Comparison of short-term diet and exercise on insulin action in individuals with abnormal glucose tolerance

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Clinical trials have shown that diet and physical activity interventions are effective in decreasing the incidence and severity of Type 2 diabetes (4, 40, 41). However, there is little information regarding the relative effectiveness of moderately severe caloric restriction and an exercise-training program that is feasible for previously sedentary obese individuals without a major disruption of their lives. In this context, the purpose of this study was to quantitatively compare the effectiveness of 10 days of moderately severe caloric restriction with that of an aerobic exercise program in reversing insulin resistance. Previous studies in this area have used the oral glucose tolerance test (OGTT) to evaluate the effect of exercise on insulin resistance (6, 23). While providing important information, the fact that both the glucose and insulin responses to a glucose load are altered by exercise training makes it impossible to accurately evaluate the effect of an intervention on insulin secretion and insulin action. To avoid this problem, we utilized a modified hyperglycemic clamp to quantify the effect of the diet and exercise intervention on insulin secretion and insulin action.

METHODS

Subjects. Obese men (n = 9) and women (n = 7), aged 53 ± 1 yr, with either IGT (n = 9) or mild Type 2 diabetes mellitus (DM) (n = 7), as defined by the American Diabetes Association (1), provided informed written consent to participate in this study, which was approved by the Washington University Human Studies Committee. All subjects were nonsmokers, had sedentary occupations, and had not exercised regularly (20 min of aerobic activity, 2 days/wk) for 12 mo before the study. This was documented by a physical activity questionnaire (39). All of the women were postmenopausal. The physical and metabolic characteristics of the subjects are detailed in Table 1. The volunteers were randomized to either a low-calorie diet (LCD) group or an exercise-training program (ET) group. All volunteers completed the study. The LCD group consisted of four subjects with IGT and four with Type 2 DM, and the ET group was composed of five subjects with IGT and three with Type 2 DM.

OGTT. A 75-g OGTT was administered in the morning after a 12-h fast to identify eligibility for the study. Only volunteers with IGT or mild Type 2 DM with insulin resistance were enrolled. Volunteers with more severe DM, defined as a significantly blunted insulin response to the OGTT, concurrent with sustained hyperglycemia, were excluded from participation.

Volunteers were instructed to eat a weight-maintaining diet containing at least 150 g/day of carbohydrate for 3 days before the OGTT. These instructions were given orally and in writing and were verified with a 3-day food record (see Diet evaluation). Venous blood samples were obtained in the...
different from LCD, the General Clinical Research Center (GCRC) dietary volunteers received all meals, including a daily multivitamin, estimated from body density by using the equation of Brozek et al. (9).

Maximal aerobic power ($V_{\dot{O}_2max}$) and leisure time physical activity. Treadmill tests with electrocardiogram and blood pressure (BP) monitoring were performed to determine $V_{\dot{O}_2max}$, as described by Kohrt et al. (28). Volunteers were excluded from the study if they had evidence of ischaemia or abnormal changes in BP during the treadmill test. The energy expended in leisure time physical activity during the past year was assessed by a structured interview (39).

Diet evaluation. Energy intake was estimated from a 3-day food record before the study was commenced. Each subject was asked to record all foods and beverages ingested for 2 weekdays and 1 weekend day. Subjects were instructed how to carefully record dietary intake. The Nutritionist IV computer program (N-Squared Computing, v3.21; Salem, OR) was used to analyze the diets for energy content as well as relative and absolute quantities of macronutrients.

LCD. The LCD consisted of 50% of the calories required to maintain energy balance. This was determined by predicting resting metabolic rate (RMR) by using the equations of Arciero et al. (2, 3) and multiplying by an activity factor between 1.2 and 1.4, depending on occupation. The composition of the diet, expressed as a percentage of total energy content, was as follows: good quality protein, 35%; carbohydrate, 50%; and fat, 15%. This diet provided ~1.5 g protein/kg fat-free mass (FFM) and a minimum of 150 g of complex carbohydrate for the duration of the study.

ET. The ET program consisted of 50–60 min of daily supervised exercise for 10 days while the subjects maintained normal energy intake based on the method used above (predicted RMR $\times$ activity factor). Thus the negative energy balance induced by ET was equal to the effect of the exercise. The exercise sessions were supervised and consisted of a 10-min warm-up followed by 50 min of aerobic exercise, such as walking, jogging, cycle ergometry, rowing ergometry, or simulated cross-country skiing, concluding with a 10-min cooldown. The exercise intensity was adjusted to require between 60 and 65% of $V_{\dot{O}_2max}$ by monitoring heart rate during the exercise sessions. This was accomplished by using the heart rate values obtained at 60–65% of the measured $V_{\dot{O}_2max}$.

Meal provisions. To precisely control food intake, all of the volunteers received all meals, including a daily multivitamin, from the General Clinical Research Center (GCRC) dietary kitchen. If there was a problem with eating certain meals in the GCRC during the course of a day, meals were provided in a “carryout” fashion. Volunteers were instructed not to alter their current level of physical activity during the 10-day intervention, with the exception of the exercise session for those in the ET group.

Hyperglycemic clamp procedure. Insulin action and secretion were evaluated during a hyperglycemic clamp procedure during which an arginine infusion and fat meal were superimposed on the hyperglycemia (25). Raising blood glucose to a high level, as is routinely done in the hyperglycemic clamp, results in only a modest increase in plasma insulin levels. By superimposing the two additional stimuli to $\beta$-cell insulin secretion, it is possible to raise plasma insulin levels sufficiently in most people to obtain information regarding the increase in glucose disposal induced by a maximally effective insulin stimulus. Furthermore, by using the three stimuli, it is possible to evaluate maximal insulin secretory capacity (25). This protocol also more closely resembles what happens in response to a mixed meal containing protein and fat in addition to carbohydrate.

The clamp procedures were performed at the beginning and end of the 10-day intervention. In the ET group, the final clamp procedure was 14–16 h after the last exercise session. Subjects in both treatment groups consumed at least 150 g carbohydrate/day for the entire treatment period. The meals provided the evening before the initial and final clamp procedures were identical in energy content and composition. Subjects arrived at the GCRC at 7:00 AM after an overnight fast, were asked to void, and were weighed. Subjects remained supine for the duration of the procedure. A polyethylene catheter was inserted into an antecubital vein for the infusion of glucose (20% dextrose), arginine, and potassium phosphate. A second catheter was inserted retrograde into the distal portion of a dorsal hand vein. The hand was kept in a box warmed to 70°C for the duration of the hyperglycemic clamp for sampling of arterialized blood. After 30 min, three baseline blood samples were drawn at 5-min intervals for the determination of fasting glucose and insulin concentrations.

The hyperglycemic clamp procedure involved superimposing on hyperglycemia an infusion of arginine and ingestion of a liquid-fat meal. Plasma glucose concentration was raised to 250 mg/dl within 15 min by using a primed infusion of 20% dextrose. Blood samples for determination of plasma glucose and insulin were obtained at 2, 4, 6, 8, and 10 min to determine the early insulin secretory response to hyperglycemia. The plasma glucose concentration was maintained at 250 mg/dl for an additional 105 min by determining the plasma glucose concentration at 5-min intervals and adjusting the rate of glucose infusion. Plasma insulin concentrations were determined on samples obtained at 10-min intervals throughout the procedure.

Arginine infusion. Forty-five minutes after the start of the glucose infusion, a 5-g dose of arginine hydrochloride (Critical

Table 1. Age, height, weight, and body composition

<table>
<thead>
<tr>
<th></th>
<th>LCD</th>
<th>ET</th>
</tr>
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<tbody>
<tr>
<td>n, women/men</td>
<td>3/5</td>
<td>4/4</td>
</tr>
<tr>
<td>Age, yr</td>
<td>53 ± 1</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 ± 3</td>
<td>170 ± 3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>114.4 ± 5.2</td>
<td>110.3 ± 4.9</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>66.6 ± 4.8</td>
<td>65.9 ± 4.3</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>47.8 ± 3.5</td>
<td>44.4 ± 3.3</td>
</tr>
<tr>
<td>Leisure time physical activity, kcal/day</td>
<td>170 ± 50</td>
<td>128 ± 28</td>
</tr>
<tr>
<td>Food intake during intervention, kcal/day</td>
<td>1,154 ± 53</td>
<td>2,078 ± 74*</td>
</tr>
</tbody>
</table>

Values are means ± SE for n = 8 subjects in each group. LCD, low-calorie diet; ET, exercise training. *Different from LCD, P < 0.01.

Table 2. Effects of interventions on maximal aerobic power, plasma glucose, and plasma insulin

<table>
<thead>
<tr>
<th></th>
<th>Low-Calorie Diet</th>
<th>Exercise Training</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>$V_{\dot{O}_2max}$, ml·min⁻¹·kg⁻¹ FFM⁻¹</td>
<td>32.5 ± 2.2</td>
<td>35.1 ± 3.3</td>
</tr>
<tr>
<td>Fasted plasma glucose, mg/dl</td>
<td>115 ± 10</td>
<td>99 ± 4</td>
</tr>
<tr>
<td>Fasted plasma insulin, µU/ml</td>
<td>23.9 ± 5.6</td>
<td>15.2 ± 3.9</td>
</tr>
</tbody>
</table>

Values are means ± SE. $V_{\dot{O}_2max}$, maximal aerobic power; FFM, fat-free mass. Significantly different from before, *P < 0.05, 1P < 0.01.
Care America, St. Louis, MO) diluted to a total volume of 50 ml with 0.9% NaCl was given over a 1-min period. This is a maximally stimulating dose of arginine. A continuous infusion of arginine at a rate of 15.0 g·m⁻²·h⁻¹ was then started and continued for the remaining 75 min of hyperglycemia.

High-fat meal. Seventy-five minutes into the clamp, volunteers were fed a liquid-fat meal (37.5 ml) containing 25 g of fat (corn oil) (Lipomul; Upjohn, Kalamazoo, MI). After 120 min of glucose infusion, the infusion of arginine was stopped, and the glucose infusion was continued as needed to maintain the plasma glucose concentration at or above the fasting value. Urine was collected throughout the infusion period and immediately after the 120 min of hyperglycemia and pooled for determination of glucose concentration in the urine.

Chemical analyses. The plasma glucose concentration was determined by using the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin was determined with a double-antibody radioimmunoassay (17).

Calculations and statistical analyses. The glucose disposal rate was calculated during each phase of the hyperglycemic clamp (0–45, 45–75, 75–120, 0–120 min) to assess insulin action before and after the intervention programs. The glucose disposal rates (GDRs) are expressed as milligrams per minute per kilogram FFM.

Data were analyzed with a 2 × 2 (group by time) repeated-measures analysis of variance. Insulin responses to hyperglycemia, arginine, and a fat meal were calculated using a computer-based trapezoidal model that summated the area under the curve. Regression equations were generated for the glucose disposal rates relative to the plasma insulin concentrations across the three stages of the clamp procedure for each treatment group before and after treatment. The slopes and intercepts of the regression lines were compared by using t-statistics (15). Statistical significance was accepted at P < 0.05. All data are expressed as means ± SE.

RESULTS

Body weight and composition. As shown in Table 1, the two groups had similar degrees of obesity as reflected in body fat content and body mass index. There were significant decreases in body weight and fat mass within each treatment group, but the changes were significantly greater in response to the LCD (−4.1 ± 1.7 and −3.4 ± 1.0 kg, respectively) than to the ET program (−1.4 ± 0.3 and −1.1 ± 0.8 kg, respectively). This was not surprising, because the estimated average daily energy deficit averaged 1,147 ± 80 kcal for the diet group compared with 421 ± 35 kcal for the exercise group. The fact that body weight and fat mass decreased more than expected on the basis of the estimated energy deficits probably reflects the decrease in body water content that occurs with weight loss and the variability in the estimates of energy balance and the measurement of body composition. The exercise program induced a 7% (35.1 ± 3.3 to 37.7 ± 3.0 ml·min⁻¹·kg FFM⁻¹; P < 0.05) increase in VO₂max over the 10-day period.

Plasma glucose and insulin. Fasting plasma glucose levels were significantly reduced by both the LCD and ET programs (Table 2). Fasting plasma insulin levels were also significantly lower after 10 days of the LCD or ET (Table 2).

Hyperglycemic clamp insulin responses. Data were analyzed with a 2 × 2 (group by time) repeated-measures analysis of variance. Insulin responses to hyperglycemia, arginine, and a fat meal were calculated using a computer-based trapezoidal model that summated the area under the curve. Regression equations were generated for the glucose disposal rates relative to the plasma insulin concentrations across the three stages of the clamp procedure for each treatment group before and after treatment. The slopes and intercepts of the regression lines were compared by using t-statistics (15). Statistical significance was accepted at P < 0.05. All data are expressed as means ± SE.

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Table 3. Average insulin responses during the hyperglycemic clamp before and after 10 days of low-calorie diet or exercise training

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Low-Calorie Diet Before</th>
<th>After</th>
<th>Exercise Training Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–10</td>
<td>48 ± 6</td>
<td>38 ± 7</td>
<td>32 ± 6</td>
<td>17 ± 2*</td>
</tr>
<tr>
<td>10–45</td>
<td>84 ± 20</td>
<td>51 ± 14*</td>
<td>56 ± 13</td>
<td>33 ± 10*</td>
</tr>
<tr>
<td>45–75</td>
<td>509 ± 43</td>
<td>359 ± 47</td>
<td>460 ± 58</td>
<td>271 ± 54</td>
</tr>
<tr>
<td>75–120</td>
<td>873 ± 220</td>
<td>777 ± 227</td>
<td>709 ± 115</td>
<td>462 ± 70</td>
</tr>
</tbody>
</table>

Values are means ± SE given in µU/ml. *Significantly different from before, P < 0.05.
the mean plasma glucose concentrations before and after the intervention were 252 ± 3 vs. 252 ± 1 mg/dl in the LCD group and 251 ± 2 vs. 250 ± 1 mg/dl in the ET group [P = not significant (NS) within and between groups]. Baseline plasma free fatty acid (FFA) concentrations were not significantly different between treatment groups and were not significantly changed in response to the low-calorie diet or the exercise program. FFA levels decreased significantly from 1,106 ± 94 µmol/l at the beginning to 355 ± 46 µmol/l at the end of the clamp procedure.

There was a significant decrease in the insulin response to hyperglycemia in response to the interventions in both groups (Fig. 1). The area under the insulin curve for the early phase of hyperglycemia (0–10 min) was reduced by an average of 46% (P < 0.01) in the ET group but only 21% (P = NS) in the LCD group (Table 3). The late (10–45 min)- phase insulin response to hyperglycemia was reduced by 33 and 41% in response to exercise and caloric restriction, respectively (both P < 0.05; Table 3).

The plasma insulin responses to the infusion of arginine were reduced, although not significantly, by 17 and 36% in response to LCD and ET, respectively (Fig. 1, Table 3). Similarly, the plasma insulin response to the combined stimulation by hyperglycemia, arginine, and a liquid high-fat meal was reduced, although not significantly, by an average of 25 and 41% in the LCD and ET groups, respectively (both P < 0.05; Table 3).

GDR. In the LCD group, the GDR was significantly greater (35%) during the 75- to 120-min period, i.e., in response to all three stimuli (Fig. 2; 8.7 ± 1.8 vs. 11.6 ± 1.5 mg·min⁻¹·kg FFM⁻¹; P < 0.01). However, in the ET group, the GDR was increased after the 10-day intervention by 53% in response to hyperglycemia plus arginine (5.2 ± 0.9 vs. 7.9 ± 0.6 mg·min⁻¹·kg FFM⁻¹; P < 0.01), by 87% in response to hyperglycemia plus arginine plus a fat meal (7.1 ± 1.8 vs. 13.2 ± 1.5 mg·min⁻¹·kg FFM⁻¹; P < 0.01), and by 56% during the entire clamp procedure (5.0 ± 1.0 vs. 7.7 ± 0.8 mg·min⁻¹·kg FFM⁻¹; P < 0.01).

When the GDRs during the three phases of the clamp procedure were plotted relative to the corresponding plasma insulin levels, there was no difference between the groups in insulin action before the intervention (Fig. 3). Insulin action was significantly increased in response to both the LCD and ET, as evidenced by significant increases in the slopes of the regression lines. Furthermore, the improvement was significantly greater in the ET group than in the LCD group.

**DISCUSSION**

The purpose of this study was to compare the effectiveness of a practical exercise program with that of a...
moderately severe restriction of caloric intake in reversing insulin resistance in obese individuals with IGT or mild Type 2 DM. The exercise sessions were designed to be of an intensity and duration that sedentary obese individuals could manage without becoming so fatigued as to interfere with their work or other usual activities. As a consequence, the magnitude of the negative energy balance induced by the LCD was >2.5 times greater than that caused by the ET. It appears well documented that negative caloric balance, resulting in loss, instead of storage, of fat, results in a rapid improvement in insulin action in obese individuals who are insulin resistant (18, 19, 23, 33). In this study, the ET program resulted in a significantly greater improvement in glucose disposal at the same insulin concentrations than did the LCD, despite inducing a much smaller caloric deficit. This finding is in keeping with the extensive evidence that exercise, in addition to increasing energy expenditure, induces large increases in the sensitivity and responsiveness of skeletal muscle to insulin (6, 8, 12, 13, 20).

Studies on humans have shown that individuals who exercise regularly are much less resistant to the action of insulin on glucose disposal than are otherwise comparable sedentary individuals (12, 14, 24, 30, 32, 36, 38). It is not possible to accurately distinguish between improved insulin sensitivity and improved insulin responsiveness in vivo, because glucose delivery becomes limiting at the unphysiologically high insulin concentrations needed to elicit a maximal response (7). However, studies in which muscles were perfused or incubated in vitro with different insulin concentrations have shown that exercise improves both the sensitivity and responsiveness of skeletal muscle to insulin (20). The increase in muscle insulin sensitivity after a bout of exercise occurs as the acute insulin-independent stimulation of glucose transport by exercise wears off. It appears from studies on rats that the increase in muscle insulin sensitivity persists as long as muscle glycogen supercompensation does not occur (10).

While the mechanism responsible for the increase in insulin sensitivity has not yet been elucidated, the improvement in insulin responsiveness is mediated by an exercise-induced increase in the GLUT-4 isoform of the glucose transporter in skeletal muscle (20). Large increases in muscle GLUT-4 content have been observed in skeletal muscles of humans and rats after a few days (2–10 days) of exercise (20). The GLUT-4 glucose transporter, which moves into the plasma membrane from intracellular sites in response to insulin, mediates the transport of glucose into the cell. Increases in muscle GLUT-4 content are associated with increases in insulin-stimulated glucose transport (20). Muscle biopsies for measurement of GLUT-4 were not obtained in the present study. However, exercise programs of similar or shorter duration have been shown to induce increases in muscle GLUT-4 (16, 22, 37), and this adaptation has been observed in response to exercise in similarly deconditioned middle-aged obese patients with Type 2 DM (13). We therefore think that the large improvements in GDR at the same insulin concentrations in the exercised compared with the calorie-restricted subjects in this study are most probably explained by an increase in muscle GLUT-4. This beneficial effect of exercise is short lived because of the rapid turnover of the GLUT-4 protein and therefore requires regularly performed exercise for its maintenance (20).

There is considerable evidence that it is central-visceral obesity, rather than generalized obesity, that is associated with insulin resistance (5, 26). The mechanism by which visceral obesity causes muscle insulin resistance is still not clear. One possibility is that abdominal-visceral fat cells that are in highly positive fat balance produce an insulin resistance factor such as tumor necrosis factor-α (21). Whatever the mechanism, it appears that reversal of insulin resistance occurs rapidly in response to negative energy balance, possibly as a result of fat loss instead of storage in adipocytes, long before there is a major reversal of obesity (18, 19, 23, 33). A LCD is clearly more effective in causing a negative fat balance than is an ET program that is feasible for sedentary obese people with a low exercise capacity. However, as is clearly shown by the present results, even an ET program that is practical for middle-aged obese people has a major beneficial effect on insulin action above and beyond that induced by negative energy balance. Our results provide strong support for the commonly made recommendation that a combination of diet and exercise should be used for the prevention and treatment of the insulin resistance associated with obesity.

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