Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial\(^{1-3}\)

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**ABSTRACT**

**Background:** Weight loss, through calorie restriction or increases in energy expenditure via exercise, improves glucose tolerance and insulin action. However, exercise-induced energy expenditure may further improve glucoregulation through mechanisms independent of weight loss.

**Objective:** The objective was to assess the hypothesis that weight loss through exercise-induced energy expenditure improves glucoregulation and circulating factors involved in insulin action to a greater extent than does similar weight loss through calorie restriction.

**Design:** Sedentary men and women aged 50–60 y with a body mass index (kg/m\(^2\)) of 23.5–29.9 were randomly assigned to 1 of 2 weight-loss interventions [12 mo of exercise training (EX group; \(n = 18\)) or calorie restriction (CR group; \(n = 18\))] or to a healthy lifestyle (HL) control group (\(n = 10\)). The insulin sensitivity index and areas under the curve for glucose and insulin were assessed with an oral-glucose-tolerance test. Adiponectin and tumor necrosis factor \(\alpha\) concentrations were measured in fasting serum. Fat mass was measured by dual-energy X-ray absorptiometry.

**Results:** Yearlong energy deficits were not significantly different between the EX and CR groups, as evidenced by body weight and fat mass changes. The insulin sensitivity index increased and the glucose and insulin areas under the curve decreased in the EX and CR groups, remained unchanged in the HL group, and did not differ significantly between the EX and CR groups. Marginally significant increases in adiponectin and decreases in the ratio of tumor necrosis factor \(\alpha\) to adiponectin occurred in the EX and CR groups but not in the HL group.

**Conclusions:** Weight loss induced by exercise training or calorie restriction improves glucose tolerance and insulin action in nonobese, healthy, middle-aged men and women. However, it does not appear that exercise training–induced weight loss results in greater improvements than those that result from calorie restriction alone. *Am J Clin Nutr* 2006;84:1033–42.

**KEY WORDS** Aging, calorie restriction, exercise training, glucose tolerance, weight loss, overweight humans

**INTRODUCTION**

Reductions in body weight and abdominal fat, induced by calorie restriction or by increasing exercise expenditure, improve insulin action and glucose tolerance (1), which are often impaired in overweight and obese persons (2, 3). In addition to weight loss induced by an energy deficit, exercise induces increases in muscle insulin sensitivity and responsiveness that are independent of weight loss (4). Previous studies have compared the effects of exercise training with those of calorie restriction on weight loss; however, exercise training in these studies was accompanied by an increase in energy intake such that little or no weight loss occurred (5–7). Although these studies provide information about the weight-loss–independent benefits of exercise training, they may underestimate the beneficial effects of exercise training because exercise training in the absence of changes in energy intake results in weight loss (8, 9). The purpose of the present study was to test the hypothesis that exercise training–induced weight loss results in greater improvements in glucose tolerance and insulin action than does similar weight loss induced by calorie restriction. We also assessed changes in circulating glucoregulatory factors [ie, adiponectin, tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), cortisol, and free fatty acids (FFAs)] that might contribute to changes in insulin action to gain preliminary insights regarding the mechanisms for improvements in glucoregulation induced by exercise training or calorie restriction. The data reported in this article were obtained as part of an investigation (CALERIE—Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) of the feasibility of long-term calorie restriction on potential markers of aging and risk factors for age-related diseases.

**SUBJECTS AND METHODS**

**Participants**

Men and women aged 50–60 y with a body mass index (BMI; in kg/m\(^2\)) of 23.5–29.9 were recruited from the St Louis metropolitan area. After screening and before baseline testing, the...
participants were randomly assigned (stratified by sex) to 1 of 2 weight-loss interventions [12 mo of exercise energy expenditure (EX group; \(n = 18\)) or calorie restriction (CR group; \(n = 18\)) or to a healthy lifestyle (HL) control group \((n = 10)\). Although the selection criterion included the high end of the range for normal BMI, only 9 enrolled subjects (5 in the EX group and 4 in the CR group) had a BMI \(< 25.0\). Candidates for the study were excluded if they had a history of diabetes or a fasting blood glucose value \(\geq 126 \text{ mg/dL}\); a history or clinical evidence of coronary artery disease, stroke, or lung disease; a resting blood pressure \(\geq 170 \text{ mm Hg (systolic)} \times 100 \text{ mm Hg (diastolic)}\); or a recent history or evidence of malignancy. Furthermore, all candidates had to be nonsmokers, had to be sedentary (defined as exercising \(< 20 \text{ min/d, twice per week, during the 6 mo before baseline testing}\), and had to not be taking medications that could affect study outcomes. The women had to be postmenopausal. All participants gave their informed written consent to participate in the study, which was approved by the Human Studies Committee and the General Clinical Research Center Advisory Committee at the Washington University School of Medicine.

**Calorie restriction intervention**

The objective of the calorie restriction intervention was to decrease calorie intake by 16% during the first 3 mo and by 20% during the remaining 9 mo. The initial calorie intake was assumed to be equal to total daily energy expenditure (TEE) as determined by the doubly labeled water (DLW) method over 2 consecutive 2-wk assessment periods. Calorie intake prescriptions were calculated as baseline TEE minus the desired magnitude of calorie restriction (ie, 16% or 20% of TEE). The participants met with the study dietitians weekly, at which time body weight was measured and consultation was provided to maximize compliance with the prescribed calorie restriction. The participants frequently recorded their food consumption. The dietitians used these records, qualitatively, as a basis for personalized dietary changes that would help the participants achieve the prescribed calorie restriction. The general strategy was to encourage reductions in portion size and to substitute foods with a low calorie density with those with a high calorie density.

**Exercise training intervention**

The goal of the exercise training intervention was to induce the same calorie deficit as was induced by the calorie restriction intervention by holding energy intake constant at baseline levels and increasing exercise energy expenditure by 16% of baseline TEE for the first 3 mo and by 20% for the subsequent 9 mo. Exercise energy expenditure goals were given to the participants during weekly meetings with exercise trainers. The participants exercised, either in our facility or on their own, while using wrist watch–type heart rate (HR) monitors (S610; Polar Electro Oy, Kempele, Finland) that stored exercise-specific data for gross energy expenditure, HR, exercise duration, and the number of exercise sessions performed. Maximal oxygen uptake \((V_\text{O}_2\text{max})\), maximal HR, and body weight, which the monitors use to estimate gross energy expenditure, were measured and updated every 3 mo. Because the study goals were based on net exercise energy expenditure, whereas the Polar HR monitors quantified gross energy expenditure, the number of calories that would have been expended during the exercise time, if the participant did not exercise, was added to the net exercise energy expenditure goal, according to the following formula, to give the prescribed gross exercise energy expenditure goal:

\[
\text{Prescribed gross exercise energy expenditure (kcal/wk)} = (\text{TEE}_{\text{week}} \times G) + (t \times \text{TEE}_{\text{min}}) \tag{1}
\]

where \(\text{TEE}_{\text{week}}\) and \(\text{TEE}_{\text{min}}\) are baseline DLW-based estimates of TEE in kcal/wk and kcal/min, respectively; \(G\) is the goal for the increase in energy expenditure expressed as a decimal (ie, 0.16 or 0.20); and \(t\) is the estimated time (in min/wk) required for the participant to achieve the weekly gross exercise energy expenditure goal. For the first week of the intervention, \(t\) was fixed at 630 min (equivalent to 90 min/d). Thereafter, \(t\) was estimated as the amount of time that would have been required during the previous week to exactly meet the exercise energy expenditure prescription if all of the exercise was performed at the measured average rate of gross exercise energy expenditure [where average rate of gross exercise energy expenditure = gross calorie expenditure (kcal/wk) \div exercise duration (min/wk)]. For post hoc reporting, average net exercise energy expenditure (kcal/d) was calculated as the average gross exercise energy expenditure minus the product of the baseline TEE (kcal/min) and the average duration of exercise (min/d).

Our exercise technician trainers stayed in close contact with the participants, providing advice, encouragement, and weekly exercise prescription updates. The participants were weighed, and data from their HR monitors were downloaded weekly. They were also questioned about any exercise sessions that were performed but not recorded on the HR monitors and were asked to rank order the times spent performing various exercise modes (ie, walking and cycling) during the preceding week.

**Healthy lifestyle intervention**

Participants in the HL group did not receive instructions to change either exercise or diet behaviors. These participants were offered advice for eating a healthy diet, but only if they requested it. Furthermore, all HL group participants were provided with passes to offsite yoga classes to use as they desired. Although the frequencies of dietary consultations and yoga class attendance were not documented, both were minimal.

**Oral-glucose-tolerance test and fasting blood collection**

Two-hour, 75-g oral-glucose-tolerance tests (OGTTs) were performed at baseline and at the end of the intervention as described previously (10). All OGTTs began between 0700 and 0900. The participants in the EX, CR, and HL groups were instructed to refrain from exercise for \(\geq 48 \text{ h before the baseline and final OGTTs}\). Plasma glucose was measured with the glucose oxidase method (YSI Stat Plus; YSI, Yellow Springs, OH) and insulin with a double-antibody radioimmunoassay (11). Total areas under the curve (AUCs) were calculated for the OGTT plasma glucose and insulin responses using the trapezoidal rule (12). An insulin sensitivity index (ISI) was calculated according to the method of Matsuda and DeFronzo (13). Serum from fasting blood samples was assessed for concentrations of FFA (NEFA C; Wako Chemicals USA, Richmond, VA), adiponectin (B-Bridge International, Sunnyvale, CA), TNF-\(\alpha\), (Quantakine High Sensitive, R&D Systems, Minneapolis, MN), and cortisol (Cortisol RIA DSL-2100; Diagnostic Systems Laboratories Inc, Webster, TX).
Body weight and composition

Body weight and composition were measured at baseline and at 1, 3, 6, 9, and 12 mo. Body weight was measured in duplicate in the morning, after the subjects fasted overnight, while the participants were wearing only underwear and a hospital gown. Body weight at each time point was calculated as the mean of multiple (up to 5 for baseline and up to 3 for each follow-up) weekly weights. Fat mass, fat-free mass, and percentage body fat were measured by dual-energy X-ray absorptiometry (DXA) with a Delphi W (software version 11.2; Hologic Corporation, Waltham MA). DXA was also used to quantify truncal and abdominal fat mass. The trunk was defined as the region above the iliac crests and below the inferior aspect of the mandible after exclusion of the upper extremities. The abdomen was defined as the region between the 12th thoracic vertebra and the inferior end of the sacroiliac joint. Body-composition data for each subject at each time point were calculated as the mean of up to 3 assessments at baseline and of 1 to 2 assessments at the follow-up time points, except for abdominal fat mass, the data for which were based on single assessments at each time point and were only available for baseline and 12 mo.

Energy intake

Energy intake was quantified at baseline and at 1, 3, 6, 9, and 12 mo with DLW, DXA, and 7-d food records. Each DLW-based assessment of TEE was 2 wk in duration and was performed by the method of Schoeller et al (14, 15). Duplicate TEE assessments were made at baseline, and single assessments were made at all time points thereafter. Baseline energy intake was assumed to equal TEE because body weight was stable. For the follow-up assessments, average energy intake for each 3-mo segment of the intervention was calculated as the average of the TEE measurements made during the 3-mo segment, with adjustments for change in total-body energy stores as determined by using DXA-based measures of body composition during the same 3-mo interval. For the estimation of changes in total-body energy stores, fat and fat free mass were assumed to contain 9.3 and 1.1 kcal/g, respectively. Energy intake was also determined by using food diaries, which were analyzed for energy intake by using Nutrition Data System for Research nutrition analysis software (versions 4.05, 4.06, and 5.0; Nutrition Coordination Center, University of Minnesota, Minneapolis, MN).

Aerobic capacity

VO_{2}\text{max} was determined at baseline and at 12 mo by indirect calorimetry during an incremental treadmill exercise test to exhaustion as described elsewhere (16).

Physical activity levels

A modified version of the Stanford 7-d Physical Activity Recall Questionnaire (PAR) (17, 18) was administered at baseline and at 3, 6, 9, and 12 mo. Physical activities were classified as light, moderate, hard, or very hard based on provided examples of activities, and these categories were assumed to require 1.5, 4.0, 6.0, and 10.0 resting metabolic equivalents (METs), respectively. Because PAR data are provided in the present study as an index of absolute physical activity levels (ie, time-weighted averages of light, moderate, hard, and very hard activities), the data are presented as MET-h/d. We chose to not present the data in terms of the calorie cost of the activities because the calorie cost of physical activity decreases with weight loss, even if habitual activities remain constant.

Statistical analyses

All analyses were performed with the inclusion of all subjects who provided follow-up OGTT data. Baseline characteristics were compared between groups by using chi-square tests for sex, Fisher’s exact test for race, and analysis of variance (ANOVA) for all quantitative variables with subsequent Tukey’s tests for post hoc comparisons. For outcomes in which only baseline and final data were available, paired t tests or Wilcoxon’s signed-rank tests were used to assess within-group changes, and analysis of covariance (ANCOVA) was used for the comparison of final values between groups after adjustment for the initial values. Post hoc comparisons between groups were performed by using Tukey’s tests. For outcomes in which data were available from ≥5 time points, the analyses were performed with mixed-model repeated-measures ANOVA. When interactions between group and time point were significant, contrasts assessing the equality of changes from baseline to 1 y were examined by using Tukey’s tests. Associations between changes in selected variables were assessed by using Pearson’s correlations from which the effects of initial ISI values were parsed out. Fisher’s z transformation was used to compare partial correlation coefficients. The analyses were performed by using SAS software (version 9.1.3 of the SAS System for Linux; SAS Institute Inc, Cary, NC). All statistical tests were two-tailed, and significance was accepted at $P \leq 0.05$. Data are presented as arithmetic means ± SDs unless noted otherwise.

RESULTS

Participants

Sample sizes for recruitment and for each stage and arm of the study are diagramed in Figure 1. Of the 48 participants who started the study, 2 dropped out before the follow-up OGTT and were therefore not included in the analyses for the present report. Sex and racial group representations were not different in the EX, CR, and HL groups: 67%, 61%, and 60% female, respectively ($P = 0.92$) and 89%, 94%, and 70% white, respectively ($P = 0.32$). Participants in the EX group were slightly older than those in the CR ($P = 0.0006$) and HL ($P = 0.02$) groups (59 ± 3, 55 ± 3, and 56 ± 3 y, respectively). Inclusion of age as a covariate in the outcome analyses did not affect the study findings (data not shown); therefore, age was not included as a covariate in the reported data.

Physical activity levels

Physical activity, as assessed with the 7-d PAR, increased from baseline during the intervention in the EX group and remained unchanged in the CR and HL groups (Figure 2). The interaction between group and time for physical activity levels was significant ($P = 0.0497$) after baseline physical activity levels were accounted for.

Exercise training volume and mode

According to HR monitor data, net exercise energy expenditure for participants in the EX group averaged 228 ± 131 kcal/d over the 12-mo intervention, and this was accomplished in 5.8 ± 2.5 exercise sessions per week at an average exercise duration of 62 ± 18 min per session. These estimates of exercise quantity are...
conservative because the participants did not record 13.5 ± 16.8% of the exercise sessions on the HR monitors according to the weekly questionnaires. Exercise intensity was 71 ± 9% of maximal HR measured during the most recent \( \dot{V}O_2 \text{max} \) test. Walking, elliptical machine exercise, cycling, and running were the most common exercises performed.

**Aerobic capacity**

Baseline \( \dot{V}O_2 \text{max} \) did not differ significantly between the EX, CR, and HL groups, whether expressed in absolute terms or relative to body weight (Table 1). \( \dot{V}O_2 \text{max} \) increased from baseline to 12 mo in the EX group, whether expressed in absolute or relative terms (Table 1). \( \dot{V}O_2 \text{max} \) decreased from baseline to 12 mo in the CR group; however, this reduction was more than fully offset by the reduction in body weight such that relative \( \dot{V}O_2 \text{max} \) increased by the end of the intervention (Table 1). Neither absolute nor relative \( \dot{V}O_2 \text{max} \) changed from baseline to 12 mo in the HL group (Table 1).

**Energy intake**

According to DLW-based estimates, energy intake during the intervention in the EX and HL groups was not significantly different from baseline (Figure 2). Energy intake in the CR group was significantly lower than baseline during months 0–9. During the last 3 mo of the study, energy intake in the CR group was not significantly different from baseline (\( P = 0.10 \)). The interaction between group and time for the DLW-based estimates of energy intake was significant (\( P = 0.01 \)) after baseline energy intake was accounted for.

According to the 7-d food records, calorie intake in the EX and HL groups was not significantly different from baseline during the intervention. Energy intake in the CR group was lower than baseline at all time points during the intervention (Figure 2). The interaction between group and time for the food record–based estimates of energy intake was significant (\( P = 0.003 \)) after baseline energy intake was accounted for.

**Body weight and composition**

Total body weight, BMI, total fat mass, truncal fat mass, and abdominal fat mass all decreased in the EX and CR groups but remained unchanged in the HL group (Table 2). As a result, the final values for weight and all of the body-composition measures were lower in the EX and CR groups than in the HL group after adjustment for baseline values. Body weight did not change

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**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline ( \dot{V}O_2 \text{max} ) (L/min/m²)</th>
<th>Intervention (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EX</td>
<td>3.5 ± 0.5</td>
<td>4.2 ± 0.6</td>
</tr>
<tr>
<td>CR</td>
<td>3.0 ± 0.4</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>HL</td>
<td>2.8 ± 0.3</td>
<td>2.8 ± 0.3</td>
</tr>
</tbody>
</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>EX</td>
<td>72 kg</td>
<td>68 kg</td>
</tr>
<tr>
<td>CR</td>
<td>75 kg</td>
<td>72 kg</td>
</tr>
<tr>
<td>HL</td>
<td>78 kg</td>
<td>78 kg</td>
</tr>
</tbody>
</table>

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**FIGURE 1.** Consort diagram indicating sample sizes at each stage and in each arm of the study.
during the 3 wk before the final OGTT in either the EX group (3 wk before the OGTT: 70.4 ± 9.6 kg; day of the OGTT: 69.8 ± 9.0 kg) or the CR group (3 wk before the OGTT: 70.7 ± 11.0 kg; day of the OGTT: 70.8 ± 11.0 kg).

Body weight, total fat mass, energy intake, aerobic capacity, and physical activity data are included as indicators of compli-

ance and to help in the interpretation of results for the primary outcomes. These outcomes were also published elsewhere (19).

**Insulin action and OGTT insulin concentrations**

ISI increased in the exercise and CR groups but not in the HL group. As a result, and after adjustment for baseline values, ISI was greater in the EX and CR groups than in the HL group at the end of the intervention (Table 3). The final adjusted ISI means were not different between the exercise and CR groups. Like-

wise, fasting insulin and insulin AUC decreased in the EX and CR groups but not in the HL group, such that the final adjusted values were significantly lower in the EX and CR groups than in the HL group. Because of baseline differences in ISI, we evaluated the OGTT insulin data after adjusting for baseline ISI; however, this did not change the statistical significance of the find-

ings for OGTT insulin.

**Oral glucose tolerance**

Although fasting glucose decreased in the CR group but not in the EX or HL group, the final fasting glucose values were not significantly different between the groups after adjustment for baseline values (Table 3), and these results were unaffected after baseline ISI was included as a covariate. Final glucose AUC values were not significantly different between study groups after adjustment for baseline values. However, after baseline ISI was added as a covariate, the P value of 0.11 for glucose AUC (Table 3) became significant (P = 0.03) and there were significant differences between both intervention groups and the control group.

**Adiponectin, TNF-α, cortisol, and FFA**

Serum adiponectin concentration tended to increase in the exercise (P = 0.06) and the CR (P = 0.07) groups and decreased significantly in the HL group (P = 0.05) (Table 4). At the end of the intervention, adiponectin concentrations were higher in the EX and CR groups than in the HL group but were not significantly different between the EX and CR groups. Final adjusted serum TNF-α concentrations were not significantly different between study groups. The ratio of TNF-α to adiponectin tended to decrease in the EX group (P = 0.06), decreased significantly in the CR group, but remained unchanged in the HL group. As a result, the final adjusted ratios of TNF-α to adiponectin were significantly lower in the EX and CR groups than in the HL group. Final ratios of TNF-α to adiponectin were not significantly different between the EX and CR groups. Final serum cortisol concentrations, after adjustment for baseline values, did not differ significantly between the 3 study groups. Serum FFAs did not change significantly in any of the study groups, and the final adjusted values were not significantly different between groups. None of the statistical results for the outcomes reported in Table 4 were affected by the inclusion of baseline ISI as a covariate.

To gain insight into the mechanism of improvements in ISI that resulted from exercise and calorie restriction, the correlations between changes in ISI, after accounting for the effects of baseline ISI, and the changes in adiponectin, TNF-α, and the ratio of TNF-α to adiponectin, were assessed. No significant difference (P = 0.37) was evident between the EX and CR groups with respect to the correlations between change in adiponectin and the...
change in ISI (EX group: \( r = 0.47 \); CR group: \( r = 0.17 \)). Likewise, the correlations for change in TNF-\( \alpha \) and change in ISI were not significantly different \((P = 0.06)\) between groups (EX group: \( r = -0.34 \); CR group: \( r = 0.33 \)). In contrast, the correlation between the change in the ratio of TNF-\( \alpha \) to adiponectin and the change in ISI was stronger in the EX group \( (r = -0.67,\)

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>EX ((n = 18))</th>
<th>CR ((n = 18))</th>
<th>HL ((n = 10))</th>
<th>( P^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
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<td>0.0003</td>
</tr>
<tr>
<td>Baseline</td>
<td>67.6 \pm 10.5^6</td>
<td>78.9 \pm 9.4</td>
<td>81.9 \pm 11.3</td>
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</tr>
<tr>
<td>Final</td>
<td>69.9 \pm 8.9^6</td>
<td>70.6 \pm 11.1^6</td>
<td>80.7 \pm 12.3</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-6.6 \pm 5.5^5</td>
<td>-8.2 \pm 4.8^5</td>
<td>-12.2 \pm 2.1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
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<td>0.0002</td>
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<tr>
<td>Baseline</td>
<td>27.1 \pm 1.9</td>
<td>27.1 \pm 2.5</td>
<td>27.9 \pm 1.3</td>
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<tr>
<td>Final</td>
<td>24.8 \pm 2.6^4</td>
<td>24.2 \pm 2.8^4</td>
<td>27.4 \pm 1.8</td>
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</tr>
<tr>
<td>Change</td>
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<td>-2.9 \pm 1.7^5</td>
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<tr>
<td>Total fat mass (kg)</td>
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<td>0.0009</td>
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<tr>
<td>Baseline</td>
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<td>26.4 \pm 5.4</td>
<td>26.5 \pm 3.3</td>
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<tr>
<td>Final</td>
<td>20.1 \pm 7.6^4</td>
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<tr>
<td>Change</td>
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<td>-6.3 \pm 3.8^5</td>
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<td>Trunk fat mass (kg)</td>
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<td>Baseline</td>
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<tr>
<td>Final</td>
<td>9.7 \pm 4.0^4</td>
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<tr>
<td>Change</td>
<td>-3.3 \pm 3.1^3</td>
<td>-3.5 \pm 2.2^3</td>
<td>-0.2 \pm 0.9</td>
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<tr>
<td>Abdominal fat mass (kg)</td>
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<td>0.009</td>
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<tr>
<td>Baseline</td>
<td>7.9 \pm 1.9</td>
<td>8.5 \pm 2.0</td>
<td>8.2 \pm 1.3</td>
<td></td>
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<tr>
<td>Final</td>
<td>6.0 \pm 2.6^6</td>
<td>6.4 \pm 2.6^6</td>
<td>8.2 \pm 1.5</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-1.9 \pm 2.1^7</td>
<td>-2.1 \pm 1.6^7</td>
<td>-0.02 \pm 0.7</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) EX, exercise training; CR, calorie restriction; HL, healthy lifestyle (control). For brevity, body-composition data are presented only for baseline and the final time points. None of the baseline values were significantly different between groups (ANOVA). Tukey’s tests were used for all post hoc comparisons between groups; ANCOVA was used for abdominal fat mass because it was measured only at the beginning and end of the study (all other body-composition variables were measured at 6 time points).

\(^2\) Reflects the significance of the interaction between study group and time, except for abdominal fat mass, in which it reflects the significance of the between-group comparison of final values after adjustment for baseline values by ANCOVA.

\(^3\) Arithmetic \( \bar{x} \pm SD \) (all such values).

\(^4\) The change from baseline was significantly different from that in the HL group: \( ^6 \) \( P \leq 0.05 \) (mixed-model repeated-measures ANOVA), \( ^5 \) \( P \leq 0.05 \) (ANOVA that included baseline values as the covariate).

\(^5\) Significantly different from zero: \( ^7 \) \( P \leq 0.05 \) (paired \( t \) test).
The main finding of the present study was that weight losses achieved by 12 mo of exercise training with no change in food intake and 12 mo of calorie restriction resulted in significant improvements in glucose tolerance and insulin action that were not significantly different between groups. Furthermore, these 2 interventions resulted in marginally significant improvements in circulating adiponectin concentrations and in the ratio of TNF-α to adiponectin.

The only other direct comparisons of exercise training– and calorie restriction–induced weight loss on improvements in insulin action are those of Ross et al (8, 9), who reported enhancements in insulin action in response to exercise training–induced weight loss and calorie restriction–induced weight loss that were not significantly different between groups. Most of the participants in the studies by Ross et al were obese at baseline and were still overweight or obese after the intervention. In contrast, the subjects in the present study were, on average, overweight (BMI: 27.1 ± 1.9)—none were obese—and the weight losses normalized body weight (BMI < 25.0) in 52% of the overweight participants in the exercise and calorically restricted groups. Whereas Ross et al’s interventions lasted 12–14 wk, we used a more gradual 1-y intervention to reduce body weight. Despite the differences in baseline body weight and the duration and intensity of the interventions between these studies, the findings of the present study agree with those of Ross et al (8, 9).

There are several possible explanations for why exercise training–induced weight loss did not result in greater improvements in insulin action than did calorie restriction, as we had hypothesized. One possibility is that the main factor responsible for the improvements was the decrease in body fat, particularly abdominal fat, which was not significantly different between the 2 groups. Another possibility is that the weight loss–independent benefits of exercise training on insulin action might have worn off before the final OGTT, because these effects are lost rapidly (20, 21). The participants in the EX group were asked to refrain from exercise for ≥48 h before the final OGTT, and the median amount of time between the last exercise bout and the OGTT was 58 h. In this time frame, it is unlikely that the exercise training

\[ P = 0.005 \] than in the CR group \( (r = 0.005, P = 0.98) \); \( P = 0.03 \) for the comparison between the EX and CR groups (Figure 3).

DISCUSSION

The main finding of the present study was that weight losses achieved by 12 mo of exercise training with no change in food intake and 12 mo of calorie restriction resulted in significant improvements in glucose tolerance and insulin action that were not significantly different between groups. Furthermore, these 2 interventions resulted in marginally significant improvements in circulating adiponectin concentrations and in the ratio of TNF-α to adiponectin.

The only other direct comparisons of exercise training– and calorie restriction–induced weight loss on improvements in insulin action are those of Ross et al (8, 9), who reported enhancements in insulin action in response to exercise training–induced weight loss and calorie restriction–induced weight loss that were not significantly different between groups. Most of the participants in the studies by Ross et al were obese at baseline and were still overweight or obese after the intervention. In contrast, the subjects in the present study were, on average, overweight (BMI: 27.1 ± 1.9)—none were obese—and the weight losses normalized body weight (BMI < 25.0) in 52% of the overweight participants in the exercise and calorically restricted groups. Whereas Ross et al’s interventions lasted 12–14 wk, we used a more gradual 1-y intervention to reduce body weight. Despite the differences in baseline body weight and the duration and intensity of the interventions between these studies, the findings of the present study agree with those of Ross et al (8, 9).

There are several possible explanations for why exercise training–induced weight loss did not result in greater improvements in insulin action than did calorie restriction, as we had hypothesized. One possibility is that the main factor responsible for the improvements was the decrease in body fat, particularly abdominal fat, which was not significantly different between the 2 groups. Another possibility is that the weight loss–independent benefits of exercise training on insulin action might have worn off before the final OGTT, because these effects are lost rapidly (20, 21). The participants in the EX group were asked to refrain from exercise for ≥48 h before the final OGTT, and the median amount of time between the last exercise bout and the OGTT was 58 h. In this time frame, it is unlikely that the exercise training

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Furthermore, it has been reported that glucose tolerance and insulin measured 48–72 h after the cessation of exercise (22–24). Enhanced glucose uptake in trained muscle are still evident when shown that the myocellular adaptations associated with effects would have worn off because studies in humans have results in modestly higher serum adiponectin concentrations than during the healthy lifestyle intervention. Although adiponectin concentrations have been shown to increase after weight loss induced by medication use (31) or by gastrointestinal bypass surgery (32), weight loss induced by diet or exercise training has generally not been shown to alter adiponectin concentration (33–36). A likely explanation for this discrepancy is that the other investigators studied obese individuals, whereas most of our participants were overweight and none were obese (BMI < 30). On the basis of cross-sectional data, adiponectin concentrations are associated with BMI but only when BMI is below ≈29 (37). It seems reasonable, therefore, that changes in BMI lead to changes in adiponectin concentrations, but only with weight losses that result in BMIs < 29. The inflammatory cytokine TNF-α has been shown to decrease insulin action (38, 39). In the present study, circulating TNF-α did not differ significantly in response to the different interventions. However, in light of recent evidence, which suggests that TNF-α and adiponectin may be reciprocally regulated (40–42), we assessed the effects of our interventions on the ratio of TNF-α to adiponectin. Both exercise training and calorie restriction resulted in lower ratios by the end of the study.

Although changes in the ratio of TNF-α to adiponectin were not significantly different between the EX and CR groups, these changes only correlated with the changes in insulin action in the EX group (Figure 3). This finding suggests that the changes in these cytokines are a more important mechanism for the improvement in insulin action in response to exercise training–induced weight loss than for that in response to calorie restriction. This is evidence, albeit preliminary, that some of the mechanisms are distinct for the improvements in insulin action that result from

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>EX (n = 18)</th>
<th>CR (n = 18)</th>
<th>HL (n = 10)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.0 ± 3.8</td>
<td>13.3 ± 6.8</td>
<td>8.6 ± 3.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Final</td>
<td>12.9 ± 4.7</td>
<td>15.5 ± 6.8</td>
<td>6.7 ± 1.6</td>
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</tr>
<tr>
<td>Change</td>
<td>1.9 ± 4.0</td>
<td>2.2 ± 4.7</td>
<td>−1.9 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.34 ± 0.70</td>
<td>1.13 ± 0.52</td>
<td>1.17 ± 0.89</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>1.09 ± 0.56</td>
<td>0.93 ± 0.46</td>
<td>1.11 ± 0.70</td>
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</tr>
<tr>
<td>Change</td>
<td>−0.25 ± 0.56</td>
<td>−0.20 ± 0.26</td>
<td>−0.06 ± 0.41</td>
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</tr>
<tr>
<td>TNF-α/adiponectin (×10⁻⁸)</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Baseline</td>
<td>13.2 ± 7.7</td>
<td>11.0 ± 6.7</td>
<td>13.8 ± 7.9</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>10.1 ± 7.5</td>
<td>7.2 ± 4.0</td>
<td>15.7 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>−3.0 ± 6.4</td>
<td>−3.9 ± 4.1</td>
<td>1.9 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Cortisol (µg/mL)</td>
<td></td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Baseline</td>
<td>11.9 ± 4.1</td>
<td>15.4 ± 4.7</td>
<td>12.8 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>11.8 ± 4.9</td>
<td>11.4 ± 3.2</td>
<td>10.6 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>−0.1 ± 4.4</td>
<td>−4.0 ± 4.1</td>
<td>−2.2 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>FFA (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Baseline</td>
<td>646 ± 210</td>
<td>569 ± 231</td>
<td>603 ± 207</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>586 ± 254</td>
<td>501 ± 203</td>
<td>616 ± 175</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>−60 ± 336</td>
<td>−68 ± 306</td>
<td>13 ± 152</td>
<td></td>
</tr>
</tbody>
</table>

1 EX, exercise training; CR, calorie restriction; HL, healthy lifestyle (control).
2 Reflects the significance of the between-group differences in final values for each outcome after adjustment for baseline values (ANCOVA).
3 Arithmetic x ± SD (all such values).
4 Significantly different from the HL group, P ≤ 0.05 (baseline-adjusted final values by ANCOVA and Tukey’s tests).
5 Significantly different from zero, P ≤ 0.05 (paired t test).
6 Significantly different from the EX group, P ≤ 0.05 (ANOVA and Tukey’s test).
was significantly greater than that in the CR group, however, the associations were assessed by using Pearson’s correlations after 2). According to the DLW method, energy intake in the CR group these methods conflict with each other in the CR group (Figure 3). Raw data were used for presentation; however, the associations were assessed by using Pearson’s correlations after the effects of baseline ISI were accounted for. The correlation in the EX group was significantly greater than that in the CR group, $P = 0.03$ (Fisher’s z transformation).

exercise training–induced weight loss compared with those that result from calorie restriction–induced weight loss.

Two methods were used to measure energy intake in the present study. To some extent, the energy intake estimates from these methods conflict with each other in the CR group (Figure 2). According to the DLW method, energy intake in the CR group was $\approx 340$ kcal/d below baseline during the first 6 mo of the intervention but only $\approx 128$ kcal/d below baseline and not significantly different from baseline ($P = 0.10$) during the last 3 mo of the intervention. In contrast, food record–based estimates of energy intake for the CR group indicate that energy intake was $\approx 300$ kcal/d below baseline throughout the intervention. In light of the difficulties of using DLW to estimate energy intake during weight loss and considering the well-known limitations of food record–based estimates of energy intake, it is difficult to know which of these estimates of change in energy intake is more accurate. It is important to note, however, that body weight and body fat mass decreased substantially in the CR group (Table 2) and remained remarkably stable during the last 3 wk of the intervention. In the absence of increases in physical activity levels, as evidenced by the PAR data (Figure 2) and a lack of increase in absolute V̇O₂max (Table 1), it is likely that energy intake was below baseline and stable at the end of the intervention as evidenced by the absence of weight gain.

The results of this trial have clinical ramifications, especially in light of the growing epidemic of type 2 diabetes. Although diet and exercise training can greatly reduce the incidence of type 2 diabetes (43, 44), the relative contributions of exercise training and calorie restriction to these protective effects are not known. Data from the present study suggest that weight loss induced by exercise training and by calorie restriction are not different with respect to their abilities to improve glucose tolerance and insulin action and, presumably, to lower the risk of type 2 diabetes.

In summary, data from the present study suggest that exercise training– and calorie restriction–induced weight loss are effective means for improving glucose tolerance and insulin action in nonobese, healthy, middle-aged men and women. It does not appear that exercise training–induced weight loss provides benefits above and beyond those that can be achieved by calorie restriction alone if exercise training is discontinued for $\geq 2$ d.

We are grateful to the study participants for their cooperation and to the staff of the Applied Physiology Laboratory and Nurses of the General Clinical Research Center at Washington University School of Medicine for their skilled assistance.

JOH and SK designed the study. EPW, SBR, DTV, LF, KS-M, and JOH collected the data and supervised its collection. EPW, SBR, KS-M, KBS, and JOH analyzed and interpreted the data. EPW, SBR, KS-M, SK, and JOH wrote the manuscript. None of the authors had a conflict of interest.

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