Effects of an Ad Libitum, High-Carbohydrate Diet and Aerobic Exercise Training on Insulin Action and Muscle Metabolism in Older Men and Women

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Background. Previous studies have demonstrated that aerobic exercise training and weight loss have independent effects on insulin-stimulated glucose disposal (ISGD). We hypothesized that ad libitum consumption of a high-carbohydrate diet would result in weight loss and improved ISGD, and that aerobic exercise training would facilitate greater improvements in ISGD compared with diet alone.

Methods. Older participants (13 women, 9 men; age = 66 ± 1 year) with impaired glucose tolerance were randomly assigned to an ad libitum diet alone (18% fat, 19% protein, 63% carbohydrate) or this diet plus aerobic exercise training (4 d/wk, 45 min/d, 80% VO2peak) for 12 weeks. ISGD, abdominal fat distribution, muscle glycogen, and glycogen synthase activity were assessed pre- and postintervention.

Results. Consumption of the diet resulted in significant weight loss and an improvement in ISGD. Consumption of the diet plus exercise training also resulted in weight loss and increased ISGD, but results were not significantly different from those in the diet-alone group. Mean abdominal visceral and subcutaneous adipose tissue cross-sectional areas were smaller postintervention compared to baseline with no difference between groups. Exercise training and consumption of the diet increased muscle glycogen content (344.7 ± 21.3 to 616.7 ± 34.4 μmol·g−1) and decreased glycogen synthase activity (0.21 ± 0.02 to 0.13 ± 0.01) compared to the diet alone.

Conclusions. These results demonstrate that consumption of an ad libitum, high-carbohydrate diet alone or in combination with aerobic exercise training results in weight loss and improved insulin sensitivity. Furthermore, exercise combined with this diet appears to limit additional increases in insulin sensitivity due to muscle glycogen supercompensation with a concomitant adaptive response of glycogen synthase.

The onset of type 2 diabetes in at-risk populations may be delayed or prevented by moderate decreases in body weight and/or increases in physical activity (1–3). Previous studies also indicate that the effect of lifestyle intervention on insulin sensitivity and diabetes incidence may vary with age, with older adults reported to be both more (2) and less (4) responsive. Uncertainty remains regarding the specific lifestyle modifications that result in the greatest improvement in insulin action in overweight, older men and women with impaired glucose tolerance. In particular, reduction in energy intake in elderly people with low energy requirements may increase the risk of micronutrient and/or protein deficiencies.

A review of epidemiological studies has shown that physically active older individuals exhibit greater glucose tolerance and reduced diabetes incidence compared to sedentary controls, even in statistical models adjusted for age and body mass index (BMI) (5). The results from intervention studies suggest that the effect of exercise on glucose tolerance may be influenced by concomitant losses of body weight. Most studies that have reported an improvement in glucose tolerance with exercise have allowed the exercising participants to lose weight or body fat, making the independent effects of weight loss and aerobic exercise difficult to distinguish. Earlier work by our laboratory (6) and others (7,8) indicated that aerobic exercise training without weight loss results in a small but significant improvement in insulin-stimulated glucose disposal (ISGD) in older men and women with impaired glucose tolerance. A subsequent study demonstrated that consumption of a high-carbohydrate, eucaloric diet abolished the positive effects of aerobic exercise training on insulin action (9). This lack of an exercise effect on ISGD was associated with a doubling of muscle glycogen content which likely greatly reduced the rate of nonoxidative ISGD, and thus limited the effects of exercise on insulin action. Weight loss can be achieved with ad libitum consumption of a low-fat diet (10) potentially without compromising nutritional status. We therefore conducted a study to examine the influence of an ad libitum, low-fat/high-carbohydrate diet, with and without aerobic exercise training, on ISGD, abdominal fat distribution, skeletal muscle glycogen concentration, and glycogen synthase activity in older individuals with impaired glucose tolerance. We hypothesized that consumption of the diet would result in weight loss and thus improved insulin action, and that participants who also aerobically exercise would experience greater improvement in insulin action, due to greater nonoxidative ISGD compared to that observed following a eucaloric high-carbohydrate diet.
DIET, EXERCISE, AND INSULIN ACTION

METHODS

Participants

Men and women aged 55–80 years were recruited using newspaper advertisements. Individuals who reported being overweight or obese (BMI ≥ 26 and <37 kg/m²), non-smoking, sedentary (≤ 2 d/wk of structured physical activity), weight stable (± ≤ 5 kg) over the past 6 months, and who were not consuming medications known to influence glucose metabolism were eligible for medical screening. Individuals with a blood glucose concentration of 140–199 mg/dL 2 hours after the consumption of a 75-g oral glucose load, but who were otherwise healthy, were eligible for study participation. Written informed consent was obtained; study procedures were approved by the Institutional Review Board of the University of Arkansas for Medical Sciences. Two participants withdrew from the study for personal reasons. The remaining 22 participants were randomly assigned to either the diet alone (n = 11) or an identical diet plus aerobic exercise training (n = 11). Baseline reported dietary intake, reported physical activity as measured by using the Yale Physical Activity Questionnaire (11), and body weight and body composition variables did not significantly differ between groups, as previously reported (12).

Experimental Protocol

The study was a block-randomized (stratified on gender), 12-week intervention trial. Each participant was provided a mixed diet (35% fat, 20% protein, 45% carbohydrate) during the 3-day baseline testing period to standardize dietary intake and maintain body weight.

Following baseline measures, participants were provided the ad libitum diet by our metabolic kitchen for 12 weeks. The macronutrient composition of the diet (based on amounts of food consumed) was 18% fat, 19% protein, 63% carbohydrate, and 26 g of fiber/1000 kcal. The diet was designed to provide 150% of predicted energy requirements, and participants were instructed to consume foods ad libitum for the duration of the study. Participants were instructed to return any unconsumed food along with empty food containers; food consumption was measured by subtracting the weight of unconsumed food from the recorded weight of provided food. Dietary intake data over the course of the study did not significantly differ between groups (2250 ± 146 and 2413 ± 155 kcal/d for diet alone and diet plus exercise groups, respectively), as reported previously (12). Postintervention testing was performed with participants continuing to consume the diet (ad libitum) until completion of testing procedures.

Participants who were randomized to the exercise group trained in our laboratory 4 d/wk, 45 min/d, at an intensity initially set at 80% VO₂peak during weeks 1–12 on a cycle ergometer (model 818E; Monarch, Varberg, Sweden). Participants’ adherence to the exercise regimen was closely supervised. Nonexercising participants were instructed to maintain their habitual physical activity, and physical activity did not change over time in the nonexercising group, as previously reported (12).

Testing Procedures

Insulin sensitivity.—A 4-hour euglycemic–hyperinsulinemic (40 mU·m⁻²·min⁻¹) clamp corrected for hepatic glucose production with [6,6-H₂]glucose was used to assess ISGD at baseline (Week 0) and Week 13 following an overnight fast as previously described (9). Postintervention clamps were completed 3 days after the last exercise session (in those participants randomized to the exercise group) to minimize acute effects of exercise on ISGD (13). Mean ISGD (mg·kg body weight⁻¹·min⁻¹) was calculated as glucose infusion plus isotopically derived endogenous glucose production during the final 30 minutes of the clamp, and measurement of substrate oxidation was performed by continuous, open-circuit indirect calorimetry (Vmax 29N; SensorMedics Corp., Yorba Linda, CA) during this same time period. Nonoxidative ISGD was calculated by subtracting carbohydrate oxidation rates from the sum of exogenous glucose infusion plus endogenous glucose production rates. Technical problems with the indirect calorimetry equipment prevented completion of this measure for one participant, and an additional participant could not complete the postintervention clamp measurement due to difficulty starting an intravenous line.

Body weight and body composition.—Fasting body weight, standing height without shoes, and body composition (BOD-POD; Life Measurement Instruments, Concord, CA) were measured (12). A computed tomography scan at the L4-L5 vertebral disc space of the abdomen was obtained at Weeks 0 and 13 to assess visceral and subcutaneous adipose tissue cross-sectional area (cm²) (12). Visceral and subcutaneous adipose tissue boundaries were manually determined.

Maximal aerobic capacity.—Participants cycled at a warm-up intensity (50 W for men, 25 W for women) for 3 minutes on a cycle ergometer (Excalibur Sport; Lode, Groningen, Netherlands), followed by another 3-minute period at a slightly higher intensity (+25 W), with incremental increases (+25 W) in intensity every minute until volitional fatigue. Verbal encouragement was used to motivate participants to exercise at a maximal effort during each test. Concentrations of expired O₂ and CO₂ were analyzed (Models S-3A/I and CD-3A, respectively; AEI Technologies, Pittsburgh, PA), and gas volume was measured using a dry-gas meter (Rayfield Equipment, Waitsfield, VT).

Specimen Analyses

Glucose kinetics and insulin.—Analysis of enrichment of plasma [6,6-H₂]glucose was performed by gas chromatography–mass spectrometry (Agilent Technologies, Palo Alto, CA) with standard derivatization procedures (14). Rates of endogenous glucose production were calculated using a modification of the Steele equation (15). Insulin concentration was measured from thawed plasma samples as previously described (16).
according to the procedure of Passonneau and Lowry (17) for FreeZone 4.5; Labconco Corp., Kansas City, MO) for until analysis. For measurement of glycogen content, a piece of the vastus lateralis from the tissue (approximately 10 mg wet weight) was homogenized with no outliers identified. Statistical analyses were performed using SPSS 12.0.0 (SPSS, Chicago, IL) and SigmaStat 2.0 (Systat Software, Richmond, CA).

**RESULTS**

Participant characteristics are shown in Table 1. No differences between groups were observed at baseline. Final weight, BMI, and percentage of body fat were lower than initial values for both groups. No Group × Time interactions for body composition variables were observed. Final peak VO₂ was significantly higher than initial peak VO₂ for the exercising group only, indicating improved fitness in this group, as previously described (12). No differences were observed when comparing participants’ age or BMI by group and sex.

Total, oxidative, and nonoxidative ISGD rates during the euglycemic–hyperinsulinemic clamp are shown in Table 2. Group × Time interaction terms for each analysis of variance model were not significant, indicating that changes in ISGD rates over time did not vary by group. A time effect was observed, however, with mean (± standard error of the mean) total ISGD greater at postintervention compared to baseline (3.67 ± 0.32 vs 2.96 ± 0.19 mg·kg⁻¹·min⁻¹; p = .018). Changes in ISGD in each group were not different from each other. Group differences in ISGD values at pre-intervention were not significant, nor were values for endogenous glucose production at baseline or changes in this variable over time. Mean pre- and postintervention steady-state plasma insulin values were not different (92.7 ± 6.7 and 90.3 ± 7.2 vs 99.4 ± 10.2 and 106.7 ± 16.7 μU·ml⁻¹ for diet and diet plus exercise groups, respectively).

Differences in nonoxidative ISGD are further illustrated in Figure 1. Skeletal muscle glycogen concentration increased

### Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diet (N = 11)</th>
<th>Diet + Exercise (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.5 ± 2.2</td>
<td>64.8 ± 2.0</td>
</tr>
<tr>
<td>Initial weight, kg</td>
<td>89.6 ± 3.4</td>
<td>82.9 ± 3.4</td>
</tr>
<tr>
<td>Final weight, kg</td>
<td>86.6 ± 3.8*</td>
<td>78.6 ± 3.0*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.9 ± 3.2</td>
<td>164.3 ± 2.9</td>
</tr>
<tr>
<td>Initial BMI, kg/m²</td>
<td>31.0 ± 0.8</td>
<td>30.8 ± 1.1</td>
</tr>
<tr>
<td>Final BMI, kg/m²</td>
<td>30.0 ± 0.9*</td>
<td>29.1 ± 1.1*</td>
</tr>
<tr>
<td>Initial body fat, %</td>
<td>42.1 ± 2.2</td>
<td>41.2 ± 2.9</td>
</tr>
<tr>
<td>Final body fat, %</td>
<td>39.8 ± 2.7</td>
<td>37.6 ± 3.1*</td>
</tr>
<tr>
<td>Initial fat free mass, kg</td>
<td>52.4 ± 3.5</td>
<td>48.9 ± 3.4</td>
</tr>
<tr>
<td>Final fat free mass, kg</td>
<td>52.4 ± 3.7</td>
<td>49.2 ± 3.4</td>
</tr>
<tr>
<td>Initial peak VO₂, ml·kg⁻¹·min⁻¹</td>
<td>17.8 ± 0.9</td>
<td>18.5 ± 1.3</td>
</tr>
<tr>
<td>Final peak VO₂, ml·kg⁻¹·min⁻¹</td>
<td>17.8 ± 1.0</td>
<td>23.1 ± 1.3*</td>
</tr>
<tr>
<td>Initial peak VO₂, L·min⁻¹</td>
<td>1.62 ± 0.13</td>
<td>1.55 ± 0.15</td>
</tr>
<tr>
<td>Final peak VO₂, L·min⁻¹</td>
<td>1.58 ± 0.13</td>
<td>1.83 ± 0.14*</td>
</tr>
</tbody>
</table>

*Final value significantly different from initial value (p < .05) as previously described (12).

N = 10.

Diet = ad libitum low-fat/high-carbohydrate diet; Diet + Exercise = ad libitum low-fat/high-carbohydrate diet plus aerobic exercise training; BMI = body mass index; VO₂ = oxygen consumption.

### Table 2. Effect of Intervention on Euglycemic–Hyperinsulinemic Clamp Variables

<table>
<thead>
<tr>
<th>Clamp Variables</th>
<th>Diet (N = 10)</th>
<th>Diet + Exercise (N = 10)</th>
<th>Time</th>
<th>p Time × Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total glucose disposal (mg·kg⁻¹·min⁻¹)</td>
<td>2.48 ± 0.17</td>
<td>3.43 ± 0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxidative glucose disposal (mg·kg⁻¹·min⁻¹)</td>
<td>2.95 ± 0.30</td>
<td>4.39 ± 0.48</td>
<td>.019</td>
<td>.005 NS</td>
</tr>
<tr>
<td>Nonoxidative glucose disposal (mg·kg⁻¹·min⁻¹)</td>
<td>1.08 ± 0.14</td>
<td>1.35 ± 0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous glucose production (μmol·kg⁻¹·min⁻¹)</td>
<td>1.26 ± 0.19</td>
<td>1.54 ± 0.17</td>
<td>NS NS NS NS NS</td>
<td></td>
</tr>
</tbody>
</table>

*Final value significantly different from initial value (p < .05) as previously described (12).

N = 10.

Diet = ad libitum low-fat/high-carbohydrate diet; Diet + Exercise = ad libitum low-fat/high-carbohydrate plus aerobic exercise training; NS = not significant.

Notes: Values are mean ± standard error of the mean. Initial total glucose disposal significantly higher in Diet + Exercise group compared to Diet-alone group (p = .01); differences in other initial values were not significant.

Diet = ad libitum low-fat/high-carbohydrate diet; Diet + Exercise = ad libitum low-fat/high-carbohydrate plus aerobic exercise training; NS = not significant.

Skeletal muscle glycogen concentration and glycogen synthase activity.—A biopsy of the vastus lateralis from the dominant leg was obtained during the initial 60 minutes of the glucose clamp procedure. Tissue was immediately plunged into liquid nitrogen and stored at this temperature (~190°C) until analysis. For measurement of glycogen content, a piece of tissue (approximately 10 mg wet weight) was lyopholized (FreeZone 4.5; Labconco Corp., Kansas City, MO) for 24 hours and weighed. Glycogen content was measured according to the procedure of Passonneau and Lowry (17) and expressed as mmol glycosyl units·g dry weight⁻¹.

For assessment of glycogen synthase activity, a piece of tissue (approximately 10 mg wet weight) was homogenized on ice, and enzyme activity (μmol·g wet weight⁻¹·h⁻¹) was measured according to a standard protocol (17). The “I” form of the enzyme (active form; independent of glucose-6-phosphate) and the “D” form (inactive form; dependent on glucose-6-phosphate) were both measured, and enzyme activity was expressed as an activity ratio (I/D).

Data Analysis

Independent samples t tests were used to examine differences in participant characteristics between groups at baseline and at postintervention. Two-factor repeated measures analysis of variance was used to compare the groups with regards to changes in ISGD, abdominal fat, glycogen concentration, and glycogen synthase activity over time. The groups were considered to have significantly different rates of change in a variable if the Group × Time interaction term was significant at the p < .05 level. Data were approximately normally distributed as assessed by the Shapiro–Wilks test and visual examination of normal probability plots; data were also assessed for potential outliers with no outliers identified.
over time in the diet plus exercise group (344.7 ± 6.21.3 vs 616.7 ± 34.4 \text{mmol} \cdot \text{g}^{-1} \cdot \text{cm}^{2}, p < .001), and decreased over time in the diet-alone group (371.3 ± 15.2 vs 319.4 ± 19.9 \text{mmol} \cdot \text{g}^{-1} \cdot \text{cm}^{2}, p = .038). Change over time in each group was analyzed separately because the Group × Time interaction term was significant. Significant changes in glycogen synthase activity occurred over time as well, with an increase in activity observed in the diet-alone group (0.18 ± 0.02 vs 0.23 ± 0.02, \( p = .006 \)) and a decrease in activity in the diet plus exercise group (0.21 ± 0.02 vs 0.13 ± 0.01, \( p < .001 \)). Differences between groups for both glycogen and glycogen synthase at postintervention were also significant (\( p < .001 \)).

Changes in cross-sectional area of abdominal adipose tissue as assessed by computed tomography are illustrated in Figure 2. The Group × Time interaction was not significant, but there was a Time effect, indicating that mean postintervention values for both visceral and subcutaneous adipose tissue area were lower than were mean preintervention values (203.0 ± 11.7 and 363.4 ± 24.4 vs 233.9 ± 9.6 and 401.1 ± 27.4 cm\(^2\), \( p = .001 \) and <.001, for mean visceral and subcutaneous fat areas, respectively).

**DISCUSSION**

The results of this study indicate that an ad libitum, high-carbohydrate diet promoted weight and body fat losses, decreased abdominal adiposity, and increased ISGD in older, overweight individuals with impaired glucose tolerance. Persons who consumed this diet and who also participated in aerobic exercise training demonstrated similar changes plus improvement in fitness, but no additional effect of the exercise on ISGD. Participants in the diet plus exercise group had greater muscle glycogen content than did nonexercisers, and this was associated with a lower proportion of active muscle glycogen synthase relative to inactive enzyme. A lower active to inactive glycogen synthase activity ratio limits glycogen storage (18) and thus the major site of ISGD during a euglycemic–hyperinsulinemic clamp (19). These findings amplify those of our previous study, which indicated that a eucaloric low-fat/high-carbohydrate diet abolishes the improvement in ISGD observed following aerobic exercise training alone. By stimulating glucose uptake in muscle, exercise plus a high-carbohydrate diet results in a greatly increased muscle glycogen content with a concomitant decrease in active glycogen synthase, limiting the effects of exercise under these dietary conditions.

Previous studies have demonstrated that diabetes incidence in at-risk individuals can be reduced by changes in
diet and physical activity (2,3), with even greater reduction in older compared to younger adults reported in one study (2). Weight loss has also been shown to result in improved insulin action and/or glucose tolerance in individuals with normal glucose tolerance and type 2 diabetes (20), thus leading to subsequent reductions in morbidity and mortality (21). The combination of regularly performed aerobic exercise with weight loss has been shown to result in a greater, additive effect on insulin action (7). Increased leisure-time physical activity (independent of changes in body weight) has also been shown to reduce diabetes incidence (22). Others have reported that, although weight loss was effective in lowering fasting and postprandial insulin concentrations, this effect was not enhanced by the addition of either aerobic or resistance exercise (23).

Regularly performed aerobic exercise without associated weight loss has been shown to increase ISGD, glucose tolerance, and muscle glucose transporter 4 (GLUT 4) concentration in men and women with impaired glucose tolerance (6–8), although this observation is not universal (24–26). Short and colleagues (4) reported that aerobic exercise training without weight loss resulted in improved insulin sensitivity in young but not old adults; however, ISGD as measured by a euglycemic glucose clamp was not assessed in this study. In the present study, we hypothesized that the effects of a high-carbohydrate diet would be mediated through weight and abdominal fat mass loss, and that further improvements would be observed with the addition of aerobic exercise training.

It is clear from our earlier work that a low-fat/high-carbohydrate diet, when administered at a calorie level necessary to maintain body weight, abolishes the improvement in glucose tolerance and insulin action observed with aerobic exercise alone (9). In the present study, muscle glycogen concentration in the diet plus exercise group was more than double that of the diet-alone group. Richter and colleagues (27) examined the effects of a 7-hour infusion of insulin and glucose on glycogen storage and found that a large decrease in ISGD was associated with greatly elevated muscle glycogen stores. Elevated glycogen stores appear to play a role in decreasing the proportion of the active form of glycogen synthase relative to the inactive form, thereby decreasing nonoxidative ISGD. Whereas both groups had improved ISGD in the current study, the lack of additional increase in ISGD in the diet plus exercise group compared to the diet-alone group was potentially due to elevated muscle glycogen stores and subsequently reduced glycogen synthase activity, which may have limited any potential additional exercise-induced increases in peripheral ISGD in these individuals. Thus, the results of the present study demonstrate that an ad libitum, high-carbohydrate diet coupled with a regular exercise program does not promote any incrementally greater increase in ISGD compared to diet alone, and previous studies suggest that this lack of additional effect may be due to a metabolic adjustment driven by glycogen supercompensation or an impairment in the ability of exercise to improve ISGD mediated by older age.

Our study may be limited by several factors. In particular, the clamp may have been too short to achieve a steady state for ISGD. The mean difference between measured and goal plasma glucose values and the mean coefficient of variation of the glucose infusion rates during the final 30 minutes of the clamp were both small, suggesting that steady state was achieved. Another potential limitation was the small but significant difference in baseline total ISGD between groups (despite randomization), which may have resulted in confounding. The lack of significant difference in other variables at baseline suggests that the difference between groups was minor. In addition, the small sample size and the absence of an exercise-only control group may limit the interpretation and generalizability of our findings.

Conclusion

Our data indicate that consumption of an ad libitum, high-carbohydrate diet resulted in decreased abdominal fat mass and increased ISGD compared to baseline, with no apparent decrease in energy intake. These results demonstrate that elderly people at highest risk of developing type 2 diabetes may reduce this risk by a shift in macronutrient intake with no compromise in protein or micronutrient nutrition. Addition of aerobic exercise training resulted in greater skeletal muscle glycogen concentration compared to that in the diet-alone group, but differences in body composition and ISGD were not significantly different and no significant additional increase in the rate of total and nonoxidative ISGD was observed. In our study, aerobic exercise did result in significant improvement in fitness; this finding suggests that exercise has an important role in weight loss programs in older adults, primarily as a means to improve physical functioning. Given the increasing emphasis on lifestyle versus pharmacologic interventions in decreasing the onset and prevalence of type 2 diabetes in the U.S. population (28), our results may provide additional guidance toward the development of diabetes risk reduction strategies that will benefit the overall health of overweight and glucose-intolerant older adults.

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