancer were cleared by their oncologist to participate in physical activity whereas all control subjects completed a physical screening and 12-lead resting electrocardiogram (ECG) at our laboratory for clearance to participate. All subjects were given preassessment guidelines to follow before any exercise testing occurred. Subjects were excluded from the study based on the following criteria: an abnormal ECG, a recent history of smoking (quit ≤ 2 years ago), any known metabolic disease, acute or chronic illness (besides breast cancer for the treatment group), elevated resting vitals, physical injury, or inability to complete a submaximal cycle ergometer test.

Maximal Oxygen Consumption Test

Once the subjects had been cleared for participation, they reported to our laboratory for their first exercise test. This exercise test was used to predict their $\dot{V}O_{2max}$ value. Once at the laboratory, subjects sat down with a researcher to record menstrual status and verify that preassessment guidelines had been followed. Subjects were fit with a heart rate (HR) monitor (Polar Electro, Inc, Lake Success, NY) and asked to rest in a seated position for 5 minutes. After 5 minutes of quiet rest, HR, blood pressure (BP), and blood

oxygen saturation levels (SpO_2 ; BCI International pulse oximeter (BCI International, Waukesha, WI) were recorded. Once resting HR was recorded, 70% of heart rate reserve (HRR) was calculated using the Karvonen formula, which has an associated error rate of ~5%.¹⁹ Subjects did not continue with the exercise session if any of the following resting vitals were observed: HR \geq 100 beats per minute (bpm), systolic BP \geq 140 mm Hg, diastolic BP \geq 90 mm Hg, or SpO_2 saturation \leq 90%. Age, weight, and height were recorded and skin fold measurements (Lange calipers, Beta Technology, Santa Cruz, CA) were taken at the triceps, suprailiac, and abdomen to determine body composition using the Jackson and Pollock equation for women.¹⁹ For cycle ergometry, each subject was fit onto the “Lode” ergometer (Lode BV, Groningen, The Netherlands) and the seat height was adjusted so that there was a 5° to 10° bend in the knee of the extended leg. Subjects were also fit with a “Oro-Nasal 7400 Vmask” facemask (Hans Rudolph, Inc, Shawnee, KS) secured tightly around their head that was worn throughout testing to collect respiratory gases via the Parvo Medics TrueMax2400 Metabolic System (Parvo Medics, Salt Lake City, UT). Resting respiratory gases were taken for 3 to 5 minutes while the subject was seated in a resting position on the ergometer. Subjects then immediately began a 3- to 5-minute warm-up at a low intensity (25 W) on the electric cycle ergometer.

The $\dot{V}O_{2max}$ testing protocol consisted of the YMCA submaximal test as described by the American College of Sports Medicine (ACSM) guidelines.¹⁹ The YMCA protocol was chosen as a means to predict $\dot{V}O_{2max}$ based on recommendations in the literature and to ensure subject safety.^{2,15,19} All subjects began the first 3 minute stage at 25 W. HR was recorded during the last 15 seconds of the second and third minute of each stage whereas the rate of perceived exertion (RPE) was recorded during the last 30 seconds of each stage using Borg’s (6-20) scale. The workload of the second stage was determined by the steady-state HR attained in the first stage as reported in the literature.¹⁹ The exercise test continued until the subject completed 2 stages in which their HR was between 110 bpm and 70% of their HRR. The exercise test was also terminated if a subject obtained a HR > 150 bpm, they could not maintain the workload, the subject requested to stop, or the investigator felt that the test should be terminated for safety reasons. Immediately after the exercise test was completed the workload was reduced to 20 W for a cool down of 3 to 5 minutes. During the cool-down period the subjects were able to remove the facemask and consume fluids ad libitum. Vital signs were continually monitored throughout the recovery period and the subjects were able to stop pedaling and dismount the ergometer when vitals had appreciably decreased and stabilized. Subjects were cleared to leave the laboratory when HR was \leq 100 bpm, systolic BP was within 20 mm Hg of resting values, SpO_2 was within 5% of resting values, and showed no other signs of distress or discomfort.

Workload Calculations

Based on the results of the $\dot{V}O_{2max}$ prediction test, the subject’s predicted maximal workloads were determined using a regression equation of workload versus HR response.¹⁹ This workload was then used to predict $\dot{V}O_{2max}$ using the ACSM equation: Leg cycling $\dot{V}O_2$ (mL/kg/min) = [1.8 × work rate (kg m/min)]/body mass (kg) + 3.5 (mL/kg/min) + 3.5 (mL/kg/min).¹⁹ A regression of actual/predicted workloads and $\dot{V}O_2$ values was used to prescribe workloads for submaximal exercise sessions.

Submaximal Exercise Sessions

Each subject completed 3 submaximal exercise sessions that corresponded with 40% (low intensity), 60% (moderate intensity), and 70% (high intensity) of their predicted $\dot{V}O_{2max}$. These intensities were chosen to correspond with the earlier work of Evan et al,¹⁵ and because of the range representing what values are typically encountered in exercise programs with cancer patients. The 3 exercise sessions were randomly assigned to each subject in an attempt to minimize confounding outcomes. Subjects returned 2 to 7 days after the $\dot{V}O_{2max}$ test to begin their submaximal exercise sessions.

Once at the laboratory, subjects were fit with a HR monitor and sat upright in a resting position for 5 to 10 minutes. During this rest period, subjects were prompted by the investigator to complete a 24-hour recall of their diet. The information from the dietary recall was entered into the website <http://www.sparkpeople.com> to determine total caloric intake, percentage of carbohydrate consumed, and percentage of fat consumed in the previous 24 hours. This was performed to ensure that the subjects were in a eucaloric state and that their carbohydrate intake was within a normal range of 45% to 55% of daily caloric intake.²⁰ The investigator also confirmed that the subjects had been fasting for the past 2 hours and documented any changes in the subject’s menstrual status. Next, detailed information regarding testing equipment and exercise protocol were reviewed with the subject. Resting HR, BP, and SpO_2 were then recorded, and just as with the $\dot{V}O_{2max}$ test, the exercise session did not progress forward if HR \geq 100 bpm, systolic BP \geq 140 mm Hg, diastolic BP \geq 90 mm Hg, or $SpO_2 \leq$ 90% were observed. A resting blood lactate and blood glucose sample were then taken using a finger puncture technique and immediately analyzed (described in the Blood Analysis section).

The subject then positioned themselves on the electric cycle ergometer and secured the facemask tightly around their head to collect resting metabolic data for 3 to 5 minutes. Once the respiratory gas calorimetry system had stabilized, the subject then began a 3- to 5-minute warm-up period at 20 W on the ergometer. Exercise sessions were based on recommendations in the literature and consisted of 9 minutes of

steady-state exercise at the randomly chosen prescribed workload for the day and started immediately after the warm-up.^{2,15} All subjects were blinded to the specific exercise workload for each session. Respiratory gases were collected continuously throughout the exercise sessions. The HR and RPE were taken during the last 15 seconds of every minute during the exercise session to ensure safety.

Following the submaximal exercise, the workload was reduced to 20 W for an active recovery of 2 minutes and the facemask was removed. After 2 minutes of active recovery the subjects were asked to stop pedaling and remain seated on the cycle ergometer. A final blood lactate and blood glucose measurement were taken during the last 30 seconds of the third minute into recovery. Once the last blood sample had been taken, the subjects were able to consume fluids and dismount the cycle ergometer. Vital signs were continually monitored throughout the recovery period and the subjects were cleared to leave the laboratory when HR was ≤ 100 bpm, BP was within 20 mm Hg of resting values, SpO_2 was within 5% of resting values, and subjects were showing no other signs of distress or discomfort. The same protocol was repeated for the other 2 exercise intensities, with at least 48 hours between sessions, over the next 2 weeks.

Blood Analysis

Finger punctures were used throughout the testing for blood analysis. For resting measurements, the fingertip was placed in a cup of warm water to increase blood flow to the area. The fingertip was dried and then cleaned with an alcohol pad and then wiped with a sterile gauze pad to remove any residue of sweat or alcohol. A lancet device was used for the skin puncture and the finger was gently massaged distally until a small bead of blood appeared. A blood lactate measurement was taken first and a blood glucose measurement was taken immediately afterward from the same site. Duplicate determination blood samples were obtained whenever possible and averaged to represent values.²¹ The finger puncture was then covered with a sterile gauze pad and the subject was asked to apply compression for about 1 to 2 minutes or until bleeding stopped. These steps were replicated for the resting and postexercise blood sampling. A "Lactate Plus" lactate analyzer (Nova Biomedical, Waltham, MA) was used for all blood lactate measurements. Tests in our laboratory indicated this was a highly reliable (intraclass correlation coefficient $>.90$) and valid (± 0.2 mmol/L) unit. A "One Touch Ultra" glucometer (Lifescan, Inc, Milpitas, CA) was used for all blood glucose measurements. All appropriate and necessary quality control steps were taken in the handling and processing of blood samples as recommended in the literature in order to assure viable specimens.²¹

Respiratory Gas Analysis

Both the oxygen consumption (V_{O_2}) and respiratory exchange ratio (RER) were averaged for the last 5 minutes (minute 4 to minute 9) of the 40%, 60%, and 70% $V_{O_{2max}}$ exercise sessions. If the subject did not complete all 9 minutes, only the minutes completed after minute 4 were averaged. Based on these averages, the amount of calories expended per minute was calculated. The RER data was then broken down into the percent of fats and carbohydrates oxidized per minute.^{22,23} Finally, the total amount of grams oxidized per minute for each substrate was calculated for the 5-minute steady-state period.^{22,23}

Statistical Analysis

All statistical procedures were performed using version 17.0 of Statistical Package for the Social Sciences (SPSS) software (SPSS Inc, Chicago, IL). Statistical significance was set a priori at an α level of $P \leq .05$. A one-way analysis of variance (ANOVA) was performed to compare the physical characteristics of the treatment and control groups. For the metabolic data, a 2×3 mixed model ANOVA (group \times intensity) was used to examine the effect of group and intensity on the rate of fat and carbohydrate oxidation (g/min) averaged over the last 5 minutes of steady-state submaximal exercise sessions. A Tukey honestly significant difference (HSD) post hoc test was used to determine mean differences when a significant effect was found. A $2 \times 3 \times 2$ mixed model ANOVA (group \times intensity \times time) was used to examine the effect of group, intensity and time on blood lactate and blood glucose measurements. A Tukey HSD post hoc test was used to determine mean differences if a significant effect was found. A Pearson product moment correlation was performed to examine the relationship between carbohydrate oxidation and recovery blood lactate across all 3 exercise intensities within each of the groups. A Hotelling test was applied between groups to determine if the correlation for each group was significantly different.

Results

Subjects

There were 14 subjects who participated in the study; 7 women in the treatment group and 7 women in the control group. All women in the treatment group had been diagnosed with breast cancer, had undergone surgery, and had completed their major medical treatments (chemotherapy and radiation therapy) within the past 6 months. One woman had been diagnosed with stage I breast cancer whereas 3 women had been diagnosed with stage II, and 3

Table 1. Subject Physical Characteristics, Physical Activity Level, and Menopausal Status^a

Group	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Body Fat (%)	Activity Level (MET h/wk)	Menopausal Status (No. of Women)
Treatment	50.6 ± 3.3	166.5 ± 2.6	81.6 ± 4.2	29.4 ± 1.1	31.8 ± 1.6	77 ± 6	Pre = 1 Peri = 3 Post = 3
Control	50.9 ± 3.6	162.8 ± 1.6	75.4 ± 5.4	28.2 ± 1.9	31.2 ± 2.2	65 ± 10	Pre = 3 Peri = 2 Post = 2

Note: BMI = body mass index; MET = metabolic equivalent task.

^aData are presented as mean ± standard error.

had been diagnosed with stage III breast cancer. Four of the women received both chemotherapy and radiation treatment, whereas 1 woman received only chemotherapy and 2 women received only radiation therapy as their major medical treatments. Six out of the 7 women in the treatment group were also on adjuvant therapies (ie, herceptin, tamoxifen, femara) during this research study. All women in the control group had no history of any preexisting major medical conditions that affected their health and all had been essentially sedentary for the past year.

The subject groups were matched on physical characteristics, which are reported in Table 1. There were no significant differences ($P > .05$) between the groups in their physical characteristics. Furthermore, the groups did not differ ($P > .05$) on their physical activity level or menopausal status (Table 1).

Subjects were asked to consume their typical diet over the course of the research study and a 24-hour dietary recall was administered before each submaximal exercise session to confirm dietary intakes. There were no significant differences ($P > .05$) for total caloric intake, percentage of carbohydrate consumed, or percentage of fats consumed between groups before each of the submaximal exercise sessions (ranges for caloric intake = 2207-1940 vs 1878-1479 kcal/d; carbohydrate intake = 53%-51% vs 57%-52%; fat intake = 33%-28% vs 34%-28%; for treatment vs control groups, respectively).

Exercise Responses

The results of the $\dot{V}O_{2max}$ prediction test are reported in Table 2. Table 2 also displays the calculated workloads to elicit the low, moderate, and high submaximal exercise sessions for each of the subjects. The predicted $\dot{V}O_{2max}$, predicted maximal workload (Wkld_{max}), and workloads at all of the submaximal exercise intensities were not significantly different between groups ($P > .05$).

During the submaximal exercise sessions there was a significant ($P \leq 0.05$) effect of intensity on both steady-state HR and RPE responses; however, there was no significant

Table 2. Estimated Maximal Oxygen Consumption (Aerobic Capacity; $\dot{V}O_{2max}$), Maximal Workload (Wkld_{max}), and Workload for Each Submaximal Exercise Session^a

Group	$\dot{V}O_{2max}$ (mL/kg/min)	Wkld _{max} (W)	Low	Moderate	High
			40% $\dot{V}O_{2max}$ (W)	60% $\dot{V}O_{2max}$ (W)	70% $\dot{V}O_{2max}$ (W)
Treatment	22.0 ± 1.5	108 ± 6	39 ± 4	61 ± 4	75 ± 5
Control	24.1 ± 1.7	115 ± 10	43 ± 4	69 ± 5	79 ± 6

^aData are presented as mean ± standard error.

difference between HR responses (mean ± standard error [SE]) for the treatment group (120 ± 6, 130 ± 5, 147 ± 5 bpm) versus the control group (115 ± 4, 135 ± 4, 145 ± 4 bpm; $P > .05$) group at the low, moderate, and high submaximal exercise intensities, respectively. Similarly, RPE responses (mean ± SE) for the treatment group (11 ± 1, 13 ± 1, 14 ± 1 Borg units) versus the control group (10 ± 1, 12 ± 1, 14 ± 1 Borg units; $P > .05$) did not differ at the low, moderate, and high submaximal exercise intensities, respectively.

Based on the steady-state $\dot{V}O_2$ responses achieved by the subjects in each of the groups for the low-, moderate-, and high-intensity exercise, the actual percentage of $\dot{V}O_{2max}$ were calculated. These percentages did not differ significantly ($P > .05$) between the groups at each of the various respective intensities examined and were in line with desired prescribed intensities (40%, 60%, and 70% $\dot{V}O_{2max}$).

There was a significant ($P < .05$) effect of exercise intensity for both carbohydrate and fat oxidation rates at steady-state exercise (see Figure 1). As exercise intensity increased there was greater carbohydrate oxidation rates and decreased fat oxidation rates. There was also a significant between groups effect for both carbohydrate and fat oxidation rates (Figure 1). That is, the treatment group oxidized significantly less carbohydrate and significantly more fat across all exercise intensities when compared with the control group.

There was a significant interaction effect for exercise intensity and time (ie, preexercise vs postexercise) on the

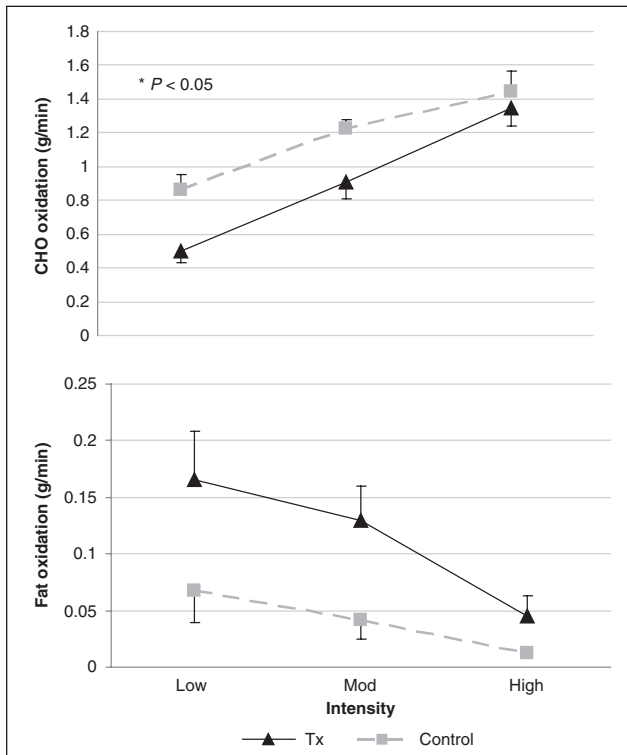


Figure 1. Steady-state carbohydrate (CHO) and fat oxidation rates at different submaximal exercise intensities (mean \pm SE; Mod, moderate intensity; Tx, treatment group). The treatment group (patients with cancer) had higher fat oxidation and lower CHO oxidation rates across all exercise intensities than the control group.

blood lactate responses to the submaximal exercise sessions ($P < .05$). Specifically, the postexercise lactate response became greater as exercise intensity increased in both groups (Figure 2); but a lower concentration of blood lactate in response to the exercise was observed (ie, postexercise) across all submaximal exercise sessions in the treatment group compared to the control group ($P < .05$).

The blood glucose responses to exercise approached significance ($P = .079$) for an interaction of group, exercise intensity, and time. In this case, the control group tended to have lower resting glucose and a more pronounced and consistent decreases in glucose concentrations postexercise than the treatment group across all exercise intensities (see Figure 3).

Carbohydrate oxidation and postexercise blood lactate responses were significantly correlated ($P < .05$) within both the treatment ($r = .549$) and control groups ($r = .635$). Although there was a stronger correlation in the control group, it was not significantly different ($P > .05$) from the treatment group coefficient (see Figures 4 and 5).

None of the women in either group displayed or reported any adverse events because of the exercise sessions. However, 2 subjects (one in each group) requested to stop exercise because of general fatigue before completing all 9

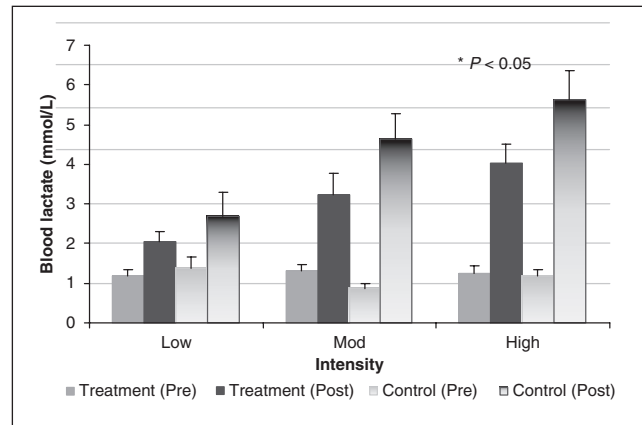


Figure 2. Preexercise and postexercise blood lactate values at different submaximal exercise intensities (mean \pm SE; Mod, moderate intensity). The treatment group (patients with cancer) had lower lactate responses to exercise at all exercise intensities than the control group

minutes of the high-intensity (70% VO_{2max}) exercise session. These subjects did reach a steady-state response and only those values were used in all analysis/calculations.

Discussion

The general objective of this study was to develop a better understanding of energy metabolism at different exercise intensities in posttreated patients with breast cancer compared with healthy women. The goal of obtaining this information was to provide insight into aspects of the physiological and metabolic responses to exercise in patients with breast cancer in order to ultimately aid in the development of more accurate and precise exercise prescriptions for such patients.

The subjects recruited into both groups of this study were predominantly sedentary in nature. This fact is confirmed by the predicted VO_{2max} in each group; treatment group = 22.0 ± 1.5 mL/kg/min, and control group = 24.1 ± 1.7 mL/kg/min. According to the ACSM, these outcomes classify the groups at low levels of aerobic physical fitness.¹⁹

The subjects of each group responded appropriately to all submaximal exercise sessions. Specifically, there was a significant increase in VO_2 , RER, HR, and RPE from rest to exercise during all submaximal exercise sessions in both groups. Both groups also elicited significantly greater increases in VO_2 , RER, HR, and RPE during exercise as the intensity of the submaximal sessions increased from low (40% VO_{2max}) to moderate (60% VO_{2max}) to high (70% VO_{2max}). Such findings are in agreement with the physiological responses to exercise in healthy persons and patients with cancer.^{11,15,19}

Blood lactate levels also increased from rest to postexercise in all sessions and the responses became significantly

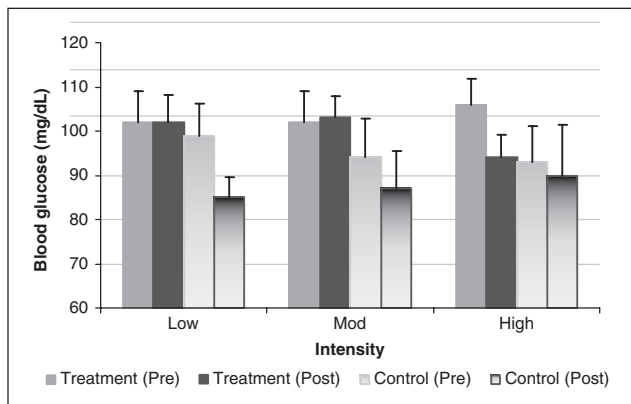


Figure 3. Preexercise and postexercise blood glucose values at different submaximal exercise intensities (mean \pm SE; Mod, moderate intensity).

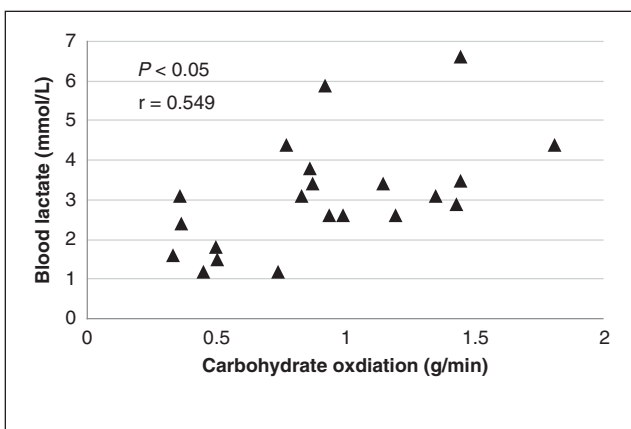


Figure 4. Correlation between carbohydrate oxidation rate and postexercise blood lactate response ($P < .05$) at all submaximal exercise intensities in the treatment group (patients with cancer).

greater as the exercise sessions became more intense. This type of response agrees with previous findings.^{11,15} However, there was a significantly lower overall response in blood lactate to exercise in the treatment group compared with the control group. This finding agrees in part with the work of Evans and associates.¹⁵ In their study, the lactate responses of cancer patients were significantly less than that of healthy control subjects only after high-intensity exercise ($\sim 70\%$ $\dot{V}O_{2max}$). Why the results of Evans et al and the present study are somewhat conflicting is uncertain. These differences may be attributed to the mode of exercise (treadmill vs cycle ergometer; which can have differing type of muscle fiber recruitment pattern), the subject group characteristics relative to training level status, or the small sample sizes used in each of the studies. Regardless of these differences, there is evidence in both studies for decreased blood lactate accumulation during exercise in patients with breast cancer when compared with healthy women.

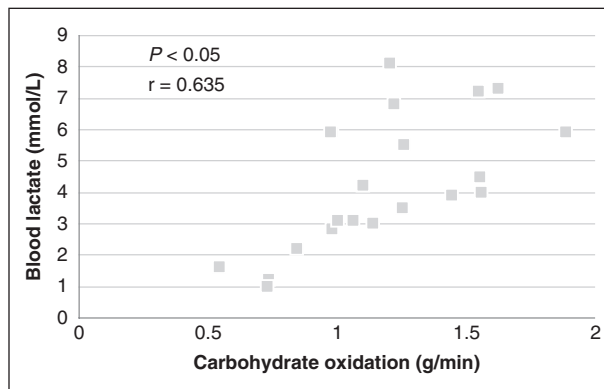


Figure 5. Correlation between carbohydrate oxidation rate and postexercise blood lactate response ($P < .05$) at all submaximal exercise intensities in the control group.

The findings of lower postexercise lactate responses at all exercise intensities (low, moderate, and high) in patients with cancer is a new and novel finding. These lower lactate responses in the cancer group are in line with the reduced carbohydrate oxidation and greater fat oxidation found in this group compared with the control group across all the exercise intensities. This finding concerning substrate oxidation is also a new and novel finding. These physiological events for lactate and oxidation are in agreement; that is, if less carbohydrate is being oxidized, then a reduced amount of lactate should be produced.^{24,25} It is well established that as exercise intensity increases there is a greater reliance on carbohydrate and a reduction in fat as an energy source, which was observed in both study groups.^{11,24} But, the finding of between-group differences in the magnitude of the oxidation rates of carbohydrate and fat has never been previously reported in the literature. It is unknown specifically whether this reduced oxidation of carbohydrate in the cancer group is producing the reduced lactate responses in the blood because (a) the substrate glucose is unavailable to the skeletal muscle, (b) there is a reduced glucose uptake mechanism within the muscle, or (c) perhaps the biochemical pathway glycolysis or related controlling factors within the muscle is compromised. These last points cannot be determined from the present data but are in need of evaluation within future studies.

Why carbohydrate oxidation is reduced and fat oxidation is enhanced during exercise in the patients with cancer is uncertain too. Some of the possibilities may be related to preexisting conditions (such as increased adiposity and menopausal status) the actual cancer disease process itself or side effects of the anticancer treatments administered to the subjects in the treatment group. Although all of the women were considered healthy (other than breast cancer in the treatment group), some women within each group were also classified as overweight, obese, or menopausal. Metabolic alterations have been

displayed in overweight and obese populations, which may increase lipolysis.²⁶ During exercise, obese populations have blunted sympathetic nervous system and catecholamine responses, which may alter the extent of lipolysis occurring; however the rate of fat oxidation does not seem to differ between obese and normal weight individuals.²⁶ Figure 1 indicates, however, that there was a significant difference in the rate of fat oxidation between groups. The difference in fat oxidation observed does not seem attributable to adiposity related factors since there were no differences in BMI or body fat percentage between the groups (Table 1).

Women who have begun menopause begin to produce less estrogen from their ovaries, which can affect energy metabolism.^{26,27} Lower levels of circulating estrogen are associated with increased carbohydrate oxidation and blood lactate responses during exercise; that is, opposite of what was seen in the treatment group.^{26,27} The results of this study show that there was no significant difference between groups for menopausal status; although there were slightly more menopausal women in the treatment group than the control group. Therefore, a highly divergent menopausal status between the groups would also not seem to explain the difference in fat and carbohydrate oxidation observed between the groups.

The disease process of cancer has been associated with endocrine changes that may affect metabolism.^{12,13,28,29} For example, Sommers²⁹ found that the majority of patients with breast cancer presented with endocrine abnormalities; in particular, the pituitary and ovary glands were found to be in a hyperfunctional state. It is believed that these abnormal endocrine gland actions cause an increase in estrogen release from either the ovaries or the adrenal cortex, which is stimulated through the pituitary–adrenal pathway.²⁹ Estrogen can directly and indirectly increase lipolysis and fat oxidation both at rest and during exercise.²⁷ However, the role of cancer-associated endocrine changes on glucose metabolism in the context of this study is speculation on our part since hormonal measurements were not performed.

The disease state of cancer has also been associated with mild to moderate hyperglycemia, glucose intolerance, and insulin resistance, which may affect energy metabolism too.^{12,13,28} There was no significant difference between groups for resting blood glucose in the current study, which is consistent with some previous literature.^{12,13} However, resting levels of blood glucose did tend to be slightly higher in the cancer treatment group compared with the control group. Interestingly, there was a tendency for less of a decrease in blood glucose after exercise in the treatment group when compared with the control group (Figure 2). Although these glucose findings only approached significance ($P < .08$), they nonetheless support the concept of glucose intolerance in cancer populations, which could be driven in part by a developing insulin resistance.^{12,13,28}

Perhaps to some degree this effect is persisting even into exercise within the cancer patients and compromises their ability to metabolize carbohydrate. Again, this is only speculation and would need to be confirmed with an oral glucose tolerance test and hormonal measurements, which were not possible in the current study.

Specific cancer treatments may also be affecting metabolism in these patients with breast cancer. The goal of cancer treatments is to destroy cancerous tissues and cells.³⁰ Radiation therapy is localized and destroys cancerous cells by fracturing their DNA sequence.³¹ Chemotherapy, antihormonal drug treatments such as tamoxifen and femara, and biological therapies such as herceptin, are all systemic therapies used to treat breast cancer.³¹ Although these treatments are meant to affect cancerous tissue primarily, they are not always selective and healthy systemic tissue may also be negatively affected by these harsh treatments causing unwanted side effects.³⁰ All the patients with cancer had undergone some type of systemic treatments (ie, chemotherapy, antihormonal therapy, biological therapy) and some of them were undergoing hormonal therapy at the time of the study. It is highly possible that when these systemic treatments target the cancer cells and destroy their metabolic process, some healthy cells are also affected. Decreasing carbohydrate metabolism ability within the cancer cell is essential to destroy the tumor but consequently it can be detrimental to healthy cells attempting to produce energy from carbohydrate during exercise.

Most of the patients (5 out of 7) in the current study were also receiving antihormonal therapies such as tamoxifen or drug agents that mimic tamoxifen. Although tamoxifen works against the harmful actions of estrogen at breast tissue, it actually acts in the same way as estrogen at many other tissues in the human body.³² As stated earlier, increased amounts of circulating estrogen has both a direct and indirect effect on increasing fat metabolism and inhibition of carbohydrate metabolism.²⁷ Not only does estrogen have direct effects on lipolysis, it may also directly reduce glucose uptake in the muscle.²⁶ The current results support this concept through the observed decreased carbohydrate oxidation as well as the tendency for less of a reduction in blood glucose in the cancer group during exercise.

Exogenous estrogens, such as oral contraceptives or hormonal therapies, can also have indirect effects on substrate oxidation. Bunt²⁷ has reported that estrogen can result in increased levels of cortisol, a result of estrogen stimulating the adrenal cortex. In addition, tamoxifen has been shown to substantially increase plasma cortisol concentrations in patients with breast cancer.³³ Cortisol is a powerful lipolytic hormone and is connected to increased fat metabolism at rest and during exercise.³⁴ The resulting lipolysis from cortisol elevation can be further enhanced through estrogen (or tamoxifen acting like estrogen), by its

action of promoting growth hormone (hGH) release from the anterior pituitary.²⁷ Growth hormone is likewise known to promote lipolysis and free fatty acid mobilization at rest and in response to exercise.^{27,34} Furthermore, these actions of cortisol and hGH can promote a reduction in glycogenolysis, which in turn decreases glycolytic substrate availability and lactate production.^{26,27}

Additionally, estrogens have been shown to result in a chronic elevation of the insulin:glucagon (I:G) ratio, which further reduces the rate of glycogenolysis.^{26,27,34} Such actions on the I:G ratio can lead to decreased insulin sensitivity, promote glucose intolerance and hyperglycemia.²⁷ Changes in glucose tolerance have been observed in women who receive exogenous estrogen through oral contraceptives or hormone replacement therapy.²⁷ Furthermore, women using exogenous estrogen have exhibited higher blood glucose levels, greater hGH and cortisol responses, and slightly greater fat oxidation and reduced glycogenolysis during submaximal exercise when compared with women not using exogenous estrogen.²⁷

Thus, chemotherapy treatments and the use of tamoxifen-like drugs may be compounding this myriad of events to further disrupt normal energy metabolism in patients with cancer during exercise. This means that some drug therapies used by these patients may contribute in part to their altered energy metabolism during exercise which promotes the reduced lactate responses observed in this study. Obviously, without hormonal measurements from this study to confirm this hypothesis, the above must be considered speculation. Nonetheless, this does provide a plausible explanation for the metabolic findings in the study.

Practical Implications

The present results combined with those of Evans et al¹⁵ suggest that blood lactate responses postexercise are not a good indicator of exercise intensity in patients with breast cancer, especially at higher intensities ($\geq 70\% V_{O_{2max}}$). This is contrary to findings in normal healthy individuals where lactate responses are used as accurate indicators of exercise intensity.¹¹ Furthermore, the ability to produce energy from carbohydrate metabolism during exercise is significantly diminished in patients with breast cancer compared with healthy women. Since glucose and glycogen (ie, carbohydrate) are the predominant choices for energy production during high-intensity exercise, this diminished capacity has implications for exercise prescription for this select group. Clinicians should understand that energy cannot be produced as rapidly through anaerobic-aerobic glycolytic means in these patients, making exercise at higher intensities more challenging to perform. Relative to exercise prescription, additional research is necessary to determine what are the most appropriate

physiological choice (lactate, HR, RPE, etc) for the monitoring of aerobic exercise intensity in posttreated patients with breast cancer. However, the present data do call into question the validity of lactate response measurements in this clinical population.

Conclusion

In summary, this study showed that there is a reduced blood lactate response, decreased carbohydrate oxidation rate, and increased fat oxidation rate in patients with breast cancer during exercise, which may compromise their capacity to perform higher intensity exercise. These findings need to be considered preliminary in nature because of the small sample size used. Regardless, these results are striking, and much more research needs to be performed to replicate, confirm, and expand on the evidence presented here. Clinicians and exercise trainers working with patients with breast cancer should keep these physiological limitations in mind while developing exercise prescriptions and programs for such patients. Finally, it is important to note, these findings can only be generalized to women who have been diagnosed with stage I-III breast cancer and have finished all of their major medical treatments within the past 6 months.

Declaration of Conflicting Interests

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