Dose Response of Exercise Training Following Roux-en-Y Gastric Bypass Surgery: A Randomized Trial

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Objective: Roux-en-Y gastric bypass (RYGB) surgery can cause profound weight loss and improve overall cardiometabolic risk factors. Exercise (EX) training following RYGB can provide additional improvements in insulin sensitivity (SI) and cardiopulmonary fitness. However, it remains unknown whether a specific amount of EX post-RYGB is required to achieve additional benefits.

Methods: We performed a post hoc analysis of participants who were randomized into either a 6-month structured EX program or a health education control (CON). The EX group (n = 56) was divided into tertiles according to the amount of weekly exercise performed, compared with CON (n = 42): low-EX = 54 ± 8; middle-EX = 129 ± 4; and high-EX = 286 ± 40 min per week.

Results: The high-EX lost a significantly greater amount of body weight, total fat mass, and abdominal deep subcutaneous abdominal fat compared with CON (P < 0.005). SI improved to a greater extent in both the middle-EX and high-EX compared with CON (P < 0.04). Physical fitness (VO2 max) significantly improved in the high-EX (9.3% ± 4.2%) compared with CON (−6.0 ± 2.4%) (P < 0.001). Skeletal muscle mitochondrial State 4 (P < 0.002) and 3 (P < 0.04) respiration was significantly higher in the high-EX compared with CON.

Conclusions: A modest volume of structured exercise provides additional improvements in insulin sensitivity following RYGB, but higher volumes of exercise are required to induce additional weight loss, changes in body composition, and improvements in cardiopulmonary fitness and skeletal muscle mitochondrial capacity.

Introduction

Diet and increased physical activity (1) can be effective interventions for all grades of obesity (2), including morbid obesity (3), and their cardiovascular and metabolic risk factors (4). The increasing use of bariatric surgery to treat obesity has rapidly gained widespread acceptance, owing, in part, to greater weight loss (5) and effective treatment of diabetes and other cardiometabolic risk factors (6). Although bariatric surgery can cause marked weight loss and remission of type 2 diabetes (7), many patients lose much less weight, have significant weight regain (8), or do not experience diabetes remission (9). There have been few studies to determine whether interventions such as exercise could effectively promote greater weight loss and better health outcomes following bariatric surgery. Moreover, although the amount of weekly exercise has been associated with greater weight loss (10) and improvements in both insulin sensitivity (11) and β-cell function (12) among non-severely obese subjects, the amount of exercise required to improve health outcomes in bariatric surgery patients is not clear.

To address this deficiency, we recently performed a randomized trial to determine the potential benefit of an exercise program in participants following Roux-en-Y gastric bypass (RYGB) surgery (13). We reported that an exercise program could significantly improve insulin sensitivity and cardiopulmonary fitness compared with a health education control.
group. Although we had a 93% completion rate, there was considerable variability in the compliance and adherence to the structured exercise program. This left us with questions about the minimum or specific amount of exercise that was associated with these positive health benefits. Therefore, we conducted a post hoc outcomes analysis of participants in our trial (13) according to their amount of objectively recorded exercise. Our overall hypothesis was that RYGB surgery patients who performed more total weekly exercise will achieve greater health benefits, including greater body fat and abdominal adipose tissue (AAT) loss, better insulin sensitivity, cardiorespiratory fitness, and skeletal muscle mitochondrial metabolism.

Methods
Participant recruitment, inclusion/exclusion criteria, and randomization
RYGB participants were recruited and randomized as previously described (13). In brief, RYGB participants were recruited 1-3 months after RYGB and randomized into a 6-month semi-supervised exercise (EX) program or health education control (CON). Participants in the EX group were asked to participate in three to five exercise sessions per week, with at least one supervised session per week to assure that the target exercise intensity (60%-70% of maximal heart rate) and duration achieved and to document number of exercise sessions and time.

The post hoc analysis and flow of participants through the study is depicted in Figure 1. From two clinical research centers, 128 RYGB patients were randomized (n = 62 in CON and n = 66 in EX). In the CON group, although 59 completed the study, 17 were excluded from the analysis because of self-reported participation in some form of structured exercise. In the EX group, although 60 participants completed the study, four were excluded in the post hoc analysis because of missing minutes per week of exercise data during the last 3 months of the intervention. Overall, 15 were men and 83 were women; 22 were African American and 76 were of mixed European descent. There were no gender or race imbalances between the groups. There were no differences in demographics or characteristics contributing to outcomes between study groups. The time from surgery to randomization was 80.5 ± 25.6 days (range = 35-156 days) for the entire study cohort, and this was not different among the study groups, nor did this significantly confound the differences in outcomes among the groups. Baseline characteristics of the subjects are shown in Table 1.

Participants in the EX group were prescribed a progressive exercise program during the first 3 months of exercise in order to reach the 120 min per week. Participants in the CON group were asked to attend monthly educational sessions and to report on any physical activity habits. Minutes per week of supervised and nonsupervised exercise during the last 3 months of the intervention was then quantified at the completion of the study to determine group adherence.

Outcomes
The primary outcome variables were insulin sensitivity, body composition, and cardiorespiratory fitness. Secondary outcome variables were resting metabolic rate, postabsorptive respiratory exchange quotient, described previously (14), and skeletal muscle mitochondrial performance. We conducted the insulin sensitivity and muscle biopsy measurements 36-48 h after the last exercise bout to reduce the influence of acute exercise and to concentrate the effects of chronic exercise on these outcomes.

Glucose and insulin homeostasis (minimal model)
A 3-h insulin-modified intravenous glucose tolerance test was performed as previously described by Coen et al. (13) to determine insulin action parameters (insulin sensitivity (S_I), glucose effectiveness (S_G), disposition index (D_I), and acute insulin response (AIR_G)). Blood glucose was determined via an oxidation reaction (YSI Model 2300 Stat plus; Yellow Springs, OH), and insulin was measured with an immunoassay (Access Immunoassay Systems, Beckman Coulter; Fullerton, CA).

Weight and body composition
Weight loss was accessed in five intervals: 1: presurgery to baseline, 2: first half of intervention: baseline intervention to mid-intervention, 3: second half of intervention: mid-intervention to postintervention, 4: intervention: baseline to postintervention, 5: total: presurgery to postintervention. Body mass index (BMI) was calculated.

Body composition was assessed at pre- and postintervention in both groups. Briefly, whole body fat mass (FM) and fat-free mass (FFM) were determined by dual-energy X-ray absorptiometry (DXA) utilizing a GE iDXA (GE Healthcare). Total AAT, superficial adipose tissue, deep adipose tissue, visceral adipose tissue, and subcutaneous adipose tissue were quantified by computed tomography (CT) using SliceOmatic image analysis software (TomoVision, Montreal, CA).

Cardiorespiratory fitness (VO2 max)
Indirect calorimetry was used to measure physical fitness and target work rate used to prescribe exercise during the intervention. In brief, VO2 max was measured during a 5- to 12-min graded exercise test (13).

Percutaneous muscle biopsy
Fasting percutaneous muscle biopsies of the vastus lateralis were performed as previously described (13). Each muscle biopsy was partitioned for fresh tissue measures of oxygen consumption (10-20 mg) and 14C-palmitate oxidation (30-50 mg).

Skeletal muscle mitochondrial respiration
High-resolution O2 consumption measurements were conducted as previously described by Anderson et al. (15). In brief, Complex I supported Leak (State 4, L4), Complex I and II supported OXPHOS (P4H), and maximal uncoupled respiration EAT were analyzed in permeabilized fiber bundles using high-resolution respirometry (Oroboros, Oxygraphy-2K, Oroboros Instruments, Innsbruck, Austria).

In vitro fat oxidation
Complete and incomplete 14C-palmitate oxidation was determined in a subset of CON and EX subjects (16). In brief, skeletal muscle homogenates were accessed for complete and incomplete oxidation of 14C-palmitate.
Data analysis

In the post hoc analysis, the EX group in all performed an average of 158 ± 18 min per week measured over the last 3 months of the intervention. There was substantial variability in the amount of exercise performed (minimum = 1; maximum = 729; and median = 128). The EX group was divided into tertiles based on the mean minutes per week of exercise during the last 3 months of the intervention (low-EX = 54 ± 8; middle-EX = 129 ± 4; and high-EX = 286 ± 40; Figure 2).

Results

Weight change

Short-term weight loss was determined as the weight loss from the time of RYGB to randomization, i.e., the start of either the control/educational or the exercise training intervention. There was substantial variability (4.6 to −47.9 kg) in the short-term weight loss among the participants in each group, as well as an (unexpectedly) significantly greater weight loss in the low-EX group (Table 2). Therefore, we included the short-term weight loss as a covariate in the outcomes analysis.

Weight loss during the first half of the intervention was significantly different in each EX tertile when compared with CON, with no significant differences between the EX tertiles (Table 2). % weight loss during the first half of the intervention was also significantly greater between the high-EX groups and both the CON group and the low-EX group ($P < 0.05$), with a trend for a significant difference between the CON group and middle-EX group ($P = 0.08$). Weight loss during the second half of the intervention was significantly different between the middle and high-EX groups, and the % weight loss was significantly greater in the high-EX group when compared with both the middle-EX and CON. Similar results were observed for change in BMI (Table 2). Thus, increased minutes per week of exercise training elicits additional decreases in weight and BMI post-gastric bypass surgery.

Body composition

Body composition was assessed by both DXA and CT. Both groups lost a significant amount of total FM (Figure 3) over the course of the intervention. Both the pre- to postintervention change and the % change in total FM were significantly different between the high-EX and CON groups, with no significant differences between CON and the low- or middle-EX groups or between the EX tertiles (Figure 3).
There was no significant difference in the change in FFM between the CON group and the EX groups or within the EX tertiles as measured by DXA.

All groups also lost a significant amount of AAT as measured by CT (Figure 4), with no significant differences between the CON and EX groups or among the exercise tertiles. There was a trend, however, for a greater decrease in total AAT in the high-EX group when compared with the CON (Figure 3). All groups lost a significant amount of adipose tissue from all abdominal compartments (Table 2). Only the change in deep adipose tissue was significantly different between the CON group and both the high-EX and middle-EX groups, with no difference among the EX tertiles (summary of changes given in fat Table 2).

Resting metabolic rate

Resting metabolic rate decreased from 1725 ± 344 at randomization to 1627 ± 304 kcal/24 h postintervention for all subjects, but this was not different among groups. The postabsorptive respiratory quotient as a measure of substrate oxidation increased from 0.75 ± 0.10 to 0.77 ± 0.07, and this also was not different among the groups.

### TABLE 1 Baseline characteristics of the study participants

| Parameter                        | CON     | Low-EX | Middle-EX | High-EX |
|----------------------------------|---------|--------|-----------|---------|
| N                                | 42      | 18     | 19        | 19      |
| Age (years)                      | 43 ± 2  | 39 ± 2 | 43 ± 2    | 41 ± 2  |
| Presurgery weight (kg)           | 123.9 ± 4.4 | 127.8 ± 3.8 | 120.9 ± 3.5 | 132.7 ± 6.9 |
| Pre-intervention weight (kg)     | 108.1 ± 4.4 | 106.4 ± 3.7 | 105.7 ± 3.3 | 113.1 ± 6.0 |
| Pre-intervention fat-free mass (kg) | 52.95 ± 1.30 | 50.79 ± 1.94 | 52.24 ± 1.94 | 56.44 ± 2.00 |
| Pre-intervention BMI (kg/m²)     | 38.5 ± 0.9 | 38.9 ± 1.6 | 37.8 ± 1.5 | 39.7 ± 1.4 |

All data shown as loss, mean ± SEM.

### TABLE 2 Weight and fat loss

| Parameter                        | CON     | Low-EX | Middle-EX | High-EX |
|----------------------------------|---------|--------|-----------|---------|
| Weight (kg)                      |         |        |           |         |
| Surgery to prerandomization      | 15.8 ± 1.2 | 21.3 ± 1.4\(^a\) | 15.2 ± 1.2\(^b\) | 19.5 ± 2.0 |
| First half of intervention       | 13.5 ± 0.9 | 16.9 ± 1.2\(^a\) | 16.4 ± 1.5\(^a\) | 17.1 ± 1.1\(^a\) |
| Second half of intervention      | 5.7 ± 1.3 | 7.8 ± 1.4 | 4.7 ± 0.6\(^c\) | 9.1 ± 1.2 |
| Intervention                     | 20.0 ± 1.7 | 22.9 ± 2.0 | 21.0 ± 1.3\(^c\) | 26.3 ± 1.9\(^a\) |
| Total                            | 35.5 ± 2.0 | 44.3 ± 2.3\(^a\) | 36.2 ± 1.9\(^c\) | 45.9 ± 3.0\(^a\) |
| % Change                         | 13.2 ± 1.0 | 16.8 ± 1.2\(^a\) | 12.6 ± 1.0\(^b\) | 14.6 ± 1.0 |
| Surgery to prerandomization      | 12.5 ± 0.7 | 16.1 ± 1.1\(^a\) | 15.7 ± 1.4 | 15.4 ± 0.7\(^a\) |
| First half of intervention       | 5.7 ± 1.5 | 8.6 ± 1.5 | 5.4 ± 0.7\(^c\) | 9.3 ± 0.8\(^a\) |
| Second half of intervention      | 18.0 ± 1.3 | 21.6 ± 1.7 | 20.1 ± 1.3\(^c\) | 23.2 ± 1.0\(^a\) |
| Total                            | 28.6 ± 1.2 | 34.8 ± 1.7\(^a\) | 30.1 ± 1.8\(^c\) | 34.5 ± 1.2\(^a\) |
| Abdominal adipose tissue (cm²)   |         |        |           |         |
| Visceral                         | 63.4 ± 9.1 | 57.9 ± 9.6 | 57.0 ± 6.9 | 73.2 ± 13.0 |
| Subcutaneous                     | 170.9 ± 20.0 | 210.1 ± 38.4 | 217.5 ± 30.4 | 210.3 ± 27.3 |
| Deep                             | 70.1 ± 9.7 | 94.3 ± 14.4 | 105.3 ± 14.6\(^a\) | 98.2 ± 10.8\(^a\) |
| Superficial                      | 100.8 ± 12.7 | 88.9 ± 17.8 | 114.4 ± 22.1 | 105.3 ± 19.3 |
| % Change                         | 41.8 ± 3.3 | 42.7 ± 5.0 | 38.9 ± 4.8 | 45.3 ± 4.6 |
| Visceral                         | 30.2 ± 3.3 | 39.5 ± 7.0 | 35.8 ± 4.9 | 39.7 ± 5.5 |
| Subcutaneous                     | 29.0 ± 3.6 | 38.7 ± 5.0\(^a\) | 38.2 ± 4.5\(^a\) | 41.9 ± 5.6\(^a\) |
| Deep                             | 32.0 ± 3.3 | 31.8 ± 6.2 | 34.5 ± 6.7 | 36.5 ± 7.1 |

All data shown as loss, mean ± SEM.

\(^a\)Versus CON.

\(^b\)Versus low-EX.

\(^c\)Versus high-EX.

All \(P < 0.05\).
Cardiorespiratory fitness
The change in absolute VO₂ max (ml/min) was only significantly different between CON and the high-EX group pre- to postintervention (Figure 4). VO₂ max per kg FFM followed the same pattern; the change in VO₂ max/FFM was significantly different between CON and high-EX (-2.15 vs. +4.70 ml/kg FFM/min, P = 0.0002).

Intravenous glucose tolerance test
S_I significantly improved in each group pre- to postintervention. But, the change in S_I was only significantly different between the CON group when compared with the high-EX or middle-EX groups. D_I also significantly improved from pre- to postintervention in all groups, with a significant group effect between the CON group when compared with either the high-EX or middle-EX groups (Figure 5). Acute insulin responsiveness (AIRG), glucose effectiveness (S_G), and homeostatic model assessment of insulin resistance (HOMA-IR) improved over time (data not shown), but there was no dose response to increased minutes per week of exercise.

O₂ flux (glycolytic protocol)
Oxygen consumption was measured in response to glycolytic substrates. The change in State 4 respiration supported by glutamate and malate was significantly higher in the high-EX group when compared with the CON, low-EX, and middle-EX groups (Figure 6). The change in State 3 respiration pre- to postintervention supported by glutamate, malate, and ADP as well as State 3 respiration supported by glutamate, malate, ADP, and succinate was significantly higher in the middle-EX and high-EX groups when compared with CON. Carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (FCCP)-supported uncoupled respiration was higher in the middle group compared with CON, with a trend to also be higher in the high-EX group compared with CON (P = 0.068) (Figure 6).

14C-palmitate oxidation
Only a subset of subjects had sufficient biopsy material available for the analysis of in vitro fat oxidation; therefore, the EX group was combined (n = 16) versus CON (n = 19) for this analysis. Complete fat oxidation significantly decreased in the CON group, with no significant change in the exercise group pre- to postintervention, suggesting better maintenance of fat oxidation with exercise training. Incomplete fat oxidation as measured by acid-soluble metabolites significantly decreased in the EX group, with no significant change in the CON group, suggesting enhanced complete oxidation and an increased flux of metabolites through β-oxidation and the TCA cycle in response to exercise training. There was a trend for an increased ratio of CO₂/acid-soluble metabolites in the EX group.
Discussion

The use of bariatric surgery can effectively treat obesity (17) and type 2 diabetes (18). Many patients, however, do not experience robust weight loss (17), have weight regain (8,17), and do not have diabetes resolution (18). Thus, adjunct therapies, such as exercise after bariatric surgery, could improve weight loss and other health outcomes. We recently reported that patients who were randomized to a structured exercise program following RYGB surgery had significantly greater improvements in insulin sensitivity and physical fitness compared with control subjects who lost similar amounts of weight but who did not perform exercise (13). One of the limitations in that study, however, was that the wide variation in compliance to the exercise program precluded us from determining more precisely how much exercise is needed to elicit these additional health benefits.

The primary findings in this study were that patients in the highest two tertiles of weekly exercise had greater improvements in insulin sensitivity, but only the highest tertile lost more weight, body fat, and AAT, as well as significantly greater cardiorespiratory fitness and enhanced mitochondrial function within skeletal muscle. Although exercise dose recommendations for achievement of health benefits exist for the general population as well as for weight maintenance in formerly obese people (10), the minimum amount or specific dose of exercise training needed post-RYGB to achieve additional health benefits is virtually unknown. In a systematic review, Egberts et al. (19) found that increased physical activity post-gastric bypass surgery is correlated with additional weight loss. The vast majority of studies published to date, however, have relied on self-reported subjective physical activity metrics (19,20). Few prospective structured exercise training studies have been performed post-bariatric surgery.

One shorter-term 12-week study employing a high-volume exercise program post-gastric bypass surgery had no effect on weight loss (21). In this analysis, the minutes per week of exercise spanned from almost no exercise to a maximum of 729 min per week of combined supervised and unsupervised exercise sessions. The low-EX group averaged 53 min per week, whereas the middle-EX group averaged 128 and the high-EX group averaged 238. Therefore, the middle-EX group’s minutes per week was very similar to the amount of exercise recommended to the general population, whereas the high-EX group’s minutes per week was very similar to the amount of exercise previously demonstrated to be effective in a weight-matched population. Exercise intensity could also play a role in improved insulin sensitivity (11) and other health outcomes. Intensity of exercise expressed as %HR_max was not different across EX: 81.7%, 78.0%, and 83% for low-EX, middle-EX, and high-EX, respectively (P > 0.05). Although we focused this analysis on the influence of intentional structured exercise post-RYGB, we recognize the potential important role that lower doses of unstructured physical activity, or decreased sedentary time, may play in promoting health benefits. We need to understand the role of objectively measured physical activity in bariatric surgery patients. In addition, although we did not quantify energy or macronutrient intake, subjects who performed more exercise experienced greater weight and fat loss relatively soon after surgery. As exercise can affect appetite and energy intake (22), and exercise and macronutrient intake can synergistically influence insulin sensitivity (23),
additional studies are needed to assess the effects of physical activity on energy intake, in association with weight loss and improved health post-bariatric surgery.

Remission of type 2 diabetes and improvements in insulin sensitivity are considered a key beneficial outcome post-RYGB. In our post hoc analysis, we recapitulate previous findings that have demonstrated improvements in $S_I$ in patients post-RYGB (9,13,24); however, we go on further to investigate the potential additive improvements in $S_I$ with increasing amount of weekly exercise training. We demonstrate that 120 min or more per week improves both $S_I$ and $D_I$ over RYGB CON. These data are the first, to our knowledge, to hone in on a specific exercise prescription post-RYGB that provides additive improvements in both $S_I$ and $D_I$. These observations are in agreement with not only our previously published per-protocol analysis (13), but others who found improvements in glucose tolerance after 12 weeks of exercise training post-RYGB (21). Although the high-EX group lost more weight and body fat, it is difficult to imagine how this relatively small additional weight loss could induce the observed improvement in insulin sensitivity, particularly because the low-EX group who lost no additional weight had significant improvements in $S_I$. The amount of weekly exercise was more strongly associated with weight loss in the second half of the intervention, suggesting that the amount of physical activity is more strongly related to weight loss over a protracted time following surgery.

The amount of weekly exercise was associated with greater improvements in cardiorespiratory fitness (VO2 max). This finding is in agreement with our previously published data as well as other reports of improvements in fitness with exercise post-RYGB (21). More specifically, VO2 max was only significantly increased in the high-EX group, indicating that the improvements documented in our previously published work (13) were truly driven by those subjects who exercise an average of $\frac{24}{280}$ min per week, whereas those who exercised an average of $\frac{24}{120}$ min per week or less maintained—but did not increase—their fitness compared with control subjects who had a decline in fitness over the course of the intervention. This significant decrease in fitness could be attributed to a trend for a greater loss of lean mass. Thus, our data indicate a dose-dependent improvement in cardiorespiratory fitness, suggesting that a minimum exercise threshold is needed to improve VO2 max in these patients.

Exercise training can have profound effects on skeletal muscle metabolism in subjects with normal weight and obesity (27,28). Much less is known about whether exercise can improve skeletal muscle mass in the face of decreasing total body FM (26). In our post hoc analysis, we demonstrate a dose-dependent effect of exercise training on total weight loss, whereas with regards to body composition, we demonstrated that only the high-EX group lost significantly more total FM when compared with CON, as well as a trend for less lean mass loss. The amount of weekly exercise was more strongly associated with weight loss in the second half of the intervention, suggesting that the amount of physical activity is more strongly related to weight loss over a protracted time following surgery.

The weight loss induced by RYGB includes body fat as well as lean body mass. Exercise training has been shown to maintain muscle mass in the face of decreasing total body FM (26). In our post hoc analysis, we demonstrate a dose-dependent effect of exercise training on total weight loss, whereas with regards to body composition, we demonstrated that only the high-EX group lost significantly more total FM when compared with CON, as well as a trend for less lean mass loss. The amount of weekly exercise was more strongly associated with weight loss in the second half of the intervention, suggesting that the amount of physical activity is more strongly related to weight loss over a protracted time following surgery.

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muscle metabolism in subjects with severe obesity, particularly following bariatric surgery. Subjects with severe obesity (BMI ≥ 45) seem to have an “obesity metabolic program” (29), by which there is a significant reduction in skeletal muscle fat metabolism when compared with lean subjects (BMI < 25). Though exact mechanisms for this diminished fat oxidation have not been elucidated, mitochondria within skeletal muscle likely play a role. Within this context, it was important to determine whether skeletal muscle mitochondria could be modified in severe obesity—either by marked weight loss or with the addition of structured exercise. Surgery-induced weight loss without concomitant exercise (CON subjects) in our study decreased complete fatty acid oxidation by mitochondria, which was corroborated by a trend toward a decrease in maximal uncoupled mitochondrial respiration. These data support prior studies demonstrating that the reduced fat metabolism in subjects with severe obesity persists after weight loss (30,31). In stark contrast, our data demonstrate a dose response of exercise training on both State 4 and State 3 respiration, as well as FCCP-supported uncoupled respiration. In addition, the combined EX group demonstrated a significant decrease in incomplete palmitate oxidation within muscle tissue. These data are in agreement with Cortright et al. (27) who reported an increase in palmitate oxidation after 10 days of exercise training in subjects with severe obesity. Taken together, the data derived from muscle biopsies indicate that mitochondrial respiration is not improved by the marked weight loss but that exercise robustly improves mitochondrial respiration in a dose-dependent manner during surgery-induced weight loss.

Conclusion

RYGB subjects who exercise more than ~238 min per week achieve significantly greater improvements in insulin sensitivity, lose more weight and body fat, and have significantly greater improvements in cardiorespiratory fitness and greater improvements in skeletal muscle metabolism. This study provides direct evidence supporting an important role for specific amounts of adjunct exercise to provide additional health benefits in patients following bariatric surgery.

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