Published in final edited form as:
Obesity (Silver Spring). 2015 December ; 23(12): 2454–2461. doi:10.1002/oby.21332.

Dose-Response of Exercise Training following Roux-en-Y gastric bypass surgery: A randomized trial

Tracey L. Woodlief[1], **Elvis A. Carnero**[1], **Robert A. Standley**[1], **Giovanna Distefano**[1], **Steve J. Anthony**[4], **Gabe S. Dubis**[3], **John M. Jakicic**[5], **Joseph A. Houmard**[3], **Paul M. Coen**[1], and **Bret H. Goodpaster**[1,*]

[1]Translational Research Institute for Metabolism and Diabetes, Florida Hospital, Orlando, FL 32804, USA

[2]Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA

[3]Health and Human Performance, East Carolina University, Greenville, NC 27858, USA

[4]Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA

[5]Department of Health and Physical Activity, University of Pittsburgh, PA 15260, USA

Abstract

Objective—Roux-en-Y gastric bypass(RYGB) can cause profound weight loss and improve overall cardiometabolic risk factors. Exercise (EX) training following RYGB can provide additional improvements in insulin sensitivity(S_I) and cardiorespiratory fitness. However, it remains unknown if 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). EX(N=56) were divided into tertiles according to the amount of weekly exercise performed, compared to CON(N=42): Low-EX=54±8; Middle-EX=129±4; High-EX=286±40 minutes per week.

Results—The High-EX lost a significantly greater amount of body weight, total fat mass and abdominal deep subcutaneous abdominal fat compared to CON($p<0.005$). S_I improved to a greater extent in both the Middle-EX and High-EX compared to CON($p<0.04$). Physical fitness (VO_2max) significantly improved in the High-EX(+9.3±4.2%) compared to 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 to CON.

Address correspondence to: Bret H. Goodpaster, Ph.D., Translational Research Institute for Metabolism and Diabetes, Florida Hospital • Sanford | Burnham | Prebys Medical Discovery Institute, 301 East Princeton Street, Orlando, FL 32804, Bret.Goodpaster@FLHosp.org, Office: 407.303.1305.

[*] new affiliation for this author

TLW and BHG researched the data; contributed to study execution, interpretation of the data; and wrote the manuscript. RAS, GD, SJA, GSD and JMJ contributed to study execution and researched the data. EAC and PMC contributed to the statistical analyses, interpretation of the data and reviewed the manuscript. BHG and JAH contributed to the study concept and design and the analysis and interpretation of the data and reviewed the manuscript. BGH and TLW are the guarantors of the data.

DISCLOSURE STATEMENT: No potential conflicts of interest relevant to this article were reported.

Conclusion—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 cardiorespiratory 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). And while bariatric surgery can cause dramatic weight loss and remission of type 2 diabetes (T2D) (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 cardiorespiratory fitness compared to 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 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 post 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 3 to 5 exercise session 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.

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/wk. 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 non-supervised exercise during the last three 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 (RMR), postabsorptive respiratory exchange quotient (RQ) described previously (14) and skeletal muscle mitochondrial performance. We conducted the insulin sensitivity and muscle biopsy measurements 36–48 hours 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-hour insulin-modified IVGTT 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 5 intervals: 1: pre-surgery to baseline, 2: first half of intervention: baseline intervention to mid-intervention, 3: Second half of intervention: mid intervention to post intervention, 4: Intervention = baseline to post intervention, 5: Total: pre-surgery to post intervention. Body mass index (BMI) was calculated.

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

Cardiorespiratory fitness (VO_2max)

Indirect calorimetry was utilized to measure physical fitness and target work rate used to prescribe exercise during the intervention. In brief, VO_2peak was measured during a 5- to 12- minute 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 (10–20mg) and ^{14}C palmitate oxidation (30–50mg).

Skeletal muscle mitochondrial respiration

High-resolution O_2 consumption measurements were conducted as previously described by Anderson et al (15). In brief, complex I supported Leak (State 4, L_I), complex I&II supported OXPHOS ($P_{I\&II}$) and maximal uncoupled respiration, $E_{I\&II}$ were analyzed in permeabilized fiber bundles using high-resolution respirometry (Oroboros, Oxygraphy-2K, Oroboros Instruments, Innsbruck, Austria).

In vitro fat oxidation

Complete and incomplete 14-C-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 ^{14}-C palmitate.

Data Analysis

In the post-hoc analysis, the EX group in all performed an average of 158±18 minutes 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;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; High-EX=286±40 (Figure 2)).

Results

Study participants

The post-hoc analysis and flow of participants through the study is depicted in Figure 1. 128 post RYGB participants from two clinical research centers were randomized (n = 62 health education controls [CON] and n = 66 exercise program [EX]). In the CON group, although 59 completed the study, 17 were excluded from the analysis due to self-reported participation in some form of structured exercise. In the EX group, while 60 participants completed the study and 4 were excluded in the post-hoc analysis due to missing minutes per week of exercise data during the last 3-months of the intervention. Overall, 15 were male and 83 were female; 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 to 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.

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 to the control group, 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 control group and the low EX-group ($p<0.05$), with a trend for a significant difference between the control 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 group, the % weight loss was significantly greater in the high-EX group when compared to both the middle-EX group and CON (Table 2). Lastly, both weight loss and % weight loss during the intervention were significantly greater in the high-EX group compared to both the middle-EX and CON. Similar results were observed for change in BMI (Table 2). Thus, increased minutes per week of EX-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 fat mass (Figure 3) over the course of the intervention. While both the change pre to post intervention and the % change in total fat mass were significantly different between the high-EX and control group, with no significant differences between control and the low or middle-EX groups or between the EX tertiles (Figure 3). There was no significant difference in the change in FFM mass between the CON group and the EX group or within the EX tertiles as measured by DXA.

All groups also lost a significant amount of abdominal adipose tissue (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 abdominal adipose tissue in the high EX group when compared to the control (Figure 3). All groups lost a significant amount of adipose tissue from all abdominal compartments (Table 2). Only the change in DSAT was significantly different between the CON group and both the high-EX and middle-EX groups, with no difference among the EX teritles [Summary of changes in fat Table 2].

Resting metabolic rate (RMR)

RMR decreased from 1725±344 at randomization to 1627±304 Kcal/24 hr post-intervention for all subjects, but this was not different among groups. The postabsorptive respiratory quotient (RQ) 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.

Cardiorespiratory fitness

The change in absolute VO_2max (ml/min) was only significantly different between CON and the high-EX group pre to post intervention (Figure 4). VO_2max per kg FFM followed the same pattern; the change in VO_2max/FFM was significantly different between Control 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 post intervention. While the change in S_I was only significantly different between the CON group when compared to the high-EX or middle-EX group. D_I also significantly improved from pre to post intervention in all groups, with a significant group effect between the CON group when compared to either the high-EX or middle-EX group (figure 5). Acute insulin responsiveness (AIRg), glucose effectiveness (S_G) and HOMA-IR improved over time, but there was no dose-response to increased minutes per week of exercise.

O_2 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 to the CON, low-EX and middle-EX group (figure 6). The change in state 3 respiration pre to post intervention 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 group when compared to CON. FCCP supported uncoupled respiration was higher in the middle group compared to the CON, with a trend to also be higher in the high-EX group compared to control (p=0.068) (figure 6).

^{14}C palmitate oxidation

Only a subset of subjects had sufficient biopsy material available for the analysis of in vitro fat oxidation, therefore the exercise group was combined (N= 16) versus CON (N=19) for this analysis. Complete fat oxidation significantly decreased in the control group, with no significant change in the exercise group pre to post intervention suggesting better maintenance of fat oxidation with exercise training. Incomplete fat oxidation as measured by acid soluble metabolites (ASM) significantly decreased in the exercise group, with no significant change in the control 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 CO_2/ASMs 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 post bariatric surgery could improve weight loss and other health outcomes. We recently reported that patients who were randomized to a structured exercise program following Roux-en-Y gastric bypass (RYGB) surgery had significantly greater improvements in insulin sensitivity and physical fitness compared to 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 the current 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 abdominal adipose tissue, 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 formally obese people (19), 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 found that increased physical activity post-gastric bypass surgery is correlated with additional weight loss (20). The vast majority of studies published to date, however, have relied on self-reported subjective physical activity metrics (20, 21). 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 (22). In the current analysis the minutes per week of exercise spanned from almost no exercise to a maximum of 729 minutes per week of a combined supervised and unsupervised exercise sessions. The low-Ex group averaged 53 minutes per week, while 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, while 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 %HRmax 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 (23), and exercise and macronutrient intake can synergistically influence insulin sensitivity (24), 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 is 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, 25); 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 minutes 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 (22). 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 since the Low-EX group who lost no additional weight had significant improvements in S_I. Our results are also supported by a report by Slentz et al. (26) demonstrating that low to moderate doses of exercise robustly improves S_I and D_I in non-diabetic subjects. Additional studies are needed to determine the potential benefits of exercise post-RYGB on insulin sensitivity and β-cell function in patients with type 2 diabetes.

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 fat mass (27). In our post-hoc analysis, we demonstrate a dose-dependent effect of exercise training on total weight loss, while with regards to body composition we demonstrated that only the high-EX group lost significantly more total fat mass when compared to 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 post surgery.

The amount of weekly exercise was associated with greater improvements in cardiorespiratory fitness (VO_2max). This finding is in agreement with our previously published data as well as other reports of improvements in fitness with exercise post-RYGB (22). More specifically, VO_2max was only significantly increased in the high-EX group, indicating that the improvements documented in our previously published work (13) was truly driven by those subjects who exercise an average of ~280 minutes per week, while those who exercised and average of ~120 minutes per week or less maintained – but did not increase - their fitness compared to 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 a minimum exercise threshold is needed to improve VO_2max in these patients.

Exercise training can have profound effects on skeletal muscle metabolism in normal weight and obese subjects (28, 29). Much less is known about whether exercise can improve skeletal muscle metabolism in severely obese subjects, particularly following bariatric surgery. Subjects with severe obesity (BMI > 45) seem to have a “obesity metabolic program” (30), by which there is a significant reduction in skeletal muscle fat metabolism when compared to 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 dramatic weight loss or with the addition of structured exercise. Surgery-induced weight loss without concomitant exercise (control subjects) in our study decreased complete fatty acid oxidation by mitochondria, which was corroborated by a trend towards a decrease in maximal uncoupled mitochondrial respiration. These data support prior studies demonstrating that the reduced fat metabolism in severely obese subjects persists post weight loss (31, 32). 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. who reported an increase in palmitate oxidation after 10-

days of exercise training in severely obese subjects (28). Taken together, the data derived from muscle biopsies indicate that mitochondrial respiration is not improved by the dramatic 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/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.

Acknowledgments

Funding: This study was supported by funding from the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK078192, R01DK078192-02S1, BHG), and the University of Pittsburgh Clinical Translational Research Center (M01RR00056).

References

1. Johns DJ, Hartmann-Boyce J, Jebb SA, Aveyard P. Behavioural Weight Management Review G. Diet or exercise interventions vs combined behavioral weight management programs: a systematic review and meta-analysis of direct comparisons. Journal of the Academy of Nutrition and Dietetics. 2014; 114:1557–1568. [PubMed: 25257365]
2. Wu T, Gao X, Chen M, van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: a meta-analysis. Obesity reviews: an official journal of the International Association for the Study of Obesity. 2009; 10:313–323. [PubMed: 19175510]
3. DeLany JP, Kelley DE, Hames KC, Jakicic JM, Goodpaster BH. Effect of physical activity on weight loss, energy expenditure, and energy intake during diet induced weight loss. Obesity. 2014; 22:363–370. [PubMed: 23804562]
4. Gaesser GA, Angadi SS, Sawyer BJ. Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. The Physician and sportsmedicine. 2011; 39:87–97. [PubMed: 21673488]
5. Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. The Cochrane database of systematic reviews. 2014; 8:Cd003641.
6. Mehaffey JH, LaPar DJ, Turrentine FE, Miller MS, Hallowell PT, Schirmer BD. Outcomes of laparoscopic Roux-en-Y gastric bypass in super-super-obese patients. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2014
7. English TM, Malkani S, Kinney RL, Omer A, Dziewietin MB, Perugini R. Predicting remission of diabetes after RYGB surgery following intensive management to optimize preoperative glucose control. Obesity surgery. 2015; 25:1–6. [PubMed: 25052254]
8. Himes SM, Grothe KB, Clark MM, Swain JM, Collazo-Clavell ML, Sarr MG. Stop regain: a pilot psychological intervention for bariatric patients experiencing weight regain. Obes Surg. 2015; 25:922–927. [PubMed: 25750006]
9. Reed MA, Pories WJ, Chapman W, Pender J, Bowden R, Barakat H, et al. Roux-en-Y gastric bypass corrects hyperinsulinemia implications for the remission of type 2 diabetes. The Journal of clinical endocrinology and metabolism. 2011; 96:2525–2531. [PubMed: 21593117]
10. Jakicic JM, Marcus BH, Lang W, Janney C. Effect of Exercise on 24-Month Weight Loss Maintenance in Overweight Women. Arch Intern Med. 2008; 168:1550–1559. [PubMed: 18663167]

11. Dube JJ, Allison KF, Rousson V, Goodpaster BH, Amati F. Exercise dose and insulin sensitivity: relevance for diabetes prevention. Medicine and science in sports and exercise. 2012; 44:793–799. [PubMed: 22051572]

12. Malin SK, Solomon TP, Blaszczak A, Finnegan S, Filion J, Kirwan JP. Pancreatic beta-cell function increases in a linear dose-response manner following exercise training in adults with prediabetes. American journal of physiology Endocrinology and metabolism. 2013; 305:E1248–1254. [PubMed: 24045867]

13. Coen PM, Tanner CJ, Helbling NL, Dubis GS, Hames KC, Xie H, et al. Clinical trial demonstrates exercise following bariatric surgery improves insulin sensitivity. Journal of Clinical Investigation. 2015; 125:248–257. [PubMed: 25437877]

14. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes. 1999; 48:839–847. [PubMed: 10102702]

15. Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, et al. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. The Journal of clinical investigation. 2009; 119:573–581. [PubMed: 19188683]

16. Privette JD, Hickner RC, Macdonald KG, Pories WJ, Barakat HA. Fatty acid oxidation by skeletal muscle homogenates from morbidly obese black and white American women. Metabolism: clinical and experimental. 2003; 52:735–738. [PubMed: 12800100]

17. Courcoulas AP, Belle SH, Neiberg RH, Pierson SK, Eagleton JK, Kalarchian MA, et al. Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Clinical Trial. JAMA Surg. 2015

18. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012; 366:1567–1576. [PubMed: 22449319]

19. Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss maintenance in overweight women. Archives of internal medicine. 2008; 168:1550–1559. discussion 1559–1560. [PubMed: 18663167]

20. Egberts K, Brown WA, Brennan L, O’Brien PE. Does exercise improve weight loss after bariatric surgery? A systematic review. Obesity surgery. 2012; 22:335–341. [PubMed: 22038571]

21. Josbeno DA, Jakicic JM, Hergenroeder A, Eid GM. Physical activity and physical function changes in obese individuals after gastric bypass surgery. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2010; 6:361–366. [PubMed: 18996771]

22. Shah M, Snell PG, Rao S, Adams-Huet B, Quittner C, Livingston EH, et al. High-volume exercise program in obese bariatric surgery patients: a randomized, controlled trial. Obesity (Silver Spring, Md). 2011; 19:1826–1834.

23. King NA, Horner K, Hills AP, Byrne NM, Wood RE, Bryant E, et al. Exercise, appetite and weight management: understanding the compensatory responses in eating behaviour and how they contribute to variability in exercise-induced weight loss. Br J Sports Med. 2012; 46:315–322. [PubMed: 21596715]

24. Kirwan JP, Barkoukis H, Brooks LM, Marchetti CM, Stetzer BP, Gonzalez F. Exercise training and dietary glycemic load may have synergistic effects on insulin resistance in older obese adults. Ann Nutr Metab. 2009; 55:326–333. [PubMed: 19844089]

25. Bikman BT, Zheng D, Pories WJ, Chapman W, Pender JR, Bowden RC, et al. Mechanism for improved insulin sensitivity after gastric bypass surgery. The Journal of clinical endocrinology and metabolism. 2008; 93:4656–4663. [PubMed: 18765510]

26. Slentz CA, Tanner CJ, Bateman LA, Durheim MT, Huffman KM, Houmard JA, et al. Effects of exercise training intensity on pancreatic beta-cell function. Diabetes Care. 2009; 32:1807–1811. [PubMed: 19592624]

27. Willis LH, Slentz CA, Bateman LA, Shields AT, Piner LW, Bales CW, et al. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. Journal of applied physiology (Bethesda, Md: 1985). 2012; 113:1831–1837.

28. Cortright RN, Sandhoff KM, Basilio JL, Berggren JR, Hickner RC, Hulver MW, et al. Skeletal muscle fat oxidation is increased in African-American and white women after 10 days of endurance exercise training. Obesity (Silver Spring, Md). 2006; 14:1201–1210.

29. Bamman MM, Cooper DM, Booth FW, Chin ER, Neufer PD, Trappe S, et al. Exercise biology and medicine: innovative research to improve global health. Mayo Clinic proceedings. 2014; 89:148–153. [PubMed: 24485128]
30. Houmard JA, Pories WJ, Dohm GL. Severe obesity: evidence for a deranged metabolic program in skeletal muscle? Exercise and sport sciences reviews. 2012; 40:204–210. [PubMed: 22710702]
31. Kim JY, Hickner RC, Cortright RL, Dohm GL, Houmard JA. Lipid oxidation is reduced in obese human skeletal muscle. American journal of physiology Endocrinology and metabolism. 2000; 279:E1039–1044. [PubMed: 11052958]
32. Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol. 1999; 277:E1130–1141. [PubMed: 10600804]

What is already known about this subject?

- Bariatric surgery can cause profound weight loss
- Exercise can provide additive improvements in insulin sensitivity and physical fitness in patients following bariatric surgery

What does this study add?

- Bariatric surgery-induced weight loss does not improve skeletal muscle mitochondrial capacity, nor does it improve physical fitness.
- There is a dose-response association between the amount of moderate exercise post bariatric surgery and improvements in insulin sensitivity, cardiorespiratory fitness, and in loss of body fat.
- A moderate amount of exercise following bariatric surgery increases mitochondrial capacity within skeletal muscle

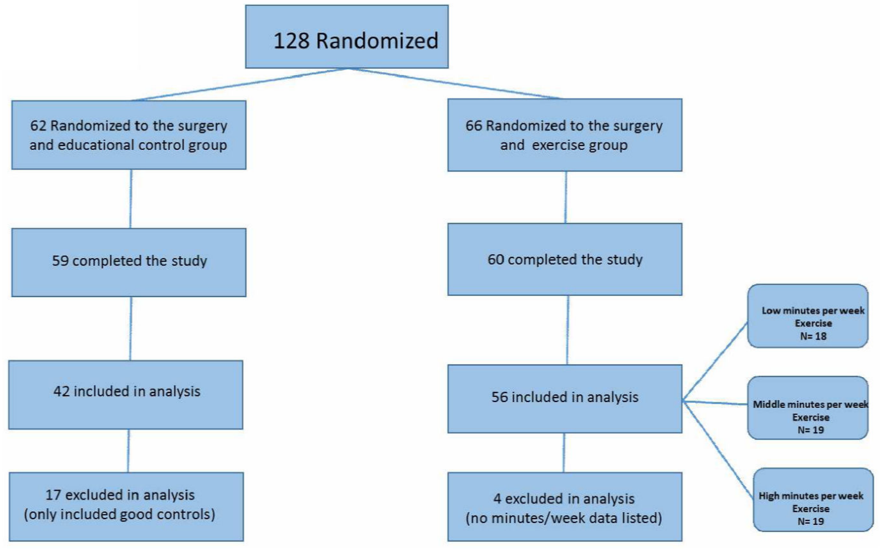
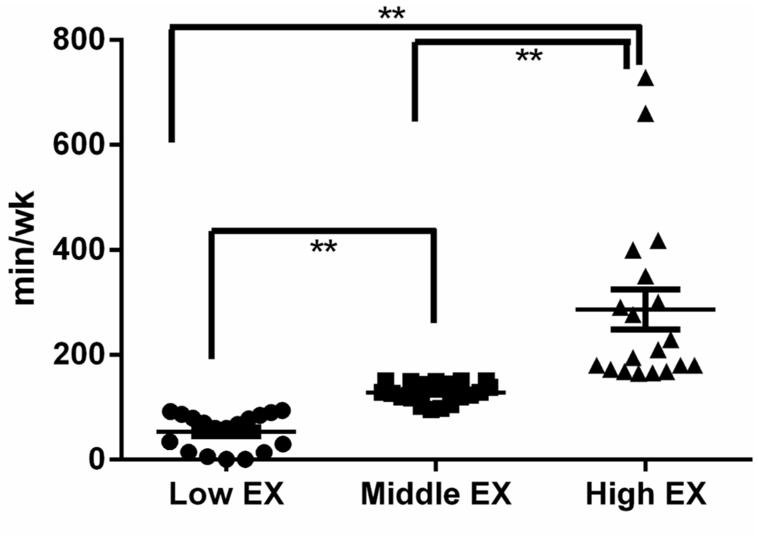


Figure 1.

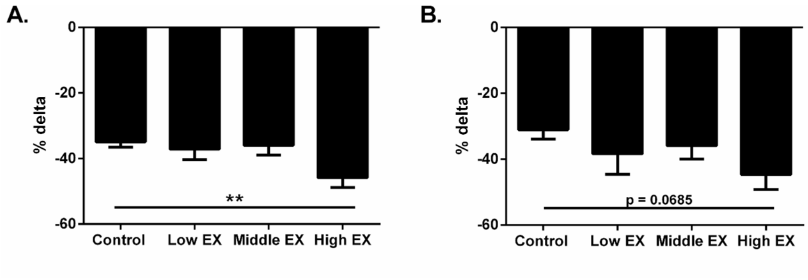
Flow of participant assessment and post-hoc analysis.



** $p < 0.05$

Figure 2.

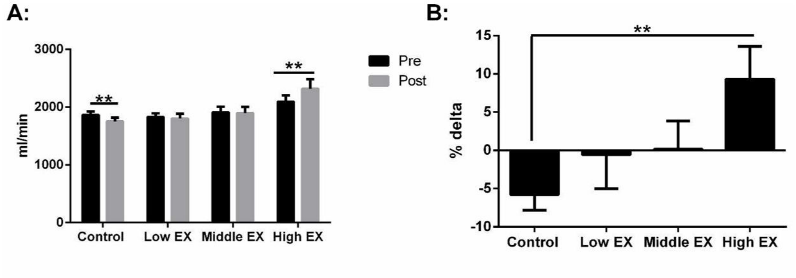
Tertiles of minutes per week of exercise training. Data are mean ± SEM, post-hoc analysis of the average minutes per week of exercise training during the last 3-months of the intervention.



** $p < 0.05$

Figure 3.

A: Percent change in total fat mass. B: Percent change in abdominal fat. Data are shown as mean ± SEM. ** different across groups, $p < 0.05$



** P < 0.05

Figure 4.

Cardiorespiratory fitness (VO$_2$peak). A: Pre intervention (black bars) and post intervention (gray bars). B: percent change from pre intervention. Data are mean ± SEM. ** post different from pre, $p<0.05$.

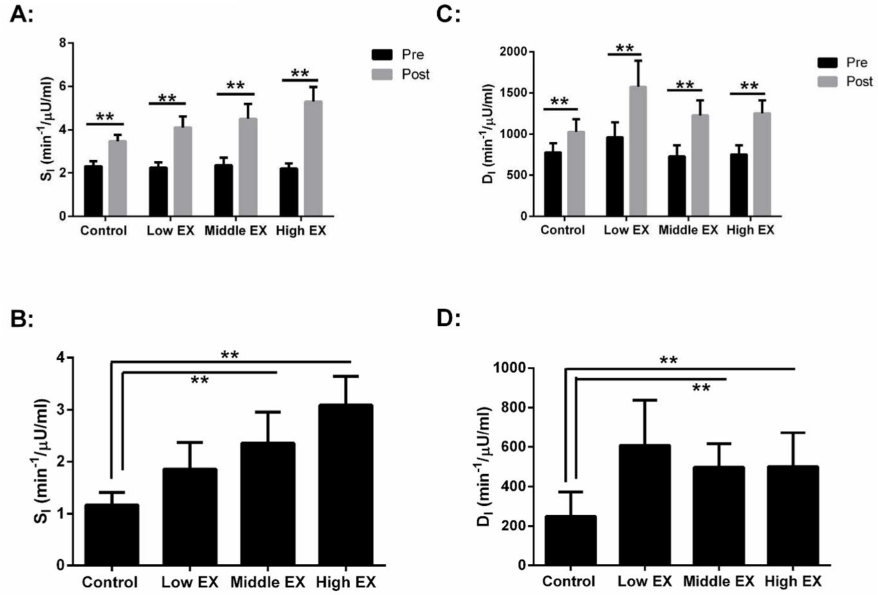


Figure 5.

A and B, Insulin sensitivity (S_I); and C and D, disposition index (D_I). Data are mean ± SEM. A and C, pre intervention (black bars) and post intervention (gray bars), ** post different from pre. B and D, ** different between groups, all $p<0.05$.

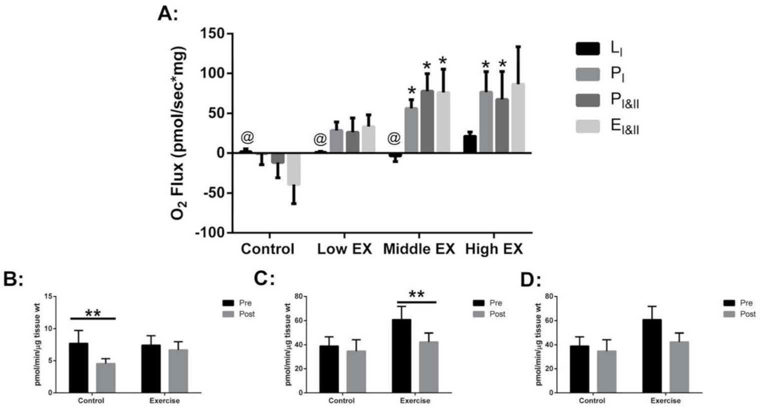


Figure 6.

A: Mitochondrial respiration in various respiratory states, including Leak (LI) respiration, complex I supported OXPHOS (PI) respiration, complex I and II supported OXPHOS respiration (PI&II) and electron transfer system capacity or maximal uncoupled respiration (EI&II). O2 flux was normalized to the fiber bundle dry weight. B: Complete Palmitate Oxidation. C: Incomplete palmitate oxidation. D: Ratio of complete/incomplete. Data are mean ± SEM. ** post different from pre; all $p < 0.05$

Table 1
Baseline characteristics of the study participants

Data show mean ± SEM.

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
Preintervention weight (kg)	108.1 ± 4.4	106.4 ± 3.7	105.7 ± 3.3	113.1 ± 6.0
Preintervention Fat free mass (kg)	52.95 ± 1.30	50.79 ± 1.94	52.24 ± 1.94	56.44 ± 2.00
Preintervention BMI, kg/m^2	38.5 ± 0.9	38.9 ± 1.6	37.8 ± 1.5	39.7 ± 1.4

Table 2

Weight and fat loss

All data shown as loss, mean ± SEM.

Parameter	CON	Low-EX	Middle-EX	High-EX
Weight (kg)				
Surgery to pre-randomization	15.8 ± 1.2	21.3 ± 1.4[*]	15.2 ± 1.2[^]	19.5 ± 2.0
First half of intervention	13.5 ± 0.9	16.9 ± 1.2[*]	16.4 ± 1.5[*]	17.1 ± 1.1[*]
Second half of intervention	5.7 ± 1.3	7.8 ± 1.4	4.7 ± 0.6[@]	9.1 ± 1.2
Intervention	20.0 ± 1.7	22.9 ± 2.0	21.0 ± 1.3[@]	26.3 ± 1.9[*]
Total	35.5 ± 2.0	44.3 ± 2.3[*]	36.2 ± 1.9[@][^]	45.9 ± 3.0[*]
% change				
Surgery to pre-randomization	13.2 ± 1.0	16.8 ± 1.2[*]	12.6 ± 1.0[^]	14.6 ± 1.1
First half of intervention	12.5 ± 0.7	16.1 ± 1.1[*]	15.7 ± 1.4	15.4 ± 0.7[*]
Second half of intervention	5.7 ±1.5	8.6 ± 1.5	5.4 ± 0.7[@]	9.3 ± 0.8[*]
Intervention	18.0 ± 1.3	21.6 ± 1.7	20.1 ± 1.3[@]	23.2 ± 1.0[*]
Total	28.6 ±1.2	34.8 ± 1.7[*]	30.1 ± 1.6[@][^]	34.5 ± 1.2[*]
Abdominal adipose tissue (cm^2)				
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[*]	98.2 ± 10.8[*]
Superficial	100.8 ± 12.7	88.9 ± 17.8	114.4 ± 22.1	105.3 ± 19.3
% change				
Visceral	41.8 ± 3.3	42.7 ± 5.0	38.9 ± 4.8	45.3 ± 4.6
Subcutaneous	30.2 ± 3.3	39.5 ± 7.0	35.8 ± 4.9	39.7 ± 5.5
Deep	29.0 ± 3.6	38.7 ± 5.0[*]	38.2 ± 4.5[*]	41.9 ± 5.6[*]
Superficial	32.0 ± 3.3	31.8 ± 6.2	34.5 ± 6.7	36.5 ± 7.1

[^] vs Low EX,

[*] vs CON,

[@] vs High EX; all $p < 0.05$