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A 12-Month Moderate-Intensity Exercise Intervention Does Not Alter Serum Prolactin Concentrations

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Abstract

Introduction—Many studies have investigated the immediate impact of physical activity on prolactin concentrations; however, it is currently unclear what impact exercise may have on prolactin concentrations in the long-term, particularly among women. Understanding the role of exercise on prolactin is important because epidemiologic studies have reported increased risks of breast cancer in association with high prolactin concentrations. We investigated whether exercise alters serum prolactin concentrations at two time points within a one-year exercise intervention.

Methods—Out of 96 women aged 40-75 years, 47 were randomized to a 12-month regimen of moderate-intensity physical activity and 49 were randomized to the control group. Participants in the exercise group (exercisers) took part in exercise at gym facilities 3 times per week and 3 times per week on their own. Serum prolactin was collected from participants at baseline, 3 and 12 months. Using generalized linear models, we compared the percent change in prolactin concentrations from baseline to the two follow-up time points in the exercisers versus the control group.

Results—While we observed the suggestion of differences in the change in serum prolactin concentrations in some subgroups, overall there was no difference in the change in prolactin concentrations between exercisers and controls at 3 months (P=0.84) or 12 months (P=0.19).

Conclusion—Our study does not support the hypothesis that long-term exercise influences serum prolactin concentrations.

Keywords

adherence; biomarker; exercise trial; randomized control trial

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Introduction

Epidemiologic studies have reported an increased risk of several diseases associated with high prolactin concentrations.[1-3] In breast cancer while there exists some debate over the role of prolactin [4,5], a pooled analysis of two large, prospective cohorts observed a 1.3-fold increased risk of breast cancer comparing the highest to lowest quartiles of prolactin concentrations (p-trend = 0.002) [3]. The support from experimental studies linking higher prolactin concentrations to breast cancer risk includes associations between prolactin and cellular proliferation [6-9], inhibition of apoptosis [4,10], and increased estrogen receptor expression [8,11].

Given the potential role of high prolactin concentrations in breast cancer, [3] it is important to understand whether modifiable factors, such as physical activity, could reduce prolactin concentrations. Multiple studies have reported on the impact of exercise on serum prolactin concentrations over differing time intervals [12-20]. Early studies reported increased prolactin concentrations immediately after intensive exercise among women [12,13,15-17] and indicated that prolactin levels returned to baseline within 24 hours [15]. Until recently the studies looking at the long-term effects of exercise on prolactin were all conducted in men. Of these studies in men, one study reported a significant increase in prolactin concentrations over an eight-week, intensive exercise regimen [18] and two others reported significantly reduced prolactin concentrations associated with intensive exercise among athletes [19,20]. Of the single study investigating long-term impacts of exercise on prolactin levels in women is a report from a 12-month moderate intensity exercise intervention describing a decrease in prolactin concentrations associated with exercise, but only among those with the highest changes in their physical fitness [14]. No study has reported on an attempt to replicate this finding.

In addition, because physical activity has been associated with a lower breast cancer risk [21], understanding whether exercise impacts prolactin concentrations can help elucidate the mechanisms by which exercise lowers breast cancer risk. In the current analysis conducted within an ancillary study of a randomized controlled trial [22], we investigated the long-term impact of physical activity on serum prolactin concentrations in middle-aged women.

Methods

Study participants were recruited into a 12-month moderate-intensity exercise intervention trial (60 min/day, 6 days/wk) among adults aged 40-75 yrs in the Seattle-Puget Sound region. This analysis was limited to the 100 women recruited into the study, of which 96 had blood samples available at all time points. The study methods, including a flow chart depicting the number of participants from recruitment through follow-up, have been described previously [22,23]. Briefly, participants were eligible for this trial if they had a colonoscopy in the previous 3 years, no history of cancer or other serious illness (including cardiovascular disease, stroke, or diabetes), a normal response to an exercise tolerance exam, engaged in less than 90 minutes of moderate to vigorous exercise per week at the time of recruitment, and consumed less than 2 alcoholic beverages/day.

Invitation letters were mailed to 9,828 gastroenterology patients, of whom 2,033 completed the interest survey, and 956 were interviewed. In addition, there were 1,328 responses to media placements, of whom 1,092 were interviewed. Of those potentially eligible, a total of 395 attended an information session, 311 were screened in clinic, and 202 were randomized. The primary reasons for ineligibility were unwillingness to be randomized (n =297), being too physically active (n= 339), and insufficient time availability (n = 48). Of those randomized, 100 were women.

After providing informed consent, each participant provided 12-hour fasting blood samples at baseline, 3-months, and 12-months, as well as completed a baseline questionnaire ascertaining information on body weight history, health habits, and medical history. Body fat percentage was determined for each participant using a DXA whole-body scanner (GE Lunar, Madison, WI). Intra-abdominal,fat was determined with computerized tomography (CT) scans (General Electric model CT 9800 scanner, Waukesha, WI).

Participants were randomized into an exercise group and control group using stratified blocked randomization on NSAID use, current smoking, menopausal status, and current hormone therapy use. Controls were waitlisted for a lifestyle intervention for 12 months.

Exercise Protocol

Participants in the exercise group, henceforth referred to as exercisers, were asked to take on 6 days/wk of 60 min/session of moderate-to-vigorous aerobic exercise gradually achieved over the first 12 weeks. The intervention was structured such that exercisers participated in exercise at one of four facilities (one located at the Fred Hutchinson Cancer Research Center Prevention Center [FHCRC] and 3 private health clubs) on treadmills, stationary bikes, elliptical machines, and rowers with an exercise specialist present for 3 days/wk. Exercisers were given heart rate monitors with instructions to reach between 60% to 85% of their maximal heart rate (established from their baseline VO_2 max test). Exercisers were also asked to exercise at home or at a gym an additional 3 days/wk with the same instructions regarding duration and heart rate goal ranges. Exercisers recorded maximal session heart rate in a daily physical activity log.

All participants underwent a physical-activity interview adapted from the Minnesota Leisure Time Physical Activity (MNLTPA) Questionnaire [24] at baseline to determine eligibility, and at 3, 6, 9, and 12 months to estimate adherence and control contamination. We assessed VO_2 max once each at baseline and 12 months with participants completing a maximal-graded treadmill test. All participants wore Accusplit pedometers while awake for 1 week at baseline and quarterly thereafter, and recorded their total daily steps in a log. This study was approved by the FHCRC Institutional Review Board.

Laboratory Analysis

Serum prolactin concentrations (ng/mL) were quantified by a chemiluminescent immunometric assay using the Immulite® analyzer (Siemens Medical Solutions Diagnostics, Malvern, PA) at the Reproductive Endocrine Research Laboratory (University of Southern California). The interassay coefficients of variation (CV) were 6.9%, 5.8% and 3.9% at 6.7, 15.8, and 32.4 ng/mL, respectively. Laboratory personnel were blinded to participants' study group.

Statistical Analysis

Serum prolactin concentrations were log-transformed due to the lack of normality. We calculated the Intraclass Correlation Coefficient (ICC) using one-way ANOVA. For our primary analysis, we calculated the percent change in prolactin concentrations from baseline to 2 follow-up time points. To evaluate whether the exercise intervention impacted prolactin concentrations, we compared the percent change in prolactin concentrations from baseline to follow-up in the exercisers versus the control groups using generalized linear models (SAS 9.1). We did not observe effects of confounding factors in our analysis, including history of breastfeeding, parity, and medications that can affect prolactin concentrations (e.g. anti-depressant medications). In secondary analyses, we stratified by age, BMI, menopausal history, first-degree family history of breast cancer, and levels of adherence to exercise program in order to compare our findings to the previous report on exercise and prolactin concentrations [14].

Our study was sufficiently powered to detect associations between exercise and prolactin. Assuming 80% power and a 2-sided significance test ($\alpha = 0.025$), we calculated that a sample of 44 women in each group was needed to detect a difference of 0.35 ng/mL in the geometric mean of prolactin. Considering that the prior report describing an association between exercise and prolactin observed a net difference for the change in the geometric mean of prolactin of 0.77 ng/mL (i.e. + 0.30 change in controls minus a - 0.47 change in exercisers with the highest change in fitness) [14], our study was amply powered to detect a similar difference.

Results

Exercisers and controls were similar in their distribution of demographic, anthropometric, and exercise-related factors at baseline such that none of these factors were statistically different between the two groups (Table 1). As reported previously, the exercise group exercised a mean of 295 and a median of 292 min/wk (82% of goal); the exercisers achieved a mean increase of 2.5 ml/kg/min (+10.5%) in VO_2 max compared to a mean decrease of 1.2 ml/kg/min (−4.8%) in controls (P <0.001) [22].

Baseline prolactin concentrations were somewhat correlated with age (r=−0.19; P = 0.06), although not statistically significantly. Baseline prolactin concentrations were not correlated with other steroid hormones, including androstendione, testosterone, free testosterone, DHEAS, SHBG, and insulin. Nor was baseline prolactin correlated with BMI or percent body fat at baseline. The ICC for prolactin concentrations at the 3 time points in control women was 0.56.

Overall, we observed no difference in the change in prolactin concentrations at 3-months or 12-months in exercisers versus controls (Table 2). Within our analyses stratified by age, we observed a slight difference between exercisers and controls among women aged 55 years and older at the end of 3 months in which exercisers had a greater increase in prolactin concentrations, although this difference was not statistically significant (P = 0.08), and this difference did not persist at the 12-month time point.

When investigated by adherence to the exercise program as measured by change in VO_2 max, change in steps/day, and minutes of exercise/day (Table 3), there again was no difference in prolactin concentrations between exercisers and controls. Nor did the results differ by family history of breast cancer (data not shown). Additionally, we investigated the potential for anti-depressants to modify the effect of exercise on prolactin but our results remained unchanged when analyses were limited to women who were not users of anti-depressant medications.

Discussion

Increased prolactin concentrations have been associated with an increased risk of breast cancer [3]. In addition, physical activity has been associated with a reduced risk of breast cancer [21], but whether physical activity impacts on prolactin concentrations has been unclear. Early reports demonstrated that intensive exercise acutely increased prolactin concentrations [12,13,15-17]; however, more recently an exercise intervention reported that long-term exercise decreased prolactin concentrations when the analysis was limited to exercisers with the highest change in physical fitness [14]. Specifically, this study reported that prolactin concentrations decreased by 10.9% (from 6.99 ng/mL at baseline to 6.23 ng/mL at 12-months) among women who gained between 5% and 15% in VO_2 max, while concentrations in controls increased by 4.0% (from 7.47 ng/mL at baseline to 7.77 ng/mL at 12-months; *P*=0.03).

The findings from the current study, however, do not support the hypothesis that physical activity affects serum prolactin concentrations either in the short-term or long-term. The current study observed no evidence that adherence, as measured by VO_2 max, steps per day, or minutes of exercise per day, affected our findings. While there was some suggestion in the current study that results differed by age, due to the small number of women within this subset, this estimate is not as reliable as the overall estimates observing no difference. Compared to the prior exercise intervention study [14], the present study population was younger and fitter at baseline. In reconciling the findings from these two studies, it is possible that if age and fitness modify the effect of prolactin these differences in study populations could contribute to the conflicting findings.

Despite being adequately powered to detect differences in the overall group, our study was limited in its ability to reliably investigate potential differences in prolactin concentrations within subgroups; however, subgroup analyses were conducted in order to compare the findings from the current study to the study previously reporting an association between prolactin and exercise [14]. An additional limitation was that a portion of the intervention was home-based, and thus, we relied on self-reported daily logs to assess some aspects of adherence. This concern is ameliorated by the finding that improvements inVO_2 max among the exercisers supported the data from participants' daily exercise logs such that reduction in body fat percentages were associated both with increasing minutes of exercise reported in daily logs and increasing levels of VO_2 max [22]. An additional limitation was the moderate reproducibility of prolactin concentrations which could limit our ability to detect an effect of the exercise intervention. However, previous studies have reported similar levels of reproducibility for prolactin measurements, demonstrating that prolactin concentrations do not differ in relation to the menstrual cycle but that ICCs for prolactin may be somewhat lower in pre-menopausal versus post-menopausal women [25-27]. Finally, with only a portion of people responding to our recruitment and meeting eligibility requirements, our study may have limited generalizability. However, approximately 25% of the study's participants were recruited through the media (and the remaining through gastroenterology clinics), indicating that our findings may be generalizable to people in the overall population who are interested in changing their sedentary lifestyle to a more physically active one.

Our findings suggest that a 12-month moderate-intensity aerobic exercise intervention does not alter serum prolactin concentrations. While this study confirmed the prior finding of no main effect of long-term exercise on prolactin concentrations [14], we could not rule out the possibility of a subgroup effect. Additional studies which are powered to detect differences by age and fitness would be needed to address this question.

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Abbreviations

CI	confidence interval

CV	coefficients of variation
DHEAS	dehydroepiandrosterone sulfate
ICC	intraclass correlation coefficient
min	minutes
MNLTPA	Minnesota Leisure Time Physical Activity
ng/mL	nanograms per milliliter
SHBG	sex hormone binding globulin
VO_2 max	maximal volume of oxygen uptake
wk	week

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Table 1

Baseline Demographic and Anthropometric Characteristics in Exercisers and Control Women

	Baseline	
	Exercisers n=49 Mean (SD) or n (%)	**Controls n=51 Mean (SD) or n (%)**
Age (yrs)	54.4 (7.1)	53.7 (5.6)
Race		
American Indian/Alaskan Native	1 (2.0)	1 (2.0)
Asian or Pacific Islander	4 (8.2)	1 (2.0)
African-American	1 (2.0)	2 (3.9)
White	42 (85.7)	47 (92.2)
Other	0 (0.0)	0 (0.0)
Anti-depressant medication use	5 (10.2)	7 (13.7)
Height (cm)	164.0 (6.9)	165.5 (6.4)
Weight (kg)	78.0 (17.8)	77.9 (12.8)
BMI (kg/m^2)	28.9 (5.5)	28.5 (4.8)
Body fat (%)	43.3 (7.2)	43.0 (6.8)
Intra-abdominal fat (cm^2)	106 (60.8)	103 (55.8)
Subcutaneous fat (cm^2)	372.0 (178.2)	373.8 (144.8)
VO_2 max (ml/kg/min)	23.8 (5.09)	24.8 (4.34)
Moderate-to-vigorous exercise in past 3 months (min/wk)	26.8 (47.7)	24.0 (55.3)

Table 2

Baseline and Follow-up Prolactin Geometric Means (ng/mL) in Women Overall and within Subgroups

	Baseline		3-mos Follow-up					12-mos Follow-up				
	Exercisers	Controls	Exercisers		Controls			Exercisers		Controls		
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Change (%)	Mean (95% CI)	Change (%)	P [1]	Mean (95% CI)	Change (%)	Mean (95% CI)	Change (%)	P [2]
Overall	7.3 (6.4, 8.4) (n=49)	7.8 (6.7, 9.1) (n=51)	7.8 (7.0,8.7) (n=48)	0.5 (6.8)	7.9 (7.1, 8.8) (n=49)	0.1 (1.3)	0.57	7.9 (7.0,9.0) (n=47)	0.6 (8.2)	7.8 (6.9, 8.8) (n=49)	0 (0.0)	0.42
Age (yrs)												
<55	8.1 (6.7, 9.7) (n=26)	8.4 (6.9, 10.3) (n=32)	7.8 (6.9, 8.9) (n=25)	−0.3 (3.7)	8.8 (7.6, 10.2) (n=31)	0.4 (4.8)	0.50	8.5 (7.0, 10.2) (n=24)	0.4 (4.9)	8.7 (7.4, 10.3) (n=31)	0.2 (2.4)	0. 92
55+	6.6 (5.4, 8.1) (n=23)	6.9 (5.6, 8.5) (n=19)	7.8 (6.6, 9.3) (n=23)	1.2 (18.2)	6.6 (5.7, 7.6) (n=18)	−0.3 (−4.3)	0.08	7.3 (6.2, 8.7) (n=23)	0.7 (10.6)	6.4 (5.5, 7.5) (n=18)	−0.5 (−7.2)	0.14
BMI (kg/m^2)												
<25	7.6 (5.9, 9.8) (n=16)	6.9 (5.5, 8.5) (n=14)	8.1 (6.8, 9.8) (n=16)	0.5 (6.6)	7.8 (6.6, 9.3) (n=13)	0.9 (13.0)	0.69	8.2 (6.3, 10.8) (n=16)	0.6 (7.9)	8.2 (6.8, 10.0) (n=13)	0 (0.0)	0.57
25-29	7.9 (6.0, 10.5) (n=14)	9.8 (7.1, 13.5) (n=18)	8.1 (6.6, 9.9) (n=14)	0.2 (2.5)	9.4 (7.7, 11.6) (n=18)	−0.4 (4.1)	0.67	8.0 (6.7, 9.6) (n=14)	0.1 (1.2)	8.8 (6.9, 11.3) (n=17)	0.8 (10.0)	0.48
30+	6.7 (5.4, 8.3) (n=19)	6.9 (5.8, 8.4) (n=19)	7.4 (6.2, 8.9) (n=19)	0.7 (10.5)	6.7 (5.7, 7.8) (n=18)	−0.2 (−2.9)	0.37	7.5 (6.1, 9.2) (n=17)	0.8 (11.9)	6.7 (5.7, 8.0) (n=19)	−0.8 (−10.7)	0.22
Menopausal status												
Pre-	9.1 (7.0, 11.7) (n=16)	8.0 (6.2, 10.3) (n=18)	8.4 (7.0, 10.0) (n=15)	−1.3 (−14.3)	7.8 (6.9, 8.9) (n=17)	−0.2 (−2.5)	0.72	9.1 (7.1, 11.6) (n=14)	0 (0.0)	8.0 (6.6, 9.7) (n=17)	0 (0.0)	0.99
Peri- and Post-	6.6 (5.6, 7.8) (n=33)	7.7 (6.4, 9.3) (n=33)	7.6 (6.6, 8.7) (n=33)	1.0 (15.2)	8.0 (6.8, 9.3) (n=32)	0.3 (3.9)	0.19	7.4 (6.4, 8.6) (n=33)	0.8 (12.1)	7.7 (6.6, 9.1) (n=32)	0.3 (4.1)	0.24

[1] Testing the difference between prolactin concentrations at 3-months and baseline in exercisers versus controls

[2] Testing the difference between prolactin concentrations at 12-months and baseline in exercisers versus controls

Table 3

Baseline and 12-Month Follow-up Prolactin Geometric Means (ng/mL) by Adherence

		Baseline	12-mos Follow-up			
		Mean (95% CI)	Mean (95% CI)	Change (%)	*P*[1]	*P*[2]
Increase in Min/Wk						
	Controls	7.8 (6.7, 9.1) (n=51)	7.8 (6.9, 8.8) (n=49)	0 (0.0)	Ref	N/A
	Exercisers					
	<250 Min/Wk	6.8 (5.4, 8.6) (n=15)	8.2 (6.5, 10.3) (n=13)	1.4 (20.6)	0.28	Ref
	250-300 Met Min/Wk	6.1 (4.7, 7.9) (n=10)	6.6 (5.4, 7.9) (n=10)	0.5 (8.2)	0.71	0.32
	300+ Met Min/Wk	8.3 (6.7, 10.3) (n=24)	8.4 (6.9, 10.2) (n=24)	0.1 (1.2)	0.73	0.11
					(p_{trend} = 0.70)	(p_{trend} = 0.15)
Increase in steps/day						
	Controls	7.8 (6.7, 9.1) (n=51)	7.8 (6.9, 8.8) (n=49)	0 (0.0)	Ref	N/A
	Exercisers					
	<1760 steps/day	7.1 (5.5, 9.1) (n=18)	7.7 (6.3, 9.4) (n=18)	0.6 (8.5)	0.63	Ref
	1760-3519 steps/day	8.1 (5.3, 12.3) (n=8)	9.0 (5.7, 14.4) (n=8)	0.9 (11.1)	0.29	0.90
	3520+ steps/day	7.3 (5.8, 9.2) (n=15)	7.9 (6.4, 9.6) (n=15)	0.6 (8.2)	0.77	0.86
					(p_{trend} = 0.33)	(p_{trend} = 0.93)
Change in VO_2 max						
	Controls	7.8 (6.7, 9.1) (n=51)	7.8 (6.9, 8.8) (n=49)	0 (0.0)	Ref	N/A
	Exercisers					
	Decreased or <5% increase	7.2 (5.4, 9.7) (n=15)	8.3 (6.5, 10.6) (n=15)	1.1 (15.3)	0.35	Ref
	Increased 5% - 15%	7.1 (5.2, 9.5) (n=15)	7.1 (6.1, 8.2) (n=15)	0 (0.0)	0.94	0.42

	Baseline	12-mos Follow-up			
	Mean (95% CI)	**Mean (95% CI)**	**Change (%)**	***P*[1]**	***P*[2]**
Increased < 15%	7.3 (6.0, 8.7) (n=14)	7.7 (5.9, 9.9) (n=14)	0.4 (5.5)	0.57	0.43
				(p_{trend} = 0.70)	(p_{trend} = 0.46)

[1] Testing a difference between the change from baseline to 12 months in the exercise group versus controls

[2] Testing a difference between the change from baseline to 12 months in middle or high exercise adherence groups versus low adherence group (controls excluded)