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Coker, Robert H.; Williams, Rick H.; Yeo, Sophie E.; Kortebein, Patrick M.; Bodenner, Don L.; Kern, Philip A.; and Evans, William J., "The Impact of Exercise Training Compared to Caloric Restriction on Hepatic and Peripheral Insulin Resistance in Obesity" (2009). *Clinical and Translational Science Faculty Publications*. 33.

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Digital Object Identifier (DOI)

10.1210/jc.2008-2033

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The Impact of Exercise Training Compared to Caloric Restriction on Hepatic and Peripheral Insulin Resistance in Obesity

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Context: It has been difficult to distinguish the independent effects of caloric restriction versus exercise training on insulin resistance.

Objective: Utilizing metabolic feeding and supervised exercise training, we examined the influence of caloric restriction vs. exercise training with and without weight loss on hepatic and peripheral insulin resistance.

Design, Participants, and Intervention: Thirty-four obese, older subjects were randomized to: caloric restriction with weight loss (CR), exercise training with weight loss (EWL), exercise training without weight loss (EX), or controls. Based on an equivalent caloric deficit in EWL and CR, we induced matched weight loss. Subjects in the EX group received caloric compensation. Combined with [6,6²H₂]glucose, an octreotide, glucagon, multistage insulin infusion was performed to determine suppression of glucose production (SGP) and insulin-stimulated glucose disposal (ISGD). Computed tomography scans were performed to assess changes in fat distribution.

Results: Body weight decreased similarly in EWL and CR, and did not change in EX and controls. The reduction in visceral fat was significantly greater in EWL ($-71 \pm 15 \text{ cm}^2$) compared to CR and EX. The increase in SGP was also almost 3-fold greater ($27 \pm 2\%$) in EWL. EWL and CR promoted similar improvements in ISGD [$+2.5 \pm 0.4$ and $2.4 \pm 0.9 \text{ mg} \cdot \text{kg fat-free mass (FFM)}^{-1} \cdot \text{min}^{-1}$], respectively.

Conclusions: EWL promoted the most significant reduction in visceral fat and the greatest improvement in SGP. Equivalent increases in ISGD were noted in EWL and CR, whereas EX provided a modest improvement. Based on our results, EWL promoted the optimal intervention-based changes in body fat distribution and systemic insulin resistance. (*J Clin Endocrinol Metab* 94:4258–4266, 2009)

Obesity and/or the lack of physical activity are two of the primary factors in the development of insulin resistance that precede the diagnosis of type 2 diabetes (T2D) (1). Studies such as the Diabetes Prevention Program have demonstrated the positive influence of lifestyle interventions in preventing the onset of T2D (2). However, a number of questions remain.

Decreased physical activity is a major cause of obesity (3), and weight loss induced entirely through exercise training seems difficult to achieve in most obese individuals. Also, of the individuals who do attempt weight loss, approximately 70% use dietary modification as their only strategy (4). Despite studies employing some combination of caloric restriction and/or exercise training to investigate

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

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doi: 10.1210/jc.2008-2033 Received September 16, 2008. Accepted July 29, 2009.

First Published Online October 6, 2009

Abbreviations: BMI, Body mass index; CR, caloric restriction with weight loss; EWL, exercise training with weight loss; EX, exercise training without weight loss; FFA, free fatty acid; FFM, fat-free mass; HbA1c, glycosylated hemoglobin; MSI, multistage insulin infusion; OGTT, oral glucose tolerance test; R_a, rate of appearance; T2D, type 2 diabetes; VO_{2peak}, peak oxygen consumption.

changes in glucose metabolism (5–10), it has been difficult to distinguish the independent impact of exercise training compared with dietary modification alone. In addition, studies that have employed behavioral, dietary, and/or exercise interventions are subject to large measurement errors (11–14). Moreover, most obese individuals that attempt exercise training do not lose weight (15), and the benefits of exercise training under those circumstances *vs.* exercise training that results in weight loss have not been sufficiently investigated.

Although obesity is also associated with hepatic and peripheral insulin resistance and may have a deleterious influence on the regulation of glucose homeostasis (16, 17), most studies examining the impact of lifestyle interventions have paid little attention to insulin resistance in the liver. Furthermore, there are no data examining the independent influence of caloric restriction *vs.* exercise training on hepatic insulin resistance in obese persons at risk for T2D.

We hypothesized that: 1) exercise training-induced weight loss would induce greater improvements in hepatic and peripheral insulin sensitivity compared with caloric restriction-induced weight loss; and 2) weight loss would be of critical importance in the efficacy of exercise training toward the facilitation of improvements in hepatic and peripheral insulin sensitivity. To test these hypotheses, we employed controlled metabolic feeding that ensured caloric balance during testing and precise manipulation of caloric intake during the intervention (*i.e.* caloric restriction or supervised exercise training) periods. Before and after these interventions, we used [6,6²H₂]glucose, a continuous octreotide/glucagon infusion, and a multistage insulin infusion (MSI) to examine hepatic and peripheral insulin resistance. To measure changes in body fat distribution, computed tomography was also performed during pre- and postintervention testing periods as previously described (18).

Subjects and Methods

Subjects

Men and women aged 50–80 yr were recruited from the central Arkansas area using newspaper advertisements. Subjects who reported being overweight or obese [body mass index (BMI) ≥ 26 and $< 40 \text{ kg/m}^2$], nonsmoking, sedentary (≤ 2 d/wk of structured physical activity), and were weight stable ($\pm \leq 5$ kg) over the past 6 months were invited to our laboratory for a comprehensive medical screening. Screening procedures included a medical history, physical examination, routine blood and urine chemistries, oral glucose tolerance test (OGTT), and a maximal exercise test on a bicycle ergometer. Subjects with a plasma glucose concentration of 100–199 mg/dl 2 h after the oral consumption of 75 g glucose, but who were otherwise healthy, were eligible for study participation. No subpopula-

tion was targeted for recruitment, and subjects were recruited without regard to sex, race, or ethnic status. Patients with a history of cardiovascular disease, diabetes, or cancer were excluded. Subjects taking medicines or supplements that might have had potential effects on carbohydrate or lipid metabolism were excluded.

Each subject provided written informed consent, and study procedures were approved by the Institutional Review Board of the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System Research and Development Committee.

Experimental protocol

After medical evaluation, eligible subjects were randomly assigned into one of four groups: exercise training without weight loss (EX); exercise training with weight loss (EWL); caloric restriction with weight loss (CR); or controls. In the experimental groups, we used controlled metabolic feeding (EX, EWL, and CR) and supervised exercise training (EX and EWL) to ensure equivalent caloric expenditure via exercise training and dietary control of caloric and macronutrient intake. In controls, caloric intake and macronutrient intake were standardized through consumption of a mixed diet (35% fat, 20% protein, 45% carbohydrate) that began 4 d before pre- and posttesting sessions. Controls were advised to maintain their normal diet during the rest of the study. Nonexercising subjects were instructed to maintain their habitual physical activity.

Controlled metabolic feeding and exercise training

All subjects except for controls consumed a weight maintenance diet for a 4-wk period before preintervention testing (Fig. 1). Body weights were recorded on a regular basis, and adjustments to the weight maintenance diet were made to ensure caloric balance by the end of the 4-wk period. Subjects were also instructed to save food that was not eaten so that we were able to use a food weigh-back method in our calculation of caloric intake.

In CR, the reduction in caloric intake began immediately after the completion of the weight maintenance phase and the pretesting session. To match the progressive increase in caloric deficit to EWL, caloric intake in CR was reduced by 1000 kcal the first week, and decreased by 500 kcal each week until total caloric restriction has reached 2500 kcal/wk. After the weight maintenance phase and preintervention testing, subjects randomized to EX and EWL began their training regimen at 50% of peak oxygen consumption ($\text{VO}_{2\text{peak}}$) (Fig. 1). All subjects were trained under direct supervision at the Donald W. Reynolds Institute on Aging using a cycle ergometer as previously described (19).

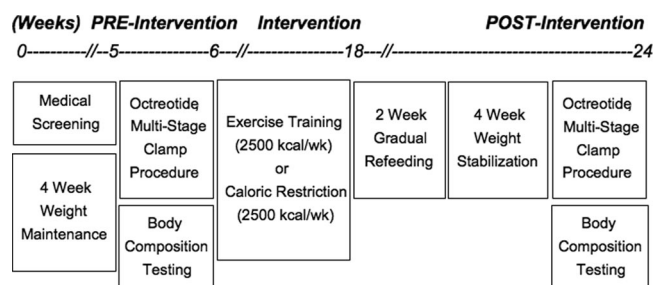


FIG. 1. Study paradigm.

To acclimatize volunteers to the training and minimize dropouts, volunteers began supervised cycle exercise training (50% of VO_{2peak}) by expending 1000 kcal/wk, and gradually increased their training (500 kcal each week) until they were expending 2500 kcal/wk. Subjects assigned to the EX group performed an identical amount of exercise training relative to intensity and caloric expenditure. Although no caloric compensation was provided for the increase in caloric expenditure in the EWL group, subjects in the EX group received complete caloric compensation for their exercise-induced caloric expenditure. Thus, the weekly and 12-wk theoretical caloric deficit of the subjects in the CR and EWL groups were almost identical, and no caloric deficit was induced in the EX group. Other than 4 d of controlled metabolic feeding before testing, subjects in the control group consumed normal diets without any dietary manipulation or change in physical activity. After the completion of the 12-wk period of caloric deficit, subjects in CR and EWL groups underwent 2 wk of gradual refeeding followed by a 4-wk weight stabilization phase (Fig. 1). Postintervention testing sessions for EX and EWL subjects were completed approximately 72 h after the last exercise session (in those subjects randomized to one of the exercise groups) to minimize acute effects of exercise on insulin sensitivity (20).

Accurate determination of energy requirements and dietary compliance in these studies allowed us to: 1) ensure weight maintenance in the EX group; 2) facilitate equivalent weight loss in the CR and EWL groups; 3) eliminate the confounding influence of acute caloric deficit; and ultimately 4) determine the importance of weight loss and physical activity on the reduction of hepatic and peripheral insulin resistance.

Aerobic capacity test

An exercise stress test was performed as part of the screening visit as well as immediately after the completion of the posttesting session to determine VO_{2peak} (Fig. 1). VO_{2peak} was determined using an incremental protocol to voluntary exhaustion on an electronically braked stationary bicycle (Lode, Groningen, Netherlands). Respiratory gases were collected continuously and analyzed using indirect calorimetry.

Body weight and body composition

Body mass, height, and body composition testing were measured during the pre- and posttesting sessions. During pre- and posttesting sessions, fat mass and lean tissue mass were measured by dual-energy x-ray absorptiometry using a Hologic QDR 2000 densitometer (Hologic Inc., Bedford, MA).

Computed tomography

During pre- and posttesting sessions, sc abdominal adipose tissue and visceral adipose tissue were determined from computed tomography scans. From these images, fat, lean tissue, and bone were clearly identified and quantified. The scans were completed using a GE High-Speed Advantage scanner (General Electric Medical Systems, Milwaukee, WI), as previously described (17, 18).

Hepatic and peripheral insulin sensitivity

We used an octreotide, MSI with basal glucagon replacement to examine changes in insulin-stimulated suppression of glucose rate of appearance (R_a) and insulin-stimulated glucose disposal. To measure basal glucose R_a and insulin-stimulated suppression of glucose R_a , a priming dose (3.27 mg/kg of

[6,6²H₂]glucose) was administered, followed by an infusion of 0.22 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from time = -120 to 120 min, and then increased to 0.44 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from time = 120 to 240 min to minimize changes in enrichment. To ensure precise control of pancreatic hormone levels, infusions of octreotide (60 $\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and glucagon (0.65 $\text{ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were started at $t = 0$ min and continued throughout the clamp. Insulin was infused at a rate of 0.25 $\text{mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from $t = 4$ to 120 min (first stage) to evaluate insulin-stimulated suppression of glucose R_a , and 1.0 $\text{mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ from $t = 120$ to 240 min in the second stage to evaluate insulin-stimulated glucose disposal.

Plasma samples were obtained every 5 min for determination of glucose by the glucose oxidase method (Glucose Analyzer 2; Beckman Coulter Inc., Brea, CA), and euglycemia was maintained by a variable 20% dextrose infusion spiked with 8 mg of [6,6²H₂]glucose/g dextrose to prevent an underestimation of glucose R_a (21). The insulin infusion rate in the first stage was representative of insulin levels approximately 2-fold greater than fasting levels and provided an ideal scenario to measure insulin-stimulated suppression of glucose R_a by mild hyperinsulinemia (17). After the initial insulin infusion rate, the rate was increased 4-fold in the second stage of the MSI, and represented the level of hyperinsulinemia necessary for the measurement of insulin-stimulated glucose disposal (22, 23).

Blood samples collected every 20 min during the MSI were centrifuged at 1200 force $\times g$ for 20 min at 4 C, and the plasma was stored at -70 C for future analysis. Plasma insulin and glucagon levels were determined using a double-antibody system, as previously described (19). Plasma deproteinization and purification were completed, and glucose enrichments were determined using gas chromatography/mass spectrometry (Agilent Technologies, Palo Alto, CA) as previously described (19).

Calculations

Glucose R_a was estimated for the basal period and modified for transitions in steady-state conditions (24) using the original equations of Steele (25). Insulin-stimulated suppression of glucose R_a was calculated as $1 - (\text{mild hyperinsulinemia glucose } R_a / [\text{insulin}]) / \text{basal glucose } R_a / [\text{insulin}] \times 100$ and indicates the degree of glucose R_a suppressed under basal glucagon/mild hyperinsulinemic conditions. Therefore, insulin-stimulated suppression of glucose R_a reflects hepatic insulin sensitivity or the degree to which mild hyperinsulinemic conditions suppress basal rates of glucose R_a . Under the mild hyperinsulinemic conditions of the first stage, the exogenous glucose infusion ranged from zero to negligible rates for the maintenance of euglycemia. In the second stage of the clamp, the M-value (adjusted for lean tissue mass), or insulin-stimulated glucose disposal was determined during the last 30 min of the 240-min clamp by subtracting glucose R_a from the exogenous glucose infusion rate, and it reflects peripheral insulin sensitivity.

Statistical analyses

Statistical comparisons between groups and over time were made using two-way ANOVA designed to account for repeated measures, and Tukey *post hoc* tests were applied to significant group \times time in interactions. Data are reported as means \pm SEM.

TABLE 1. Clinical characteristics (pre- and postintervention)

| | Control | | EX | | EWL | | CR | |
|--|-----------|-----------|-----------|------------------------|-----------|------------------------|-----------|-----------------------|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Gender (M/F) | 3/5 | | 2/6 | | 3/6 | | 3/6 | |
| Race (C/AA) | 8/0 | | 6/2 | | 7/2 | | 7/2 | |
| Age (yr) | 59 ± 2 | | 55 ± 2 | | 54 ± 2 | | 58 ± 2 | |
| Weight (kg) | 89 ± 4 | 91 ± 4 | 91 ± 3 | 91 ± 3 | 87 ± 5 | 82 ± 5 ^a | 86 ± 2 | 81 ± 2 ^a |
| BMI (kg/m ²) | 31 ± 1 | 32 ± 1 | 32 ± 1 | 32 ± 1 | 32 ± 1 | 30 ± 1 ^a | 30 ± 0 | 28 ± 1 ^a |
| Body fat (%) | 39 ± 2 | 41 ± 2 | 41 ± 2 | 41 ± 2 | 40 ± 2 | 37 ± 3 ^a | 40 ± 2 | 37 ± 2 |
| VO _{2peak} (liters/min) | 1.7 ± 0.1 | 1.7 ± 0.1 | 1.8 ± 0.1 | 2.1 ± 0.2 ^a | 1.8 ± 0.1 | 2.1 ± 0.2 ^a | 1.7 ± 0.2 | 1.7 ± 0.1 |
| Subcutaneous abdominal adipose tissue (cm ²) | 349 ± 24 | 340 ± 29 | 387 ± 41 | 397 ± 43 | 422 ± 46 | 370 ± 42 ^a | 343 ± 22 | 301 ± 19 ^a |
| Visceral adipose tissue (cm ²) | 198 ± 17 | 205 ± 24 | 245 ± 31 | 228 ± 34 ^a | 236 ± 24 | 165 ± 12 ^a | 199 ± 12 | 170 ± 11 ^a |
| Thigh lean tissue (cm ²) | 124 ± 8 | 121 ± 8 | 133 ± 9 | 135 ± 7 | 129 ± 9 | 136 ± 9 ^a | 140 ± 11 | 133 ± 9 ^a |

Values are means ± SEM. There were no significant baseline age differences. C/AA, Caucasian/African American; %, body fat/total body mass; M, males; F, females.

^a Significant difference from pre- to postintervention ($P < 0.05$).

Results

Subjects

We enrolled 42 volunteers, and eight subjects dropped out due to their inability to comply with the protocol. Therefore, 34 obese women and men completed all facets of the protocol (Table 1).

Maximal exercise capacity

Baseline VO_{2peak} was similar in all groups (Table 2). VO_{2peak} increased in EX and EWL from pre- to postint-

ervention ($P < 0.05$), but there were no significant changes in controls or CR (Table 1).

Anthropometrics

All groups were similar at baseline with respect to body weight, BMI, and percentage fat (Table 1). In controls and EX subjects, there was no change in body weight (Table 1). However, there was a similar decline in body weight in CR and EWL groups ($P < 0.05$) (Table 1). In controls, there was no change in sc or visceral adipose tissue from pre- to

TABLE 2. Metabolism variables during fasting conditions and during the first and second stage of the MSI procedure (pre- and postintervention)

| | Control | | EX | | EWL | | CR | |
|--|-----------|------------------------|-----------|------------------------|-----------|-------------------------|-----------|------------------------|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| HbA1c (%) | 5.6 ± 0.1 | 5.7 ± 0.1 | 5.6 ± 0.1 | 5.5 ± 0.1 | 5.5 ± 0.1 | 5.7 ± 0.1 | 5.5 ± 0.1 | 5.6 ± 0.1 |
| Fasting plasma glucose (mg · dl ⁻¹) | 97 ± 4 | 102 ± 3 | 99 ± 4 | 97 ± 4 | 95 ± 2 | 96 ± 2 | 95 ± 3 | 95 ± 4 |
| 2-h OGTT plasma glucose (mg · dl ⁻¹) | 139 ± 9 | 136 ± 13 | 134 ± 6 | 127 ± 13 | 129 ± 7 | 117 ± 7 | 137 ± 10 | 127 ± 4 |
| Plasma FFAs (μU/ml) | 72 ± 9 | 78 ± 10 | 74 ± 10 | 70 ± 15 | 73 ± 9 | 68 ± 10 | 78 ± 9 | 77 ± 4 |
| Basal period of MSI | | | | | | | | |
| Plasma insulin (μU/ml) | 7 ± 2 | 6 ± 1 | 7 ± 2 | 7 ± 2 | 6 ± 1 | 5 ± 1 | 5 ± 1 | 5 ± 1 |
| Basal glucose R _a (mg · kg ⁻¹ · min ⁻¹) | 2.8 ± 0.2 | 3.3 ± 0.2 ^a | 3.4 ± 0.4 | 2.8 ± 0.2 | 3.6 ± 0.4 | 3.3 ± 0.2 | 2.8 ± 0.1 | 2.9 ± 0.3 |
| First stage of MSI | | | | | | | | |
| Plasma insulin (μU/ml) | 18 ± 3 | 14 ± 3 | 18 ± 2 | 16 ± 2 | 14 ± 1 | 14 ± 2 | 18 ± 4 | 14 ± 2 |
| Glucose R _a (mg · kg ⁻¹ · min ⁻¹) | 1.8 ± 0.2 | 2.0 ± 0.3 | 2.7 ± 0.4 | 2.0 ± 0.2 | 2.4 ± 0.2 | 1.4 ± 0.2 | 2.0 ± 0.3 | 1.8 ± 0.5 |
| Second stage of MSI | | | | | | | | |
| Plasma insulin (μU/ml) | 86 ± 3 | 74 ± 3 | 80 ± 2 | 84 ± 1 | 83 ± 3 | 72 ± 3 | 71 ± 2 | 76 ± 2 |
| Insulin-stimulated glucose disposal (mg · kg ⁻¹ · min ⁻¹) | 6.6 ± 0.2 | 6.4 ± 1.3 | 7.3 ± 0.5 | 8.3 ± 0.6 ^a | 7.8 ± 0.6 | 10.2 ± 0.9 ^a | 6.8 ± 0.6 | 9.2 ± 0.6 ^a |

Values are means ± SEM. There were no baseline or pre- and postintervention differences in HbA1c or OGTT results in controls. In the second stage of the MSI, glucose R_a was less than 0.1 mg · kg⁻¹ · min⁻¹.

^a Significant change from pre- to postintervention ($P < 0.05$).

postintervention (Table 1). In EX subjects, there was no change in sc adipose tissue, but there was a significant decline in visceral adipose tissue ($-17 \pm 7 \text{ cm}^2$; $P < 0.05$) from pre- to postintervention (Table 1). There was a similar reduction in sc adipose tissue in CR ($-42 \pm 12 \text{ cm}^2$; $P < 0.05$) and EWL ($-51 \pm 12 \text{ cm}^2$; $P < 0.05$) groups (Table 1). Moreover, the decrease in visceral adipose tissue was 2-fold greater in EWL ($-71 \pm 15 \text{ cm}^2$; $P < 0.01$) compared with CR ($-36 \pm 10 \text{ cm}^2$; $P < 0.05$) subjects (Table 1) and supports the significant influence of exercise training-induced weight loss toward the reduction of visceral adipose tissue. Lastly, EWL promoted an increase in thigh lean tissue ($7 \pm 1 \text{ cm}^2$; $P < 0.05$), whereas CR induced a significant reduction in thigh lean tissue ($-7 \pm 1 \text{ cm}^2$; $P < 0.05$) (Table 1).

Caloric and macronutrient intake

Before the preintervention testing session, the weight maintenance period ensured that caloric and macronutrient intake was similar in EX, EWL and CR subjects (see Fig. 4). In EX, caloric intake increased significantly during the intervention period and remained stable during the gradual refeeding and weight stabilization periods (Fig. 2). In EWL, caloric intake remained stable during the intervention period and increased ($P < 0.05$) during gradual refeeding and weight stabilization (see Fig. 4). Caloric intake decreased ($P < 0.05$) in CR during the intervention period (Fig. 2). After the intervention period, caloric intake was stabilized during the gradual refeeding and weight stabilization periods in CR (Fig. 2).

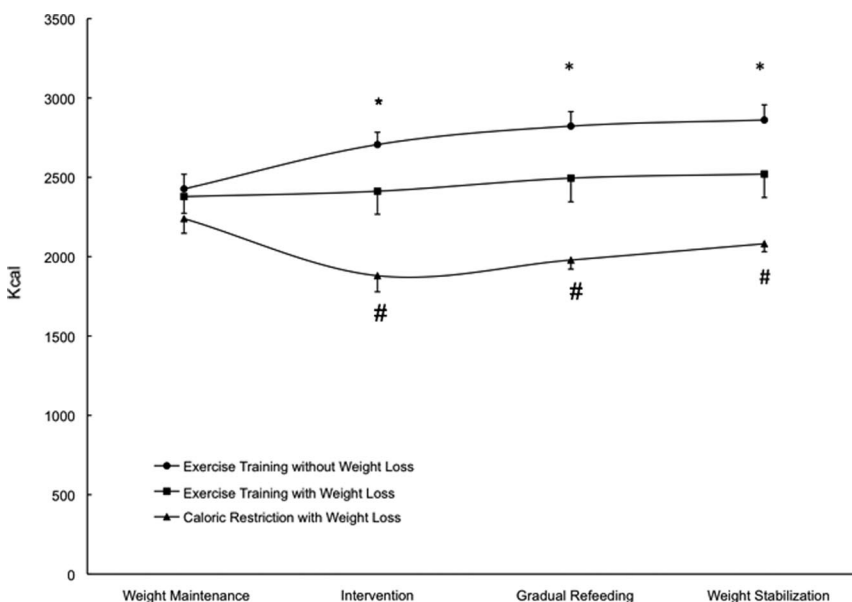


FIG. 2. Caloric intake during the weight maintenance, intervention, gradual refeeding, and weight stabilization phases in EX, EWL and CR. *, Significant increase from weight maintenance phase; #, significant decrease from weight maintenance phase.

Plasma glucagon and insulin

Mean pre- and postintervention plasma glucagon was similar in all four groups during the basal period and the first stage of the MSI (data not shown) ($P < 0.05$). Because the exogenous glucagon infusion rate remained at the same rate during the second stage of the MSI, plasma glucagon was not measured during this stage. Basal pre- and postintervention plasma insulin was similar in controls, EX, EWL, and CR ($P < 0.05$). In the first stage of the preintervention MSI, the approximately 2-fold increase ($P < 0.05$) in plasma insulin was similar in controls and EX, EWL, and CR subjects (Table 2). In the second stage of the MSI, the plasma insulin concentration reached approximately 10-fold that of basal levels ($P < 0.05$) and was similar in controls and EX, EWL, and CR subjects (Table 2) ($P > 0.05$).

Glucose metabolism

Preintervention values for glycosylated hemoglobin (HbA1c), and the 2-h plasma glucose from the OGTT were similar in all four groups (Table 2). Also, there were no differences between the pre- and postintervention values for HbA1c and the 2-h glucose from the OGTT in any of the four groups (Table 2).

Basal glucose R_a was not different in controls and EX, EWL, and CR subjects (Table 2). There was no significant change in the insulin-stimulated suppression of glucose R_a from pre- to postintervention in controls ($-1 \pm 1\%$; $P > 0.05$). On the contrary, there was a similar, significant increase in insulin-stimulated suppression of glucose R_a in EX ($12 \pm 2\%$; $P < 0.05$) and CR ($10 \pm 2\%$; $P < 0.05$)

(Fig. 3). Moreover, the increase in insulin-stimulated suppression of glucose R_a from pre- to postintervention was almost 3-fold greater in EWL ($27 \pm 2\%$; $P < 0.001$) (Fig. 3) and suggests the combined influence of exercise training and caloric deficit induced by the exercise training ($P < 0.05$). In all four groups, negligible rates of glucose R_a were subtracted from our calculation of insulin-stimulated glucose disposal. In controls, there was no significant change in insulin-stimulated glucose disposal from pre- to postintervention testing (Fig. 4). In EX, there was a significant increase in insulin-stimulated glucose disposal from pre- to postintervention ($0.95 \pm 0.41 \text{ mg} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$) ($P < 0.05$) (Fig. 4). Moreover, the increase in insulin-stimulated glucose disposal was approxi-

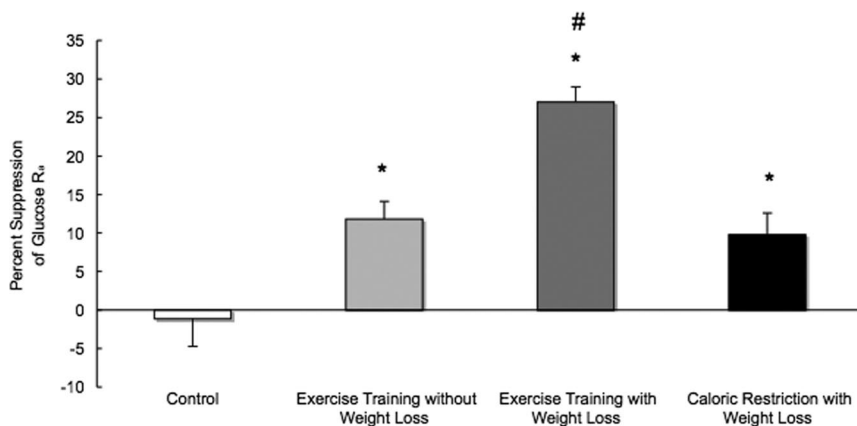


FIG. 3. Change in insulin-stimulated suppression of glucose R_a in controls, EX, EWL, and CR. Values are means \pm SEM for 34 subjects. *, Significant increase from pre- to postintervention; #, significant difference between EWL, and EX and CR.

mately 2-fold greater in EWL ($2.45 \pm 0.43 \text{ mg} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$; $P < 0.001$) and CR ($2.46 \pm 0.69 \text{ mg} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$; $P < 0.03$) (Fig. 4).

Discussion

Using metabolic feeding and supervised exercise training, we have distinguished the influence of exercise training-induced weight loss *vs.* caloric restriction-induced weight loss on hepatic and peripheral insulin resistance. In addition, we used caloric compensation under conditions of equivalent caloric expenditure to directly compare the influence of exercise training (with and without weight loss) on hepatic and peripheral insulin resistance. Compared with EX and CR groups, our results demonstrate that EWL subjects promoted the greatest reductions in visceral adipose tissue and hepatic insulin resistance. Moreover, EX subjects had only a modest influence on peripheral insulin resistance, whereas induction of weight loss (either through EWL

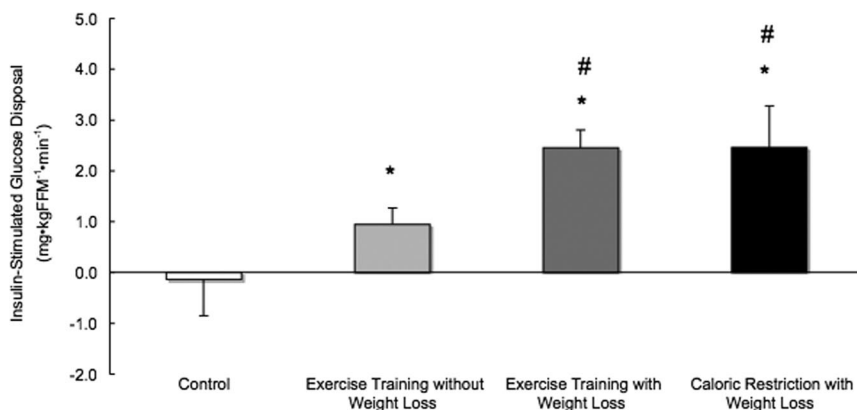


FIG. 4. Change in insulin-stimulated glucose disposal in controls, EX, EWL, and CR. Values are means \pm SEM for 34 subjects. *, Significant increase from pre- to postintervention; #, significant difference between EWL and CR, and EX.

or CR) proved similarly effective in the reduction of peripheral insulin resistance.

Our interest in the influence of lifestyle-induced changes on liver metabolism have stemmed from cross-sectional studies that suggested enhanced hepatic insulin sensitivity in trained *vs.* untrained individuals (26). To our knowledge, our findings represent the first in which exercise-induced weight loss promoted greater improvements in hepatic insulin sensitivity compared with caloric restriction-induced weight loss. Although previous studies using a caloric restriction/low-fat diet to induce weight loss reported a more profound

reduction in hepatic insulin resistance than examined in our caloric restriction group (27), the consumption of the low-fat diet may have also contributed toward a reduction in circulating free fatty acid (FFA) levels (28). It is also important to mention that the individuals in the previous study had already been diagnosed with T2D, and as a result, it was necessary to use a higher insulin infusion rate to evaluate hepatic insulin resistance. Therefore, differences in dietary manipulation and disease etiology make it difficult to draw clear interpretations (27). Based on our current results under conditions of equivalent weight loss, exercise training was superior in fostering a greater, concomitant reduction in visceral adipose tissue and hepatic insulin resistance.

EX promoted a significant improvement in hepatic insulin sensitivity that was equivalent to the adaptations induced by CR. The mechanisms responsible for the favorable changes in all of the intervention groups may be partially due to a reduction in visceral adipose tissue-derived lipolysis (29). The portal concentration of FFA may have decreased and promoted an improvement in insulin-stimulated suppression of glucose R_a under equivalent conditions of mild hyperinsulinemia (30). Support for this rationale has been provided by the results of animal studies where training-induced loss of body fat and visceral adipose tissue was directly linked to the decreased portal vein concentration of FFA (31). As such, there may be an additive influence of exercise training and weight loss on these factors. Therefore, our findings extend beyond the previous link between visceral adipose tissue and pe-

peripheral insulin resistance (5, 8, 32) and demonstrate the powerful effects of EWL in the augmentation of hepatic insulin sensitivity.

Ross *et al.* (5) demonstrated similar improvements in insulin-stimulated glucose disposal with exercise- and caloric restriction-induced weight loss, whereas only modest changes in insulin-stimulated glucose disposal were noted with exercise training in the absence of weight loss. Although these results related to changes in insulin-stimulated glucose disposal were equivocal to the results of our present study, we did find that EWL promoted a significantly greater reduction in visceral adipose tissue. On the contrary, a recent meta-analysis of studies involving a wide variety of exercise training and/or dietary modification also suggested that exercise training (with or without weight loss) provided no additional benefit in the reduction of visceral adipose tissue (33). From this meta-analysis, only two of the 37 studies directly compared exercise-*vs.* caloric restriction-mediated weight loss, and whereas these two studies noted similar reductions in visceral adipose tissue, significant changes in insulin-stimulated glucose disposal were inconsistent with caloric restriction-mediated weight loss (5, 34). Fundamental differences in the level of methodological control may have influenced these outcomes. As such, these results pose interesting questions as to the primary factors that may have an influence on the etiology of peripheral insulin resistance such as alterations in adiposity, triglycerides, ectopic lipid deposition, and the molecular signals influenced by these factors (35). Therefore, our study design may have provided a more well-controlled experimental paradigm that was necessary to elicit a response similar to the previously reported training-induced loss of visceral fat from animal studies (31).

For example, studies that have used behavioral modification methodologies are prone to the inaccurate assessment of dietary intake and/or exercise-induced caloric expenditure (36, 37). Moreover, the lack of weight stabilization periods may result in an assessment of insulin sensitivity that did not reflect the precise influence of the intervention (38). Similar to the acute effects of dietary intake, acute exercise has an acute influence on peripheral insulin sensitivity, even when assessed through indirect methodologies that lack a high degree of sensitivity (39). In the study by Dengel *et al.* (40), the considerable variability of weight loss (*i.e.* approximately one third of entire amount of weight lost) may have been an indication of poor metabolic control during the intervention. We supervised all exercise training, and our dietary control included a dietary feeding paradigm that has been validated using the doubly labeled water method (37). Therefore, these methods provide our study with the additional

level of metabolic control necessary for accurate data interpretation.

Contrary to hyperinsulinemic clamp methodology that provides a direct examination of insulin sensitivity, methods like the OGTT represent a nonspecific technique largely developed as a screening tool for large-scale epidemiological studies, and not small-scale intervention-based studies (41). Previous results from our laboratory have determined that indirect assessments of insulin sensitivity lack the specificity necessary to detect direct mechanisms induced by interventions (42). In fact, indirect assessments of insulin sensitivity involve a combination of hepatic and peripheral insulin sensitivity and may even be further complicated by β -cell response. Changes in “pre to post” pancreatic release of insulin may have potentially influenced the results termed as “insulin sensitivity” without the ability to discriminate between hepatic or peripheral insulin sensitivity (41). For these reasons, conclusions drawn from intervention-based studies that have used indirect assessments of glucose metabolism should be viewed with caution.

Using our MSI procedure, we were able to selectively control insulin and glucagon levels in pre- and postintervention testing sessions. It was important to control and replicate glucagon levels during each pre- and postintervention testing session due to the influence of small changes in hormone concentrations and their impact on glucoregulatory feedback loops responsible for control of glucose metabolism (43). Also, exercise training may result in the modification of hepatic insulin extraction, and control of insulin levels was important in the accurate measurement of insulin sensitivity (44). In addition, stable isotope methodology provided us with the assessment of insulin-stimulated suppression of glucose R_a that represented an actual physiological scenario in obesity during which this physiological parameter may be impaired (45, 46). Because absolute suppression of glucose R_a may also be impaired at high physiological plasma insulin levels, we subtracted glucose R_a from our dextrose infusion rate to provide an accurate calculation of insulin-stimulated glucose disposal in our study. This was another factor that might have contributed to somewhat different conclusions compared with other studies investigating exercise and/or diet-induced changes in peripheral insulin resistance (5, 40).

In summary, our studies have demonstrated that whereas exercise training- and caloric restriction-induced weight loss promoted the reduction of visceral adipose tissue and hepatic insulin resistance, exercise-induced weight loss was more than twice as effective in this regard. Therefore, our results have provided additional support for the link between visceral adipose tissue and insulin

resistance in the liver (16, 17). Exercise training in the absence of weight loss still promoted a modest decrease in peripheral insulin resistance, and yet, weight loss (either through exercise training or caloric restriction) promoted more significant reductions in peripheral insulin resistance. In conclusion, our results confirm our hypotheses that weight loss induced by exercise training alone promoted greater retention of lean tissue and superior reductions in visceral adipose tissue and hepatic insulin resistance, and it also induced a significant decrease in peripheral insulin resistance.

Acknowledgments

We extend our gratitude for the expert nursing assistance of Amy Sadler and Leizleigh Robinette, the coordinator support of Maria Bogachova, and the dietary support of Amanda Wells and her technical staff. We also extend our sincere appreciation to our volunteers for their effort toward the completion of this demanding study.

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This work was supported by National Institutes of Health (NIH) Grant KO1 DK 64716-01 (to R.H.C.) and American Heart Association Grant SDA 0335172N (to R.H.C.). We acknowledge the support of the University of Arkansas for Medical Sciences General Clinical Research Center funded through NIH Grant M01 RR14288.

This material is based upon work supported in part by the Department of Veterans Affairs, and Health Services Research and Development.

Disclosure Statement: The authors have nothing to disclose.

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