Enhanced Fat Oxidation Through Physical Activity Is Associated With Improvements in Insulin Sensitivity in Obesity

Bret H. Goodpaster, Andreas Katsiaras, and David E. Kelley

Skeletal muscle insulin resistance entails dysregulation of both glucose and fatty acid metabolism. This study examined whether a combined intervention of physical activity and weight loss influences fasting rates of fat oxidation and insulin-stimulated glucose disposal. Obese (BMI >30 kg/m^2) volunteers (9 men and 16 women) without diabetes, aged 39 ± 4 years, completed 16 weeks of moderate-intensity physical activity combined with caloric reduction. Body composition was determined by dual-energy X-ray absorptiometry and computed tomography. Glucose disposal rates (R_d) were measured during euglycemic hyperinsulinemia (40 mU · m^{-2} · min^{-1}), and substrate oxidation was determined via indirect calorimetry. Fat mass and regional fat depots were reduced and Vo_{2max} improved by 19%, from 38.8 ± 1.2 to 46.0 ± 1.0 ml · kg fat-free mass (FFM)$^{-1}$ · min^{-1} ($P < 0.05$). Insulin sensitivity improved 49 ± 10% (6.70 ± 0.40 to 9.51 ± 0.51 mg · min^{-1} · kg FFM^{-1}; $P < 0.05$). Rates of fat oxidation following an overnight fast increased (1.16 ± 0.06 to 1.36 ± 0.05 mg · min^{-1} · kg FFM^{-1}; $P < 0.05$), and the proportion of energy derived from fat increased from 38 to 52%. The strongest predictor of the improved insulin sensitivity was enhanced fasting rates of fat oxidation, accounting for 52% of the variance. In conclusion, exercise combined with weight loss enhances postabsorptive fat oxidation, which appears to be a key aspect of the improvement in insulin sensitivity in obesity. *Diabetes* 52:2191–2197, 2003

Obesity and physical inactivity are risk factors for the development of type 2 diabetes and other aspects of the metabolic syndrome and are attributed to insulin resistance (1–5). Currently, it is recommended that overweight and obese individuals undertake moderate weight loss combined with increased physical activity to lessen these risks (6,7) and reduce the risk for developing type 2 diabetes (8–10). While physical activity and weight loss are generally recommended as a combined intervention, there continues to be uncertainty and debate regarding their respective effects on insulin resistance. There is a clear consensus that weight loss reduces insulin resistance (11). It is less clear whether exercise achieves this effect independent of concomitant weight loss. A single bout of exercise can acutely improve insulin sensitivity, but this effect dissipates over several days (12–15). Longer-term exercise interventions revealed little effect to improve insulin sensitivity if changes in weight were prevented (16) or if changes in weight attained during increased physical activity are matched to those attained by restriction of calorie intake (17). These data raise questions as to whether physical activity has effects additive to weight loss in the treatment of insulin resistance.

To address this issue, it is potentially valuable to ascertain several aspects of skeletal muscle insulin resistance that can be characterized by both reduced rates of insulin-stimulated glucose utilization and reduced reliance upon fat oxidation during fasting conditions (18,19). Our group has shown that metabolic inflexibility in fat oxidation is a component of skeletal muscle insulin resistance in obesity and type 2 diabetes (18). Other investigators have also noted an impaired capacity for lipid oxidation in skeletal muscle in obesity (20). Lower rates of fat oxidation predict weight gain (21) and risk for weight regain following weight loss (22). In contrast, it is noteworthy that physically trained individuals typically manifest both a high degree of insulin sensitivity for glucose disposal (23) and a high reliance upon fat oxidation by skeletal muscle during physical activity (24). In a recent intervention study in overweight and obese individuals, we observed that weight loss improved insulin-stimulated glucose utilization but did not alter fasting rates of lipid oxidation (18). Therefore, in the current study, we sought to determine whether the addition of physical activity to a weight loss program would influence fasting patterns of lipid oxidation and contribute to improved insulin resistance. To provide an appropriate context for assessing the additional effect of physical activity to those of weight loss, the current study also included several measures of body composition with emphasis upon regional fat distribution and, in particular, accumulation of fat within the abdomen and skeletal muscle.

RESEARCH DESIGN AND METHODS

Subjects. The primary study group consisted of 25 obese (BMI >30 kg/m^2) volunteers (9 men and 16 women), aged 39.0 ± 4 years, who participated in a combined program of exercise and caloric restriction–induced weight loss. An additional seven normal weight volunteers (four women and three men)

From the Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to David E. Kelley, Division of Endocrinology and Metabolism, University of Pittsburgh Department of Medicine, 3459 Fifth Ave., Montefiore Hospital, N809, Pittsburgh, PA 15213. E-mail: kelley@msx.dept-med.pitt.edu.

Received for publication 24 December 2002 and accepted in revised form 19 May 2003.

CT, computed tomography; FFM, fat-free mass; FM, fat mass; OGTT, oral glucose tolerance test; R_d, glucose disposal rate; RQ, respiratory quotient.

completed an identical physical activity program but without weight loss. Improvements in insulin sensitivity in these two groups were also compared with a subset of obese men ($n = 6$) and women ($n = 10$) in a separate intervention (18) who had lost a similar amount of weight and total body fat through caloric restriction but without exercise. Baseline characteristics, including BMI, insulin sensitivity, and age, were similar in these two obese groups.

Volunteers were weight stable (±2 kg body wt) for at least 6 months before the study. None of the volunteers had type 2 diabetes, nor were they participating in any regular exercise before the study. Individuals with coronary heart disease, peripheral vascular disease, or clinically significant hyperlipidemia (plasma triglycerides >3.95 mmol/l or total cholesterol levels >7.76 mmol/l) were excluded. Individuals with treated or untreated hypertension were excluded. The protocol was approved by the University of Pittsburgh Institutional Review Board, and all volunteers gave written informed consent.

Dual-energy X-ray absorptiometry. Whole-body fat mass (FM) and fat-free mass (FFM) were assessed by dual-energy X-ray absorptiometry (Lunar model DPX-L; Lunar, Madison, WI) using software version 1.3Z.

Computed tomography. Cross-sectional areas and location of adipose tissue within the abdomen and thigh were determined using computed tomography (CT) imaging (9800 CT scanner; General Electric, Milwaukee, WI) and commercially available software (Sice-O-Matic; Tomovision, Montreal, Canada). Abdominal subcutaneous and visceral adipose tissue were measured in one image acquired at the L4-L5 vertebral disc space using an established method (25). Mid-thigh muscle, adipose tissue, and muscle attenuation characteristics were also determined with CT, defined by regions of interest with attenuation values for adipose tissue (−30 to −190 Hounsfield units; [HU]) and skeletal muscle (0–100 HU). Muscle area was further characterized by its mean attenuation value within that range, representing a marker of muscle lipid content such that lower attenuation values reflect higher lipid content (26). Thigh adipose tissue was further distinguished by manual tracings as intermuscular thigh adipose tissue, subfascial adipose tissue, and subcutaneous adipose tissue, as described previously (27).

Maximal aerobic capacity. Maximal aerobic capacity ($V_{O_{2max}}$) was measured using an incremental protocol on an electronically braked cycle ergometer (Sensormedics, Yorba Linda, CA). Heart rate, blood pressure, and electrocardiogram were recorded before, during, and immediately following this test. Oxygen consumption (V_{O_2}) was calculated via direct calorimetry (Sensormedics 2900). The heart rate–V_{O_2} relationship was plotted for each person in order to provide individualized exercise intensity prescriptions and also to estimate energy expenditure during their exercise sessions. The exercise test was terminated when the subject reached volitional exhaustion or had a respiratory exchange ratio (RER) ≥1.15.

Oral glucose tolerance test. At ~8:00 A.M. at the General Clinical Research Center, following an overnight fast, subjects ingested 40 g · body surface area (m^{-2}) of a glucose solution (NERL Diagnostics, East Providence, RI). Plasma glucose and insulin were measured before glucose ingestion and at 30, 60, 90, and 120 min following glucose ingestion. Total area under the oral glucose tolerance test (OGTT) curve for glucose was computed using a trapezoid approximation procedure, using zero as the baseline.

Insulin sensitivity. Insulin sensitivity was determined as the rate of glucose disposal R_d during the last 30 min of a 4-h hyperinsulinemic (40 mU · m^{-2} · min^{-1})-euglycemic clamp. Subjects were instructed to consume a weight-maintaining diet containing at least 200 g carbohydrate for at least 3 days before measurements of insulin sensitivity and to avoid strenuous activity for 36–48 h preceding these studies. Postintervention metabolic assessments were performed 36–48 h following the last exercise session. On the evening before measurement of insulin sensitivity, subjects received a standard dinner (42 kJ/kg; 50% carbohydrate, 30% fat, 20% protein) and then fasted overnight in the General Clinical Research Center until completion of the glucose and insulin infusions. A catheter was placed in a forearm vein for the insulin infusion (Humulin; Eli Lilly, Indianapolis, IN), and an additional catheter was inserted into a radial artery for blood sampling. Euglycemia was maintained using an adjustable infusion of 20% dextrose. No tracer was administered to determine glucose disposal since hepatic glucose production was expected to be completely suppressed at this insulin infusion rate in these nondiabetic volunteers. Plasma glucose was determined at 5-min intervals during the clamp.

Systemic fat oxidation. Whole-body indirect calorimetry was performed in the postabsorptive state and during the last 30 min of insulin infusion, using an open-circuit spirometry metabolic monitor system (DeltaTrac, Anaheim, CA), in order to calculate fat and glucose oxidation from respiratory gas exchange (28). An overnight, timed urine collection (~12 h duration) was obtained to estimate whole-body protein oxidation.

TABLE 1
Changes in body composition and physical fitness during combined exercise and caloric restriction

	n	Pre	Post
Body weight (kg)	25	98.1 ± 2.3	90.4 ± 2.6*
Total body fat (kg)	25	36.5 ± 1.7	30.5 ± 1.9*
FFM (kg)	25	61.6 ± 2.5	59.1 ± 2.4*
BMI (kg/m^2)	25	33.5 ± 0.7	30.9 ± 0.8*
Visceral adipose tissue (cm^2)	17	162.8 ± 14.4	118.0 ± 8.8*
Subcutaneous abdominal adipose tissue	15	426.9 ± 32.7	342.1 ± 33.1*
Subfascial thigh adipose tissue	17	8.9 ± 0.9	6.9 ± 0.7*
Intermuscular thigh adipose tissue	17	4.6 ± 0.6	2.9 ± 0.5*
Subcutaneous thigh adipose tissue	17	141.4 ± 19.7	114.4 ± 15.7*
Muscle attenuation (HU)	17	50.9 ± 0.6	49.6 ± 0.7
$V_{O_{2max}}$ (ml · kg FFM^{-1} · min^{-1})	25	38.8 ± 1.2	46.0 ± 1.4*

Data are means ± SE. *Significantly different from before intervention, $P < 0.05$. CT data were obtained and analyzed for 17 volunteers. HU, Hounsfield units.

Exercise training protocol. A 16-week program of exercise training was conducted after completion of baseline metabolic and body composition assessments. Subjects were asked to participate in a minimum of four and a maximum of six exercise sessions weekly. At least one exercise session per week was supervised for each participant to assure that the target exercise intensity and duration was achieved. Subjects were instructed on the proper use of a wireless heart rate monitors (Polar, Kempele, Finland) to record exercise duration and mean heart rate for estimation of weekly caloric expenditure. Logs of exercise sessions were kept, including exercise duration and average heart rate. For the first 4 weeks, subjects were instructed to exercise for at least 30 min per session at an intensity of 60–70% of their maximal heart rate. At week 8, volunteers performed a submaximal V_{O_2} exercise test on a cycle ergometer to reestablish the heart rate–energy expenditure relationship. During weeks 5–8, exercise sessions were increased to 40 min at the same intensity. During weeks 9–16, exercise sessions were continued at 40 min and the intensity increased to 75% of maximal heart rate.

Energy restriction–induced weight loss. To achieve a goal of 10% weight loss, a reduction of 500–1,000 kcal/day (based on recent food records/history) and low-fat (<30% of calories from fat) diet was implemented. The weight loss program was administered individually to subjects, so that a nutritionist/behaviorist met with each subject weekly and body weight was recorded. All subjects kept detailed 7-day food records for the entire 16-week intervention. The 16-week caloric restriction–induced weight loss program conducted in the subset of obese individuals has been described previously (29).

Analyses. Plasma glucose during the OGTT and glucose clamp were measured using an automated glucose oxidase reaction (2300 Glucose Analyzer; YSI, Yellow Springs, OH). Serum insulin was determined using commercially available radioimmunoassay kits (Pharmacia, Uppsala, Sweden).

Statistical analysis. Data are presented as mean ± SE, unless otherwise indicated. Changes in whole-body fatty acid oxidation, insulin sensitivity (R_d), physical fitness ($V_{O_{2max}}$), and body composition were compared using paired t tests. Differences in insulin sensitivity among the intervention groups were examined using a two-way ANOVA (group × time). Bivariate and multivariate linear regression analysis was used to determine whether the changes in physical fitness, fatty acid oxidation, or body composition were associated with improvements in insulin sensitivity. All statistics were performed using JMP version 3.1.6 for the Macintosh (SAS, Cary, NC).

RESULTS

Body composition changes. At completion of the intervention, volunteers had lost an average of 8% (7.7 ± 1.1 kg) of initial body weight. Most of this was comprised of the loss of fat mass (5.8 ± 0.8 kg), which represented a mean loss of 19% of fat mass, as shown in Table 1, along with

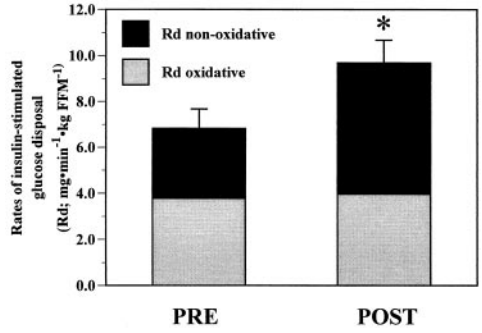

FIG. 1. Improvements in insulin sensitivity with combined diet and exercise. *Significantly different ($P < 0.05$) from before intervention.

other changes in body composition. There was a modest decrease in FFM.

All volunteers underwent CT imaging for regional fat distribution, but unfortunately CT data for eight subjects were lost due to irreparable damage to a storage disk. Of those subjects for whom CT data are available, abdominal visceral adipose tissue was reduced by 24% and, similarly, subcutaneous abdominal adipose tissue was decreased by 21% (Table 1). Within the thigh, the largest absolute loss was of subcutaneous thigh adipose tissue, but as a proportion of baseline, loss of intermuscular thigh adipose tissue was greatest at 32% ($P < 0.05$), as compared with the loss of subcutaneous (21%) or subfascial (17%) adipose tissue. Mean muscle attenuation values did not change. Of the changes in regional fat depots, only the change in visceral fat was different in men and women; men lost significantly more visceral fat than women (35 vs. 15% loss, $P < 0.05$).

Improvement in physical fitness. Physical fitness (Vo_{2max}) increased on average by 19.5 ± 2.8% (Table 1). Average weekly exercise energy expenditure for the group was 1,114 ± 124 kcal/week. The average intensity per exercise session was 7.4 ± 0.5 kcal/min, and the average energy expenditure per exercise session was 252 ± 20 kcal. Although the exercise prescription was based on uniform guidelines, there was considerable variation among participants in their average duration and intensity of exercise.

Improvement in insulin sensitivity. Exercise combined with caloric restriction improved ($P < 0.01$) insulin sensitivity by 49 ± 10% (Fig. 1) and was not different in men and women. Of the 25 volunteers who completed the intervention, only 2 subjects failed to exhibit improvements in insulin sensitivity. Improvement in insulin sensitivity was due entirely to an improvement in nonoxidative glucose disposal, which increased by 159 ± 35%. There was no change in rates of insulin-stimulated glucose oxidation (Fig. 1 and Table 2). Systemic energy expenditure during insulin-stimulated conditions was not altered by the intervention (Table 2).

Oral glucose tolerance did not change as a result of the intervention (area under the curve: pre-OGTT 846 ± 34 mmol · l^{-1} · min^{-1}; post-OGTT 849 ± 33 mmol · l^{-1} · min^{-1}), and insulin secretion during the OGTT, as reflected by the 2-h insulin value, was only modestly reduced ($P < 0.05$) from 49.9 ± 7.6 to 38.3 ± 5.6 μU/ml.

Changes in fasting substrate oxidation. The rate of systemic energy expenditure expressed per kilogram FFM did not change following intervention (Table 2), though the absolute rate of energy expenditure was reduced, reflecting a reduction in FFM (Table 1). Systemic postabsorptive respiratory quotient (RQ) was significantly lower following intervention, reflecting a 25% increase ($P < 0.01$) in resting fat oxidation. Correspondingly, postabsorptive glucose oxidation was significantly reduced (Table 2). The proportion of energy derived from fat oxidation during fasting conditions increased from 38 ± 3 to 52 ± 3%. The contribution of protein oxidation during postabsorptive conditions was minor (7.0 ± 0.5 mg/min; <4%) and did not change following intervention. The intensity of exercise and the amount of weekly exercise performed, but not changes in fat mass, were correlated with the change in fasting RQ (Table 3).

TABLE 2
Changes in systemic energy expenditure and substrate oxidation during insulin-stimulated and fasting conditions

	Pre	Post
Fasting		
Energy expenditure (kcal · kg FFM^{-1} · 24 h^{-1})	31.1 ± 0.7	31.1 ± 0.6
RQ	0.82 ± 0.07	0.79 ± 0.06*
Fat oxidation (mg · min^{-1} · kg FFM^{-1})	1.16 ± 0.06	1.36 ± 0.05*
Glucose oxidation (mg · min^{-1} · kg FFM^{-1})	1.99 ± 0.14	1.38 ± 0.14*
Insulin-stimulated		
Energy expenditure (kcal · kg FFM^{-1} · 24 h^{-1})	31.5 ± 0.6	32.2 ± 0.6
RQ	0.91 ± 0.07†	0.91 ± 0.06†
Fat oxidation (mg · min^{-1} · kg FFM^{-1})	0.48 ± 0.05†	0.42 ± 0.04†
Glucose oxidation (mg · min^{-1} · kg FFM^{-1})	3.78 ± 0.19†	3.96 ± 0.18†

Data are means ± SE. *Significantly different ($P < 0.05$) from before intervention; †significantly different ($P < 0.05$) change from fasted to insulin-simulated conditions.

Predictors of improved insulin sensitivity. We examined, initially using bivariate analyses, potential correlates of the improvement in insulin-stimulated glucose metabolism induced by the weight loss and physical activity intervention. We also examined whether there were baseline (preintervention) characteristics that were predictive of the intervention-induced change in insulin sensitivity (Table 4). Those who were more insulin resistant before the intervention had greater improvements in insulin sen-

TABLE 3
Predictors of systemic RQ following exercise and diet-induced weight loss

Change predictor variable	Δ RQ (r)	P value
Total body fat (kg)	0.03	0.44
FFM (kg)	0.06	0.24
Vo_{2max} (ml · min^{-1} · kg FFM^{-1})	0.17	0.04
Mean exercise intensity (kcal/min)	0.26	<0.01
Weekly exercise energy expenditure (kcal)	0.31	<0.01

Simple correlation coefficients (r) determined using simple linear regression analysis. Exercise intensity and energy expenditure were estimated from individual heart rate–Vo_2 relationships during each exercise session. Δ, change as a continuous variable from pre- to postintervention.

TABLE 4
Predictors of improved insulin sensitivity following exercise and diet-induced weight loss

	Δ Insulin sensitivity (r)	P value
Baseline predictor variable		
Total body fat (kg)	0.24	0.23
Subcutaneous abdominal fat (cm^2)	0.22	0.39
Visceral abdominal fat (cm^2)	0.14	0.60
Subcutaneous thigh fat (cm^2)	0.10	0.70
Subfascial thigh fat (cm^2)	0.13	0.65
$V_{O_{2max}}$ ($ml \cdot min^{-1} \cdot kg\ FFM^{-1}$)	0.30	0.14
Insulin sensitivity ($mg \cdot min^{-1} \cdot kg\ FFM^{-1}$)	0.41	0.04
Systemic RQ	0.44	0.03
Fasting fatty acid oxidation ($mg \cdot min^{-1} \cdot kg\ FFM^{-1}$)	0.30	0.15
Change predictor variable		
Δ Total body fat (kg)	0.53	<0.01
Δ Subcutaneous abdominal fat (cm^2)	0.69	<0.01
Δ Visceral abdominal fat (cm^2)	0.22	0.36
Δ Subcutaneous thigh fat (cm^2)	0.42	0.10
Δ Subfascial thigh fat (cm^2)	0.60	<0.01
Δ $V_{O_{2max}}$ ($ml \cdot min^{-1} \cdot kg\ FFM^{-1}$)	0.38	0.059
Exercise energy expenditure ($kcal \cdot week^{-1}$)	0.32	0.11
Δ Systemic RQ	0.71	<0.01
Δ Fasting fatty acid oxidation ($mg \cdot min^{-1} \cdot kg\ FFM^{-1}$)	0.62	<0.01

Simple correlation coefficients (r) determined using simple linear regression analysis. Exercise energy expenditure was estimated from individual heart rate–V_{O_2} relationships during each exercise session. Δ, change as a continuous variable from pre- to postintervention.

sitivity, as did those who had low fasting rates of fat oxidation at baseline. This may imply that those who need the intervention the most, i.e., those who are more insulin resistant, are indeed the ones who benefit the most (have greater improvements). It is possible, however, that this was influenced by regression to the mean, resulting in an overestimation of the association between baseline and change values. Initial patterns of adipose tissue distribution or level of physical fitness did not predict improved insulin sensitivity.

Next, we examined whether changes induced in body composition, fitness, and fasting metabolism predicted the improvement in insulin sensitivity (Table 4). The loss of total body fat, subcutaneous abdominal fat, and subfascial thigh fat, but not the selective loss of visceral fat or subcutaneous thigh fat, was associated with the improved insulin sensitivity. Changes in $V_{O_{2max}}$ and exercise energy expenditure tended to be associated with the improved insulin sensitivity. However, the strongest simple correlate with improved insulin sensitivity was increased fasting rates of fat oxidation and, accordingly, the reduced fasting RQ, as shown in Table 3 and Fig. 2. Similar associations were observed with respect to the nonoxidative component of insulin sensitivity.

Stepwise multivariate regression analysis was then used to examine the interaction and interdependence of these changes in physiologic and body composition parameters. Increased fasting rates of fat oxidation emerged as the strongest predictor of improved insulin sensitivity, accounting for 52% of the variance. After accounting for increases in fasting rates of fat oxidation, the selective loss of subfascial thigh fat emerged next, followed by the loss in total body fat as independent predictors of this improvement. These three variables combined to account for 84% of the variance in the improvement in insulin sensitivity. Enhanced postabsorptive fat oxidation remained a significant correlate of improved insulin sensitivity after adjusting for the loss of body fat or improved physical fitness in the model.

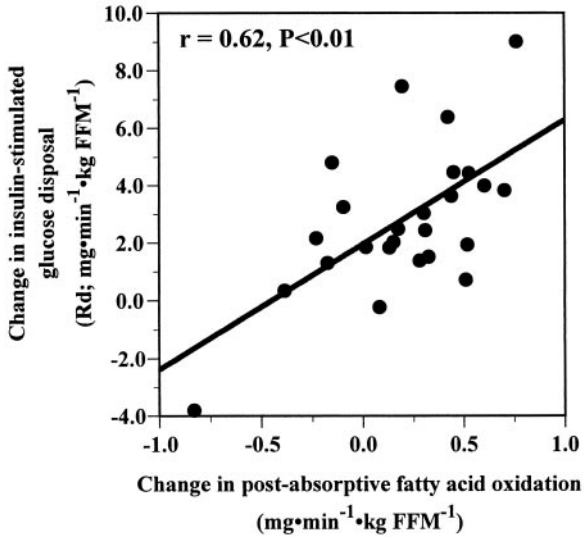

FIG. 2. Relation of fatty acid oxidation to improvement in insulin sensitivity. This association remains significant ($P < 0.05$) after omitting the apparent outlier in the bottom left.

Exercise plus weight loss versus weight loss alone. To further examine whether the addition of physical activity provided more metabolic benefit than weight loss alone, we compared the findings from the current research volunteers with that attained in a separate group of obese subjects (BMI 33.3 ± 2.7 kg/m^2) who had completed a weight loss intervention without physical activity and with a nonobese group who completed a physical activity intervention without concomitant weight loss. Figure 3 illustrates the improvements in insulin sensitivity in a subset of men and women (9 women and 7 men) who completed the exercise and caloric restriction interven-

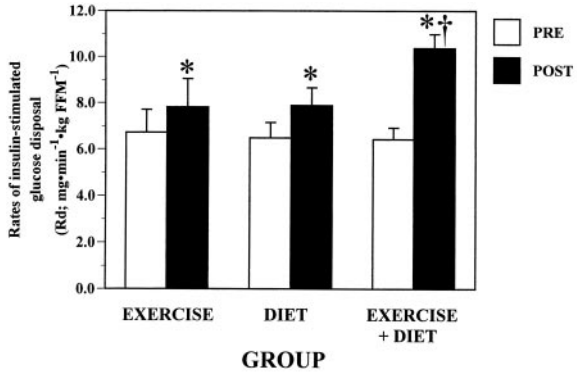

FIG. 3. Improvements in insulin sensitivity by weight loss with exercise, weight loss without exercise, or exercise without weight loss. *Significantly different ($P < 0.05$) from before intervention; †significantly greater ($P < 0.05$) improvement in insulin sensitivity compared with either the exercise or diet groups.

tion, as compared with those who either completed a program of caloric restriction only (29) (10 women and 6 men) or exercise without weight loss (4 women and 3 men). The subset of individuals from the two groups were matched for fat mass lost: 7.7 ± 0.8 kg in the group who exercised and 7.8 ± 0.7 kg for the group who lost weight without exercise. Subjects in these groups were of similar age (36 ± 5, 38 ± 6, and 39 ± 5 years for exercise-only, diet-only, and exercise plus diet groups, respectively). Identical protocols, including timing of the glucose clamps following intervention, were followed in each of these three groups, although it is possible that the separate interventions were confounded by time effects. Improvements in insulin sensitivity were similar in those who exercised without weight loss (16%) and in those who lost weight without exercise (22%). The improvement in the group who combined dieting with exercise, however, was 61%, indicating a threefold higher ($P < 0.01$) improvement in insulin sensitivity compared with either the exercise-only group or the weight loss–only group.

DISCUSSION

Physical activity and moderate sustained weight loss are advocated for the treatment of obesity, the insulin resistance syndrome, and the prevention of type 2 diabetes. It is not clear how physical activity and weight loss interact in achieving these effects. Even a single session of moderate to strenuous intensity exercise can induce a transient improvement in insulin sensitivity (13), effects that appear to wane within a few days (15). Exercise also increases oxidative enzyme activity in skeletal muscle and induces related biochemical and morphologic changes that would seem to confer a metabolic basis for improved insulin sensitivity. However, in clinical interventions carefully controlled with respect to matching energy balance, exercise in the absence of weight loss has been found to have modest (17,30) or no (16) effect on insulin sensitivity. These findings have suggested that exercise might be of lesser value than weight loss as an intervention for the insulin resistance syndrome. We sought to address this apparent conundrum in two ways. First, we employed exercise interventions in conjunction with weight loss, an intervention model that more appropriately matches clinical recommendations than either intervention in isolation. Second, we sought to employ a more comprehensive characterization of "insulin resistance," including aspects of both insulin-stimulated and fasting metabolism.

The improvement in insulin sensitivity in these obese subjects was greater than those observed for other studies examining exercise or weight loss alone (16,17). Similarly, Bogardus et al. (30) reported a 27% improvement in insulin sensitivity when exercise was superimposed upon diet, as compared with no improvement with diet only. Ross et al. (17) found that weight loss induced by either caloric restriction or exercise improved insulin sensitivity by 60%, as compared with a 30% increase with exercise without weight loss. Therefore, these results suggest a synergistic effect of weight loss and exercise to improve insulin resistance. The timing of the insulin sensitivity measure after the last exercise bout could also affect the magnitude of the improvements in insulin sensitivity across studies. It is important to account for the influence of acute exercise on insulin sensitivity. On the other hand, delaying the insulin sensitivity measure too long after the last exercise may result in a "de-training" effect and thereby mask the effects of chronic exercise. We chose 36–48 h after the last exercise bout to perform the glucose clamp to avoid both the acute exercise effects and potential de-training effects. This likely contributed to greater improvements with exercise training compared with other studies that performed the insulin sensitivity measure 4–6 days following the last exercise bout (16,17,30).

Improved insulin sensitivity through either weight loss or exercise has been associated with the loss of abdominal visceral fat (17,29). Obese subjects in the present study lost a significant amount of fat from several region-specific depots, including abdominal fat and subfascial thigh fat. In multivariate analysis, only the loss of subfascial thigh fat was independently correlated with the improvement in insulin sensitivity after adjusting for the change in systemic fatty acid oxidation. The attenuation of muscle on CT as a marker of muscle lipid (26) did not change, although muscle attenuation can increase with diet-induced weight loss (29). However, lipid within muscle can be higher in endurance-trained athletes (23), raising the possibility that weight loss and exercise have counterbalancing effects on muscle lipid, perhaps explaining the lack of change in muscle attenuation.

Our findings indicate that the combination of exercise and weight loss enhances not only the insulin-stimulated capacity for glucose utilization, but also enhances the capacity for fat oxidation during fasting conditions. The improvement in fat oxidation during fasting conditions was associated with characteristics specific for the exercise intervention, namely intensity and duration of physical activity, but was not associated significantly with overall or regional loss of adiposity. In turn, the magnitude of improvement in insulin-stimulated glucose metabolism was strongly related to the concomitant increase in fat oxidation during fasting conditions.

Impaired insulin-stimulated glucose metabolism is the most well-established manifestation of skeletal muscle insulin resistance, but it is also recognized that another very important facet of skeletal muscle insulin resistance is altered patterns of fat oxidation. Normally, insulin effectively suppresses fat oxidation (31), but this suppression of fat oxidation is impaired in insulin resistance (18). Additionally, it has long been noted that in those with normal insulin sensitivity, skeletal muscle has a high reliance upon fat oxidation during fasting conditions (32). In contrast, among those with obesity and insulin resistance, and in those with type 2 diabetes, fasting rates of fat oxidation are reduced in skeletal muscle (19). The decrease in fasting rates of fat oxidation and the lack of further suppression of fat oxidation during insulin are facets of insulin resistance that we have previously characterized as "metabolic inflexibility" (33). In prior cross-sectional studies, we observed that impaired fat oxidation during fasting predicts severity of insulin-resistant glucose metabolism (18). We had also noted that following diet-induced weight loss, but without changes in patterns of physical activity, there was improvement in insulin-stimulated glucose metabolism but there was not a significant change in fasting rates of fat oxidation (18). Thus, in

weight loss without exercise, there appeared to be a separation in the effects on those aspects of insulin resistance related to insulin-stimulated glucose metabolism from those aspects regulating rates of fat oxidation. The current study sought to probe whether the addition of exercise might address insulin resistance in a manner different from weight loss alone.

There are several conceptual reasons to postulate that physical activity might modify the aspects of insulin resistance related to the capacity for fat oxidation. First, exercise training at moderate intensity is typically associated with induction of a higher capacity for, and reliance upon, fat oxidation during the exercise session (34). Second, chronic exercise effects, namely increased activity of oxidative enzymes and increased capillary density, might facilitate fatty acid utilization both at rest and during physical activity. Another consideration is perhaps more conceptual and is related to the "negative energy balance," whereby during negative energy balance created by calorie reduction, muscle has a relatively passive role. In contrast, during physical activity, muscle generates a negative energy balance and is comprised of consumption of muscle glycogen and muscle triglyceride (24,35).

In contrast to the decrease in energy expenditure induced by weight loss through reductions in caloric intake (18), the lack of change in resting energy expenditure despite weight loss was likely due to the exercise component. Therefore, the current findings that an exercise intervention increases the reliance on fat oxidation while maintaining resting energy expenditure are in accord with these prior observations. The novel finding of the current study that helps to extend the clinical implications of these prior data is that the augmentation of resting rates of fat oxidation are a specific metabolic correlate of the amplitude of improvement in insulin sensitivity.

In summary, the improvement in insulin sensitivity resulting from a program combining exercise and diet is associated with an increased reliance on fat oxidation during fasted conditions. This enhanced fat oxidation is likely due to exercise and not caloric restriction. Therefore, the greater improvements in insulin sensitivity in obese subjects who perform regular exercise with weight loss, as compared with those who lose weight without exercise, are likely mediated by changes in skeletal muscle fatty acid metabolism.

ACKNOWLEDGMENTS

This work was funded by R01DK-49200-04 (to D.E.K), K24 DK02782 (to D.E.K), and K01-AG-00851 (to B.H.G) and by the Obesity Nutrition Research (1P30DK46204) and General Clinical Research (5 M01RR00056) Centers.

We thank the volunteers for their participation in this study. We appreciate the time, dedication, and effort of the intervention staff (Pat Harper, Juliet Mancino, Anne Mathews, Donna Wolf, Kellie McCormack, and Sara Fleet) and nurses (Carol Kelley and Janet Krulia).

REFERENCES

1. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS: Physical activity and reduced occurence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
2. Brown MD, Moore GE, Korytkowski MT, McCole SD, Hagberg JM: Improvement of insulin sensitivity by short-term exercise training in hypertensive African American women. *Hypertension* 30:1549–1553, 1997
3. Holloszy JO, Schultz J, Kusnierkiewicz J, Hagberg JM, Ehsani AA: Effects of exercise on glucose tolerance and insulin resistance. *Acta Medica Scandinavica* 711 (Suppl.):55–65, 1980
4. Kopelman PG: Obesity as a medical problem (Review). *Nature* 404:635–643, 2000
5. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN: Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279:669–674, 1998
6. Gordon NF: *The Health Professional's Guide to Diabetes and Exercise*. Alexandria, VA, American Diabetes Association, 1995
7. National Institutes of Health: Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence report. *Obes Res* 6 (Suppl. 2):461–462, 1998
8. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologica* 34:891–898, 1991
9. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
10. Group DPPR: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
11. Pi-Sunyer FX: Short-term medical benefits and adverse effects of weight loss (Review). *Ann Intern Med* 119:722–726, 1993
12. Dela F, LArsen JJ, Mikines KJ, Ploug T, Petersen LN, Galbo H: Insulin-stimulated muscle glucose clearance in patients with NIDDM. *Diabetes* 44:1010–1020, 1995
13. Devlin JT, Hirshman M, Horton ED, Horton ES: Enhanced peripheral and splanchnic insulin sensitivity in NIDDM men after single bout of exercise. *Diabetes* 36:434–439, 1987
14. Devlin JT, Horton ES: Effects of prior high-intensity exercise on glucose metabolism in normal and insulin-resistant men. *Diabetes* 34:973–979, 1985
15. King DS, Baldus PJ, Sharp RL, Kesl LD, Feltmeyer TL, Riddle MS: Time course for exercise-induced alterations in insulin action and glucose tolerance in middle-aged people. *J Appl Physiol* 78:17–22, 1995
16. Segal KR, Edano A, Abalos A, Albu J, Blando L, Tomas MB, Pi-Sunyer FX: Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. *J Appl Physiol* 71:2402–2411, 1991
17. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I: Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med* 133:92–103, 2000
18. Kelley DE, Goodpaster B, Wing RR, Simoneau JA: Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity and weight loss. *Am J Physiol* 277:E1130–E1141, 1999
19. Kelley DE, Simoneau JA: Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. *J Clin Invest* 94:2349–2356, 1994
20. Kim JY, Hickner RC, Cortright RL, Dohm GL, Houmard JA: Lipid oxidation is reduced in obese human skeletal muscle. *Am J Physiol Endocrinol Metab* 279:E1039–E1044, 2000
21. Zurlo F, Lillioja S, Esposito-DelPuente A, Nyomba BL, Raz I, Saad MF, Swiunburn WC, Knowler WC, Bogardus C, Ravussin E: Low ratio of fat to carbohydrate oxidation as a predictor of weight gain: a study of 24-h RQ. *Am J Physiol* 259:E650–E657, 1990
22. Ranneries C, Bulow J, Buemann B, Christensen NJ, Madsen J, Astrup A: Fat metabolism in formerly obese women. *Am J Physiol* 274:E155–E161, 1998
23. Goodpaster BH, He J, Watkins S, Kelley DE: Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. *J Clin Endocrinol Metab* 86:5755–5761, 2001
24. Romijn JA, Coyle EF, Sidossis LS, Gastaldelli A, Horowitz JF, Endert E, Wolfe RR: Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am J Physiol* 265:E380–E391, 1993
25. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE: Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46:1579–1585, 1997
26. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R: Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol* 89:104–110, 2000
27. Goodpaster BH, Thaete FL, Kelley DE: Thigh adipose tissue distribution is

associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr* 71:885–892, 2000
28. Frayn KN: Calculation of substrate oxidation rates in vivo from gaseous exchange. *J Appl Physiol* 55:628–634, 1983
29. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL: Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* 48:839–847, 1999
30. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EA: Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes* 33:311–318, 1984
31. Kelley DE, Reilly J, Veneman T, Mandarino LJ: The influence of physiologic hyperinsulinemia on skeletal muscle glucose storage, oxidation and glycolysis in man. *Am J Physiol* 258:E923–E929, 1990
32. Andres R, Cadar G, Zierler K: The quantitatively minor role of carbohydrate in oxidative metabolism by skeletal muscle in intact man in the basal state. *J Clin Invest* 35:671–682, 1956
33. Kelley DE, Mandarino LJ: Fuel selection in human skeletal muscle in insulin resistance. *Diabetes* 49:677–683, 2000
34. Bergman BC, Butterfield GE, Wolfel EE, Casazza GA, Lopaschuk GD, Brooks GA: Evaluation of exercise and training on muscle lipid metabolism. *Am J Physiol* 276:E106–E117, 1999
35. Goodpaster B, Wolfe R, Kelley D: Effects of obesity on substrate utilization during exercise. *Obes Res* 10:575–584, 2002