# Effects of Exercise Training on Fasting Insulin, Insulin Resistance, Insulin-like Growth Factors, and Insulin-like Growth Factor Binding Proteins in Postmenopausal Breast Cancer Survivors: A Randomized Controlled Trial[1]

**Adrian S. Fairey, Kerry S. Courneya,[2] Catherine J. Field, Gordon J. Bell, Lee W. Jones, and John R. Mackey**

University of Alberta, Edmonton, Alberta, Canada T6G 2H9

## Abstract

**Insulin, insulin-like growth factors (IGFs) I and II, and IGF binding proteins (IGFBPs) 1 and 3 have been implicated in breast cancer outcomes. We conducted a randomized controlled trial to determine the physiological effects of exercise training on changes in these biological markers in postmenopausal breast cancer survivors. Fifty-three postmenopausal breast cancer survivors were randomly assigned to an exercise ($n = 25$) or control group ($n = 28$). The exercise group trained on cycle ergometers three times per week for 15 weeks. The control group did not train. End points included changes in fasting insulin, glucose, insulin resistance, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and IGF-I:IGFBP-3 molar ratio between baseline and week 15. All of the statistical tests were two-sided ($\alpha = 0.05$). Fifty-two participants completed the trial. The exercise group completed 44.3 of 45 (98.4%) prescribed exercise sessions. Baseline hormone concentrations did not differ between groups except that IGF-II was higher in the exercise group ($P = 0.011$). No significant differences between groups were observed for changes in fasting insulin (+6.3 pmol/liter; $P = 0.941$), glucose (+0.09 mmol/liter; $P = 0.824$), insulin resistance (+0.4; $P = 0.247$), IGF-II (−40.7 ng/ml; $P = 0.101$), or IGFBP-1 (+1.4 ng/ml; $P = 0.774$). However, significant differences between groups were observed for changes in IGF-I (−7.4 ng/ml; $P = 0.045$), IGFBP-3 (+180.5 ng/ml; $P = 0.021$), and IGF-I:IGFBP-3 molar ratio (−0.006; $P = 0.017$). Exercise training had significant physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio in postmenopausal breast cancer survivors. The clinical implications of these findings remain to be defined.**

## Introduction

Insulin, IGF-I,[3] IGF-II, IGFBP-1, and IGFBP-3 have been implicated in breast cancer outcomes (1). Insulin exerts mitogenic effects on normal and malignant breast epithelial cells *in vitro* (2, 3), and high fasting insulin levels have been associated with distant recurrence and death in breast cancer survivors (4). IGF-I also has potent mitogenic and antiapoptotic properties in normal and malignant breast epithelial cells *in vitro*, whereas IGFBP-1 and IGFBP-3 restricts its availability and biological activity (1, 5, 6). Although the data are not consistent, high levels of IGF-I and/or low levels of IGFBP-3 have been associated with an increased risk of breast cancer (7–10) and adverse prognostic factors (4, 11, 12). Therefore, interventions that modify these biological markers may be important in breast cancer outcomes.

Research has shown that exercise training can reduce fasting insulin levels and insulin resistance in adults with and without type 2 diabetes (13–15). Exercise training has also been shown to alter IGF and IGFBPs in healthy women (16). To date, however, no study has examined the effect of exercise training on changes in insulin, insulin resistance, IGF, and IGFBP in breast cancer survivors. Therefore, we conducted a randomized controlled trial of exercise training in postmenopausal breast cancer survivors who had completed surgery, radiotherapy, and/or chemotherapy with or without current tamoxifen or arimidex use. We hypothesized that exercise training would have a physiological effect on fasting insulin. We prospectively tested this hypothesis in the Rehabilitation Exercise for Health after Breast Cancer trial (17).

## Materials and Methods

Details of the method have been described (17). Brief descriptions of the setting, participants, experimental design, randomization, and exercise intervention are provided below.

**Setting and Participants.** The study was conducted at the Cross Cancer Institute and University of Alberta. The Alberta Cancer Board and the University of Alberta approved the study. Written informed consent was obtained for all of the procedures.

A random sample of female breast cancer survivors was obtained from the Alberta Cancer Registry, and the referring

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[2] To whom requests for reprints should be addressed, at Faculty of Physical Education, University of Alberta, E-424 Van Vliet Center, Edmonton, Alberta, Canada, T6G 2H9. Phone: (780) 492-1031; Fax: (780) 492-2364; E-mail: kerry.courneya@ualberta.ca.

[3] The abbreviations used are: IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; CI, confidence interval.

physician was contacted for approval. A recruitment letter was mailed to each approved survivor who then contacted the project director by telephone if interested. An exercise test and blood collection was scheduled at that time. Eligibility criteria included: (*a*) histologically confirmed stage I to IIIB breast cancer; (*b*) diagnosed between January 1999 and June 2000; (*c*) completed surgery, radiotherapy, and/or chemotherapy (≥6 months before randomization) with or without current tamoxifen or arimidex therapy; (*d*) postmenopausal (not experiencing menstrual periods for previous 12 months); (*e*) nonsmokers (not smoking for previous 12 months); (*f*) between 50 and 69 years of age; (*g*) English-speaking; and (*h*) willing to travel to the exercise facility. Eligible participants were not admitted if they had: (*a*) known cardiac disease; (*b*) uncontrolled hypertension; (*c*) uncontrolled thyroid disease; (*d*) diabetes; (*e*) mental illness; (*f*) infection; (*g*) immune or endocrine abnormality; (*h*) body weight reduction ≥10% in past 6 months; or (*i*) positive exercise stress test.

**Experimental Design and Randomization.** The study was a prospective, randomized controlled trial. Participants were stratified by type of adjuvant therapy (previous chemotherapy *versus* no previous chemotherapy and current hormone therapy use *versus* no current hormone therapy use) and block randomized to an exercise or control group using a random-numbers table. A research assistant generated the allocation sequence, and the project director assigned participants to groups.

**Exercise Training Intervention.** The exercise training intervention was designed to improve cardiopulmonary fitness and was based on the fitness level of each participant at baseline. The exercise group trained three times per week for 15 weeks on recumbent or upright cycle ergometers (Lifestyle Fitness 9500HR; Lifecycle Inc.). Exercise intensity was set at the power output that elicited the ventilatory equivalent for carbon dioxide (~70–75% of peak oxygen consumption). Exercise duration began at 15 min for weeks 1–3, and then systematically increased by 5 min every 3 weeks thereafter to 35 min for weeks 13–15. Warm-up and cool-down periods consisted of 5 min of cycling at the power output that elicited the ventilatory equivalent for oxygen (~50% of peak oxygen consumption). Exercise physiologists supervised the exercise sessions, and monitored heart rate and blood pressure. The control group did not train, and were asked not to begin a structured exercise program. To reduce attrition, the control group was offered the intervention after the trial.

Several strategies were used to promote adherence to the exercise training intervention. These included individualized attention at the exercise facility, telephone calls to reschedule missed sessions, individual meetings to outline goals and provide feedback on progress, and the opportunity to exercise alone or in a small group.

**End Points and Blinding.** End points included changes in fasting insulin, glucose, insulin resistance, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and IGF-I:IGFBP-3 molar ratio between baseline and week 15. Laboratory staff and those who assessed the study end points were blinded to treatment assignment.

**Blood Collection.** Participants were instructed not to exercise for at least 48 h before blood collection. Blood was collected between 7:00 a.m. and 10:00 a.m. after a 12-h water-only fast with participants in the seated position. Blood was drawn into tubes chilled on ice treated with sodium heparin (for plasma) or no anticoagulant (for serum). Blood was centrifuged at 700 × *g* at 23°C for 10 min. Plasma and serum were aliquoted and stored at −70°C. Precautions were taken to prevent thawing or warming of specimens during storage. Blood samples were collected from 53 participants at baseline and 52 participants at week 15.

**Laboratory Analyses and Calculations.** Insulin was measured in plasma using a radioimmunoassay kit (Count-A-Count; DPC, Los Angeles, CA). Glucose was measured in plasma using a glucose analyzer (Beckman Instruments, Brea, CA). IGF-I and IGFBP-3 were measured in plasma using ELISA kits (Quantikine; R & D Systems, Inc., Minneapolis, MN). IGF-II and IGFBP-1 were measured in serum using ELISA kits (Diagnostic Systems Laboratories, Inc., Webster, TX). All of the samples were analyzed by using assay kits from a single lot before the expiration date of the assay kit. Each assay was performed in one batch (*i.e.*, baseline and week 15 assessments of each analyte for both exercise and control group participants were performed in one batch). Duplicate measurements were made for each sample, and the mean of the duplicate measurements was assigned as the sample value. Blind duplicates were used for determining coefficients of variation. The mean intra-assay coefficient of variation was 1.6% for insulin, 5.1% for IGF-I, 4.4% for IGF-II, 6.3% for IGFBP-1, and 3.0% for IGFBP-3.

Insulin resistance was estimated by homeostatic model assessment (18). It was calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting glucose level (in millimoles per liter), divided by 22.5. The IGF-I:IGFBP-3 molar ratio was calculated as the fasting plasma IGF-I level divided by the fasting plasma IGFBP-3 level.

**Baseline Characteristics.** Demographic data were collected by self-report. Medical data were abstracted from medical records.

**Dietary Intake and Daily Medication Use.** Dietary intake was assessed using 3-day diet records. Participants completed the 3-day diet records on consecutive days before blood collection at baseline. These records were photocopied and returned to participants at week 15. Participants were asked to consume the same diet on the 3 consecutive days before blood collection at week 15. No specific diet was prescribed. Diet records were analyzed using the Food Processor II program (ESHA Research, Salem, OR). Daily medication use in the 6 months before the intervention and during the intervention period was assessed by self-report.

**Adherence to the Exercise Training Intervention.** Exercise levels outside of the exercise intervention were assessed using the leisure score index of the Godin Leisure-Time Exercise Questionnaire (19). Participants completed the leisure score index on a biweekly basis during the intervention period. The exercise physiologists monitored adherence to the intervention.

**Statistical Analysis.** Data were analyzed using the intention-to-treat approach with SPSS version 10.0 software (SPSS, Inc., Evanston, IL). The last-observation-carried-forward procedure was used for participants who did not complete the trial. Therefore, if data were missing at week 15, we assumed that there was a return to the baseline value. Distributions were checked for skewness and outliers. This led to the following transformations in statistical analyses: glucose (inverse) and insulin (log). These transformations were reversed for presentation of data.

Baseline comparisons between the two groups were made using independent-samples *t* tests for continuous data and Pearson's $\chi^2$ tests for categorical data. The primary analysis used independent-samples *t* tests to compare changes between groups in end points from baseline to week 15. Change over the intervention period was calculated by subtracting the baseline value from the week 15 value. A two-sided $P < 0.05$ indicated

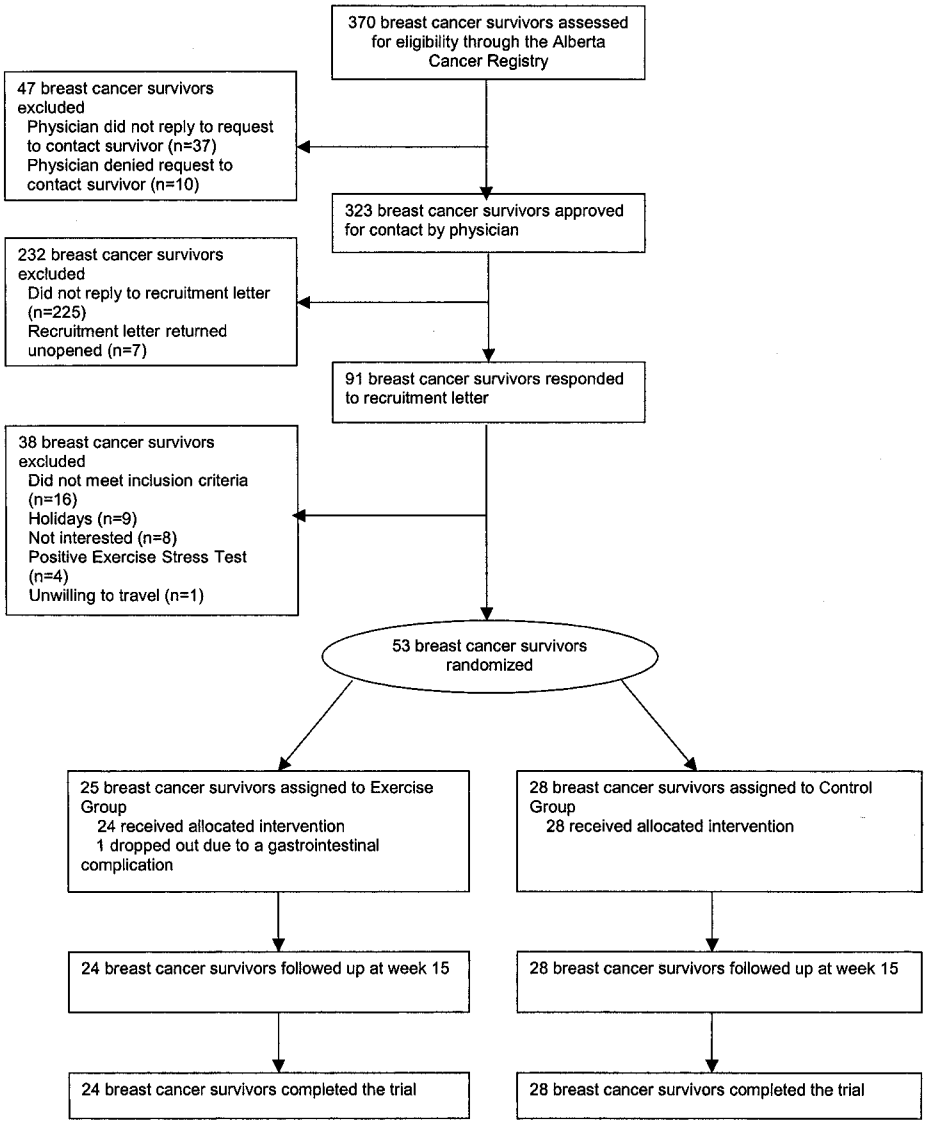


*Fig. 1.* Flow of participants through the trial. Adapted from Courneya *et al.*, J. Clin. Oncol. *21:*1660–1668, 2003 with permission from the American Society of Clinical Oncology.

statistical significance. No adjustments were made for multiple comparisons. Data are presented as the mean (±SD) with 95% CIs.

## Results

**Flow of Participants Through the Trial.** Fig. 1 shows the flow of participants through the trial. In brief, 370 breast cancer survivors were assessed for eligibility during the recruitment period, and 53 (14.3%) were randomly assigned to the exercise ($n = 25$) or control group ($n = 28$). During the intervention period, 1 participant (4.2%) dropped out in the exercise group compared with 0 participants in the control group ($P = 0.285$). Overall, 52 of 53 participants completed the trial (98.1%).

**Baseline Characteristics.** Table 1 presents the baseline characteristics. The groups were balanced in terms of demographic, medical, and past exercise variables.

**Diet Intake and Daily Medication Use.** Table 2 shows information on dietary intake and daily medication use. The groups were balanced in terms of dietary intake and daily medication use variables except that there were trends toward a difference between groups for use of acetaminophen ($P = 0.054$) and thyroid hormone ($P = 0.054$).

**Adherence to the Intervention.** The exercise group completed 44.3 of 45 (98.4%) of the prescribed exercise sessions. Nonprotocol-related exercise was low and did not differ between groups ($P = 0.890$). The exercise group reported an average of 15 min of moderate/strenuous nonprotocol-related exercise per week compared with 13 min in the control group.

**Changes in Cardiopulmonary Fitness and Body Composition.** Changes in cardiopulmonary fitness and body composition have been described (17). In brief, baseline values for peak oxygen consumption ($P = 0.254$), body weight ($P = 0.983$), body mass index ($P = 0.725$), and sum of skinfolds ($P = 0.650$) did not differ between groups. A significant difference between groups was observed for change in peak oxygen consumption (mean difference, +0.29 liters/min; 95% CI, 0.18–0.40 liters/min; $P < 0.001$). No significant differences between groups were observed for changes in body weight (mean difference,

*Table 1* Baseline Characteristics[a]

| Variable | Overall ($n$ = 52) | Exercise group ($n$ = 24) | Control group ($n$ = 28) | $P$[b] |
|---|---|---|---|---|
| Demographic | | | | |
| Age (years) | 59 (6) | 59 (5) | 58 (6) | 0.712 |
| Medical | | | | |
| Weight (kg) | 78.7 (18.1) | 78.1 (20.4) | 79.4 (16.4) | 0.801 |
| Body mass index (kg/m$^2$) | 29.2 (6.6) | 29.4 (7.4) | 29.1 (6.1) | 0.880 |
| Months postsurgery, RT, and/or CT[c] | 14 (6) | 14 (6) | 14 (7) | 0.856 |
| Stage | | | | |
| I ($T_1N_0$) | 21 (40%) | 10 (42%) | 11 (39%) | 0.862 |
| IIa ($T_1N_1$, $T_2N_0$) | 17 (33%) | 6 (25%) | 11 (39%) | 0.274 |
| IIb ($T_2N_1$, $T_3N_0$) | 11 (21%) | 6 (25%) | 5 (18%) | 0.530 |
| IIIa ($T_1N_2$, $T_2N_2$, $T_3N_{1-2}$) | 3 (6%) | 2 (8%) | 1 (4%) | 0.463 |
| Surgery | | | | |
| Mastectomy | 28 (54%) | 15 (64%) | 13 (46%) | 0.246 |
| Lumpectomy | 24 (46%) | 9 (37%) | 15 (54%) | 0.246 |
| Radiation therapy | 37 (71%) | 16 (67%) | 21 (75%) | 0.508 |
| Chemotherapy | 21 (40%) | 10 (42%) | 11 (39%) | 0.862 |
| Anthracycline regimen | 20 (38%) | 10 (42%) | 10 (36%) | 0.329 |
| Current hormone therapy use | 24 (46%) | 11 (46%) | 13 (46%) | 0.966 |
| Past exercise | | | | |
| Moderate minutes | 82 (114) | 62 (94) | 98 (126) | 0.247 |
| Strenuous minutes | 25 (61) | 23 (56) | 26 (65) | 0.897 |
| Moderate/strenuous minutes | 106 (129) | 85 (102) | 124 (146) | 0.280 |
| >90 Moderate/strenuous | 22 (42%) | 10 (42%) | 12 (42.9%) | 0.931 |

Data are presented as the mean (SD) for continuous variables and frequency (percentage) for categorical variables.
[a] Adapted with permission from Ref. 17.
[b] $P$ for difference between groups.
[c] RT, radiation therapy; CT, chemotherapy.

−0.6 kg; 95% CI, −1.6 to +0.6 kg; $P$ = 0.339) or body mass index (mean difference, −0.3 kg/m$^2$; 95% CI, −0.6 to +0.3 kg/m$^2$; $P$ = 0.337) but there was a trend toward a change in sum of skinfolds (mean difference, −10.2 mm; 95% CI, −21.6 to +1.8 mm; $P$ = 0.095).

**Changes in Insulin, Glucose, Insulin Resistance, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and IGF-I:IGFBP-3 Molar Ratio.** Table 3 presents the hormone end points. Baseline concentrations did not differ between groups except that IGF-II was higher in the exercise group ($P$ = 0.011). No significant differences between groups were observed for changes in fasting insulin (mean difference, +6.3 pmol/liter; 95% CI, −6.1 to +18.8 pmol/liter; $P$ = 0.941), glucose (mean difference, +0.09 mmol/liter; 95% CI, −0.3 to +0.5 mmol/liter; $P$ = 0.824), insulin resistance (mean difference, +0.4; 95% CI, −0.3 to +1.0; $P$ = 0.247), IGF-II (mean difference, −40.7 ng/ml; 95% CI, −89.7 to +8.3 ng/ml; $P$ = 0.101), and IGFBP-1 (mean difference, +1.4 ng/ml; 95% CI, −8.6 to +11.5 ng/ml; $P$ = 0.774). However, significant differences between groups were observed for changes in IGF-I (mean difference, −7.4 ng/ml; 95% CI, −14.6 to −0.2 ng/ml; $P$ = 0.045), IGFBP-3 (mean difference, +180.5 ng/ml; 95% CI, +28.4 to +332.5 ng/ml; $P$ = 0.021), and IGF-I:IGFBP-3 molar ratio (mean difference, −0.006; 95% CI, −0.01 to −0.001; $P$ = 0.017).

## Discussion

The Rehabilitation Exercise for Health after Breast Cancer trial is the first study to evaluate the physiological effects of exercise training on fasting insulin, glucose, insulin resistance, IGF, and IGFBP in cancer survivors. We found that exercise training had no significant physiological effects on fasting insulin, glucose, insulin resistance, IGF-II, and IGFBP-1 in postmenopausal breast cancer survivors. However, exercise training did have significant physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio.

The strengths and limitations of our data merit consideration. Strengths include the randomized controlled trial design, standardized blood collection protocols, high exercise adherence rate, and minimal loss to follow-up. Limitations include the 14% recruitment rate, small sample size, short exercise intervention with no long-term follow-up, and use of a single hormone measurement to classify participants.

Key findings of our trial were that exercise training had no significant physiological effect on fasting insulin, glucose, or insulin resistance in postmenopausal breast cancer survivors. These results are in contrast to previous observations. In a randomized controlled trial, Ross *et al.* (13) demonstrated that 3 months of exercise-induced weight loss (700 kcal/day, ≤70% of peak oxygen consumption) improved insulin sensitivity by ~60% in obese men. In a nonrandomized trial, Duncan *et al.* (15) showed that 6 months of exercise training without weight loss (3–7 sessions/week, 45–75% of heart rate reserve, 30 min/session) improved insulin sensitivity by ~70% in overweight, sedentary adults. Finally, in a meta-analysis of controlled clinical trials, Boule *et al.* (20) showed that aerobic (3.4 sessions/week, 18 weeks) or resistance (10 exercises, 2.5 sets, 13 repetitions, 2.5 times/week, 15 weeks) exercise training reduced glycosylated hemoglobin ($HbA_{1C}$) by 0.66% in adults with type 2 diabetes mellitus.

There are several possible explanations for the lack of effects on fasting insulin, glucose, and insulin resistance in our trial. First, our exercise training intervention did not induce weight loss, which is known to reverse the hyperinsulinemia and insulin resistance that is associated with overweight and obesity (13, 21, 22). However, exercise training does not necessarily need to reduce body weight to have beneficial physiological effects on insulin resistance and glycemic control (13,

*Table 2* Dietary intake and daily medication use[a]

| Variable | Overall ($n$ = 52) | Exercise group ($n$ = 24) | Control group ($n$ = 28) | $P$[b] |
|---|---|---|---|---|
| Dietary intake | | | | |
| Total calories (Kcal/day) | 1780 (389) | 1782 (391) | 1779 (395) | 0.979 |
| Percent calories from fat | 33 (6) | 34 (5) | 32 (7) | 0.288 |
| Percent calories from carbohydrates | 50 (8) | 49 (6) | 51 (8) | 0.253 |
| Percent calories from protein | 16 (3) | 16 (3) | 16 (4) | 0.440 |
| Total fat (g) | 59 (15) | 60 (14) | 58 (17) | 0.541 |
| Total carbohydrate (g) | 228 (61) | 220 (54) | 234 (67) | 0.428 |
| Total protein (g) | 73 (23) | 74 (21) | 71 (25) | 0.663 |
| Daily medication use | | | | |
| ACE inhibitor | 3 (5%) | 1 (4%) | 2 (7%) | 0.646 |
| Acetaminophen | 3 (5%) | 3 (13%) | 0 (0%) | 0.054 |
| α-Antagonist | 2 (4%) | 2 (8%) | 0 (0%) | 0.119 |
| Antibiotic | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |
| Antifungal | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |
| Anti-inflammatory | 15 (29%) | 7 (29%) | 8 (29%) | 0.962 |
| Aspirin | 3 (5%) | 2 (8%) | 1 (4%) | 0.463 |
| Atorvastatin | 3 (5%) | 1 (4%) | 2 (7%) | 0.646 |
| β-Blocker | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |
| Bisphosphonate | 11 (19%) | 7 (29%) | 4 (14%) | 0.190 |
| Calcium channel blocker | 1 (2%) | 1 (4%) | 1 (4%) | 0.911 |
| Diuretic | 2 (4%) | 1 (4%) | 1 (4%) | 0.911 |
| Hormone replacement therapy | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |
| Hydrogen ion blocker | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |
| Leukotriene antagonist | 1 (2%) | 1 (4%) | 0 (0%) | 0.275 |
| Nasal steroid | 2 (4%) | 1 (4%) | 1 (4%) | 0.911 |
| Proton pump inhibitor | 4 (7%) | 3 (13%) | 1 (4%) | 0.228 |
| Sedative | 6 (12%) | 4 (17%) | 2 (7%) | 0.284 |
| Selective serotonin reuptake inhibitor | 11 (19%) | 6 (25%) | 5 (18%) | 0.530 |
| Sumatriptan | 1 (2%) | 1 (4%) | 0 (0%) | 0.275 |
| Thyroid hormone | 13 (23%) | 3 (13%) | 10 (36%) | 0.054 |
| Ventolin | 1 (2%) | 0 (0%) | 1 (4%) | 0.350 |

[a] Data are presented as the mean (SD) for continuous variables and frequency (percentage) for categorical variables.
[b] $P$ for the difference between groups.

21). Second, blood collection was performed after a period of at least 48 h without exercise. Given that it is known that acute exercise is associated with substantial improvements in insulin resistance when measured within 48 h of the last exercise session (23, 24), it is likely that the short-term effects of exercise on insulin resistance had dissipated. Third, the sample size of our trial may have been too small to detect a treatment effect.

Other findings of our trial were that exercise training did have significant physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio. Previous trials of exercise training and IGF-I and IGFBP-3 in older women have reported mixed results (16, 25–32), making it difficult to compare our findings. However, comparison of our effects with those reported in trials of selective estrogen receptor modulator therapies is instructive. The direction and magnitude of the between-group change in IGF-I (10.9%) and IGF-I:IGFBP-3 molar ratio (18.2%) in our trial is similar to that observed in a randomized controlled trial of raloxifene in postmenopausal breast cancer survivors (33). In this trial, participants were assigned to receive 600 mg/day of raloxifene, 60 mg/day of raloxifene, or placebo for 14 days. Comparison of participants assigned to 600 mg/day of raloxifene with those assigned to placebo revealed significant between-group changes in IGF-I and IGF-I:IGFBP-3 molar ratio of 15 and 20%, respectively (33). However, nonrandomized breast cancer trials of selective estrogen receptor modulator therapies such as tamoxifen (34–37) and droloxifene (38) have reported decreases in IGF-I between 20 and 40%. Reasons for these differences in magnitude of the effect remain to be determined but may include both the dose and length of drug administration. The between-group change in IGFBP-3 (8.4%) that we observed has not been demonstrated in three previous trials of anticancer drug therapies (12, 33, 38) but is consistent with one recent prospective cohort study of tamoxifen in postmenopausal breast cancer survivors (34). Therefore, in aggregate, these data suggest that exercise training may provide similar physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio compared with selective estrogen receptor modulator therapies.

Exercise-induced modulation of fasting insulin, glucose, insulin resistance, IGF, and IGFBP is biologically plausible. Exercise training may decrease hepatic and muscle insulin resistance, and increase glucose disposal by a number of mechanisms including increased postreceptor insulin signaling, increased glucose transporter protein and mRNA, increased activity of glycogen synthase and hexokinase, decreased release and increased clearance of free fatty acids, increased muscle glucose delivery because of increased muscle capillary density, and changes in muscle composition favoring increased glucose disposal (39). This reduction in insulin resistance may lower circulating levels of insulin (24), which, in turn, may decrease IGF bioavailability via insulin-mediated changes in IGFBP concentrations. Although our findings do not provide evidence of these mechanisms and other factors may be involved (40, 41), these effects may represent clinically significant biological mechanisms of action of exercise training.

Additional studies designed to evaluate the effects of exercise training on changes in fasting insulin, glucose, insulin

*Table 3* Changes in insulin, glucose, insulin resistance, IGF-I, IGF-II, IGFBP-1, IGFBP-3, and IGF-I:IGFBP-3 molar ratio[a]

| End point | Baseline | P[b] | Week 15 | Mean change | Difference between groups in mean change (95% CI) | P value[c] |
|---|---|---|---|---|---|---|
| Insulin (pmol/liter) | | | | | | |
| Exercise group ($n$ = 25) | 60.2 (34.8) | | 67.5 (51.9) | +7.2 (26.0) | | |
| Control group ($n$ = 28) | 53.2 (36.3) | 0.381 | 54.1 (37.3) | +0.9 (18.8) | +6.3 [−6.1 to 18.8] | 0.941 |
| Glucose (mmol/liter) | | | | | | |
| Exercise group ($n$ = 25) | 5.9 (1.5) | | 5.8 (1.7) | −0.07 (1.0) | | |
| Control group ($n$ = 28) | 5.5 (0.8) | 0.255 | 5.4 (0.9) | −0.16 (0.5) | +0.09 [−0.3 to 0.5] | 0.824 |
| Insulin resistance index | | | | | | |
| Exercise group ($n$ = 25) | 2.3 (2.1) | | 2.7 (3.0) | +0.4 (1.4) | | |
| Control group ($n$ = 28) | 1.9 (1.7) | 0.424 | 1.9 (1.9) | 0.0 (0.9) | +0.4 [−0.3 to 1.0] | 0.247 |
| IGF-I (ng/ml) | | | | | | |
| Exercise group ($n$ = 25) | 67.4 (29.1) | | 62.5 (23.9) | −4.9 (10.7) | | |
| Control group ($n$ = 28) | 70.0 (21.5) | 0.705 | 72.6 (24.8) | +2.5 (14.8) | −7.4 [−14.6 to −0.2] | 0.045 |
| IGF-II (ng/ml) | | | | | | |
| Exercise group ($n$ = 25) | 824.9 (155.5) | | 805.0 (139.9) | −19.9 (97.1) | | |
| Control group ($n$ = 28) | 714.5 (148.9) | 0.011 | 735.3 (152.4) | +20.9 (80.5) | −40.7 [−89.7 to 8.3] | 0.101 |
| IGFBP-1 (ng/ml) | | | | | | |
| Exercise group ($n$ = 25) | 47.5 (32.3) | | 53.2 (30.4) | +5.6 (13.4) | | |
| Control group ($n$ = 28) | 48.2 (29.8) | 0.933 | 52.4 (34.2) | +4.2 (21.2) | +1.4 [−8.6 to 11.5] | 0.774 |
| IGFBP-3 (ng/ml) | | | | | | |
| Exercise group ($n$ = 25) | 2160.8 (421.1) | | 2264.2 (435.4) | +103.4 (224.7) | | |
| Control group ($n$ = 28) | 2146.2 (438.2) | 0.902 | 2069.1 (478.4) | −77.1 (313.5) | +180.5 [28.4 to 332.5] | 0.021 |
| IGF-I:IGFBP-3 molar ratio | | | | | | |
| Exercise group ($n$ = 25) | 0.032 (.013) | | .028 (0.012) | −0.003 (0.006) | | |
| Control group ($n$ = 28) | 0.034 (.015) | 0.518 | .037 (0.015) | +0.003 (0.01) | −0.006 [−0.01 to −0.001] | 0.017 |

[a] Data are presented as the mean (SD).
[b] $P$ for independent $t$ tests comparing the exercise group and control group at baseline.
[c] $P$ for independent $t$ tests comparing changes between the exercise group and control group from baseline to week 15.

resistance, IGF, and IGFBP in postmenopausal breast cancer survivors are needed. Researchers should attempt to confirm our findings in a larger sample of survivors and determine whether there are differential physiological effects to be achieved by altering the exercise parameters (frequency, intensity, time, and type). Studies are also needed to test underlying biological mechanisms of action and to evaluate whether exercise-induced modulation of fasting insulin, glucose, insulin resistance, IGF, and IGFBP is associated with breast cancer outcomes.

In summary, exercise training had no significant physiological effects on fasting insulin, glucose, insulin resistance, IGF-II, and IGFBP-1 in postmenopausal breast cancer survivors. However, exercise training did have significant physiological effects on IGF-I, IGFBP-3, and IGF-I:IGFBP-3 molar ratio. The clinical implication(s) of our findings remain to be defined.

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