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TITLE: Resistance Training and Protein Supplementation Increase Strength After Bariatric Surgery: a Randomized Controlled Trial

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STUDY IMPORTANCE QUESTIONS

What is already known about this subject?

- Beneficial effects of bariatric surgery include marked weight loss as well as decreased morbidity and mortality.
- Surgery-induced weight loss is also associated with decreased protein intake as well as decreased lean body mass and muscle strength.
- Physical activity and dietary regimens to optimize health outcomes including body composition and physical fitness after bariatric surgery are not well known.

What does this study add?

- We found that resistance training with added oral protein intake was associated with a significant increase in muscle strength in women with obesity undergoing Roux-en-Y gastric bypass.
- We found that changes in body weight and body composition were comparable to protein supplementation without exercise or to usual follow-up.
- These data provide new evidence to optimize post-surgery follow-up care with exercise and diet that can overcome the loss in muscle strength in people with obesity after bariatric surgery.

ABSTRACT

Objective: Physical activity and dietary regimens to optimize health outcomes after bariatric surgery are not well known. We aimed to determine whether resistance training with dietary protein supplementation is effective in maintaining body composition and physical fitness after obesity surgery.

Method: Seventy-six women with obesity undergoing Roux-en-Y gastric bypass were randomly assigned at the time of surgery to receive either usual care (controls or CON, n=22), usual care and additional (whey) protein intake (PRO, n=31), or usual care, additional protein intake and supervised strength training for 18 weeks (PRO+EX, n=23). The primary outcome was pre- to six-month post-surgery change in lean body mass (by dual-energy X-ray absorptiometry). Secondary outcomes included changes in muscle strength (by 1-RM testing).

Results: Loss over time in lean body mass did not differ between groups (mean [CI 95%]: -8.8 [-10.1;-7.5], - 8.2 [-9.3;-7.1] and -7.7 [-9.0;-6.5] kg for CON, PRO and PRO+EX, respectively, P=0.899). The increase in relative lower limb muscle strength was higher in the PRO+EX group (+0.6 [0.3;0.8]) vs. +0.1 [-0.1;0.4] and +0.2 [0.0;0.4] kg/kg body mass in CON and PRO groups, respectively (P=0.021).

Conclusions: Loss in muscle strength observed after bariatric surgery can be overcome by resistance training with additional protein intake.

INTRODUCTION

In patients with severe obesity, bariatric surgery results in marked and sustained weight loss, decreased mortality (1) and improvement in obesity comorbidities, physical function and health-related quality of life (2, 3). To enhance health benefits, lifestyle changes represent a major component of follow-up after bariatric surgery (2, 3). Physical activity is a cornerstone of obesity treatment in general (4), however, in patients undergoing bariatric surgery little is known about the effects of physical activity on health outcomes including body composition and physical fitness (5). Randomized controlled trials (RCTs) that have assessed the effects of an exercise training program in the first year post-bariatric surgery are few (6-9). Findings from a narrative review (5) suggested improvements in metabolic health and cardiorespiratory fitness after endurance training, although there was no consistent additional effect on surgery-induced loss in fat mass and lean body mass.

Resistance, or strength, training is known to increase lean body mass and muscle strength (10). Muscle strength is an important marker related to functional capacity, cardiovascular disease risk factors and mortality (11-13). Patients undergoing bariatric surgery, such as Roux-en-Y gastric bypass (RYGB), experience a substantial decrease in lean body mass (14, 15). Bariatric surgery is also associated with a decrease in absolute muscle strength (16). However, when expressed relative to muscle mass, muscle strength was found unchanged, suggesting that the loss of absolute strength might be due to the decrease in muscle mass (8). The effect of resistance training, performed alone or in combination with endurance training, on changes in lean body mass and muscle strength during the first year after bariatric surgery has been assessed in only two RCTs (8, 9). Muscle strength was found improved in both studies (8, 9), whereas lean body mass was found preserved in one study (9) and unchanged in the other (8). Therefore, additional RCTs appear needed to further investigate the effectiveness and feasibility of resistance training in the bariatric surgery setting.

Strategies to preserve lean body mass during dietary-induced weight loss in patients with obesity include a combination of resistance training and a sufficient intake of high-quality protein (17). In the first months after bariatric surgery, energy and protein intake are dramatically reduced (3, 18). Emerging evidence suggests that whey protein would help increase protein synthesis during energy deficit in patients with overweight or obesity (19). Whey protein, representing 20% of milk proteins, are rapidly digested with an early rise in blood amino acids and increased stimulation of muscle protein synthesis (20). The effect of additional protein intake in combination with exercise training after bariatric surgery is however not known.

The aim of this study was to determine whether resistance training with whey protein supplementation is effective in maintaining lean body mass and muscle strength six months after RYGB.

METHODS

Study design

We undertook this single center, open-label, parallel group, RCT between May 1, 2010 and December 31, 2014 at the Department of Nutrition of Pitié-Salpêtrière university hospital (Assistance Publique-Hopitaux de Paris), Paris, France. Patients were followed-up for six months after surgery and underwent the same assessments at visits before and after surgery. The study was approved by the Ethics Committee of Pitié-Salpêtrière hospital (Paris, France).

Participants

Bariatric surgery (RYGB) was offered to patients following current guidelines (21, 22).

Inclusion criteria were female gender, age between 18 and 65 years, place of residence in Paris

or its region, body mass index (BMI) of 40 kg/m² or higher, or a BMI of 35 kg/m² or higher with at least one obesity comorbidity. Exclusion criteria were diagnosis of recent coronary event, uncontrolled hypertension, proliferative diabetic retinopathy or disabling neuropathy, dialysis treatment, orthopedic problems limiting exercise, abnormal cardiac stress test, ongoing or planned pregnancy, refusal to participate in a physical activity program, concurrent participation in a structured physical activity program, food intolerance to milk protein products. All patients signed an informed written consent to join the study prior to surgery.

Randomization

We randomized patients at the time of surgery to receive usual care with regular medical and nutritional follow-up (control group, CON), or usual care and additional oral protein intake (protein group, PRO), or usual care, additional protein intake and supervised resistance training (protein plus exercise group, PRO+EX).

Procedures

The same RYGB surgical procedure was performed laparoscopically with an alimentary limb of 1.2 to 1.5 m in length (14). All patients underwent detailed assessments before, and 1, 3, and 6 months after surgery. At each visit, body weight and composition, dietary intake, and various blood parameters were assessed. Health-related quality of life was documented before, and 3, 6 months after surgery. Data on muscle strength, cardiorespiratory fitness, physical activity, and obesity comorbidities were collected before, and 6-months after surgery.

Usual care

General dietary and physical activity counseling was provided to all participants during planned pre- and post-surgery visits at 1, 3 and 6 months, as part of usual care (21). Dietary advice aimed to progressively increase protein intake to reach a minimum amount of 60 g/d (2, 3). Patients

were encouraged to perform at least 150 minutes/week of moderate-to-vigorous endurance-type physical activity, such as brisk walking (12). All patients received the same initial prescription to prevent vitamin and mineral deficiencies (21), starting 15 days before surgery and including iron (2×80 mg/d), calcium (1,000 mg/d), vitamin D (800 IU/d) and a multivitamin and mineral supplement. No other supplement was allowed throughout the study.

Whey protein supplementation

From the first week post-surgery, patients randomized to the PRO and PRO+EX groups were prescribed a daily protein supplementation in the form of a whey-protein enriched powder (X-treme, INKO, Peyruis, France) delivered in 750 g cans to the participant home by the supplier. Participants were instructed to consume every day two powder drinks, one in the morning, the other in the afternoon or evening, and shortly after the end of the exercise session for the PRO+EX group, for a total supplemental whey protein dose of 48 g/d (corresponding to 2 measuring spoons to mix 30 g of powder containing 24 g of whey protein with 150 ml of water). Each protein drink provided approximately 464 kJ of energy, 0.9 g of sucrose, 1 g of fat and 0.3 g of fiber. Patients were asked to return empty cans of protein powder at follow-up visits to assess compliance.

Resistance training program

From week six post-surgery, participants randomized to the PRO+EX group exercised for 1 hour, three times per week on non-consecutive days, during 18 weeks, at our center, under supervision by qualified trainers. Each session included ten minutes of light endurance warming-up, 45 minutes of strength training and five minutes of stretching and cooling-down. The program was adapted from previous studies (23, 24) that demonstrated the safety and effectiveness on body composition of progressive resistance training in patients with obesity and/or type 2 diabetes. The program consisted of six different movements (leg press, leg

extension, abdominal crunch, chest press, vertical traction and biceps curl) involving major muscle groups. Each exercise was repeated in four sets of eight to 12 repetitions. For all movements except abdominal crunch, 1-RM (repetition-maximum or maximum weight that can be used to complete 1 repetition) values estimated before surgery were used to define weight loads during exercise sessions. The starting level was eight repetitions at 50% of 1-RM. The number of repetitions was increased (from eight to nine to 12) and then weight loads were increased (from 50% to 65% to 75% of 1-RM). Resting periods between repetition sets were approximately 60 s.

Anthropometry and body composition

Body composition was measured by whole-body fan-beam Dual Energy X-ray Absorptiometry (DXA) scan (Hologic Discovery W, Hologic, Bedford, MA) (14). Lean body mass was calculated as weight minus bone mineral content minus fat mass. Body regions (upper limb, lower limb, trunk, and head) were delineated with the use of specific anatomical landmarks. For all patients, right-side half-body scans were carried out from which whole-body composition was extrapolated, as described (25).

Muscle strength

Isometric maximal grip strength was measured using a handgrip dynamometer (Jamar, Sammons Preston Rolyan, Bolingbrook, Canada) (26). The highest value of 5 maximal trials with each hand was kept for analyses (26). Dynamic maximal strength of lower and upper limbs was measured on strength training equipment (leg press, chest press) (27). After a warm-up set of ten repetitions with a light weight, subjects were asked to complete sets of three repetitions with the greatest strength and speed. Testing began at 50% of their estimated maximal strength and the load was gradually increased for subsequent sets until failure was reached. The Myotest accelerometer device (Myotest, Acceltec, Sion, Switzerland); is a valid and reliable tool

specifically designed for field-based evaluation of muscle strength, velocity and power (28, 29). During strength testing, the Myotest was laid flat on the weights that moved on the vertical plane. The Myotest measured the maximum velocity (cm/s), which we used to establish the load-velocity relationship. Given the linear relationship between load and velocity, the maximal load, i.e. load at zero velocity, can be estimated accurately using the load-velocity relationship (30). The 1-RM, which is a measure of dynamic strength, is then estimated using the following equation: $1\text{-RM} = (0.871 \times \text{load at zero velocity}) - 0.624$ (30). For analysis, strength was expressed as absolute values (kg), values relative to body weight and lean body mass and values adjusted for lean body mass.

Cardiorespiratory fitness and physical activity

VO₂peak was measured by indirect calorimetry during a graded maximal exercise test on a cycle ergometer (31). The test protocol started at a workload of 30 W and increased by 30 W every 2 min until volitional exhaustion. VO₂peak, determined as the highest attained VO₂ during the test, was expressed in absolute values and relative to body mass and to lean body mass. For assessment of habitual physical activity, participants wore the Actigraph GT3X+ (Manufacturing Technology, Pensacola, FL) accelerometer for seven consecutive days during waking hours. Time wear of at least four days and at least eight hours each day defined valid data (32). The number of counts per minute was calculated from movements on the vertical axis. Steps were calculated by censoring steps taken at intensity <500 counts/min (33). Freedson cutpoints were used to quantify sedentary behavior, light, moderate and vigorous intensity physical activity (34).

Other assessments

Health-related quality of life was assessed with the 36-item short-form (SF-36) questionnaire, and was summarized in a physical and a mental component score ranging from 0 (poor) to 100

(good) (35). Food and beverage consumption were assessed by a registered dietician using the dietary history method (36). Energy (kJ/d) and macronutrient (g/d) intakes were calculated using the national food database. Obesity comorbidities were defined through detailed assessment of each patient medical history and medication use (37). Blood samples were collected after an overnight fast to measure routine parameters (blood count, blood glucose, protein, prealbumin, albumin, 25(OH)-vitamin-D3, vitamin B12, folate, thiamine).

Outcomes

The primary outcome was pre- to 6-month post-surgery change in lean body mass. Secondary outcomes included changes in upper and lower-limb muscle strength, cardiorespiratory fitness (VO₂ peak), objectively-assessed habitual physical activity, dietary protein intake, nutritional status, obesity comorbidities and health-related quality of life.

Statistical analysis

Based on evidence available at the time of the study was designed, it was estimated that subjects lost an average 16 (7.4)% of their lean body mass 6 months after RYGB (14). Sample sizes were determined *a priori* and based on detection of preservation effect in lean body mass loss of about one third in subjects with protein supplementation (i.e. averaged loss of 10.7 [4.9]%) (38). We assumed a similar additional effect in subjects with strength training. Setting an overall power to 80% with alpha at 0.05 yielded an estimate of 75 patients (with 31 in PRO group, 22 in PRO+EX and CON groups).

Characteristics of interest were summarized with frequencies and percentages for categorical data, means and standard deviations (SDs) or medians and 25th and 75th percentiles (P₂₅-P₇₅) for continuous data. Variables that did not meet the assumption of a normal distribution were log-transformed and retested. If the assumption of normality could not be met by transformation, we used non-parametric tests for comparing groups. Baseline preoperative characteristics were

analyzed with one-way analysis of variance or Kruskal-Wallis test (for continuous data) and Chi-square test or Fisher's exact test (for categorical data) as appropriate. Linear mixed models were used to estimate and test changes over time. The terms "group", "time" and "group x time" were included as fixed effects. Each follow-up wave was added to the model as a dummy variable. Changes in muscle strength independent of changes in regional lean mass were estimated by including regional lean body mass variable as a covariate in the corresponding models. Primary analyses were intention-to-treat (ITT), involving all randomized patients (n=76). For analyses of lower limb muscle strength data, implausible values (1-RM values over 320 kg) led to exclude data from 3 subjects. All analyses were then repeated on completers defined as subjects taking ≥ 24 g/d additional protein intake (i.e. half of total supplemental whey protein dose) and participating in ≥ 2 exercise sessions/week during 16 weeks (i.e. the lower limit of prescribed exercise frequency). Two-sided P-values are reported. The dose-response relationship across randomized groups was examined by performing a test of trend and examining linear and non linear (quadratic) contrasts. Results were considered significant at P-value <0.05 . Statistical analyses were performed with STATA (release 13; Stata Corporation, College Station, TX).

RESULTS

Out of 290 subjects assessed for eligibility, 71 patients were non-included because they did not meet inclusion criteria and 125 refused to participate (Supplementary Figure 1). Ninety-four patients were included in the study, 76 were randomized to receive either usual follow-up (CON, n=22), usual follow-up and additional protein intake (PRO, n=31) or usual follow-up, additional protein intake and exercise training (PRO+EX, n=23) and included in the ITT analysis, with 47 of them meeting the definition of completers. In the PRO and PRO+EX groups, we found no difference between non completers (n=29) and completers (n=25) in baseline characteristics, except for protein intake.

Baseline characteristics were similar between groups (Table 1). Mean (SD) age was 42.4 (9.9) years, body weight: 116.2 (16.2) kg, BMI: 44.0 (5.8) kg/m², and percent body fat: 50.1 (4.0)%. Compared to non-included patients, those included had a lower BMI (BMI in non-included patients: 46.6 (6.4) kg/m², p=0.002) and had similar age (43.1 [12.6], p=0.719). The median (P₂₅-P₇₅) number of exercise training sessions attended in the PRO+EX group was 35 (15-40). The median (P₂₅-P₇₅) whey protein supplementation was 20.8 (12.5-41.7 g/d) in the PRO group and 36.5 (29.2-41.7) g/d in the PRO+EX group. At baseline, 5 participants reached the physical activity threshold of 150 min/week of 10-min bouts moderate-to-vigorous physical activity (1 from the CON group, and 4 from the PRO group).

Table 2 shows changes in anthropometry and body composition, muscle strength, cardiorespiratory fitness, habitual physical activity, quality of life, dietary intake and nutritional status after RYGB according to treatment groups in ITT analysis (Table 2A) and in completers only (Table 2B). A significant time effect was observed for almost all variables, both in ITT and completers. Overall, six months after RYGB, lean body mass decreased by 8.2 (3.1) kg in parallel with a decrease in body weight, BMI and fat mass (27.5 (7.4) kg and 10.4 (2.6) kg/m², and 19.6 (4.8) kg, respectively), without significant difference between groups. For lower limb and upper limb strength in ITT analysis, when expressed relative to body weight or to lean body mass, there was a significant group effect and group x time interaction. In completers, group x time interaction was significant for lower limb and upper limb muscle strength expressed in absolute and relative values. In completers, a dose-response relationship was evidenced for changes in lower and upper limb 1-RM between CON, PRO and PRO+EX groups (p_{linear}<0.05). The supplementary table shows details of changes in dietary intakes.

Figure 1 illustrates the relative change in lower limb and upper limb muscle strength in percent change from baseline in completers. In the PRO+EX group after RYGB, increases in muscle strength were 12 and 13% in absolute values and 43% and 44% relative to body weight, for lower and upper limb respectively (Figure 1). When muscle strength was expressed relative to lean body mass, increases equaled to 33% and 30%.

Overall, six months after RYGB, VO_2 peak increased by 2.8 (4.9) mL/kg/min and the number of steps by 1178 (3082) steps/d. A significant time effect without difference between groups was also observed for changes in handgrip strength, energy and macronutrient intakes, and nutritional parameters. Daily protein intake (including the additional protein intake) six months after RYGB was 60.2 (17.3), 74.5 (22.4) and 81.4 (27.7) g/d in CON, PRO and PRO+EX subjects, respectively. No serious adverse effect was recorded.

DISCUSSION

This is a first RCT to test whether resistance training, under supervision for 18 weeks, with protein supplementation in the form of oral intake of whey protein added to the usual diet, was effective in maintaining lean body mass after RYGB. Although body composition changes did not differ across groups, other results show an increase in muscle strength which was found two to three times higher for lower limbs in the group following the exercise training program and the protein supplementation compared to the group with protein supplementation without exercise and to the group that followed the usual post-surgery medical and nutritional care.

Results also show that surgery-induced weight loss in itself was associated with a series of beneficial health effects including increased objectively-measured habitual physical activity and cardiorespiratory fitness, adding to current evidence indicating an overall improved cardiovascular risk profile in patients after bariatric surgery. Post-surgery improvement in

cardiorespiratory fitness has been previously reported in several observational studies (39). Changes in habitual physical activity, however, are still a matter of discussion. According to recent reviews, data generated from self-reported questionnaires consistently indicated an increase in physical activity whereas data from objective measures indicated no change or only modest increases (5, 16, 40).

A unique feature of our trial is the design combining muscle strength training and protein supplementation in patients undergoing bariatric surgery. At the time the study was designed and funded, no RCT had been published testing the effects of exercise training, whatever type, on health outcomes after bariatric surgery. We initially focused on changes in lean body mass based on results of our previous observational study describing changes in body composition through serial DXA assessments after RYGB (14). In that study, in patients closely monitored and following usual care recommendations (21, 22), lean body mass loss amounted to about a third of body weight loss in the six-month to one-year time period after RYGB (14). In addition to functional consequences, risk of malnutrition and reduced capacity to cope with aggression, this loss in lean body mass would induce a decrease in energy expenditure possibly contributing to weight regain as observed in many patients at long term after surgery (3). Since then, results of several trials suggested similar changes in lean body mass with exercise training compared to usual care after bariatric surgery (5), in line with the present data. None of these previous trials however investigated the effects of combining strength training with additional protein intake. Indeed, sufficient intake of high-quality protein is necessary to preserve or increase lean body mass through strength training (17). This also explains why we decided not to include an exercise only group in our trial.

A recent review has evidenced decreased muscle strength after bariatric surgery (16). Interestingly, our findings show that gains in muscle strength can be achieved in the first months

following bariatric surgery with progressive moderate-intensity strength training. This gain in muscle strength is likely to be a beneficial effect regarding physical functioning given the major contribution of muscle strength in performing daily living physical activity in persons with obesity (41). In the PRO+EX group, we observed an increase of 12% and 43% on average in lower limb muscle strength in absolute and relative terms, respectively. Such an increase in absolute strength is lower than that usually reported after resistance training in previously untrained women (42) but is comparable to the gain observed after resistance training following bariatric surgery (8). In a non-randomized trial, Daniels et al. reported an 18 to 36% increase in lower-limb absolute strength after 12-week resistance training. Increases in muscle strength of approximately 20% have also been found after resistance training when performed during dietary-induced weight loss (43). The decrease in lean body mass associated with weight loss might prevent large gains in absolute strength, and even more so during surgery-induced weight loss. Our findings therefore add to emerging evidence showing that it is feasible to substantially increase muscle strength with physical training, even during marked negative energy balance leading to important lean body mass loss. This increase in muscle strength was not associated with additional improvements in quality of life, in line with previous studies (44).

Gains in muscle strength as found here might be attributable to neural adaptations rather than muscle hypertrophy. Neural adaptations occurring during the first months of resistance training mainly include increased motor unit activation of the trained muscles and decreased co-contraction of antagonists (10). Uncoupling between muscle strength and mass after long-term resistance training has been well described (10). For example, a 66% increase in strength after a 6-month strength training program performed in middle-aged women under normo-caloric conditions was explained by a 34% increase in muscle activation and a 9% increase in muscle cross-section (42).

Protein intake appeared sufficient to maintain protein status, although it was found insufficient to observe an effect on lean body mass. In the control group, energy and protein intakes were indeed very low during the first months after surgery, in agreement with previous literature (3). With the use of a whey protein supplement, subjects in the two intervention groups achieved increased protein intake compared to usual care. Protein intake was on average over 60 g/d 3 months after RYGB, which corresponds to thresholds suggested in recent guidelines for bariatric surgery patients (2, 3). This was however far from recommended protein intake for maintenance of muscle mass during strength training which typically exceed 1 g/kg/d (45). The very low protein intake in a context of marked negative energy balance would be a main reason to explain the absence of significant effect on lean body mass, which was our main hypothesis. Whey protein is known to induce higher increases in muscle protein synthesis compared to other proteins (20). During previous studies of dietary-induced weight loss, whey protein supplementation led to lean mass retention although the effect size was modest (22). The effect of whey protein on muscle metabolism during negative energy balance as seen after bariatric surgery has not been investigated.

Strengths of the present RCT include the supervised and progressive strength training program, the homogeneous sample, the objective assessment of a large set of health outcomes that were found favorably associated with surgery-induced weight loss, the careful follow-up of patients at pre-specified post-surgery time points that were the same for all patients. Some limitations should be noted. Adherence to additional protein intake was self-reported. We included only women and similar investigations should also be performed in men. Mean BMI was higher in non-included subjects, which might limit the generalizability of findings. Our assessment of muscle mass was indirect as it was based on DXA-measured lower limb lean body mass. Since this trial was designed, the number of sleeve gastrectomy procedures has risen sharply (3). Whether our results also apply to different bariatric procedures would need to be studied

CONCLUSION

This trial shows that significant improved muscle strength was achieved through the combination of resistance training and additional protein intake during six months after RYGB. Although no difference was found regarding weight and lean body mass loss or improvement in cardiorespiratory fitness after bariatric surgery, these findings add to the body of knowledge indicating the adjunct value of physical exercise training in the follow-up care of bariatric surgery in patients with severe obesity.

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Individual participant data or any other data will not be available.

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Table 1. Baseline Preoperative Characteristics of Patients Undergoing Roux-en-Y Gastric Bypass Surgery

	All patients N=76	Randomised N=76			
		CON N=22	PRO N=31	PRO + EX N=23	
Age, years	42.4 (9.9)	43.9 (10.7)	42.5 (8.7)	40.9 (10.8)	0.604 ^a
Anthropometry and body composition					
Body weight, kg (n=76)	116.2 (16.2)	116.3 (19.3)	115.7 (14.9)	116.7 (15.4)	0.972 ^a
BMI, kg/m ² (n=76)	44.0 (5.8)	43.6 (6.2)	43.3 (6.0)	45.2 (5.2)	0.484 ^a
Body fat, % (n=75)	50.1 (4.0)	50.2 (3.4)	49.7 (4.8)	50.4 (3.4)	0.794 ^a
Fat mass, kg (n=75)					
Total, kg	58.3 (10.9)	58.7 (11.8)	57.4 (10.8)	59.2 (10.5)	0.527 ^a
Trunk fat mass, kg	28.1 (5.5)	27.8 (6.2)	27.8 (5.4)	28.8 (5.1)	0.753 ^a
LBM, kg (n=75)					
Total, kg	55.5 (6.7)	55.6 (8.4)	55.9 (6.1)	54.8 (5.9)	0.844 ^a
Lower limb LBM, kg	19.7 (3.3)	19.6 (3.6)	19.7 (3.3)	19.8 (3.1)	0.990 ^a
Upper limb LBM, kg	4.5 (0.9)	4.3 (0.9)	4.5 (1.0)	4.5 (0.7)	0.552 ^a
Muscle strength					
Handgrip, kgF (n=76)	32.0 (6.2)	30.6 (5.7)	33.0 (7.0)	32.0 (5.6)	0.388 ^a
Lower limb 1-RM					
Absolute, kg (n=71)	179.5 (47.8)	175.7 (53.1)	174.6 (42.0)	189.2 (50.4)	0.519 ^a
Relative to body weight, kg/kg (n=71)	1.57 (0.45)	1.58 (0.59)	1.52 (0.39)	1.62 (0.38)	0.734 ^a
Relative to lower limb LBM, kg/kgLBM (n=70)	9.31 (2.85)	9.41 (3.69)	8.94 (2.54)	9.65 (2.31)	0.682 ^a
Upper limb 1-RM					
Absolute, kg (n=75)	32.1 (8.1)	31.4 (6.9)	32.1 (8.2)	32.9 (9.2)	0.836 ^a
Relative to body weight, kg/kg (n=75)	0.28 (0.07)	0.27 (0.05)	0.28 (0.08)	0.28 (0.08)	0.834 ^a
Relative to upper limb LBM, kg/kgLBM (n=74)	7.37 (1.89)	7.56 (2.03)	7.31 (1.97)	7.25 (1.70)	0.842 ^a
Cardiorespiratory fitness					
VO ₂ peak					
Absolute, L/min (=73)	2.10 (0.49)	2.21 (0.50)	2.08 (0.46)	2.02 (0.51)	0.433 ^a
Relative to body weight, mL/min/kg (=73)	18.2 (4.2)	19.2 (4.9)	18.1 (3.5)	17.4 (4.3)	0.373 ^a
Relative to LBM, mL/min/kgLBM (=73)	38.0 (9.0)	40.1 (10.4)	37.3 (7.5)	36.9 (9.3)	0.421 ^a
Habitual physical activity					
Wear-time, min/d (n=70)	786.0 (74.2)	798.2 (67.7)	784.9 (81.6)	775.2 (71.7)	0.607 ^a
Counts per minute (n=70)	314.5 (97.8)	295.7 (85.6)	344.7 (116.5)	293.2 (72.4)	0.108 ^a
Steps per day (n=70)	6450.2 (2483.5)	6573.6 (2188.7)	6966.5 (2843.7)	5638.5 (2119.0)	0.174 ^a
LPA, min/d (n=70)	286.8 (71.4)	282.0 (75.8)	293.8 (76.5)	282.2 (61.8)	0.804 ^a
MVPA, min/d (n=70), median (P ₂₅ -P ₇₅)	24.6 (16.7-35.9)	25.7 (14.7-33.8)	25.1 (17.7-41.8)	20.9 (15.9-33.7)	0.338 ^b
MVPA in ≥10 min bouts, (n=70), min/week, median (P ₂₅ -P ₇₅)	22 (0-67)	29 (0-66)	22.0 (0-109.5)	20 (10-49)	0.740 ^b
Accumulate 150 min/week MVPA in ≥10 min bouts, No. (%)	5 (7.1)	1 (4.8)	4 (14.3)	0 (0)	0.177 ^d
Quality of life					
Physical dimension (n=74)	37.7 (6.7)	38.1 (6.5)	37.1 (6.6)	38.1 (7.5)	0.839 ^a
Mental dimension (n=74)	43.1 (8.0)	44.2 (8.6)	42.8 (7.4)	42.5 (8.5)	0.759 ^a
Comorbidities					
Type 2 diabetes, No. (%) (n=76)	21 (27.6)	5 (22.7)	8 (25.8)	8 (34.8)	0.636 ^c
Sleep apnea syndrome, No. (%) (n=76)	39 (51.3)	10 (45.5)	18 (58.1)	11 (47.8)	0.613 ^c
Hypertension, No. (%) (n=75)	22 (29.3)	6 (27.3)	10 (33.3)	6 (26.1)	0.821 ^c

Dietary intake					
Energy intake, kJ/d (n=51)	7450.4 (1756.0)	7358.3 (1746.9)	7680.8 (2196.0)	7210.0 (872.1)	0.724 ^a
Protein, g/d (n=62)	78.9 (16.3)	80.3 (12.7)	82.0 (19.8)	73.1 (12.9)	0.185 ^a
Protein, g/kg/d (n=62)	0.69 (0.16)	0.71 (0.12)	0.72 (0.18)	0.65 (0.17)	0.343 ^a
Carbohydrate, g/d (n=55), median (P ₂₅ -P ₇₅)	208.0 (52.7)	216.9 (64.8)	206.8 (56.5)	199.6 (28.4)	0.673 ^b
Lipid, g/d (n=55)	69.0 (17.4)	67.3 (18.3)	69.3 (21.0)	70.4 (11.0)	0.877 ^a
Nutritional status					
Hemoglobin, g/dL (n=76)	13.1 (0.9)	13.0 (0.9)	13.0 (0.8)	13.5 (0.8)	0.078 ^a
Proteinemia, g/L (n=76)	72.0 (4.1)	72.5 (4.3)	72.0 (4.2)	71.7 (3.9)	0.829 ^a
Albumin, g/L (n=75)	36.1 (3.9)	36.0 (3.7)	36.2 (4.4)	36.1 (3.4)	0.970 ^a
Prealbumin, g/L (n=75)	0.25 (0.05)	0.24 (0.06)	0.24 (0.04)	0.25 (0.04)	0.568 ^a
Vitamins					
25(OH)-vitamin-D3, ng/mL (n=75)	16.8 (9.0)	18.3 (10.3)	17.7 (9.1)	14.2 (7.0)	0.375 ^a
Thiamine, nmol/L (n=72)	163.1 (56.1)	166.1 (36.0)	158.3 (74.7)	166.5 (43.8)	0.408 ^a
Serum folate, nmol/L (n=72)	17.3 (7.5)	19.4 (8.3)	16.7 (7.5)	16.0 (6.5)	0.278 ^a
Erythrocyte folate, nmol/L (n=54)	1248.8 (371.6)	1435.5 (346.2)	1143.0 (255.2)	1200.2 (500.9)	0.018^a
B12, pmol/L (n=74)	348.8 (162.5)	357.7 (248.2)	337.5 (97.2)	355.3 (130.0)	0.897 ^a

Data are means (standard deviations) unless otherwise indicated.

p-value from ^aone-way analysis of variance, ^bKruskal–Wallis test, ^cChi-square test or ^dFisher’s exact test.

p-value from test performed on log-transformed data for vitamins (except for serum folate).

Abbreviations. 1-RM, one repetition maximum; BMI, body mass index; CON, control group; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group; LBM, lean body mass; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity; No., frequency; n, number of observations; N, total number of observations; P_x, xth percentile.

Number of observations for each item may vary due to missing data.

Table 2. Changes in Anthropometry, Body Composition, Muscle Strength, Cardiorespiratory Fitness, Habitual Physical Activity and Quality of Life after Roux-en-Y Gastric Bypass Surgery

A. Intention-to-treat (N=76)

	Change from baseline (95% CI)			Group	P-value	
	CON	PRO	PRO + EX		Time	Group by time
	N=22	N=31	N=23			
Anthropometry and body composition						
Body weight, kg	-28.0 (-30.6;-25.4)	-27.2 (-29.4;-25.1)	-27.4 (-29.9;-24.8)	0.970	< 0.001	0.664
BMI, kg/m ²	-10.5 (-11.4;-9.6)	-10.2 (-11.0;-9.4)	-10.6 (-11.5;-9.7)	0.503	< 0.001	0.686
Fat mass, kg	-19.7 (-21.5;-17.9)	-19.8 (-21.3;-18.2)	-19.4 (-21.1;-17.6)	0.808	< 0.001	0.417
LBM, kg	-8.8 (-10.1;-7.5)	-8.2 (-9.3;-7.1)	-7.7 (-9.0;-6.5)	0.803	< 0.001	0.899
Lower limb LBM, kg	-3.6 (-4.3;-3.0)	-3.0 (-3.6;-2.5)	-3.2 (-3.8;-2.6)	0.712	< 0.001	0.557
Upper limb LBM, kg	-0.3 (-0.6;-0.1)	-0.3 (-0.5;-0.1)	-0.5 (-0.8;-0.3)	0.633	< 0.001	0.554
Muscle strength						
Handgrip, kgF	-21.0 (-43.1;1.1)	-29.1 (-47.5;-10.6)	-22.9 (-44.1;-1.4)	0.427	< 0.001	0.840
Lower limb 1-RM						
Absolute, kg	-30.4 (-55.8;-5.0)	-19.6 (-41.5;2.3)	+4.68 (-19.6;28.9)	0.012	0.032	0.128
Relative to body weight, kg/kg	+0.12 (-0.14;0.38)	+0.22 (-0.01;0.44)	+0.59 (0.34;0.84)	0.033	< 0.001	0.021
Relative to lower limb LBM, kg/kgLBM	-0.08 (-1.53;1.38)	+0.19 (-1.08;1.46)	+2.22 (0.83;3.60)	0.041	0.055	0.043
Adjusted for lower limb LBM, kg	-19.3 (-46.3;7.7)	-9.1 (-32.3;14.2)	+14.6 (-10.9;40.2)	0.010	0.584	0.136
Upper limb 1-RM						
Absolute, kg	-6.2 (-9.9;-2.6)	-4.8 (-7.9;-1.7)	-0.5 (-4.0;3.0)	0.135	< 0.001	0.061
Relative to body weight, kg/kg	+0.02 (-0.02;0.06)	+0.03 (-0.01;0.06)	+0.09 (0.05;0.12)	0.175	< 0.001	0.050
Relative to upper limb LBM, kg/kgLBM	-1.0 (-2.0;-0.1)	-0.8 (-1.6;0.1)	+0.9 (-0.1;1.9)	0.242	0.272	0.010
Adjusted for upper limb LBM, kg	-5.2 (-9.0;-1.5)	-4.1 (-7.3;0.9)	+1.2 (-2.5;4.9)	0.123	0.012	0.029
Cardiorespiratory fitness						
VO₂peak						
Absolute, L/min	-0.4 (-0.6;-0.2)	-0.3 (-0.4;-0.1)	-0.1 (-0.3;0.1)	0.759	< 0.001	0.276
Relative to body weight, mL/min/kg	+1.8 (-0.3;3.9)	+2.5 (0.7;4.3)	+4.0 (1.9;6.1)	0.764	< 0.001	0.324
Relative to LBM, mL/min/kgLBM	-1.0 (-5.1;3.1)	+0.4 (-3.1;3.8)	+3.2 (-0.8;7.3)	0.663	0.443	0.335
Habitual physical activity						
Wear-time, min/d	-7.5 (-45.7;30.6)	-3.0 (-36.4;30.4)	-8.3 (-46.5;29.8)	0.551	0.561	0.975
Counts per minute	+49.4 (-0.1;98.9)	+10.7 (-32.9;54.4)	+31.0 (-18.5;80.5)	0.337	0.031	0.515
Steps per day	+1716 (358;3074)	+629 (-560;1819)	+1022 (-336;2379)	0.164	0.004	0.496
LPA, min/d	+3.1 (-26.5;32.6)	-23.7 (-49.7;2.3)	+1.5 (-28.1;31.0)	0.995	0.445	0.311
MVPA, min/d	+9.6 (1.9;17.3)	+5.7 (-1.1;12.5)	+5.7 (-2.0;13.5)	0.178	0.001	0.717
MVPA in ≥10 min bouts, min/week	+30.5 (1.2;59.9)	+20.3 (-5.7;46.4)	+14.8 (-14.6;44.1)	0.114	0.009	0.751
Quality of life						
Physical dimension	+8.7 (6.1;11.2)	+9.4 (7.2;11.6)	+10.0 (7.4;12.7)	0.994	< 0.001	0.438
Mental dimension	+5.8 (2.3;9.3)	+8.2 (5.3;11.2)	+8.9 (5.3;12.4)	0.929	< 0.001	0.800
Dietary intake						
Energy intake, kJ/d	-2196.2 (-2920.7;-1471.7)	-2737.2 (-3362.6;-2111.8)	-1961.9 (-2715.4;-1208.5)	0.492	< 0.001	0.526

Protein, g/d	-20.8 (-30.7;-10.9)	-8.2 (-16.5;0.1)	+7.3 (-2.6;17.1)	<0.001	<0.001	<0.001
Protein, g/kg/d	-0.18 (-0.28;-0.09)	-0.07 (-0.15;0.01)	+0.06 (-0.03;0.16)	<0.001	<0.001	<0.001
Carbohydrate, g/d	-75.5 (-100.1;-50.9)	-79.1 (-101.1;-57.1)	-79.1 (-104.4;-53.8)	0.204	<0.001	0.954
Lipid, g/d	-19.6 (-27.0;-12.2)	-26.3 (-32.9;-19.7)	-23.1 (-30.7;-15.4)	0.813	<0.001	0.714
Nutritional status						
Hemoglobin, g/dL	-0.01 (-0.38;0.36)	-0.04 (-0.35;0.28)	-0.02 (-0.39;0.35)	0.030	0.150	0.937
Proteinemia, g/L	-2.0 (-3.7;-0.3)	-1.6 (-3.0;-0.1)	-2.0 (-3.7;-0.4)	0.820	<0.001	0.837
Albumin, g/L	+1.1 (-0.5;2.6)	+1.5 (0.2;2.8)	+1.0 (-0.6;2.5)	0.829	0.001	0.791
Prealbumin, g/L	-0.05 (-0.07;-0.04)	-0.05 (-0.06;-0.04)	-0.05 (-0.07;-0.04)	0.400	<0.001	0.964
Vitamins						
25(OH)-vitamin-D3, ng/mL	+11.4 (7.1;15.7)	+12.8 (9.2;16.4)	+17.6 (13.5;21.8)	0.991	<0.001	0.341
Thiamine, nmol/L	+9.9 (-28.0;47.8)	+38.3 (10.0;66.7)	+38.9 (8.0;69.9)	0.119	0.007	0.445
Serum folate, nmol/L	+3.3 (-0.2;6.9)	+4.9 (1.9;8.0)	+10.7 (7.1;14.3)	0.504	<0.001	0.047
Erythrocyte folate, nmol/L	+37.7 (-159.7;235.2)	+230.5 (60.5;400.5)	+398.8 (180.4;617.2)	0.268	<0.001	0.192
B12, pmol/L	-84.9 (-131.5;-38.3)	-62.1 (-101.7;-22.6)	-86.5 (-133.6;-39.5)	0.947	<0.001	0.777

Abbreviations. 1-RM, one repetition maximum; 95% CI, confidence interval at 95%; BMI, body mass index; CON, control group; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group; LBM, lean body mass; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity

P-values for Group, Time, interaction (Group x Time) terms in mixed models

B. Completers (N=47)

	Change from baseline (95% CI)			Group	P-value	
	CON	PRO	PRO + EX		Time	Group by time
	N=22	N=14	N=11			
Anthropometry and body composition						
Body weight, kg	-28.0 (-30.8;-25.2)	-26.7 (-30.2;-23.1)	-25.7 (-29.7;-21.8)	0.760	<0.001	0.751
BMI, kg/m ²	-10.5 (-11.4;-9.5)	-10.2 (-11.4;-9.0)	-10.1 (-11.5;-8.7)	0.291	<0.001	0.811
Fat mass, kg	-19.7 (-21.5;-17.9)	-19.6 (-21.9;-17.3)	-17.4 (-20.0;-14.8)	0.513	<0.001	0.362
Lean body mass, kg	-8.8 (-10.2;-7.5)	-7.2 (-8.8;-5.5)	-7.8 (-9.7;-5.9)	0.771	<0.001	0.624
Lower limbs LBM, kg	-3.6 (-4.3;-3.0)	-2.7 (-3.5;-1.9)	-3.3 (-4.2;-2.4)	0.695	<0.001	0.318
Upper limbs LBM, kg	-0.3 (-0.6;-0.1)	-0.2 (-0.5;0.1)	-0.6 (-0.9;0.2)	0.524	<0.001	0.798
Muscle strength						
Handgrip, kgF	-21.0 (-46.3;4.3)	-28.0 (-59.0;3.0)	-3.6 (-38.5;31.4)	0.055	0.052	0.577
Lower limb 1-RM						
Absolute, kg	-30.4 (-54.8;-6.0)	-31.5 (-64.7;1.6)	+17.6 (-15.5;50.8)	0.007	0.100	0.048
Relative to body weight, kg/kg	+0.12 (-0.11;0.35)	+0.11 (-0.20;0.43)	+0.68 (0.37;0.99)	0.071	<0.001	0.010
Relative to lower limb LBM, kg/kgLBM	-0.07 (-1.36;1.22)	-0.66 (-2.41;1.09)	+3.10 (1.35;4.85)	0.066	0.097	0.005
Adjusted for lower limb LBM, kg	-18.7 (-45.0;7.6)	-23.4 (-56.2;9.4)	+28.7 (-5.0;62.5)	0.012	0.661	0.032
Upper limb 1-RM						
Absolute, kg	-6.2 (-9.9;-2.6)	-6.0 (-10.7;-1.3)	+3.5 (-1.6;8.6)	0.002	0.028	0.006
Relative to body weight, kg/kg	+0.02 (-0.02;0.06)	+0.02 (-0.03;0.07)	+0.13 (0.07;0.18)	0.012	<0.001	0.006
Relative to upper limb LBM, kg/kgLBM	-1.0 (-2.0;-0.1)	-1.1 (-2.4;0.1)	+2.0 (0.7;3.3)	0.017	0.885	<0.001
Adjusted for upper limb LBM, kg	-5.2 (-8.9;-1.4)	-5.4 (-10.1;-0.7)	+5.3 (0.1;10.5)	0.002	0.207	0.002
Cardiorespiratory fitness						
VO ₂ peak						
Absolute, L/min	-0.4 (-0.6;-0.1)	-0.1 (-0.4;0.1)	-0.1 (-0.5;0.2)	0.277	0.011	0.364

Relative to body weight, mL/min/kg	+1.8 (-0.5;4.2)	+3.9 (1.0;6.8)	+3.1 (-0.4;6.5)	0.131	< 0.001	0.541
Relative to LBM mL/min/kgLBM	-0.9 (-5.5;3.7)	+2.4 (-3.3;8.0)	+2.8 (-3.9;9.5)	0.211	0.399	0.553
Habitual physical activity						
Wear-time, min/d	-7.5 (-43.9;28.8)	-3.3 (-50.8;44.3)	+27.4 (-24.3;79.1)	0.823	0.681	0.539
Counts per minute	+49.4 (-4.3;103.1)	+45.3 (-25.6;116.3)	+48.7 (-27.6;125.1)	0.254	0.017	0.996
Steps per day	+1726 (345;3108)	+1063 (-749;2874)	+2014 (48;3980)	0.459	0.002	0.764
LPA, min/d	+3.5 (-23.2;30.1)	-6.5 (-41.8;28.8)	+29.0 (-8.9;66.9)	0.353	0.382	0.382
MVPA, min/d	+9.6 (1.0;18.2)	+9.2 (-2.2;20.6)	+10.3 (-1.94;22.5)	0.075	0.002	0.992
MVPA in ≥10 min bouts, min/week	+30.5 (-2.40;63.5)	+15.9 (-28.1;59.8)	+17.3 (-29.4;64.0)	0.057	0.083	0.836
Quality of life						
Physical dimension	+8.7 (6.2;11.2)	+9.3 (6.2;12.5)	+10.2 (6.5;14.0)	0.764	< 0.001	0.543
Mental dimension	+5.8 (2.4;9.3)	+6.0 (1.6;10.3)	+9.8 (4.7;15.0)	0.964	< 0.001	0.442
Dietary intake						
Energy intake, kJ/d	-2182.6 (-2974.1;-1391.0)	-2628.3 (-3626.6;-1630.1)	-1668.6 (-2837.8;-499.5)	0.104	< 0.001	0.894
Protein, g/d	-20.6 (-29.9;-11.4)	+0.1 (-11.3;11.5)	+13.0 (-1.2;27.2)	< 0.001	< 0.001	< 0.001
Protein, g/kg/d	-0.18 (-0.27;-0.10)	+0.01 (-0.10;0.12)	+0.11 (-0.03;0.24)	< 0.001	< 0.001	< 0.001
Carbohydrate, g/d	-75.4 (-101.7;-49.0)	-73.4 (-107.8;-39.0)	-79.8 (-120.1;-39.5)	0.315	< 0.001	0.994
Lipid, g/d	-19.6 (-26.9;-12.2)	-21.9 (-31.6;-12.2)	-15.2 (-26.5;-3.9)	0.388	< 0.001	0.868
Nutritional status						
Hemoglobin, g/dL	-0.01 (-0.44;0.42)	+0.01 (-0.53;0.55)	-0.08 (-0.70;0.55)	0.023	0.633	0.949
Proteinemia, g/L	-2.0 (-3.7;-0.3)	-1.6 (-3.7;0.6)	-2.2 (-4.6;0.3)	0.822	0.008	0.850
Albumin, g/L	+1.1 (-0.5;2.7)	+1.3 (-0.7;3.3)	+1.5 (-0.8;3.7)	0.146	0.007	0.442
Prealbumin, g/L	-0.05 (-0.07;-0.04)	-0.05 (-0.06;-0.03)	-0.06 (-0.08;-0.04)	0.480	< 0.001	0.763
Vitamins						
25(OH)-vitamin-D3, ng/mL	+11.4 (7.6;15.2)	+12.9 (8.2;17.6)	+14.8 (9.5;20.1)	0.255	< 0.001	0.911
Thiamine, nmol/L	+9.9 (-30.1;50.0)	+23.4 (-19.9;66.7)	+21.2 (-26.1;68.6)	0.233	0.255	0.855
Serum folate, nmol/L	+3.3 (-0.4;7.1)	+4.2 (-0.6;8.9)	+11.8 (6.4;17.2)	0.558	< 0.001	0.058
Erythrocyte folate, nmol/L	+41.8 (-143.8;227.4)	+281.1 (36.5;525.8)	+417.1 (128.1;706.0)	0.450	< 0.001	0.060
B12, pmol/L	-83.3 (-126.2;-40.4)	-36.8 (-89.7;16.1)	-76.1 (-137.9;-14.2)	0.904	< 0.001	0.546

Abbreviations. 1-RM, one repetition maximum; 95% CI, confidence interval at 95%; BMI, body mass index; CON, control group; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group; LBM, lean body mass; LPA, light physical activity; MVPA, moderate-to-vigorous physical activity.

P-values for Group, Time, interaction (Group x Time) terms in mixed models.

Figures legends

Supplementary Figure 1 – Study Flow Diagram

Abbreviations. CON, control group; PA, physical activity; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group.

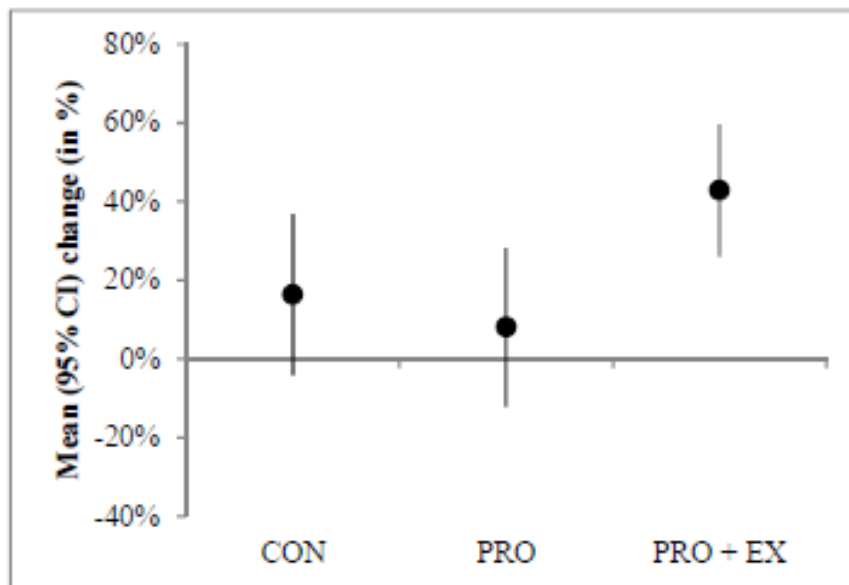
Supplementary Table - Changes in Dietary Intake 1, 3 and 6 Months after Roux-en-Y Gastric Bypass Surgery Compared to Pre-operative Values

Abbreviations. CON, control group; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group.

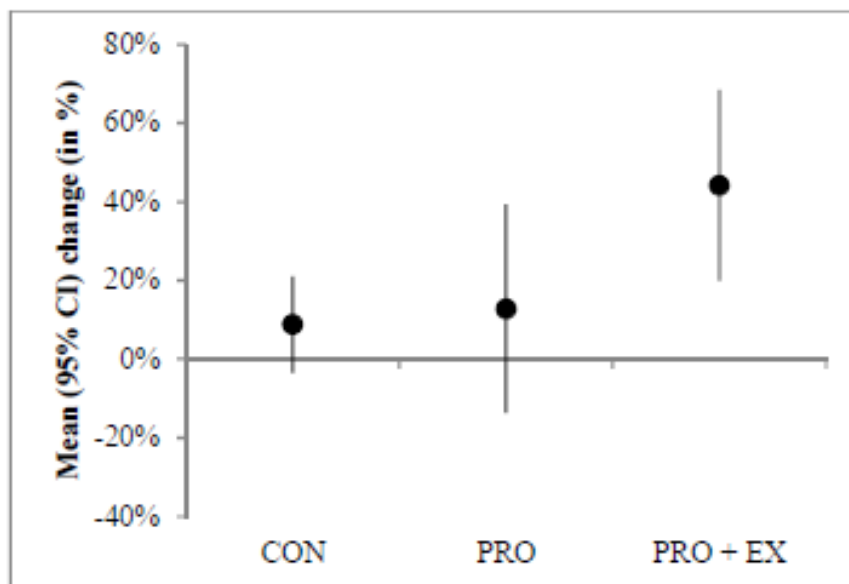
Figure 1 A-B - Percent Change in Lower Limb and Upper Limb Muscle Strength Relative to Body Weight from Baseline to 6 Months After Roux-en-Y Gastric Bypass Surgery (completers)

Abbreviations. CON, control group; PRO, protein intake group; PRO + EX, protein intake and supervised strength training group.

Note. The dots represent the mean values and the vertical bars extending from the dots in both directions represent the 95% CI.



A. Lower limb muscle strength relative to body weight



B. Upper limb muscle strength relative to body weight

Figure 1