Effects of Exercise on Metabolic Risk Variables in Overweight Postmenopausal Women: A Randomized Clinical Trial

Laura Lewis Frank,† Bess E. Sorensen,* Yutaka Yasui,* Shelley S. Tworoger,‡ Robert S. Schwartz,§ Cornelia M. Ulrich,*† Melinda L. Irwin,¶ Rebecca E. Rudolph,*‖ Kumar B. Rajan,*† Frank Stanczyk,** Deborah Bowen,* David S. Weigle,‖ John D. Potter,*† and Anne McTiernan*†‖*

Abstract

FRANK, LAURA LEWIS, BESS E. SORENSEN, YUTAKA YASUI, SHELLEY S. TWOROGER, ROBERT S. SCHWARTZ, CORNELIA M. ULRICH, MELINDA L. IRWIN, REBECCA E. RUDOLPH, KUMAR B. RAJAN, FRANK STANCZYK, DEBORAH BOWEN, DAVID S. WEIGLE, JOHN D. POTTER, AND ANNE MCTIERNAN. Effects of exercise on metabolic risk variables in overweight postmenopausal women: a randomized clinical trial. *Obes Res.* 2005;13:615–625.

Objective: This study examined the effects of exercise on metabolic risk variables insulin, leptin, glucose, and triglycerides in overweight/obese postmenopausal women.

Research Methods and Procedures: Sedentary women ($n = 173$) who were overweight or obese (BMI $\geq$ 25 kg/m^2 or $\geq$24 kg/m^2 with $\geq$33% body fat), 50 to 75 years of age, were randomized to 12 months of exercise ($\geq$45 minutes of moderate-intensity aerobic activity 5 d/wk) or to a stretching control group. Body composition (DXA) and visceral adiposity (computed tomography) were measured at baseline and 12 months. Insulin, glucose, triglycerides, and leptin were measured at baseline and 3 and 12 months. Insulin resistance was evaluated by the homeostasis model assessment formula. Differences from baseline to follow-up were calculated and compared across groups.

Results: Exercisers had a 4% decrease and controls had a 12% increase in insulin concentrations from baseline to 12 months ($p = 0.0002$). Over the same 12-month period, leptin concentrations decreased by 7% among exercisers compared with remaining constant among controls ($p = 0.03$). Homeostasis model assessment scores decreased by 2% among exercisers and increased 14% among controls from baseline to 12 months ($p = 0.0005$). The exercise effect on insulin was modified by changes in total fat mass (trend, $p = 0.03$), such that the exercise intervention abolished increases in insulin concentrations associated with gains in total fat mass.

Discussion: Regular moderate-intensity exercise can be used to improve metabolic risk variables such as insulin and leptin in overweight/obese postmenopausal women. These results are promising for health care providers providing advice to postmenopausal women for lifestyle changes to reduce risk of insulin resistance, coronary heart disease, and diabetes.

Key words: insulin, triglycerides, leptin, homeostasis model assessment, physical activity

Introduction

More than 60% of postmenopausal women in the United States are overweight or obese (1). Obesity, especially central obesity, is associated with an increased risk for diabetes (2,3), coronary heart disease (4), ischemic stroke (5), and several cancers (6–8). Obesity may contribute to the pathogenesis of these diseases by altering carbohydrate and lipid metabolism. For example, elevated concentrations of insulin and glucose are associated with an increased risk of insulin

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*Fred Hutchinson Cancer Research Center, Cancer Prevention, Seattle, Washington; †Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington; ‡Channing Laboratory, Harvard Medical School and the Brigham and Women's Hospital, Boston, Massachusetts; §Department of Internal Medicine, Division of Geriatric Medicine, University of Colorado Health Sciences Center, Denver, Colorado; ¶Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut; ‖Department of Medicine, School of Medicine, University of Washington, Seattle, Washington; and **Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, California.

Address correspondence to Anne McTiernan, Fred Hutchinson Cancer Research Center, PO Box 19024, M4-B402, Seattle, WA 98109-1024.

E-mail: amctiern@fhcrc.org

resistance and type 2 diabetes (9–11), several cancers (12–14), and cardiovascular disease (15,16). In addition, hyperleptinemia, hyperinsulinemia, hyperglycemia, and hypertriglyceridemia all play central roles in the development of the metabolic syndrome (17–19).

Previous studies have suggested that moderate-intensity exercise can result in improvements in both body composition and coronary (metabolic) risk factors in postmenopausal women (20–23). We extended these previous studies by including a larger population of postmenopausal women and by lengthening our randomized controlled clinical trial to 12 months. Furthermore, because several studies have shown that the amount of intraabdominal fat, in postmenopausal women, strongly influences insulin sensitivity and other cardiovascular disease risk factors (24–26), we further explored whether the exercise-induced changes in body composition (27) would have favorable effects on metabolic risk variables such as insulin, glucose, triglycerides, leptin, and insulin resistance [evaluated by the homeostasis model assessment (HOMA)[1] formula] (28). We also explored effects of change in total and intraabdominal body fat, as well as degree of adherence, on the effect of exercise on study endpoints.

Research Methods and Procedures

This study, conducted from 1997 to 2001, was a 12-month randomized clinical trial comparing the effect of a moderate-intensity exercise intervention vs. a stretching control program on circulating hormones and other variables at 3 and 12 months after randomization (27,29). All study procedures, including a written informed consent, were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Participants

Participants were postmenopausal women from the greater Seattle area; 50 to 75 years of age; sedentary at baseline [<60 min/wk of moderate- or vigorous-intensity recreational activity and a maximal oxygen consumption ($V\text{O}_{2\text{max}}$) < 25.0 mL/kg/min]; with a BMI ≥25.0 kg/m^2 (or a BMI between 24.0 and 25.0 kg/m^2 if percentage body fat measured by bioelectrical impedance was >33.0%); not taking menopausal hormone therapy in any form in the past 6 months; without clinical diagnosis of diabetes and fasting blood glucose levels <140 mg/dL; without significant comorbidities; and not smoking.

We recruited women through a combination of mass mailings and media placements (30). After extensive screening (Figure 1), we randomly assigned 173 women to exercise intervention (n = 87) or control (n = 86) groups, stratified by BMI (<27.5 vs. ≥27.5 kg/m^2). The primary reasons for exclusion were current use of menopausal hormone therapy, currently exercising at a nonsedentary level, and not likely to be able to meet the study requirements (30).

Exercise Intervention

The exercise prescription consisted of at least 45 minutes of moderate-intensity exercise, 5 d/wk, for 12 months. Participants attended three supervised sessions per week at one of the two study facilities (University of Washington or a commercial gym) during months 1–3 and exercised 2 d/wk at home. For months 4–12, they attended one session per week at a study facility and exercised 4 d/wk either at home or at the facility. The training program started at 40% of observed maximal heart rate for 16 min/session and gradually increased to 60% to 75% of maximal heart rate for 45 min/session by week 8. Participants wore Polar heart rate monitors during exercise sessions and engaged primarily in treadmill and outdoor walking and stationary bicycling (27).

Women randomized to the control group attended once-weekly 45-minute stretching sessions and were asked not to otherwise change their exercise habits during the study. All participants were asked to maintain their usual diet.

We used two measures of exercise adherence. We assessed baseline and 12-month $V\text{O}_{2\text{max}}$ in all participants using a maximal-graded treadmill test, with heart rate and oxygen uptake monitored by an automated metabolic cart (Medgraphics, St. Paul, MN) (27). In addition, exercise intervention participants kept daily activity logs of all sports or recreational activities of moderate or vigorous level activities [estimated to be ≥3 metabolic equivalent (MET) level, where 1 MET is equal to the oxygen cost at rest (1 kcal/kg/h)] (31). For each exercise session, participants recorded the type of exercise, peak heart rate, rating of perceived exertion, and duration of exercise.

Study Measures

At baseline and 3 and 12 months, data were collected on demographic information, medical history, health habits, medication use, reproductive and body weight history, total energy intake, using a 120-item self-administered food frequency questionnaire (32), and frequency, duration, and intensity of physical activity, using a self-administered adaptation of the Minnesota Physical Activity Questionnaire (33). Weight, height, and waist and hip circumferences were measured.

Total body fat and percentage body fat were analyzed at baseline and 12 months using a DXA whole body scanner (QDR 1500; Hologic, Waltham, MA), and intraabdominal and subcutaneous fat were analyzed with computed tomography (CT; model CT 9800 scanner; General Electric,

[1] Nonstandard abbreviations: HOMA, homeostasis model assessment; $V\text{O}_{2\text{max}}$, maximal oxygen consumption; MET, metabolic equivalent; CT, computed tomography; CV, coefficient of variation.

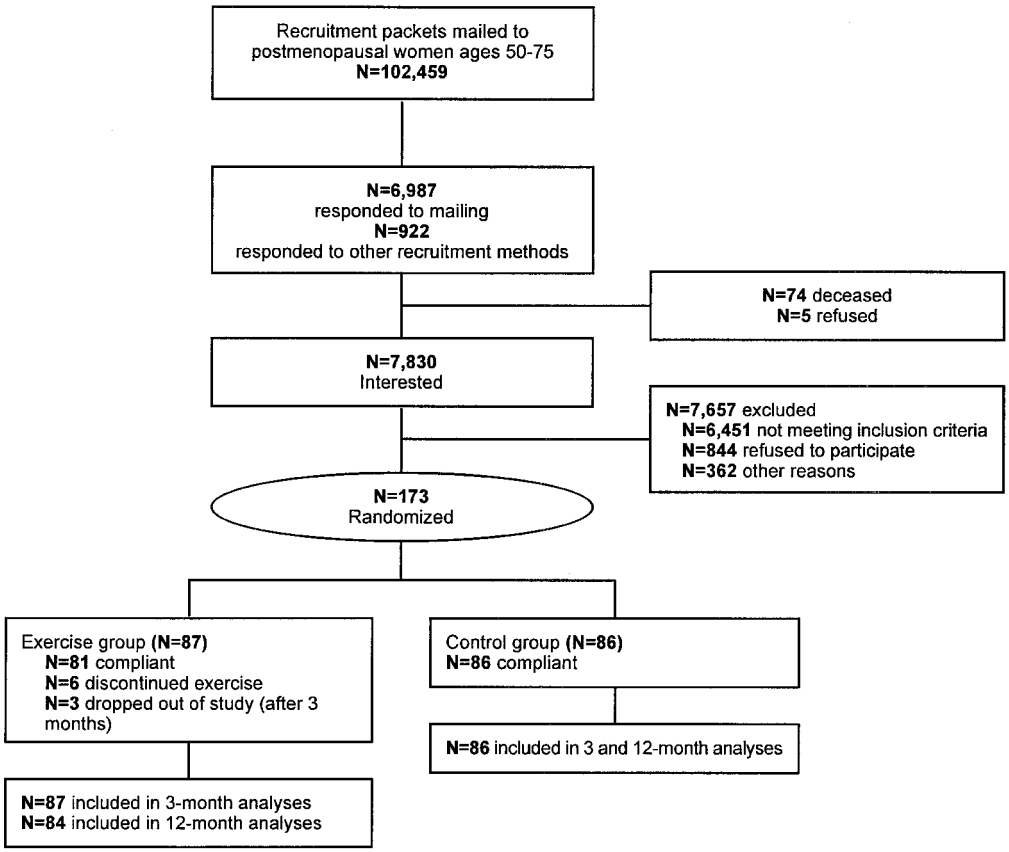

Figure 1: Flow of participants through the study.

Waukesha, WI) (34). Coefficients of variation (CVs) for repeat measurement of the CT images of subcutaneous and intraabdominal fat were 1.2% and 1.5%, respectively. At baseline and 3 and 12 months, participants provided a 12-hour fasting 50-mL sample of blood; participants were asked not to engage in exercise within 24 hours of blood draw. Blood was processed within 1 hour of collection, and serum, aliquoted into 1.8-mL tubes, was stored at –70 °C.

Serological Assays

Insulin was analyzed at the Diabetes Endocrinology Research Center Immunoassay Core Laboratory (University of Washington). Insulin was quantified by a 48-hour, polyethylene glycol-accelerated, double-antibody radioimmunoassay using primarily guinea pig anti-human insulin and secondarily goat anti-guinea pig immunoglobins. The intra- and interassay CVs were 6.5% and 9.3%, respectively.

Glucose and triglycerides were analyzed at the Northwest Lipid Research Laboratories (University of Washington). Glucose was quantified on a clinical chemistry autoanalyzer by measuring the combined catalytic activities of hexokinase and glucose-6-phosphate dehydrogenase. Spectroscopy was used to detect the solution's absorbance measured at 340/380 nm; the amount of NADH produced is directly proportional to the amount of glucose in the specimen. The intra- and interassay CVs of glucose measurements were 0.9% and 1.0%, respectively. Triglyceride concentrations in plasma were determined enzymatically on an autoanalyzer (Hitachi 917) using Boehringer Mannheim reagent. The intra- and interassay CVs of triglyceride measurements were 0.9% and 2.0%, respectively.

Leptin assays were performed at the University of Washington Harborview Medical Center using a commercially available radioimmunoassay (Linco Research, St. Charles, MO). The intra- and interassay CVs were 8.7% and 11.2%, respectively.

Samples were placed into batches such that, within each batch, all samples from a participant were included, the number of exercise and control subjects was approximately equal, the randomization dates of participants were similar, and the sample order was random. For each participant, two specimens of a quality control–pooled sample were placed in each batch, as well as a 10% random sample of repeat blood draws. Laboratory personnel were blinded to sample identity.

HOMA was used as a surrogate measure of whole body insulin sensitivity (28,35). HOMA was calculated as follows: fasting glucose (mM) $\times$ fasting insulin (μU/mL)/

22.5. This method is commonly used in clinical and population-based studies as a relative index of insulin resistance (35).

Statistical Analyses

Spearman correlations between baseline measures of body fat (including BMI, intraabdominal fat, subcutaneous fat, and percentage body fat) and concentrations of selected metabolic risk variables, insulin, leptin, glucose, triglycerides, and HOMA score, were calculated. The mean changes in levels of insulin, leptin, glucose, triglycerides, and HOMA scores from baseline to 3 and 12 months stratified by intervention group were computed. The primary analysis assessed the intervention effect based on the assigned treatment at the time of randomization, regardless of adherence or compliance status (intent-to-treat). The primary analysis considered log-transformed metabolic risk variables at baseline, 3 months, and 12 months as repeated measures, using a generalized-estimating-equation modification of linear regression models (36).

In preplanned secondary analyses, the following were examined: effect modification, or possible interactions, between the exercise effect and changes in total and intraabdominal fat mass and, among exercisers only, changes in $V\text{O}_{2\text{max}}$ and average self-reported (daily exercise logs) minutes of exercise per week. We classified participants into those who gained total fat mass or lost <0.5 kg and two equal-sized categories among those who lost ≥0.5 kg. We classified change in intraabdominal fat into two equal-sized categories among participants who gained and two equal-sized categories among those who lost intraabdominal fat. Adherence groups were based on the tertiles of average minutes of exercise per week over 12 months for self-reported exercise and on no change or gain <1%, gain of 1% to 10%, and gain of >10% for $V\text{O}_{2\text{max}}$. We also adjusted the results according to change in total caloric intake in exercisers and controls to determine whether change in energy intake could have accounted for study results. These secondary analyses were undertaken to evaluate whether specific groups of women may be more likely to benefit from the intervention and to explore possible underlying biological mechanisms.

Diagnostic thresholds for diabetes and lesser degrees of impaired glucose regulation have recently changed (37). According to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, a fasting plasma glucose concentration <100 mg/dL (<5.6 mM) is considered normal, and 100 to 125 mg/dL (5.6 to 6.9 mM) is now termed "impaired fasting glucose." A fasting blood glucose concentration ≥126 mg/dL (≥ 7.0 mM) constitutes diabetes, however, only if other confirmatory tests are positive. We analyzed our data among women with fasting blood glucose concentrations both <100 and ≥100 mg/dL to determine whether exclusion or inclusion of meeting the definition of impaired fasting glucose would affect our results.

All statistical tests were two-sided. Statistical analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC).

Results

Study Subjects

At baseline, there were no differences between the intervention and control groups in demographic characteristics, body composition, mean daily caloric intake, and fitness levels (Table 1). On average, the participants were obese, well educated, and had a low level of fitness. Less than one-third of the participants worked full-time; 86% were non-Hispanic white, 4% were African American, and 6% were Asian American.

Exercise Adherence

During the 12-month intervention, the exercise group ($N = 87$) participated in moderate-intensity sports/recreational activity on 3.7 ± 1.4 d/wk (79% of the prescribed frequency of 5 d/wk) for a total of 171 ± 88 min/wk (87% of the prescribed duration of 225 min/wk). Six (7%) exercisers "dropped out" of the exercise intervention (all after 3 months). However, three of these provided 12-month blood samples and are included in the primary analyses. Exercise adherence was significantly higher during months 1 to 3 of the intervention than during months 4 to 12 (27). Among the control group, six (7%) reported an increase of at least 225 min/wk of moderate-vigorous sports/recreational activity on the 12-month physical activity questionnaire. On average, $V\text{O}_{2\text{max}}$ increased from baseline to 12 months in exercisers by 12.7% and in controls by 0.8% ($p < 0.0001$).

Baseline Associations between Adiposity and Metabolic Risk Variables

Strong and statistically significant correlations were observed for all measures of adiposity with serum concentrations of insulin and leptin. Insulin was strongly correlated with weight, BMI, and intraabdominal fat area ($r = 0.51$, 0.44, and 0.47, respectively, all $p < 0.01$). Leptin was correlated with weight, percent body fat, and abdominal subcutaneous fat area ($r = 0.31$, 0.41, and 0.50, respectively, all $p < 0.01$). Weight, BMI, and subcutaneous abdominal fat were moderately correlated with glucose ($p < 0.05$). In addition, intraabdominal fat was statistically significantly correlated with triglyceride concentrations ($p < 0.05$).

Main Intervention Effects

Measurements of insulin, leptin, glucose, and triglycerides were obtained for all 173 women at baseline and 3

Table 1. Baseline characteristics of randomized participants ($n = 173$)

	Exercisers	Controls
N	87	86
Age (years)	60.7 ± 6.7	60.6 ± 6.8
BMI (kg/m^2)	30.4 ± 4.1	30.5 ± 3.7
Percent body fat (DXA)	47.4 ± 4.8	47.3 ± 4.6
$V\text{O}_{2\text{max}}$ (mL/kg.min)	20.0 ± 3.5	20.4 ± 3.0
Alcohol (g/day)	4.03 ± 8.4	4.62 ± 7.2
Total calories (kcal/day)	1635 ± 792.2	1722 ± 671.8
Full-time employment (%)	25 (29)	25 (29)
Education (%)		
High school graduate	10 (12)	9 (10)
Some college	36 (41)	35 (41)
College graduate	5 (6)	10 (12)
Graduate degrees	36 (41)	32 (37)
Ethnicity (%)		
Non-Hispanic white	74 (86)	75 (87)
African American	4 (5)	3 (4)
Asian/Pacific Islander	6 (7)	3 (4)
Hispanic/Latino	0 (0)	2 (2)
American Indian	0 (0)	2 (2)
Other	2 (2)	1 (1)
Family history of breast cancer		
None	59 (68)	58 (67)
First degree	14 (16)	16 (19)
Second degree	13 (15)	11 (13)
Ever used hormone replacement therapy	35 (48)	38 (52)

Values are means ± SD or *N* (%).
There were no statistically significant differences at baseline between intervention and control subjects for these variables.

months and for 170 women at 12 months. At baseline, the intervention and control groups were similar for concentrations of metabolic risk variables (Table 2).

Compared with baseline, exercisers had a 6% and 4% decline, whereas controls had a 9% and 12% increase, in insulin concentrations at 3 ($p = 0.002$) and 12 months ($p = 0.0002$), respectively (Table 2). Leptin concentrations decreased by 11% in exercisers compared with 1% in controls from baseline to 3 months ($p = 0.001$). From baseline to 12 months, exercisers decreased their leptin concentrations by 7% compared with no changes in the control group ($p = 0.03$). In addition, compared with baseline, exercisers had a 7% and 2% decline, whereas controls had a 10% and 14% increase, in HOMA scores at 3 ($p = 0.0024$) and 12 months ($p = 0.0005$), respectively. No differences were observed between exercisers and controls for changes in glucose or triglyceride concentrations at 3 or 12 months. Furthermore, the results did not differ between women with baseline fasting glucose concentrations <100 mg/dL ($n = 106$) and those with fasting glucose concentrations ≥100 mg/dL ($n = 67$; data not shown).

Modifications of Intervention Effects

The exercise effect on insulin concentrations was modified by changes in total fat mass (trend, $p = 0.03$; Table 3). This was primarily because of the exercise effect among women who gained total fat mass; in this group, exercisers had a smaller increase in insulin concentrations than controls (1% vs. 19%, respectively). Also, among exercisers, those who lost >2 kg of fat mass had a significantly larger decline in insulin over the year than those who gained fat mass ($p = 0.04$).

Glucose concentrations remained stable in both exercisers and controls who either gained or lost total fat mass (Table 3). Among women who lost >2 kg fat, exercisers ($n = 35$) had an average 4% decrease in triglyceride concentrations, whereas controls ($n = 12$) had an average 25% decrease (trend, $p = 0.05$). Furthermore, among exercisers, triglyceride concentrations were significantly different in those who lost >2 kg fat mass compared with those who gained fat mass ($p < 0.05$).

Changes in intraabdominal adiposity did not modify the exercise effect on any of the metabolic risk variables (data not shown). Changes in percentage body fat, weight, and $V\text{O}_{2\text{max}}$ also did not modify the effect of exercise on the study endpoints (data not shown).

Intervention participants who exercised for 131 to 190 min/wk had a statistically significant decrease in insulin concentrations at 12 months ($p = 0.03$) compared with women who exercised the least (≤130 min/wk; Table 4). However, >190 min/wk of exercise did not significantly lower insulin compared with the low-adherence group. Exercisers in the top two adherence groups had greater declines in leptin compared with the low-adherers ($p = 0.03$ and 0.06). There were no significant differences in glucose or triglyceride concentrations by adherence. Very similar results were observed when we classified women by change in $V\text{O}_{2\text{max}}$ rather than self-reported exercise (data not shown). Because we had $V\text{O}_{2\text{max}}$ data available for only 75 of the 87 exercisers, we chose to present only the self-reported adherence data.

Exercisers and controls did not change total caloric intake differently over the 12 months (27). When we adjusted the analysis for change in caloric intake, results did not change (data not shown).

Table 2. Concentrations of metabolic risk variables at baseline and 3 and 12 months comparing exercisers and controls

	Baseline* [mean (95% CI)]	3 months [mean (95% CI)]	ΔPercent†	*p*‡	12 months [mean (95% CI)]	ΔPercent§	*p*¶
Insulin (μU/mL)							
Exercisers**	18.4 (16.6, 20.4)	17.3 (15.6, 19.2)	−6	0.002	17.7 (16.0, 19.7)	−4	0.0002
Controls††	17.3 (15.7, 19.2)	18.9 (16.9, 21.1)	+9		19.4 (17.6, 21.4)	+12	
Leptin (ng/mL)							
Exercisers	27.3 (24.6, 30.2)	24.4 (22.0, 27.1)	0	0.001	25.3 (22.8, 28.1)	+1	0.03
Controls	26.6 (24.7, 28.6)	26.3 (23.6, 29.4)	+1		26.5 (24.0, 29.3)	+1	
Glucose (mg/dL)							
Exercisers	97.8 (81.4, 117.4)	97.4 (82.2, 115.5)	0	0.23	98.9 (81.8, 119.5)	−3	0.99
Controls	97.4 (82.5, 115.1)	98.1 (83.2, 115.5)	+3		98.4 (83.5, 115.9)	−4	
Triglycerides (mg/dL)							
Exercisers	121 (109, 134)	120 (108, 133.6)	−11	0.45	117 (105, 130)	−7	0.95
Controls	124 (112, 137)	127 (114, 142)	+4		119 (108, 131)	+5	
HOMA score‡‡							
Exercisers	4.5 (4.0, 5.0)	4.2 (3.8, 4.7)	−7	0.0024	4.4 (3.9, 5.0)	−2	0.0005
Controls	4.2 (3.8, 4.7)	4.6 (4.1, 5.2)	+10		4.8 (4.3, 5.3)	+14	

* There were no statistically significant differences between exercisers and controls for any of the metabolic risk variables at baseline.
† Percent change from baseline to 3 months.
‡ Differences in change between exercisers and controls from baseline to 3 months.
§ Percent change from baseline to 12 months.
¶ Differences in change between exercisers and controls from baseline to 12 months.
** *n*: baseline = 87, 3 months = 87, 12 months = 84.
†† *n*: baseline = 85, 3 months = 85, 12-months = 85.
‡‡ HOMA was used as a surrogate measure of whole-body insulin sensitivity. HOMA was calculated as [fasting glucose (mM) × fasting insulin (μU/mL)/22.5].

Discussion

This 12-month moderate-intensity exercise intervention program in postmenopausal, overweight/obese, sedentary women resulted in statistically significant decreases in mean insulin and leptin concentrations from baseline to 12 months. Exercisers showed greater improvements in insulin sensitivity (as estimated by HOMA scores) than controls. These results suggest that regular moderate-intensity exercise can improve metabolic disease risk profiles associated with obesity, such as high insulin and leptin concentrations. We found similar results in women meeting and not meeting criteria for impaired fasting glucose (37).

Exercise has been shown to be a viable option for the treatment of obesity (38,39). In agreement with these findings, our earlier results showed that a year-long moderate-intensity exercise intervention resulted in statistically significant ($p < 0.05$) declines in weight, BMI, percent body fat, and intraabdominal and subcutaneous abdominal fat (27). Serum insulin levels have been used as an estimate of insulin sensitivity, and a significant independent relationship between hyperinsulinemia and chronic disease risk has been reported from several large epidemiological studies (40–42). In addition, exercise has been shown to lower insulin concentrations with and without weight loss (43). Our findings in this study are in concordance with some (21,44–46) but not all (23) studies, which have found that weight loss, achieved in the context of an exercise intervention, is important for improving insulin concentrations. In contrast to our study, exercise in the absence of weight loss has also been shown to improve insulin sensitivity (47–50). Donnelly et al. (51) reported significant decreases in fasting insulin from baseline to 18 months after intermittent exercise in previously sedentary, moderately obese women (mean age, 49 ± 8 years), as well as improved insulin values under the curve from baseline to 18 months for participants randomized to either continuous or intermittent exercise. Body weight and fat decreased significantly ($p < 0.05$) for the continuous exercisers in that study across the

Table 3. Concentrations of metabolic risk variables at baseline and 12 months in exercisers and controls, stratified by changes in total fat mass

	Exercisers			Controls			
	Baseline [mean (95% CI)]	12 months [mean (95% CI)]	ΔPercent*	Baseline [mean (95% CI)]	12 months [mean (95% CI)]	ΔPercent*	*p*†
Insulin							
Gained fat mass‡	19.6 (16.0, 24.0)	19.8 (16.1, 24.3)	+1	17.1 (15.3, 19.1)	20.3 (18.0, 22.9)	+19	Ref
Lost ≤2 kg fat mass	18.3 (14.4, 23.2)	18.1 (14.4, 22.9)	−1	17.9 (14.7, 21.7)	19.9 (16.4, 24.2)	+11	0.65
Lost >2 kg fat mass	17.8 (15.6, 20.4)	15.8§ (14.0, 17.9)	−11	19.2 (14.3, 25.9)	16.9 (12.7, 22.4)	−12	0.03
Leptin							
Gained fat mass	29.9 (27.1, 33.1)	31.1 (28.2, 34.2)	+4	26.9 (20.0, 29.8)	28.3 (25.8, 31.1)	+5	Ref
Lost ≤2 kg fat mass	27.8 (25.1, 30.8)	25.1 (22.0, 28.5)	−10	26.9 (23.8, 30.5)	26.4 (23.0, 30.3)	−2	0.90
Lost >2 kg fat mass	25.7 (22.9, 28.7)	22.2 (19.5, 25.2)	−14	24.3 (19.7, 29.9)	20.4 (16.3, 25.6)	−16	0.15
Glucose							
Gained fat mass	97.0 (93.4, 100.8)	97.7 (93.7, 101.8)	+1	96.6 (94.4, 98.8)	97.6 (95.3, 99.9)	+1	Ref
Lost ≤2 kg fat mass	98.6 (94.5, 102.8)	101.1 (97.1, 105.2)	+3	98.7 (95.5, 102.0)	100.8 (98.0, 103.7)	+2	0.63
Lost >2 kg fat mass	97.4 (94.6, 100.2)	97.3 (94.8, 99.8)	0	98.1 (92.2, 104.4)	96.4 (90.74, 102.5)	−2	0.68
Triglycerides							
Gained fat mass	115 (93, 141)	117 (44, 309)	+2	116 (102, 132)	123 (107, 141)	+6	Ref
Lost ≤2 kg fat mass	123 (51, 296)	116 (42, 318)	−6	134 (111, 162)	115 (93, 143)	−14	0.22
Lost >2 kg fat mass	121 (48, 305)	116§ (48, 285)	−4	138 (111, 172)	104 (49, 252)	−25	0.05
HOMA score¶							
Gained fat mass	4.7 (3.8, 5.8)	5.0 (4.1, 6.1)	+6	4.4 (3.9, 4.9)	5.2 (4.6, 5.9)	+18	Ref
Lost ≤2 kg fat mass	4.7 (3.9, 5.9)	4.4 (3.5, 5.5)	−6	3.7 (3.1, 4.5)	4.2 (3.5, 5.1)	+11	0.81
Lost >2 kg fat mass	4.1 (3.4, 4.9)	3.7 (3.3, 4.2)	−10	5.1 (3.8, 6.9)	5.1 (4.1, 6.4)	0	0.34

* Percent change from baseline to 12 months.

† *p* value for the overall trend in the exercise-control group differences across groups of fat mass changes from baseline to 12 months.

‡ Exercise, $n = 24$, 24, and 35 and control, $n = 47$, 25, and 12, for those who gained fat mass, lost ≤2 kg fat mass, and lost >2 kg fat mass, respectively.

§ $P < 0.05$ comparing change from baseline to 12 months among exercisers who lost >2 kg fat mass vs. gained fat mass.

¶ HOMA was used as a surrogate measure of whole body insulin sensitivity. HOMA was calculated as [fasting glucose (mM) × fasting insulin (μU/mL)/22.5].

Table 4. Concentrations of metabolic risk variables at baseline and 12 months in exercisers, stratified by minutes of exercise per week

	Baseline [mean (95% CI)]	12 months [mean (95% CI)]	ΔPercent*	*p*†
Insulin				
≤130 min/wk‡	20.1 (16.7, 24.3)	21.2 (17.5, 25.7)	+5	Ref
131 to 190 min/wk	20.4 (16.9, 24.6)	18.0 (14.9, 21.8)	−12	0.03
>190 min/wk	15.6 (13.5, 18.1)	14.9 (12.8, 17.3)	−4	0.28
Leptin				
≤130 min/wk	29.3 (26.4, 32.6)	29.3 (26.9, 32.03)	0	Ref
131 to 190 min/wk	28.6 (25.2, 32.6)	25.9 (22.2, 30.3)	−9	0.03
>190 min/wk	24.6 (22.5, 26.8)	21.7 (19.1, 24.6)	−12	0.06
Glucose				
≤130 min/wk	96.9 (93.4, 100.6)	99.5 (95.3, 103.8)	+3	Ref
131 to 190 min/wk	98.9 (96.1, 101.7)	99.5 (96.3, 102.8)	+1	0.37
>190 min/wk	97.7 (94.3, 101.3)	94.8 (94.6, 101.2)	−3	0.22
Triglycerides				
≤130 min/wk	115 (96, 137)	110 (91, 135)	−4	Ref
131 to 190 min/wk	139 (102, 166)	131 (109, 158)	−6	0.73
>190 min/wk	113 (97, 131)	112 (96, 132)	−1	0.43
HOMA score§				
≤130 min/wk	4.8 (3.9, 5.9)	5.3 (4.2, 5.6)	+10	Ref
131 to 190 min/wk	5.3 (4.1, 6.2)	4.6 (3.7, 5.6)	−13	0.35
>190 min/wk	3.8 (3.2, 4.3)	3.7 (3.1, 4.3)	−3	0.48

* Percent change from baseline to 12 months.

† p value for comparing adherence groups.

‡ n = 29, 30, and 28 for an adherence of ≤130 min/wk, 131–190 min/wk, and >190 min/wk, respectively.

§ HOMA was used as a surrogate measure of whole body insulin sensitivity. HOMA was calculated as [fasting glucose (mM) × fasting insulin (μU/mL)/22.5].

18 months of exercise, but intermittent exercisers' body weight and fat decreased at 9 months and returned to baseline values at 18 months. These results suggest that insulin concentrations are affected by both intermittent and continuous exercise with or without concomitant weight loss or changes in body composition but that continuous exercise may be needed to promote changes in body composition alone.

Also consistent with the literature, our results showed that exercise resulted in reductions in leptin concentrations (52). However, several studies have shown that the impact of exercise on leptin concentrations may not be independent of exercise-induced weight loss (53). Reducing plasma leptin concentrations in postmenopausal women may be important because leptin has been shown to be related to other cardiovascular risk factors (54) and may be associated with increased risk for cancers, independently of adiposity (55–59).

There are several mechanisms by which exercise training has been shown to improve insulin sensitivity, including increasing oxidative enzymes and glucose transporters in the muscle (60). It is unclear in this study what mechanisms were at play to decrease fasting insulin, decrease fasting leptin, and improve HOMA scores in exercisers compared with controls. Further avenues of research are needed to explore such mechanisms and to determine whether changes in metabolic risk variables were caused solely by changes in body composition or by changes in molecular and intracellular actions.

With respect to effect modification, our results showed that changes in total fat mass, but not intraabdominal fat, modified the effect of exercise on insulin concentrations and marginally on triglyceride concentrations. In addition, our study showed that, among women who gained total fat mass, exercise abolished a rise in insulin concentrations. Furthermore, fat loss in both exercisers and controls resulted

in decreased leptin concentrations. Our findings are interesting because previous studies have shown that upper body obesity in women may be associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other cardiovascular risk factors (24–26,61). Furthermore, exercise may preferentially decrease visceral adiposity (62). Therefore, our findings that the exercise effect on changes in insulin and triglycerides concentrations was influenced by changes in total fat mass but not by changes in intraabdominal fat mass need further exploration.

The effect of exercise was also modified by levels of adherence. Adherence to exercise of at least 131 to 190 min/wk significantly reduced insulin and leptin concentrations compared with women who exercised ≤130 min/wk. Exercising >190 min/wk did not seem to add additional benefit. Similar results were observed when we categorized exercisers according to $V\text{O}_{2\text{max}}$. The level of adherence was reduced in months 4 to 12 compared with months 1 to 3, which may have explained the attenuation of effects of exercise on some of our endpoints. These results suggest that there is an optimal amount of exercise that may decrease cardiovascular disease risk factors.

The clinical relevance of a 5% to 10% reduction in fasting insulin and improved HOMA scores in our study population is unclear. Hyperinsulinemia has been shown to independently predict a 2-fold increase in coronary heart disease risk (46). Furthermore, the Diabetes Prevention Program reported that 30 min/d of moderate-intensity physical activity, coupled with an average 5% to 10% reduction in body weight, resulted in a 58% reduction in diabetes (63). In addition, hyperinsulinemia is associated with increased risk for several cancers, including breast and colon, independently of adiposity (64–66). Therefore, although the clinical relevance of this study may not be fully realized, it seems that exercise is a viable option for reducing fasting insulin, even among women who gain body fat, and that this may have beneficial health effects.

The strengths of this study were the randomization design, the excellent adherence and retention of the participants, the availability of diverse measures of body composition and fitness, the length of the study, and the focus on a previously understudied population of older, postmenopausal women. Furthermore, this was one of the first studies to explore interactions between the exercise effect and metabolic risk variables by changes in total vs. intraabdominal body fat. This study also had several limitations. First, we tested only one exercise intervention; thus, we cannot provide data on the effects of different types, intensities, and durations of exercise. Second, we did not test the effect of dietary change and, therefore, cannot address the overall issue of energy balance or diet composition on our study endpoints. Third, we did not perform a direct measure of insulin resistance. Although the HOMA has been reported to correlate well with the accepted "gold standard" measure of whole body insulin sensitivity, the hyperinsulinemic clamp ($r = -0.82$) (35), this calculation may be less precise, and associations with insulin sensitivity might have been distinguished if the clamp technique had been used. However, the hyperinsulinemic clamp was not feasible in a study of this size. Finally, the ultimate effects of the exercise intervention on disease incidence or mortality were not evaluated.

In summary, the results of this study show that regular, moderate-intensity exercise decreases fasting insulin and leptin concentrations in overweight/obese postmenopausal women and that the adoption of regular, moderate-intensity exercise may be particularly useful among postmenopausal women who gain fat mass over time. Finally, these findings suggest that by following the recommendations of ≥30 minutes of moderate-intensity physical activity on most, or preferably all, days of the week (67), women may achieve a more desirable metabolic profile, especially with respect to carbohydrate and lipid metabolism.

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References

1. **Mokdad A, Serdula M, Dietz W, Bowman B, Marks J, Koplan J.** The spread of the obesity epidemic in the United States, 1991–1998. *JAMA*. 1999;282:1519–22.
2. **Colditz G, Willett W, Rotnitzky A, Manson J.** Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995;122:481–6.
3. **Ohlson L, Larsson B, Svardsudd K, et al..** The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes.* 1985;34:1055–8.
4. **Hong S, Friedman J, Alt S.** Modifiable risk factors for the primary prevention of heart disease in women. *J Am Womens Assoc*. 2003;58:278–84.
5. **Rexrode K, Buring J, Manson J.** Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord*. 2001;25:1047–56.
6. **Carroll K.** Obesity as a risk factor for certain types of cancer. *Lipids*. 1998;33:1055–9.
7. **Giovannucci E, Colditz G, Stampfer M, Willett W.** Physical activity, obesity, and risk of colorectal adenoma in women (United States). *Cancer Causes Control*. 1996;7:253–63.
8. **Morimoto L, White E, Chen Z, et al.** Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control.* 2002;13:741–51.

9. **Weyer C, Hanson R, Tataranni A, Bogardus C, Pratley R.** A high fasting plasma insulin concentration predicts type 2 diabetes independent of insulin resistance. Evidence for a pathogenic role of relative hyperinsulinemia. *Diabetes*. 2000; 49:2094–101.
10. **Kekäläinen P, Sarlund H, Pyörälä K, Laakso M.** Hyperinsulinemia cluster predicts the development of type 2 diabetes independently of family history of diabetes. *Diabetes Care*. 1999;22:86–92.
11. **McCance D, Pettit D, Hanson R, Jacobsson L, Bennett P, Knowler W.** Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. *Diabetologia*. 1994;37:617–23.
12. **Hardiman P, Pillay O, Atiomo W.** Polycystic ovary syndrome and endometrial carcinoma. *Lancet*. 2003;361:1810–2.
13. **Furberg A, Thune I.** Metabolic abnormalities (hypertension, hyperglycemia, and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. *Int J Cancer*. 2003;104:669–76.
14. **Marugame T, Lee K, Eguchi H, Oda T, Shinchi K, Kono S.** Relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. *Cancer Causes Control*. 2002;13:917–21.
15. **Balkau B, Eschwege E.** Insulin resistance: an independent risk factor for cardiovascular disease? *Diabetes Obes Metab.* 1999;Suppl 1:S23–31.
16. **Haffner S.** Impaired glucose tolerance, insulin resistance and cardiovascular disease. *Diabet Med*. 1997;14(Suppl 3):S12–8.
17. **Leyva F, Godsland I, Ghatei M, et al.** Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. *Arterioscler Thromb Vasc Biol.* 1998;18:928–33.
18. **Ford E, Giles W, Dietz W.** Prevalence of metabolic syndrome among US adults. *JAMA*. 2002;287:356–9.
19. **Zimmet P, Boyko E, Collier G, deCourten M.** Etiology of the metabolic syndrome: potential role of insulin resistance, leptin resistance, and other players. *Ann N Y Acad Sci*. 1999; 892:25–44.
20. **Ready A, Drinkwater D, Ducas J, Fitzpatrick D, Brereton D, Oades S.** Walking program reduces elevated cholesterol in women postmenopause. *Can J Cardiol*. 1995;11:905–10.
21. **Ready A, Naimark B, Ducas J, et al.** Influence of walking volume on health benefits in women post-menopause. *Med Sci Sports Exerc.* 1996;28:1097–105.
22. **Asikainen T, Miilunpalo S, Oja P, Rinne M, Pasanen M, Vuori I.** Walking trials in postmenopausal women: effect of one vs. two bouts on aerobic fitness. *Scand J Med Sci in Sports*. 2002;12:99–105.
23. **Asikainen T, Miilunpalo S, Kukkonen-Harjula K, et al.** Walking trials in postmenopausal women: effect of low doses of exercise and exercise fractionization on coronary risk factors. *Scand J Med Sci Sports.* 2003;13:284–92.
24. **Rendell M, Hulthen U, Tornquist C, Groop L, Mattiasson L.** Relationship between abdominal fat compartments and glucose and lipid metabolism in early postmenopausal women. *J Clin Endocrinol Metab*. 2001;86:744–9.
25. **Ozbey N, Sencer E, Molvalilar S, Orhan Y.** Body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women with similar BMI. *Endocr J*. 2002;49:503–9.
26. **Hernandez-Ono A, Monter-Carreola G, Zamora-Gonzalez J, et al.** Association of visceral fat with coronary risk factors in a population-based sample of postmenopausal women. *Int J Obes Relat Metab Disord.* 2002;26:33–9.
27. **Irwin M, Yasui Y, Ulrich C, et al.** Effect of exercise on total and intraabdominal body fat in postmenopausal women. A randomized clinical trial. *JAMA*. 2003;289:323–30.
28. **Matthews D, Hosker J, Rudenske A, Naylor B, Treacher D, Turner R.** Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–9.
29. **McTiernan A, Ulrich C, Yancey D, et al.** The physical activity for total health (PATH) study: rationale and design. *Med Sci Sports Exerc.* 1999;31:1307–12.
30. **Tworoger S, Yasui Y, Ulrich C, et al.** Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers. *Cancer Epidemiol Biomarkers Prev.* 2002;11:73–7.
31. **Ainsworth B, Haskell W, Whitt M, et al.** Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32:S498–516.
32. **Patterson R, Kristal A, Tinker L, Carter R, Bolton M, Agurs-Collins T.** Measurement characteristics of the Women's Health Intiative food frequency questionnaire. *Ann Epidemiol.* 1999;9:178–87.
33. **Taylor H, Jacobs D, Schucker B, Knudsen J, Leon A, Debacker G.** A questionnaire for the assessment of leisure-time physical activities. *J Chronic Dis*. 1987;31:741–55.
34. **Shuman W, Morris L, Leonetti D, et al.** Abnormal body fat distribution detected by computed tomography in diabetic males. *Invest Radiol.* 1986;21:483–7.
35. **Bonora E, Targher G, Alberiche M, et al.** Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care.* 2000;23:57–63.
36. **Zeger S, Liang K.** Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–30.
37. **Genuth S, Alberti K, Bennett P, et al.** Follow-up report on the diagnosis of diabetes mellitus: the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes.* 2003;26:3160–7.
38. **Poirier P, Despres J.** Exercise in weight management of obesity. *Cardiol Clin*. 2001;19:459–70.
39. **Zachwieja J.** Exercise as treatment for obesity. *Endocrinol Metab Clin North Am*. 1996;25:965–88.
40. **Fontbonne A, Charles M, Thibult N, et al.** Hyperinsulinaemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-year follow-up. *Diabetologia.* 1991;34:356–61.
41. **Zimmet P, Collins V, Dowse G, et al.** Is hyperinsulinaemia a central characteristic of a chronic cardiovascular risk factor clustering syndrome? Mixed findings in Asian Indian, Creole and Chinese Mauritians. Mauritius Noncommunicable Disease Study Group. *Diabet Med.* 1994;11:388–96.
42. **Pyorala M, Miettinen H, Laakso M, Pyorala K.** Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. *Diabetes Care*. 2000;23:1097–102.

43. **Kelley D, Goodpastor B.** Effects of physical activity on insulin action and glucose tolerance in obesity. *Med Sci Sports Exerc*. 1999;31:S619–23.
44. **Goodpastor B, Kelley D, Wing R, Meier A, Thaete F.** Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes*. 1999;48:839–47.
45. **Tremblay A, Nadeau A, Despres J, St-Jean L, Theriault G, Bouchard C.** Long-term exercise training with constant energy intake. 2: Effect on glucose metabolism and resting energy expenditure. *Int J Obes Relat Metab Disord.* 1990;14:75–84.
46. **Watkins L, Sherwood S, Feinglos M, et al.** Effects of exercise and weight loss on cardiac risk factors associated with Syndrome X. *Arch Intern Med.* 2003;163:1889–95.
47. **Duncan G, Perri M, Theriaque D, Hutson A, Eckel R, Stacpoole P.** Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*. 2003;26:557–62.
48. **Lamarche B, Despres J, Pouliot M, et al.** Is body fat a determinant factor in the improvement of carbohydrate and lipid metabolism following aerobic exercise training in obese women? *Metabolism.* 1992;41:1249–56.
49. **Oshida Y, Yamanouchi K, Hayamizu S, Sato Y.** Long-term mild jogging increases insulin action despite no influence on body mass index or VO_2 max. *J Appl Physiol*. 1989;66:2206–10.
50. **Boulé N, Haddad E, Kenny G, Wells G, Sigal R.** Effects of exercise on glycemic control and body mass index in type 2 diabetes mellitus. A meta-analysis of controlled clinical trials. *JAMA*. 2001;286:1218–27.
51. **Donnelly J, Jacobsen D, Heelan KS, Seip R, Smith S.** The effects of 18 months of intermittent vs. continuous exercise on aerobic capacity, body weight and composition, and metabolic fitness in previously sedentary, moderately obese females. *Int J Obes Relat Metab Disord*. 2000;24:566–72.
52. **Koutsari C, Karpe F, Humphreys S, Frayn K, Hardman A.** Plasma leptin is influenced by diet composition and exercise. *Int J Obes Relat Metab Disord*. 2003;27:901–6.
53. **Kraemer R, Chu H, Castracane V.** Leptin and exercise. *Exp Biol Med (Maywood)*. 2002;227:701–8.
54. **Os I, Os A, Abdelnoor M, Larsen A, Birkeland K, Westheim A.** Plasma leptin in postmenopausal women with coronary artery disease: effect of transdermal 17beta-estradiol and intermittent medroxyprogesterone acetate. *Climacteric*. 2003;6:204–10.
55. **Ishikawa M, Kitayama J, Nagawa H.** Enhanced expression of leptin and leptin receptor (ob-R) in human breast cancer. *Clin Cancer Res*. 2004;10:4325–31.
56. **Yin N, Wang D, Zhang H, et al.** Molecular mechanisms involved in growth stimulation of breast cancer by leptin. *Cancer Res.* 2004;64:5870–5.
57. **Stattin P, Palmquist R, Soderberg S, et al.** Plasma leptin and colorectal cancer risk: a prospective study in Northern Sweden. *Oncol Rep.* 2003;10:2015–21.
58. **Hu X, Juneja S, Maihle N, Cleary M.** Leptin-A growth factor in normal and malignant breast cells and for normal mammary gland development. *J Natl Cancer Inst*. 2002;94:1704–11.
59. **Okumura M, Yamamoto M, Sakuma H, et al.** Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression. *Biochim Biophys Acta.* 2002;1592:107–16.
60. **Goodyear L, Kahn B.** Exercise, glucose transport, and insulin sensitivity. *Ann Rev Med*. 1998;49:235–61.
61. **Kissebah A, Vydelingum N, Murray R, et al.** Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab.* 1982;54:254–60.
62. **National Heart, Lung, and Blood Institute in cooperation with The National Institute of Diabetes and Digestive and Kidney Diseases.** *Clinical Guidelines on the Identification, and Treatment of Overweight and Obesity in Adults. The Evidence Report.* Bethesda, MD: National Institutes of Health; 1998.
63. **Knowler WC, Barrett-Connor E, Fowler SE, et al.** Reduction in the incidence of type 2 diabetes with lifestyle interventions or metformin. *N Engl J Med.* 2002;346:393–403.
64. **DelGuidice M, Fantus I, Ezzat S, McKeown-Eyssen G, Page D, Goodwin P.** Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res Treat*. 1998;47:111–20.
65. **Bruning P, Bonfer J, vanNoord P, Hart A, DeJong-Bakker M, Nooijen W.** Insulin resistance and breast-cancer risk. *Int J Cancer*. 1992;52:511–6.
66. **Giovannucci E, Ascherio A, Rimm E, Colditz G, Stampfer M, Willett W.** Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med*. 1995;122:327–34.
67. **Pate R, Pratt M, Blair S, et al.** Physical activity and public health: a recommendation from the Centers of Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402–7.