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Aerobic training reduces systemic oxidative stress in young women with elevated levels of F2-isoprostanes

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Abstract

The purpose of this trial was to determine whether exercise without weight loss would reduce F2-isoprostanes in previously sedentary young women. Participants (N=319) were randomized to four months of 150 min/wk aerobic exercise or a control group. Plasma free F2-isoprostanes were measured by gas chromatography-mass spectrometry. Other assessments included fitness and % body fat. Intervention groups were compared with stratification by quartiles of baseline plasma F2-isoprostane. This stratified comparison was linearly adjusted for baseline plasma F2-isoprostane and we also used baseline plasma F2-isoprostane as a propensity score to balance the intervention. Training resulted in significant improvements in aerobic fitness (0.88 METs) and body fat percent (1%) in exercisers compared to controls ($p < 0.001$). The exercise group had significantly higher mean baseline plasma F2-isoprostanes (79.1 vs 67.9 pg/mL) than the control group in the highest quartile of baseline plasma F2-isoprostanes. Within this highest quartile, exercise led to a greater decline in plasma F2-isoprostanes (-20.2 ± 2.5 pg/mL) than control (-7.4 ± 2.5 pg/mL); with adjustment for baseline plasma F2-isoprostanes and in the balanced groups, this difference was reduced but remained significant. Four months of exercise training resulted in significant reductions of systemic oxidative stress only among previously sedentary young women who were in the highest quartile of plasma F2-isoprostanes at baseline (> 57 pg/mL). Our findings indicate that the benefits of aerobic exercise in reducing systemic oxidative stress may be limited to those who present higher baseline levels of plasma F2-isoprostanes.

Keywords

F2-isoprostanes; exercise; women; body composition; fitness

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Introduction

Evidence suggests that oxidative stress is a major underlying pathogenic factor in the aging process and numerous chronic diseases associated with inflammation [1, 2]. Production of reactive oxygen species (ROS) is important to carcinogenesis because oxidant-induced DNA damage results in gene mutations and modification of gene expression [3]. Oxidative stress mediated by ROS may result in lipid peroxidation, of which F2-isoprostanes are the most frequently used clinical markers. Isoprostanes are generated from oxidation of cell membrane-bound arachidonic acid. They are cleaved by phospholipases following attack by ROS and circulate in plasma and then are excreted in urine [4]. Indeed, the risk of breast cancer has been found to be doubled in women whose urinary F2-isoprostanes, a marker of systemic oxidative stress, were in the second, third and fourth quartiles compared with those in the lowest quartile [5]. In overweight women, the levels of F2-isoprostanes were positively associated with breast cancer risk [6] and high levels of F2-isoprostanes have also been linked to risk of prostate [7] and hepatocellular carcinoma [8]. Thus, interventions to reduce oxidative stress could have important implications regarding reduction of cancer risk. Exercise training has been proposed as a means to reduce systemic oxidative stress, particularly among overweight and obese adults [2]. Our hypothesis was that exercise without weight loss would reduce F2-isoprostanes in previously sedentary young women.

Methods

The Women in Steady Exerciser Research (WISER) study was a randomized clinical trial comparing the effects of a 16-week aerobic exercise intervention *versus* no exercise on markers associated with breast cancer risk [9]. The study was approved by the University of Minnesota Human Subjects Review Committee. Participants were healthy women aged 18–30 years, with a BMI between 18.5–40 kg/m², sedentary, non-smoking, not taking hormonal contraceptives, and not dieting. Women were randomly assigned to the exercise intervention ($n = 166$) or the control group ($n = 153$) and were instructed to avoid weight change.

The exercise intervention consisted of 30 minutes of weight-bearing aerobic exercise, five times per week, at a specified intensity based on age-predicted heart rate maximum (HRmax). Exercise intensity increased every four weeks to reach 80–85% of HRmax. The control group was asked to maintain their usual levels of physical activity.

At baseline and 16-weeks the following were collected: demographic information, anthropometrics, body composition via DXA (Lunar Radiation Corp., Madison, WI), dietary intake via 3-day food records, health habits, fitness level via sub-maximal tests, and blood samples, which were collected after fasting of 12–15 hours during the morning between 6:30 am and 10:30 am during the follicular phase of participants' cycles. Blood was collected in EDTA-containing tubes and placed in dry ice immediately after separating the plasma into 0.5-mL aliquots. Plasma samples were transferred to -70°C freezer within 24 hours of collection. The average storage time of plasma samples prior to analysis ranged between 6–18 months. Free F2-isoprostanes were measured in plasma at baseline and 16 weeks by a gas chromatography-mass spectrometry (GC-MS)-based method [10] at the Molecular Epidemiology and Biomarker Research Laboratory (MEBRL), University of Minnesota, Minneapolis, MN. Intra- and inter-assay coefficients of variation were 8% and 7%, respectively.

Statistical Methods

Examination of baseline data revealed marked imbalance between intervention groups: the majority of those with high baseline levels of plasma F2-isoprostane were assigned to the exercise group (Figure 1). This was surprising given the size of the study, and of concern

because the study's primary outcome was change from baseline in plasma F₂-isoprostane, which was correlated with baseline plasma F₂-isoprostane. We used three methods to reduce bias in estimated differences between intervention groups. First, intervention groups were compared with stratification by quartiles of baseline plasma F₂-isoprostane [11]. Second, this stratified comparison was linearly adjusted for baseline plasma F₂-isoprostane [12]. Third, baseline plasma F₂-isoprostane was used as a propensity score to balance the intervention groups, a technique commonly applied in observational studies [13, 14]. Exercise and control women were paired using a caliper-matching algorithm requiring baseline F₂-isoprostane difference < 5 pg/mL within a pair [15]. Of 319 subjects, 290 were able to be matched, giving randomized intervention groups of 145 subjects who were balanced with respect to baseline in plasma F₂-isoprostane (Figure 1).

Unadjusted comparisons of demographic characteristics were performed by t-tests and chi-squares for continuous and categorical variables, respectively. Comparisons between groups were adjusted for age and BMI strata with a general linear model. Plasma F₂-isoprostane was analyzed on the log scale; change in plasma F₂-isoprostane was analyzed on the original scale. To assess whether change in fitness was a mediator for exercise effects on plasma F₂-isoprostanes, change in fitness was regressed on treatment in a strata-adjusted model, change in plasma F₂-isoprostanes was regressed on both treatment and change in fitness in a strata-adjusted model, with Sobel's test for indirect effect [16]. Statistical analysis was in SAS, version 9.2 (SAS Institute Inc., 2008, Cary, NC). The sample size for this trial was determined based on results from an uncontrolled pilot study [17] that observed a standard deviation for plasma F₂-isoprostanes of 52.1 pg/mL and a repeated measures correlation of 0.53. Based on these data and the goal of detecting a change in F₂-isoprostanes of less than 16 pg/mL (30% of the standard deviation from the pilot study), we estimated we would need data from 320 women.

Results

Screening was completed by 1684 potential women participants. Of these, 1260 were found eligible, 683 were consented and 391 enrolled in WISER, of whom 319 completed the study with both a baseline and final measurement of plasma F₂-isoprostanes. Details of enrollment have been previously published [9].

We report results from the 319 healthy women who completed the study (the study completers), and also from a subset of 290 balanced on baseline plasma F₂-isoprostanes (the balanced subset). Baseline demographics for study completers were similar between the two groups (Table 1) and in the balanced groups (data not shown). Control and exercise participants self-reported the same mean level of exercise at baseline (Table 1). One-third of participants were overweight or obese. There were no significant differences in demographic characteristics listed in Table 1 between the 319 who completed the study and the 72 (26 in the control group, 46 in the exercise group) who did not have a final measurement of plasma F₂-isoprostanes (data not shown).

In the exercise group, participants completed a mean of 92% of assigned minutes of exercise, and 140 women (86%) exercised for at least 14 weeks. Mean adherence was 97% in the first exercise, 85% in the final stage. Adherence in the balanced groups was nearly identical. Details are described elsewhere [18].

No changes in mean body weight or BMI were observed (Table 2). There was a significant increase in aerobic fitness and lean body mass in exercisers compared with controls, and exercisers lost significantly more body fat mass than controls. However, there was a

significant decrease in total calorie intake in the control group compared with the exercise group ($p < 0.001$). The same results were seen in the balanced groups (data not shown).

Change in plasma F₂-isoprostanes was strongly related to baseline plasma F₂-isoprostanes. Dividing participants into quartiles of baseline plasma F₂-isoprostanes, there were no differences in mean change in plasma F₂-isoprostanes between intervention groups in the lowest three quartiles (baseline plasma F₂-isoprostanes < 57 pg/mL). In the highest quartile of baseline plasma F₂-isoprostanes, the exercise group had significantly higher mean baseline plasma F₂-isoprostanes. Within this highest quartile, exercise led to a greater decline in plasma F₂-isoprostanes than control; with adjustment for baseline plasma F₂-isoprostanes and in the balanced groups, this difference was reduced but remained significant (Table 3).

Stratifying on BMI, there were no differences in mean change in plasma F₂-isoprostanes between intervention groups among normal weight ($18.5 \leq \text{BMI} < 25$) and overweight ($25 \leq \text{BMI} < 30$) women. Among obese ($\text{BMI} \geq 30$) women, the exercise group had significantly higher baseline plasma F₂-isoprostanes and exercise led to a greater decline in plasma F₂-isoprostanes than control (Table 4). With adjustment for baseline plasma F₂-isoprostanes and in the balanced groups, this difference was no longer significant.

Adjustment for caloric intake (kcal) did not alter the conclusions of Tables 3 and 4. There was no association of change in fitness with change in F₂-isoprostanes and a mediation analysis did not support the hypothesis that change in F₂-isoprostanes was mediated through changes in fitness (data not shown). Changes in body fat and lean mass were not associated with changes in plasma F₂-isoprostanes.

Discussion

We found that four months of exercise training of the dose recommended for cancer prevention [19] did not decrease systemic oxidative stress as measured by F₂-isoprostanes in previously sedentary young women. There seemed to be an effect of exercise on the levels of F₂-isoprostanes only in the women who were in the highest quartile of baseline F₂-isoprostanes (plasma F₂-isoprostanes ≥ 57 pg/mL). Although baseline plasma F₂-isoprostanes were elevated in obese participants, the effect of exercise was not significant after adjustment or balancing for baseline plasma F₂-isoprostanes.

Four prior small uncontrolled trials ($n = 11$ to 23) observed decreases in F₂-isoprostanes after interventions ranging from one week to four months of aerobic training of moderate to vigorous intensity, 3–7 times weekly [17, 20–22]. Participants in these previous uncontrolled studies ranged in age from 18–50 years, with the exception of one study, which recruited subjects 38–72 years of age [20]. In contrast to the positive results of these small uncontrolled trials, neither of the two prior controlled trials demonstrated an effect of exercise training on F₂-isoprostanes. Eight weeks of three times weekly aerobic exercise did not result in any change in F₂-isoprostanes in men and women with type 2 diabetes [23]. One year of five times weekly aerobic exercise also did not result in any changes in F₂-isoprostanes in previously sedentary, obese post-menopausal women in the Physical Activity for Total Health (PATH) Trial [24]. However, the authors did note a significant treatment effect in a planned subgroup analysis when comparing exercisers who increased maximal oxygen capacity by 15% or more to control group participants [24]. The WISER trial differed from prior studies by having a larger sample size, by including younger women with a broad range of BMIs, and having been designed with plasma F₂-isoprostanes as the primary outcome of interest.

Effects of exercise training on oxidative stress did not appear to be mediated by changes in fitness which differs from results in the PATH trial [24] and may be the result of using a sub-maximal rather than a maximal aerobic exercise testing protocol. This is a potential limitation of the WISER Trial. Another limitation is the use of a single measure of oxidative stress. On the other hand, a large study concluded that urinary and plasma F₂-isoprostanes are among the best available choices for reflecting overall systemic oxidative stress and demonstrated that correlations between plasma F₂-isoprostanes and other measures of oxidative stress are excellent [25]. The failure of the randomization to balance the intervention groups on the primary outcome at baseline was an unexpected limitation of this trial. Strengths of the WISER Trial include the randomized controlled trial design, large sample size, minimal loss to follow-up, excellent exercise adherence, documented improvements in aerobic fitness with objective treadmill testing, use of a well accepted marker for oxidative stress, and use of the exercise dose currently recommended by the American Cancer Society for cancer prevention [19].

The magnitude of exercise effect in plasma F₂-isoprostanes among the participants in the highest quartile for baseline F₂-isoprostanes, using the first estimate on table 3, was approximately one half of the magnitude of change observed after two weeks of smoking abstinence among smokers [26]. It is possible that these demonstrated effects on systemic oxidative stress mediate the previously published epidemiologic link between exercise and cancer prevention [27]. However, our findings suggest that habitual exercise may not have any effect on levels of F₂-isoprostanes in individuals who already have lower levels of F₂-isoprostanes (< 57 pg/mL). The benefits of aerobic exercise in reducing systemic oxidative stress may be limited to those who present higher baseline levels of plasma F₂-isoprostanes.

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Figure 1. Change in plasma F₂-isoprostanes and baseline values of BMI and plasma F₂-isoprostanes. Control participants are indicated by open circles, exercise participants by filled circles. The highest quartile of plasma F₂-isoprostanes was 57 pg/mL.

Table 1

Baseline demographics.

	Exercise (n = 166)	Control (n = 153)	P-value
Age (years)	25.4 ± 3.5	25.2 ± 3.5	0.73
Height (cm)	164.9 ± 7	165.4 ± 8	0.54
Weight (kg)	67.4 ± 15	67.6 ± 15	0.94
BMI (kg/m ²)	24.7 ± 4.7	24.7 ± 4.8	0.88
Weight categories:			
Underweight (BMI < 18.5)	1 (1%)	1 (1%)	
Normal weight (18.5 ≤ BMI < 25)	100 (60%)	100 (65%)	0.38
Overweight (25 ≤ BMI < 30)	46 (28%)	30 (20%)	
Obese (BMI ≥ 30)	19 (11%)	22 (14%)	
Education:			
High school or less	11 (7%)	7 (5%)	0.66
Some college	43 (26%)	44 (29%)	
College graduate or more	112 (68%)	102 (67%)	
Race			
White	124 (75%)	107 (70%)	
Black	13 (8%)	12 (26%)	0.66
Asian	20 (12%)	26 (17%)	
Other	9 (5%)	8 (5%)	
Hispanic	8 (5%)	6 (4%)	0.70
Prior childbirth	12 (7%)	9 (6%)	0.63
Self-reported physical activity (MET*mins/week)	22.3 ± 1.3	22.6 ± 1.4	0.88

Values are mean ± standard deviation or number (percent).

Table 2

Changes in anthropometrics, fitness, and diet. Values are mean $\pm$ standard error.

	Baseline	Change at 4 months
METs reached at 80% of Max HR		
Exercise	6.95 $\pm$ 0.1	0.88* $\pm$ 0.08
Control	7.04 $\pm$ 0.1	0.13 $\pm$ 0.08
P-value	0.59	< 0.001
Weight (kg)		
Exercise	68.0 $\pm$ 0.7	-1.2 $\pm$ 0.7
Control	68.8 $\pm$ 0.8	-1.2 $\pm$ 0.8
P-value	0.41	0.96
BMI (kg/m ²)		
Exercise	25.0 $\pm$ 0.2	-0.42 $\pm$ 0.30
Control	25.2 $\pm$ 0.2	-0.48 $\pm$ 0.30
P-value	0.45	0.88
Percent body fat		
Exercise	36.8 $\pm$ 0.4	-0.95* $\pm$ 0.20
Control	37.1 $\pm$ 0.4	-0.06 $\pm$ 0.20
P-value	0.65	<0.001
Lean mass (kg)		
Exercise	39.9 $\pm$ 0.4	0.55* $\pm$ 0.10
Control	40.3 $\pm$ 0.4	0.07 $\pm$ 0.10
P-value	0.42	0.003
Diet (kcal/day)		
Exercise	1895 $\pm$ 39	22 $\pm$ 47
Control	1919 $\pm$ 40	-204* $\pm$ 50
P-value	0.65	0.001

* Significant within-group change from baseline ($p < 0.01$).

Table 3

Comparison of exercise and control groups for baseline and adjusted change in plasma F₂-isoprostanes; comparisons are given for the highest quartile of baseline F₂-isoprostanes; there were no intervention differences in the three lower quartiles.

	Baseline	Change at 4 months
Highest 25%: Baseline F₂-isoprostanes 57 pg/mL		
<i>All study completers</i>		
Exercise (n = 48)	79.1 (74 – 84)	– 20.2* ± 2.5
Control (n = 46)	67.9 (64 – 72)	– 7.4* ± 2.5
P-value	.0005	.0002
<i>All study completers, with baseline F₂ adjustment</i>		
Exercise (n = 48)		– 8.4* ± 3.0
Control (n = 46)		0.6 ± 2.7
P-value		.0067
<i>Balanced Groups</i>		
Exercise (n = 33)	72.5 (70 – 75)	– 13.3* ± 2.5
Control (n = 39)	70.0 (68 – 72)	– 6.6* ± 2.3
P-value	.148	.047

Values are unadjusted geometric mean (95% CI) for baseline F₂; for change in F₂, mean ± standard error, adjusted for randomization age and BMI strata.

* Significant within-group change from baseline (p < 0.05).

Table 4

Comparison of exercise and control groups' mean baseline and adjusted change in plasma F₂-isoprostanes; comparisons are given for obese participants, with results from all study completers and from the balanced subset; there were no intervention differences among normal weight and overweight women.

	Baseline	Change at 4 months
Obese (BMI = 30)		
<i>All study completers</i>		
Exercise (n = 19)	72.9 (62 – 86)	– 19.5* ± 4.6
Control (n = 22)	53.6 (46 – 63)	– 2.9 ± 4.4
P-value	0.003	0.003
<i>All study completers, with baseline F₂ adjustment</i>		
Exercise (n = 19)		– 8.9* ± 4.1
Control (n = 22)		– 0.5 ± 3.8
P-value		0.095
<i>Balanced Groups</i>		
Exercise (n = 14)	60.9 (51 – 73)	– 8.3 ± 4.6
Control (n = 21)	53.2 (45 – 62)	– 1.0 ± 4.2
P-value	.190	.171

Values are unadjusted geometric mean (95% CI) for baseline F₂; for change in F₂, mean ± standard error, adjusted for randomization age and BMI strata.

* Significant within-group change from baseline (p < 0.05).