Clinical trial demonstrates exercise following bariatric surgery improves insulin sensitivity

Paul M. Coen, …, Joseph A. Houmard, Bret H. Goodpaster

BACKGROUND. Roux-en-Y gastric bypass (RYGB) surgery causes profound weight loss and improves insulin sensitivity ($S_I$) in obese patients. Regular exercise can also improve $S_I$ in obese individuals; however, it is unknown whether exercise and RYGB surgery–induced weight loss would additively improve $S_I$ and other cardiometabolic factors.

METHODS. We conducted a single-blind, prospective, randomized trial with 128 men and women who recently underwent RYGB surgery (within 1–3 months). Participants were randomized to either a 6-month semi-supervised moderate exercise protocol (EX, $n = 66$) or a health education control (CON; $n = 62$) intervention. Main outcomes measured included $S_I$ and glucose effectiveness ($S_G$), which were determined from an intravenous glucose tolerance test and minimal modeling. Secondary outcomes measured were cardiorespiratory fitness ($V_O^2$ peak) and body composition. Data were analyzed using an intention-to-treat (ITT) and per-protocol (PP) approach to assess the efficacy of the exercise intervention (>120 min of exercise/week).

RESULTS. 119 (93%) participants completed the interventions, 95% for CON and 91% for EX. There was a significant decrease in body weight and fat mass for both groups ($P < 0.001$ for time effect). $S_I$ improved in both groups following the intervention (ITT: […]

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Clinical trial demonstrates exercise following bariatric surgery improves insulin sensitivity

Paul M. Coen,1,2 Charles J. Tanner,3 Nicole L. Helbling,1 Gabriel S. Dubis,3 Kazanna C. Hames,1 Hui Xie,4 George M. Eid,5 Maja Stefanovic-Racic,1 Frederico G.S. Toledo,1 John M. Jakicic,7 Joseph A. Houmard,3 and Bret H. Goodpaster1

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BACKGROUND. Roux-en-Y gastric bypass (RYGB) surgery causes profound weight loss and improves insulin sensitivity (SI) in obese patients. Regular exercise can also improve SI in obese individuals; however, it is unknown whether exercise and RYGB surgery–induced weight loss would additively improve SI and other cardiometabolic factors.

METHODS. We conducted a single-blind, prospective, randomized trial with 128 men and women who recently underwent RYGB surgery (within 1–3 months). Participants were randomized to either a 6-month semi-supervised moderate exercise protocol (EX, n = 66) or a health education control (CON; n = 62) intervention. Main outcomes measured included SI and glucose effectiveness (SG), which were determined from an intravenous glucose tolerance test and minimal modeling. Secondary outcomes measured were cardiorespiratory fitness (VO2 peak) and body composition. Data were analyzed using an intention-to-treat (ITT) and per-protocol (PP) approach to assess the efficacy of the exercise intervention (>120 min of exercise/week).

RESULTS. 119 (93%) participants completed the interventions, 95% for CON and 91% for EX. There was a significant decrease in body weight and fat mass for both groups (P < 0.001 for time effect). SI improved in both groups following the intervention (ITT: CON vs. EX; +1.64 vs. +2.24 μU/mL, P = 0.18 for Δ, P < 0.001 for time effect). A PP analysis revealed that exercise produced an additive SI improvement (PP: CON vs. EX; +1.57 vs. +2.24 μU/mL, P = 0.019) above that of surgery. Exercise also improved SG (ITT: CON vs. EX; +0.0023 vs. +0.0063 μU/mL, P = 0.009) compared with the CON group. Exercise improved cardiorespiratory fitness (VO2 peak) compared with the CON group.

CONCLUSION. Moderate exercise following RYGB surgery provides additional improvements in SI, SG, and cardiorespiratory fitness compared with a sedentary lifestyle during similar weight loss.

TRIAL REGISTRATION. clinicaltrials.gov identifier: NCT00692367.

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Introduction

Roux-en-Y gastric bypass (RYGB) is the most commonly performed metabolic surgery in the United States and results in dramatic weight loss and type 2 diabetes (T2D) remission in a large percentage of patients (1, 2). Although insulin resistance is a central component of T2D and its control is key to the prevention and treatment of T2D, improvements in insulin sensitivity (SI) in nondiabetic patients following RYGB surgery are typically quite modest compared with the presurgery condition (3). Moreover, there appear to be 2 discrete periods of improvement. The first is immediately after surgery, at which time hepatic, but not peripheral, SI improves in response to acute energy restriction (4–6), while greater, protracted weight loss appears to be more strongly associated with improved peripheral SI (7, 8). Even with significant weight loss 1 year following RYBG surgery, peripheral SI is still low compared with that of lean metabolically healthy individuals (3, 5, 6, 9).

Exercise is considered a cornerstone for obesity treatment, and while it is not generally viewed to cause substantial body weight reduction (10), it can potently improve peripheral SI and glucose control (11–13) and can reduce the risk of T2D and cardiovascular disease (14, 15). There is general consensus that even a single session of moderate intensity exercise can induce an improvement in SI (16). There is also evidence that exercise can
Table 1. Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EX (n = 66)</th>
<th>CON (n = 62)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean yr (SD)</td>
<td>41.3 (9.7)</td>
<td>41.9 (10.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>7/59</td>
<td>8/54</td>
<td>0.69</td>
</tr>
<tr>
<td>Race, ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European descent</td>
<td>12/54</td>
<td>10/52</td>
<td>0.76</td>
</tr>
<tr>
<td>Anthropometrics, mean (SD)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Presurgery weight, kg</td>
<td>127.2 (22.6)</td>
<td>121.8 (25.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Preintervention weight, kg</td>
<td>107.3 (19.9)</td>
<td>105.7 (25.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Preintervention BMI, kg/m²</td>
<td>38.8 (6.1)</td>
<td>38.3 (6.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Preintervention waist circumference, cm</td>
<td>112.8 (15.1)</td>
<td>110.5 (15.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Plasma lipids, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>151.6 (31.5)</td>
<td>140.8 (29.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>93.1 (26.2)</td>
<td>84.4 (23.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>36.7 (9.9)</td>
<td>35.5 (10.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>108.9 (40.3)</td>
<td>104.7 (33.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>BP, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.8 (14.5)</td>
<td>121.5 (14.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74 (9.3)</td>
<td>75.4 (7.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Medication use, no. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>17 (25.8)</td>
<td>12 (19.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>6 (9.1)</td>
<td>5 (8.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>30 (45.4)</td>
<td>26 (41.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12 (18.2)</td>
<td>13 (20.9)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data show mean ± SD of all subjects. SI conversion factors: to convert total cholesterol and HDL cholesterol values from mg/dl to mmol/l, multiply by 0.0259; triglyceride values from mg/dl to mmol/l, by 0.0113; glucose values from mg/dl to mmol/l, by 0.0555; and insulin values from μU/ml to pmol/l, by 6.945.

Exercise in combination with caloric restriction can produce an additive reduction in body weight (10) and may be beneficial for weight-loss maintenance (19). However, it is not known whether exercise following bariatric surgery provides additional improvements in cardiometabolic risk factors, including $S_v$. Indeed, only one study to date has assessed whether aerobic exercise is even a feasible therapeutic option in this patient population (20). Case-controlled studies indicate that bariatric surgery patients have lower levels of physical activity than weight-matched nonsurgery controls (21–23). A number of retrospective cohort studies report a positive association between physical activity and postsurgery weight loss (24–28). However, these studies are limited by their observational nature, inclusion of only patients who return for follow-up, and subjectively measured physical activity by self-report questionnaires (29).

To date, there have been no randomized, controlled trials that have examined the effects of an exercise intervention on $S_v$ and other cardiometabolic risk factors following bariatric surgery. To address this paucity in the literature, we conducted a randomized, controlled trial to examine the effects of a 6-month semi-structured exercise intervention on $S_v$, cardiorespiratory fitness, body composition, weight, and other cardiometabolic risk factors following RYGB surgery.

Results

Study participants. The flow of participants through the study is depicted in Figure 1. Forty-eight participants were randomized at the East Carolina University site ($n = 24$, exercise program [EX]; $n = 24$, health education control [CON]) and 80 at the University of Pittsburgh site ($n = 42$, EX; $n = 38$, CON). The average time from the date of RYGB surgery to randomization into study groups was 79 ± 25 days. Retention rates for the interventions were 95% for the CON group and 91% for the EX group ($P = 0.49$). There were no serious adverse events in either study group, nor were there differences in reported adverse events between groups. In the intention-to-treat (ITT) analysis, the EX group performed an average (± SEM) of 147 ± 15 min/wk of exercise, measured over the final 12 weeks of the intervention. Forty-four out of sixty-six EX participants performed at least 120 min/wk (average: 185 ± 18 min/wk) of exercise and were thus included in the per-protocol (PP) analyses. For the 22 EX participants who were not included in the PP analysis, 5 did not complete the intervention due to time-commitment issues and 1 was lost to follow-up. The other 16 participants who did complete postintervention testing averaged only 55.7 min/wk of exercise during the final 3 months of the intervention. There were a number of reasons for noncompliance to the exercise intervention. Five participants reported health problems (knee pain, hernia, rotator cuff surgery) not related to the study that prevented 120 min/wk of exercise. Two participants lived more than 35 miles from the exercise facility, which made compliance difficult. Nine participants did not have an apparent reason for noncompliance. Six participants in the CON group reported a physically active lifestyle (exercising >1 day/wk), so 56 out of 62 CON participants randomized were included in the PP analysis.

Baseline characteristics of the study groups are shown in Table 1. Of the 128 participants randomized, 15 were male and 113 were female, and 22 were African-American and 106 were of mixed European descent. There were no race or sex imbalances between groups. There were no differences in demographics or characteristics contributing to outcomes between study groups. Total and LDL cholesterol tended to be higher in the EX group than in the CON group. The groups had similar body weight pre-surgery and preinterventions. Both groups also reported similar...
medication use at baseline. There were no group differences in medication use following intervention.

Intravenous glucose tolerance test. Preintervention $S_g$ measurements for both groups were similar, but substantially lower than those observed for normal-weight subjects of a similar age (3). Following the interventions, there was a significant time effect ($P < 0.001$), with both groups showing improved $S_g$ (Table 2 and Figure 2). In the ITT analysis, $S_g$ tended to improve to a greater degree for the EX group compared with the CON group, but this was not statistically different between groups (Figure 2: EX vs. CON; $+2.24$ vs. $+1.64 \text{ min}^{-1}/\mu\text{U}/\text{ml}$, $P = 0.18$). Next, in a PP analysis, we examined the effects of exercise for individuals who met the a priori–defined intervention protocol criteria (Table 3 and Figure 2). In this analysis, those subjects who performed more than 120 min/wk of exercise in the final 3 months of the intervention had significantly greater improvements in $S_g$ compared with those observed for RYGB surgery–induced weight loss alone (Figure 2: EX vs. CON; $+2.69$ vs. $+1.57 \text{ min}^{-1}/\mu\text{U}/\text{ml}$, $P = 0.019$). The plasma insulin and glucose excursions during the intravenous glucose tolerance test (IVGTT) for the PP analysis are presented in Figure 3.

$S_g$ refers to the ability of glucose per se to stimulate glucose uptake and is an important component of glucose metabolism. $S_g$ was similar at baseline (EX vs. CON; $0.015$ vs. $0.017 \text{ min}^{-1}$). ITT analysis revealed that there was a main effect of surgery (time) for $S_g$ (Table 2: $P < 0.001$) and that there was a greater improvement observed in the EX group (Figure 4: EX vs. CON; $+0.0063$ vs. $+0.0023 \text{ min}^{-1}$, $P = 0.009$). The exercise effect on $S_g$ was also robust in the PP analysis (Figure 4: EX vs. CON; $+0.0071$ vs. $+0.0023 \text{ min}^{-1}$, $P = 0.011$). Thus, regular exercise following RYGB surgery elicits a powerful effect on the ability of glucose per se to stimulate glucose uptake. Acute insulin response (AIRg) and disposition index ($D_1$) improved over time, but there was no additional improvement with exercise (Tables 2 and 3).

Weight, body composition, and waist circumference. Both study groups exhibited similar mass, BMI, waist circumference, and total and depot-specific fat mass at baseline and similar reductions when the data were analyzed with ITT and PP approaches (Tables 2 and 3). There was no difference in the loss of subcutaneous and visceral fat depots after the interventions. We did not observe a difference in proportionate weight loss between fat depots.
Other cardiometabolic risk factors. Compared with CON, EX significantly improved VO₂ peak (Figure 5), an index of cardiorespiratory fitness and an effective predictor of future morbidity and mortality (30). Blood pressure (BP) (systolic and diastolic), cholesterol (total, LDL, and HDL), and triglycerides were reduced to a similar degree in the EX and CON groups (ITT, Table 2; PP, Table 3); there was no additional effect of exercise on these cardiometabolic risk factors.

Discussion

RYGB surgery is a highly effective treatment option for severe obesity, as it results in substantial weight loss and improved cardiometabolic risk profile, including S_I. Although exercise can also reduce cardiometabolic risk independently of weight, it is not known whether exercise can promote additional improvements in RYGB surgery patients concomitant with their robust weight loss. Our results indicate that moderate aerobic exercise elicits additional improvements in S_I as well as S_G, i.e., the ability of glucose per se to facilitate glucose disposal, along with improved cardiorespiratory fitness concomitant with RYGB surgery-induced weight loss. These data advocate for the inclusion of an exercise program to optimize health benefits during active weight loss following RYGB surgery.

The improvement in glucose control in T2D patients following RYGB surgery may be due to energy restriction-induced improvements in hepatic S_I and a modified postprandial gut hormone response in the days to weeks after the operation (7). Improved peripheral S_G, however, appears to be more strongly associated with longer-term weight loss (3, 7). Here, we recapitulate these findings and demonstrate that, despite substantial initial weight loss (~20 kg), within 1 to 3 months after surgery, peripheral S_G remains approximately 60% lower compared with that of metabolically healthy lean individuals of similar age and the same sex (31). Our data affirm that there is capacity for further improvements through lifestyle interventions, such as exercise.

Our PP analysis demonstrates that an exercise program of more than 120 min/wk effectively improved S_I in RYGB surgery patients, by approximately 30% over a sedentary lifestyle. These data are the first, to our knowledge, to suggest that an exercise intervention was not only feasible, but was efficacious in improving S_I in severely obese RYGB surgery patients. This observation is congruent with the finding that a 12-week exercise program following RYGB and gastric banding improved glucose tolerance (20). In the current study, exercise-induced improvements in S_I and S_G cannot be accounted for by any additional effect of exercise on reduced body mass or adiposity. This does not, however, preclude the possibility that improvements in S_I with exercise were related to changes in intramyocellular lipids, inflammation, or other factors that influence insulin action (32).

We observed a robust and statistically significant improvement in S_G with exercise after surgery. These data indicate that an exercise program during RYGB surgery-induced weight loss may improve metabolic health by both insulin-dependent and -independent mechanisms (at basal insulin levels). S_G reflects the capacity of glucose per se to enhance cellular glucose uptake and accounts for approximately 50% of glucose disposal following a meal (33, 34). The cellular mechanisms that mediate S_G are unclear, but are thought to relate to glucose mass action (35). S_G is an independent predictor of diabetes across race/ethnic groups and varying degrees of obesity and is reduced with impaired
Table 2. ITT analysis of weight, body composition, cardiorespiratory fitness, and IVGTT variables

<table>
<thead>
<tr>
<th>Weight, body composition, and cardiorespiratory fitness, mean (SD)</th>
<th>CON (n = 62)</th>
<th>EX (n = 66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>105.7 (25.0)</td>
<td>83.7 (20.9)</td>
<td>107.3 (19.8)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>38.3 (6.9)</td>
<td>30.2 (5.6)</td>
<td>38.8 (6.0)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>110.6 (15.2)</td>
<td>94.7 (13.6)</td>
<td>113.4 (15.6)</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>49.6 (14.9)</td>
<td>30.6 (11.4)</td>
<td>51.6 (10.8)</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>50.1 (10.1)</td>
<td>49.2 (10.2)</td>
<td>50.5 (7.7)</td>
</tr>
<tr>
<td>Weight, body composition, and cardiorespiratory fitness, mean (SD)</td>
<td>CON (n = 62)</td>
<td>EX (n = 66)</td>
<td>P value</td>
</tr>
<tr>
<td>Total fat, cm²</td>
<td>679.1 (164.8)</td>
<td>427.8 (184.4)</td>
<td>703.8 (144.3)</td>
</tr>
<tr>
<td>Superficial subcutaneous fat, cm²</td>
<td>287.4 (104.4)</td>
<td>182.4 (86.8)</td>
<td>296.6 (59.8)</td>
</tr>
<tr>
<td>Deep subcutaneous fat, cm²</td>
<td>236.0 (71.0)</td>
<td>150.6 (65.1)</td>
<td>249.6 (75.5)</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat, cm²</td>
<td>537.2 (149.6)</td>
<td>345.4 (145.5)</td>
<td>560.0 (126.4)</td>
</tr>
<tr>
<td>Visceral fat, cm²</td>
<td>141.9 (53.1)</td>
<td>77.9 (39.5)</td>
<td>143.3 (49.6)</td>
</tr>
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<td>BP and plasma lipids, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>121.5 (13.9)</td>
<td>117.3 (12.8)</td>
<td>122.8 (14.3)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>75.4 (7.8)</td>
<td>70.9 (8.4)</td>
<td>74.0 (9.2)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>140.6 (28.6)</td>
<td>144.6 (28.1)</td>
<td>150.9 (31.6)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>84.6 (22.9)</td>
<td>80.3 (20.9)</td>
<td>92.5 (26.2)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>35.6 (10.7)</td>
<td>48.3 (11.0)</td>
<td>36.7 (10.0)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>104.5 (33.0)</td>
<td>80.6 (33.5)</td>
<td>108.8 (39.1)</td>
</tr>
</tbody>
</table>

Data show mean ± SD of all subjects, with MCMC MI for missing data. *Within group, significant difference from before to after, with FDR P < 0.05. **Between groups, significant difference at before and after, with FDR P < 0.05. FFM, fat-free mass; HOMA-IR, homeostasis model assessment of insulin resistance (fasting glucose × fasting insulin)/22.5. S conversion factors: to convert total cholesterol and HDL cholesterol values from mg/dl to mmol/l, multiply by 0.0259; triglyceride values from mg/dl to mmol/l, by 0.0113; glucose values from mg/dl to mmol/l, by 0.0555; and insulin values from µIU/ml to pmol/l, by 6.945.

The physical activity habits of bariatric surgery patients have not been clearly described. Case-control studies report significantly lower levels of physical activity than weight-matched nonsurgery controls (21–23). Indeed, it is not clear whether an exercise training intervention is even a feasible therapeutic option in this unique patient population. Here, we show that 91% of patients randomized to the exercise group completed the intervention. We also used a PP approach using only data from subjects who adhered to the a priori–defined exercise prescription and intervention, which is within recommended guidelines. The exercise program (>120 min/wk) was adhered to by two-thirds of the patients randomized to the exercise group, who exercised an average of 185 min/wk. These data indicate that exercise training is a feasible treatment option for this patient population. Of the 22 participants who did not strictly adhere to the intervention, 13 reported reasons for noncompliance, while 9 did not. It has been well documented that bariatric surgery patients have psychosocial barriers to exercise, including low self efficacy and exercise motivation, and social stigma (39, 40). The aim of this study was to not to determine psychosocial barriers to exercise, and while we didn’t measure these factors, it is likely that they contributed to noncompliance in these 9 participants.

Exercise following RYGB surgery also significantly improved cardiorespiratory fitness (VO₂ peak). This finding is similar to other reports of improvements in fitness with exercise in post–bariatric surgery patients (20) and is clinically important, as cardiorespiratory fitness is inversely correlated with BMI (41) and improved cardiorespiratory fitness is associated with a reduced risk of all-cause mortality (42). Therefore, not only is an aerobic exercise training program feasible in this population, it is also effective at...
improving cardiorespiratory fitness, a result that directly counters the perception that severely obese individuals cannot respond to lifestyle interventions. Our data highlight the need for additional randomized controlled exercise trials to better understand the implications of components of exercise prescription (dose, duration, intensity) on long-term weight loss maintenance and health in RYGB surgery patients.

Increased physical activity after bariatric surgery has been reported to provide additional weight loss (43). However, most of these studies were nonrandomized, retrospective, and observational in nature and measured physical activity by questionnaire and self report (43), methods that may lead to overestimation of exercise participation in obese subjects (44, 45), including those who have undergone bariatric surgery (29). Our observations using a semi-supervised exercise intervention are in line with those of Shah et al., who showed that a high-volume exercise prescription following bariatric surgery had no impact on body weight and waist circumference when patients were compared with a control group (20). We extend these observations by demonstrating that abdominal adipose depots, measured by computed tomography (CT), are not uniquely influenced by a 6-month exercise training intervention in RYGB surgery patients.

Strengths and limitations. A particular strength of this study is that it is, we believe, the first randomized controlled trial in a reasonably large sample of RYGB surgery patients to examine the efficacy of a semi-supervised exercise program on SI. Although the adherence was high in our study, we did not determine the feasibility or the efficacy of exercise in a broader group of patients or across different bariatric surgery procedures. Therefore, we cannot generalize the potential benefits of exercise after bariatric surgery. Additional studies are needed to determine the optimal dose and modality of exercise and whether exercise-induced benefits extend to other bariatric surgery procedures. The semi-supervised nature of the intervention indicates that it is clinically practical and the prescription performed is feasible and well tolerated by RYGB surgery patients, which has important implications for refining future physical activity recommendations. Our study had some additional limitations. Participants were mostly younger to middle-age women, and although randomized groups were stratified by sex, it is difficult to determine sex-specific responses. Nutritional intake was not controlled or monitored and may represent an important factor that contributes to affecting outcome measures, including SI, weight loss, and other cardiometabolic risk factors.

Conclusions. RYGB surgery patients who regularly perform a modest amount (>120 min/wk) of exercise achieve significant improvements in SI and S_c beyond those derived from RYGB surgery-induced weight loss alone. Thus, exercise can be a useful tool for optimizing weight loss and improving cardiometabolic health in this population.
The Journal of Clinical Investigation

**Table 3. PP analysis of weight, body composition, cardiorespiratory fitness, and IVGTT variables**

<table>
<thead>
<tr>
<th>Weight, body composition, and cardiorespiratory fitness, mean (SD)</th>
<th>CON (n = 56)</th>
<th>EX (n = 44)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>106.3 (25.8)</td>
<td>84.2 (21.3)</td>
<td>108.3 (21.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>38.4 (7.1)</td>
<td>30.4 (5.6)</td>
<td>38.3 (5.9)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>110.6 (15.4)</td>
<td>94.7 (12.7)</td>
<td>112.9 (16.7)</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>50.4 (15.2)</td>
<td>31.2 (11.0)</td>
<td>50.7 (10.3)</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>49.8 (9.6)</td>
<td>48.7 (9.4)</td>
<td>50.8 (8.2)</td>
</tr>
<tr>
<td>Total fat, cm²</td>
<td>692.6 (164.0)</td>
<td>431.8 (143.9)</td>
<td>707.3 (150.9)</td>
</tr>
<tr>
<td>Superficial subcutaneous fat, cm²</td>
<td>294.9 (99.4)</td>
<td>185.0 (76.7)</td>
<td>294.3 (73.8)</td>
</tr>
<tr>
<td>Deep subcutaneous fat, cm²</td>
<td>238.7 (74.0)</td>
<td>152.0 (57.6)</td>
<td>250.6 (75.5)</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat, cm²</td>
<td>547.8 (148.5)</td>
<td>350.4 (125.5)</td>
<td>558.5 (129.7)</td>
</tr>
<tr>
<td>Visceral fat, cm²</td>
<td>144.8 (54.1)</td>
<td>81.4 (41.0)</td>
<td>148.8 (54.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>106.3 (25.8)</td>
<td>84.2 (21.3)</td>
<td>108.3 (21.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>38.4 (7.1)</td>
<td>30.4 (5.6)</td>
<td>38.3 (5.9)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>110.6 (15.4)</td>
<td>94.7 (12.7)</td>
<td>112.9 (16.7)</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>50.4 (15.2)</td>
<td>31.2 (11.0)</td>
<td>50.7 (10.3)</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>49.8 (9.6)</td>
<td>48.7 (9.4)</td>
<td>50.8 (8.2)</td>
</tr>
<tr>
<td>Total fat, cm²</td>
<td>692.6 (164.0)</td>
<td>431.8 (143.9)</td>
<td>707.3 (150.9)</td>
</tr>
<tr>
<td>Superficial subcutaneous fat, cm²</td>
<td>294.9 (99.4)</td>
<td>185.0 (76.7)</td>
<td>294.3 (73.8)</td>
</tr>
<tr>
<td>Deep subcutaneous fat, cm²</td>
<td>238.7 (74.0)</td>
<td>152.0 (57.6)</td>
<td>250.6 (75.5)</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat, cm²</td>
<td>547.8 (148.5)</td>
<td>350.4 (125.5)</td>
<td>558.5 (129.7)</td>
</tr>
<tr>
<td>Visceral fat, cm²</td>
<td>144.8 (54.1)</td>
<td>81.4 (41.0)</td>
<td>148.8 (54.1)</td>
</tr>
<tr>
<td>BP and plasma lipids, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.4 (14.0)</td>
<td>117.0 (13.0)</td>
<td>121.7 (13.7)</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>75.9 (7.9)</td>
<td>70.8 (8.6)</td>
<td>73.1 (9.4)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>142.5 (28.7)</td>
<td>146.5 (27.5)</td>
<td>149.6 (31.7)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>85.6 (23.2)</td>
<td>81.7 (20.3)</td>
<td>92.7 (25.3)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>36.0 (10.9)</td>
<td>48.7 (10.9)</td>
<td>35.7 (9.9)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>105.3 (33.3)</td>
<td>80.1 (33.9)</td>
<td>106.3 (40.7)</td>
</tr>
</tbody>
</table>

Data are mean ± SD for all subjects. For the PP analysis, only subjects who complied with intervention protocols and completed the intervention were included. *Within group, significant difference from before to after, with FDR P < 0.05. †Between groups, significant difference at before and after, with FDR P < 0.05. HOMA-IR: (fasting glucose × fasting insulin)/22.5. Conversion factors: to convert total cholesterol and HDL cholesterol values from mg/dl to mmol/l, multiply by 0.0259; triglyceride values from mg/dl to mmol/l, by 0.0113; glucose values from mg/dl to mmol/l, by 0.0555; and insulin values from μIU/ml to pmol/l, by 6.945.

adjunct therapy for RYGB surgery patients to promote additional improvements in cardiometabolic risk and physical fitness.

**Methods**

**Patient recruitment.** RYGB surgery patients (1 to 3 months after surgery) were recruited from the University of Pittsburgh Medical Center and East Carolina University bariatric surgery centers in Pittsburgh, Pennsylvania, USA, and Greenville, North Carolina, USA. The study setting was an academic clinical translational research center. Recruitment commenced in September 2008, the last participant was randomized in March 2012, and data were available for analysis in October 2012.

**Inclusion/exclusion criteria.** Male and female participants were eligible if they were between 21 and 60 years, had a BMI below 55 kg/m², and underwent RYGB surgery 1 to 3 months previously. Race/ethnicity was self reported. Participants were required to walk without assistance. If on hormone replacement therapy, participants remained on the same dose throughout the study. Participants were excluded if they had a diagnosis of diabetes, hypertension, anemia, hypothyroidism, elevated liver enzymes, current malignancy or history of cancer within past 5 years, or stent placement within the past 3 years. Participants were also excluded if there was a history of myocardial infarction, angioplasty, angina, liver disease, or neuromuscular disease. Medication exclusions included the following: anticoagulation therapy, steroids or other drugs that would alter metabolism, glucose homeostasis, or medications that would confound study results. Participants were also excluded if they reported being physically active, defined as participating in planned exercise (>30 min in duration) more than 1 day a week, as determined by self report.

**Randomization.** A permuted-blocks approach was used, with subjects stratified by gender. Blocks of random sizes of 4 and/or greater were used to achieve the goal sample size in each group between both study sites. The study clinical coordinator at Pittsburgh conducted randomization for both sites. The study was single blind, with assessors for all outcomes blinded to participant group assignment.

**Intervention groups.** Participants (1 to 3 months following surgery) were randomized to 6-month semi-supervised EX or CON intervention. Participants were required to participate in 3 to 5 exercise sessions per week, with at least 1 directly supervised session per week.
Primary and secondary outcome measures. Study measurements were made over separate clinic visits before and after the 6-month interventions. A 3-hour insulin-modified IVGTT was performed in the morning hours after a 12-hour fast to determine insulin action parameters based on the Bergman minimal model calculations (46). A 50% dextrose bolus (0.3 g/kg body mass) was administered after fasting samples were collected, and insulin (0.025 U/kg body mass) was then injected at minute 20. Blood samples were collected in EDTA tubes at minutes 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180. Plasma insulin was determined by enzyme immunoassay (Access Immunoassay System, Beckman Coulter) and glucose by the oxidation reaction (Sycron Dxc600i, Beckman Coulter). SI, SG, DI, and AIRg were calculated with MINMOD millennium software (version 5.10, 2002) (47).

Secondary measures included fat and lean mass determined by dual-energy x-ray absorptiometry (DXA) using a GE Lunar (GE Healthcare). Abdominal visceral and subcutaneous adipose tissue area were quantified by CT using SliceOmatic image analysis software (Tomovision) (48).

Cardiorespiratory fitness (VO2peak) was measured by indirect calorimetry during a 5- to 12-minute graded exercise test on a cycle ergometer (Lode) (49). Twelve-lead ECG recordings were monitored by the study physician and interpreted for contraindications to exercise. Body weight, BP, and plasma lipids and hepatic enzymes were measured by standard clinical protocols.

Power and sample size calculations. Power analyses were conducted a priori based on data from pilot studies at our 2 centers and indicated that a sample size of 63 subjects per group would provide 80% power.
participants provided written informed consent prior to their participation in the study. The study was registered at www.clinicaltrials.gov (trial ID NCT00692367).

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to detect a medium effect size (0.55) for statistically significant differences in $S_i$ and visceral abdominal fat.

Statistics. Group differences in baseline characteristics were determined using 2-sample Student’s $t$ test (2 tailed) or $\chi^2$ or Fisher exact tests. The primary analyses were as follows: (a) ITT approach, in which all 128 randomized participants were assumed to adhere to treatment assignments and complete follow-up assessment and (b) a PP approach. Only EX participants who performed at least 120 min/wk of exercise on average during the last 3 months of the intervention and CON participants who maintained a physically inactive lifestyle (exercising an average of <1 day/wk during the last 3 months of the intervention) were included in the PP analysis.

The multiple imputation (MI) method with Markov chain Monte Carlo (MCMC) algorithms was used to estimate missing data. Before MI, any variables with high skew were log- or square-root transformed to achieve a normal distribution. These variables were antitransformed after MI procedure. The general linear mixed model with repeated measures (PROC MIXED) was performed to detect group and time effects on the outcome variables. Group, time, and group multiplied by time were treated as fixed effects and subjects nested within each group as random effect. Age, sex, and race were covariates. We applied PROC MIANALYSIS to combine the statistical results generated from PROC MIXED based on each imputation data. $P$ values for post-hoc tests were adjusted by false discovery rate (FDR). A $P$ value of less than 0.05 was considered significant. Analyses were performed using SAS version 9.1 (SAS Institute Inc.).

Study approval. The study protocol was approved by the University of Pittsburgh and East Carolina University Institutional Review Boards and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to their participation in the study. The study was registered at www.clinicaltrials.gov (trial ID NCT00692367).

Figure 5. ITT and PP analysis for change in cardiorespiratory fitness in exercise and control groups. Data shown are mean ± SD for all subjects, with MCMC MI for missing data in ITT analysis. For the PP analysis, only subjects who complied with intervention protocols and completed at month 6 were included. *$P < 0.05$; **$P < 0.01$. 
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