Obesity Surgery (2021) 31:1635–1646
https://doi.org/10.1007/s11695-020-05172-1

ORIGINAL CONTRIBUTIONS

Effects of Resistance Training With or Without Protein Supplementation on Body Composition and Resting Energy Expenditure in Patients 2–7 Years PostRoux-en-Y Gastric Bypass: a Controlled Clinical Trial

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Received: 4 July 2020 / Revised: 9 December 2020 / Accepted: 10 December 2020 / Published online: 6 January 2021

Abstract

Background Resistance training (RT) and adequate protein intake are recommended as strategies to preserve fat-free mass (FFM) and resting metabolic demand after bariatric surgery. However, the effect of both interventions combined in the late postoperative period is unclear. This study investigated the effects of RT, isolated and combined with protein supplementation, on body composition and resting energy expenditure (REE) in the late postoperative period of Roux-en-Y gastric bypass (RYGB).

Methods This controlled trial involved patients who were 2–7 years postRYGB. Participants were partially matched on body mass index (BMI), age, sex, and years after surgery, and divided into four groups, placebo maltodextrin (control [CON]; $n = 17$), whey protein supplementation (PRO; $n = 18$), RT combined with placebo (RTP; $n = 13$), and RT combined with whey protein supplementation (RTP + PRO; $n = 15$)—considering the participants who completed the protocol. REE was measured by indirect calorimetry and body composition by multifrequency electrical bioimpedance.

Results Participant characteristics (40.3 ± 8.3 years old; average BMI 29.7 ± 5.3 kg/m^2; 88.9% females) were similar among groups. The RTP+PRO group showed an increase of 1.46 ± 1.02 kg in FFM and 0.91 ± 0.64 kg in skeletal muscle mass (SMM), which was greater than the equivalent values in the CON group (− 0.24 ± 1.64 kg, $p = 0.006$ and − 0.08 ± 0.96 kg, $p = 0.008$, respectively). There was no significant time-by-group interaction for absolute or relative REE.

Conclusion Combined RT and adequate protein intake via supplementation can increase FFM and SMM in the late postoperative period without changing REE. These associated strategies were effective in improving muscle-related parameters and potentially in improving the patients' physical function.

Keywords Bariatric surgery · Body composition · Energy metabolism · Resistance training · Roux-en-Y gastric bypass · Whey protein

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Introduction

Roux-en-Y gastric bypass (RYGB) frequently helps in achieving satisfactory weight loss, improved quality of life, and better control of comorbidities in patients with severe obesity [1–4]. However, in the second year after RYGB, many patients have difficulty in maintaining a low weight [5], which is associated with reduced adherence to systematic clinical monitoring [6–8]. Adoption of healthy lifestyle habits is paramount to long-term satisfactory excess weight loss after bariatric surgery [9, 10].

In individuals undergoing bariatric surgery, exercise has consistently been shown to provide positive effects, focusing on body weight, physical fitness, and cardiovascular health [11–14]. Meanwhile, training effects on resting energy expenditure (REE) remain poorly understood. REE is believed to be positively related to body mass, particularly fat-free mass (FFM) [15], to reduce abruptly in the first 6–12 months after bariatric surgery [16], and to remain decreased two years after that [17]. Therefore, in addition to bodyweight monitoring, information on alterations to body composition after bariatric surgery could provide insights for improved long-term management of patients' postRYGB [18].

Resistance training (RT) improves body composition and increases FFM in diverse clinical populations, including those with obesity [19, 20]. The effects of RT, either isolated [21, 22] or combined with other types of exercise [23–25], have been studied during the first 2 years after bariatric surgery [21–25], but they remain unclear [14].

In addition to RT, adequate protein intake is essential for maintaining FFM and for avoiding a positive energy balance in patients undergoing RYGB because FFM is one of the most metabolically active compartments in the body. Relevant studies indicate that a protein intake ≥ 60 g/day is positively associated with better FFM preservation [26, 27]. However, protein intake is usually lower than recommended in patients who underwent bariatric surgery [28–30] owing to the reduction of the overall food consumption or because of intolerance to the protein sources present in food [29, 30]. Thus, high-quality protein supplements have been used to help achieve minimum intake recommendations. Whey protein is an example of a high-quality supplement that is easy to digest, quick to absorb [31, 32], and rich in all essential amino acids. Whey protein enhances muscle protein synthesis and can contribute to training-induced muscular hypertrophy [32–34]; hence, this is considered the first choice of protein supplementation in clinical practice.

To our knowledge, the only clinical trial that evaluated the effect of RT combined with protein supplementation found no changes in the body composition of women in the first 6 months after bariatric surgery [35]. However, the effect of these interventions combined with long-term postsurgery is yet to be investigated. Given that it is important to investigate effective and feasible strategies for the improvement of muscle-related parameters in patients who are at risk of weight regain and have low adherence to systematic clinical monitoring over time, this study aimed to investigate the effects of RT with and without whey protein supplementation on body composition and REE in the late postoperative period of RYGB.

Materials and Methods

Study Design

This study was part of the Nutrition and Resistance Exercise in Obesity (NERO) project, which was a controlled clinical trial with parallel groups. This study was registered (RBR-9k2s42) with the Brazilian Clinical Trials Registration Platform (ReBEC). The study was approved by the local Research Ethics Committee.

Participants

Adult individuals of both sexes who were at 2–7 years postRYGB were invited to participate through posters and social media announcements.

Patients with diabetes mellitus, heart disease, hormones or appetite regulator use, severe psychiatric disorders, recent elective surgery, and current pregnancy or breastfeeding were excluded. Individuals who used protein supplementation regularly and those who had been engaging in physical exercise since at least 2 months before the study were also excluded. To calculate the desired sample size, an effect size of 0.8 (a large effect size, according to Cohen [36]) was considered as indicative of a significant difference between the two groups. This calculation considered a level of significance of 5% and power of 80%, resulting in a minimum sample of 13 individuals in each group, with a total of 52 participants required for the study. Considering the high dropout rate found in this type of study, wide announcement of the study was made, and finally 119 participants were assessed after the exclusion criteria were applied.

Study Protocol

Allocation

Participants were paired according to body mass index (BMI), age, sex, and years after surgery and allocated to two separate groups that would or would not perform RT considering their ability to reach the place where the study was being conducted. Briefly, matched sets were created, bringing together four participants with similar characteristics. As the groups of participants were formed over time, the sets were filled in whole or in part, based on the characteristics of each set. Thus, the gaps observed in some matching sets were filled as new groups of volunteers were formed whenever possible, but it was not possible to guarantee the same number of participants in all groups.

Allocation to receive a protein supplement or placebo followed a randomized, double-blind procedure performed by an external researcher using the Research Randomizer® online software, version 4.0 (http://www.randomizer.org/). The protocol comprised two combined or isolated interventions, each lasting 12 weeks.

All assessments were performed before and after 12 weeks of the intervention, except for food intake, which was also evaluated at 6 weeks.

Sociodemographic and Clinical Characteristics

Sociodemographic and clinical data were collected with a questionnaire that included closed and open questions regarding sex, date of birth, education level (in years of study), and surgery date (in months and years).

Resistance Training Intervention

Volunteers allocated to either RTP or RTP+PRO took part in a 12-week RT program, performed thrice per week on nonconsecutive days. Before the training period, participants received three familiarization sessions to ensure that they had properly understood the technique. The training targeted all major muscle groups and involved the following exercises: chest press, knee extension, hamstring curl, leg press, hip abduction, latissimus pulldown, shoulder abduction, and plantar flexion (Rotech® Fitness Equipment, Brazil). Training loads were monitored and carefully adjusted using the OMNIResistance Exercise Scale (OMINI-RES) [37]. During the first 4 weeks of the training period, loads were carefully adjusted to correspond to 6 points on the OMINI-RES scale ("somewhat hard"), to 7 points (from "somewhat hard" to "hard") during the next 4 weeks, and to 8 points ("hard") in the last 4 weeks; repetitions were decreasing from 12 to 10 and 8, respectively, throughout the training period. Each exercise was performed in three sets with approximately 1-min breaks between sets. Each session lasted approximately 60 min and was preceded by a 10-min warm-up and followed by a 10-min cooldown. In order to assess the effectiveness of the RT program, knee extension isokinetic peak torque at 60°/s was measured before and after the intervention period using an isokinetic dynamometer (Biodex System 3®, Biodex Medical Systems, Inc., Shirley, NY, USA). All training sessions were closely supervised by qualified professionals. During the intervention period, participants were instructed to retain their usual physical activities and to refrain from joining any other exercise programs. Attendance at the training sessions was recorded; attendance < 70% was considered loss of follow-up.

Nutritional Intervention

The nutritional intervention consisted of whey protein supplementation or placebo (Maltodextrin). A concentrated 30-g portion of whey protein powder included the following: 120 kcal, 1.80 g of carbohydrates, 1.38 g of total fats, 23.10 g of proteins (5.61 g of branched-chain amino acids [BCAA] and, of these, 2.70 g of leucine), while a 30-g portion of Maltodextrin included 112 kcal and 28 g of carbohydrates.

Whey protein supplements or placebo portions were provided every 15 days, delivered in opaque packaging in the form of sachets, containing the amount corresponding to each individual daily dose. Participants were instructed to consume the entire dose at once with the last meal of the day. Empty packaging and sachets not used were returned to the researchers during scheduled consultations and duly registered.

Whey protein supplementation was prescribed at a dose of 0.5 g/kg of ideal body weight/day to the PRO and RTP+PRO groups. Maltodextrin was offered as a placebo to the CON and RTP groups at the same dose. A supplement or placebo intake < 70% was considered a loss to follow-up. All participants received general training on healthy eating.

Anthropometry and Body Composition Assessment

Anthropometric and body composition assessments were performed in the morning with the participant standing barefoot and wearing light clothing. Height measurement was performed using a portable stadiometer (Sanny®, American Medical of Brazil). Bodyweight and body composition were determined using a multifrequency bioelectrical impedance analysis (BIA) (InBody720®, Biospace, Korea). Participants were requested to refrain from physical activity and caffeine consumption in the 24 h before the exam; participants were also asked to fast for at least 8 h beforehand, present at a time outside a menstrual period, as relevant, and have an empty bladder. The variables obtained were body weight (BW; kg), FFM (kg), skeletal muscle mass (SMM; kg), fat mass (FM; kg), and the percentage of body fat (BF; %). Body weight and height were used to calculate BMI (kg/m^2). Excess weight loss (EWL) and total weight loss (TWL) were considered satisfactory when greater than 50% and 20% [38], respectively. Weight regain was defined as weight gain greater than 10% of the lowest weight recorded during the postoperative period, and the ideal body weight was calculated using BMI equivalent to 25 kg/m^2.

Resting Energy Expenditure Measurement

REE was analyzed by an open-circuit metabolic system IC (Vmax 29®, Sensor Medic Corp, Yorba Linda, CA, USA), as described elsewhere [39, 40]. In the morning before the test, participants remained at rest for 10 min in a supine position under thermoneutral conditions (22–24 °C) in a quiet and dimly lit room. They were instructed to remain awake, keep quiet, avoid hyperventilation and sudden movements, and breathe for 30 min through a transparent plastic ventilated canopy placed over the head. Oxygen and carbon dioxide sensors were calibrated using a reference mix of gases of known composition before each test. The average of measurements acquired in the last 20 min was used to determine the REE based on the Weir formula [41]; REE was expressed as kcal/day. A "steady state" was defined as a period when the average consumption of O_2 and production of CO_2 varied by less than 10% [42]. The variables thus obtained were absolute REE (kcal/day), relative REE by BW (REE/BW; kcal/kg), relative REE by FFM (REE/FFM; kcal/kg), and respiratory quotient (RQ).

Blood Parameters

Participants were instructed to undergo blood tests in the same week as the other tests. Blood samples were collected in the morning by qualified professionals, after an overnight fast of 8–14 h and measured by standard procedures. Levels of the following parameters were analyzed: serum albumin (colorimetric bromocresol green method), blood glucose (hexokinase method), basal insulin (chemiluminescence method), creatinine (amidinohydrolase/oxidase method), and lipid profile, including levels of total cholesterol (esterase/oxidase method), triglycerides (oxidase/peroxidase method), HDL-c (direct method), and LDL-c (calculated by Martin's formula [43]). Homeostatic model assessment of insulin resistance and beta-cell function (HOMA-IR and HOMA-β) were calculated by standard formulas [44].

Dietary Intake

Energy and protein intake were analyzed using multiple 24-h dietary recalls (24hR) at baseline and after 6 and 12 weeks of intervention. At each evaluation point, two 24hR were made on non-consecutive days according to the 5-step multiple-pass method [45]. Data were analyzed using the Nutrition Data System for Research (NDSR®) software, version 2018 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA). Participants' usual food consumption, with correction for intrapersonal variance in the complete sample [46], was performed at each of the follow-up assessments with PC-SIDE® software, version 1.0 (Iowa State University, Ames, IA, USA). Energy and protein intake were reported as absolute values and adjusted for the current and/or ideal BW.

To assess total protein intake during the follow-up period, the evaluation point at 6 weeks was chosen to analyze both dietary protein intake and protein supplementation. In addition, mean protein supplementation intake during the entire intervention was described in absolute values/day.

Data Analysis

Categorical variables were presented as frequencies and compared between groups with the chi-square test. Continuous variables were expressed as mean and standard deviation. To verify data distribution normality assumption, the Kolmogorov–Smirnov test was applied. A comparison between participants who completed the protocol and those who left the study was performed using the Student *t* test or the Mann–Whitney *U* test, as appropriate. Baseline among-group comparisons were performed with one-way ANOVA with Tukey's post hoc test or the Kruskal–Wallis *H* test followed by Müller–Dunn post-hoc test, as appropriate. The effects of isolated and combined interventions were analyzed by testing the interaction effect in a two-way mixed ANOVA test with repeated measures, considering time as an intraindividual factor and group as an interindividual factor. A p value < 0.05 was indicative of statistical significance. All analyses were performed using the SPSS software, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Among the 119 participants included in the study, a total of 63 completed the entire study protocol (Fig. 1). There was no difference in demographic or clinical characteristics between participants who completed ($n = 63$) and those who left the study ($n = 56$). The baseline characteristics of participants were similar among groups. Almost 90% of the participants were female, with a mean age of approximately 40 years old and BMI close to the upper limit of overweight classification. Participants exhibited adequate weight loss; however, approximately half of them showed weight regain, on average, 4 years after surgery (Table 1).

Mean adherence to the RT program was above 80%, with no difference between groups with this intervention. The adherence rates of protein supplementation and placebo were similar among the groups and above 90%.

Usual energy and protein intake were similar among the groups, except for a higher absolute protein intake of the PRO group than that of the CON group at 12 weeks ($p = 0.031$). The groups that received protein supplement had a usual protein intake approximately 30 g higher than placebo groups ($p < 0.001$), including after adjustment for the current and ideal weight (Table 2). Average levels of blood parameters were within normal reference ranges for all groups, without among-group differences (Table 3).

For anthropometric, body composition, and strength parameters, ANOVA demonstrated significant time-by-group interactions. Post hoc analyses revealed significant increases in the RTP+PRO group, relative to the CON group, observed for BW ($p = 0.012$), BMI ($p = 0.012$), FFM ($p = 0.006$), and

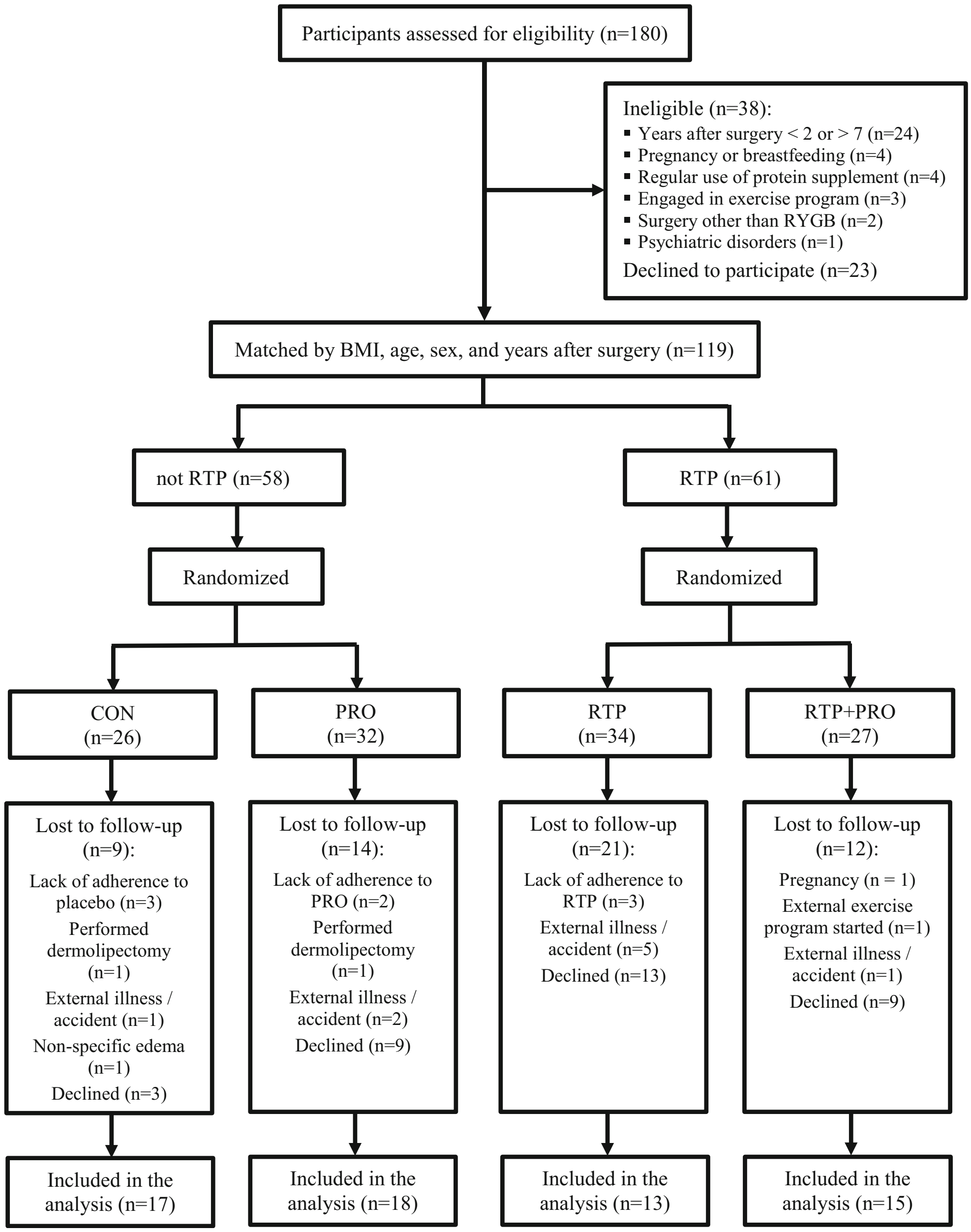

Fig. 1 Flowchart capturing participant allocation process, sample randomization, and drop-out rates at each study stage. Abbreviations: RYGB: Roux-en-Y gastric bypass; BMI: Body mass index; CON: Control; PRO: Whey protein supplementation; RTP: Resistance training program. External illness/accident: car accident, musculoskeletal problems, diseases in the family, gout. Total sample loss $n = 56$

SMM ($p = 0.008$). A significant post hoc analysis was also noted for knee extension isokinetic peak torque. These results were driven by significant improvements in the groups subjected to the RT program, and these results were not seen in the nonexercise groups (RTP: $p = 0.001$ and $p < 0.001$; RTP+PRO: $p = 0.011$ and $p = 0.005$; when compared to CON and PRO, respectively). There was no significant time-by-group interaction for absolute or relative REE, nor RQ (Table 4).

Discussion

To our knowledge, this is the first clinical trial that evaluated the effects of RT, separate or combined with protein supplementation, on body composition, relative REE, and blood parameters during the late postoperative period of RYGB. In patients in the "late" postRYGB period, RT combined with whey protein supplementation was associated with increased FFM. Although patients in the RTP group also exhibited an absolute mean increase in FFM, this change was not statistically significant.

Typically, 2 years postsurgery, patients achieve weight stabilization, and weight regain is often observed [47, 48]. In the present study, despite meeting the success criteria after surgery, as noted by EWL and TWL, weight regain was observed in about half of the sample. These findings might be due to participants not using protein supplementation and practicing physical exercise for at least two months, which were the

Table 1 Baseline demographic and clinical characteristics of participants in the late postoperative period of Roux-en-Y gastric bypass, divided into dropout, attended sample and intervention groups

Variables	Discontinued the study ($n = 56$)	Completed the study ($n = 63$)	p value	Groups				p value
				CON ($n = 17$)	PRO ($n = 18$)	RTP ($n = 13$)	RTP + PRO ($n = 15$)	
Female [n (%)]	50 (89.3%)	56 (88.9%)	0.945 [1]	17 (100%)	16 (88.9%)	11 (84.6%)	12 (80.0%)	0.312 [1]
Age (years)	37.7 ± 6.7	40.3 ± 8.3	0.064 [2]	39.8 ± 7.8	40.6 ± 10.4	40.0 ± 8.7	41.0 ± 6.4	0.978 [4]
Education level (years of study)	15.5 ± 3.8	16.0 ± 4.0	0.178 [3]	14.3 ± 4.2	16.4 ± 4.1	16.5 ± 4.8	17 ± 2.6	0.126 [5]
Years after surgery (years)	3.9 ± 1.4	4.1 ± 1.4	0.522 [2]	3.7 ± 1.4	4.3 ± 1.4	4.4 ± 1.7	4.0 ± 1.2	0.430 [4]
Preoperative body mass index (kg/m^2)	43.2 ± 4.9	41.8 ± 5.7	0.089 [3]	41.6 ± 5.2	43.2 ± 5.8	42.0 ± 6.3	40.1 ± 5.8	0.494 [4]
Current Body Mass Index (kg/m^2)	29.7 ± 4.7	29.7 ± 5.3	0.666 [3]	29.3 ± 4.4	30.1 ± 5.7	29.8 ± 6.1	29.4 ± 5.4	0.969 [4]
Excess weight loss (%)	74.1 ± 18.4	74.0 ± 21.2	0.973 [2]	75.3 ± 20.8	73.9 ± 20.9	73.8 ± 22.7	72.9 ± 22.9	0.992 [4]
Total weight loss (%)	38.8 ± 8.3	36.0 ± 7.0	0.055 [2]	36.5 ± 8.3	37.9 ± 6.4	35.5 ± 6.8	33.7 ± 6.3	0.459 [5]
Weight regain [6] [n (%)]	30 (53.6%)	30 (47.6%)	0.517 [1]	9 (52.9%)	8 (44.4%)	5 (38.5%)	8 (53.3%)	0.826 [1]
Mean of weight regain ($n = 30$) (%)	21.2 ± 10.4	17.9 ± 7.2	0.249 [3]	16.8 ± 6.6	21.3 ± 9.5	17.4 ± 7.8	15.9 ± 4.8	0.468 [4]

[1] Chi-square test; [2] Student's t test for independent samples; [3] Mann–Whitney U test; [4] One-way ANOVA; [5] Kruskal–Wallis H test; [6] Weight regain when > 10% of the lowest weight obtained in the postoperative period. *CON* Control; *PRO* whey protein supplementation; *RTP* resistance training program

inclusion criteria; they might also be associated with the end of adequate postoperative follow-up. Thus, at the beginning of the study, participants were not receiving any specific treatment, regardless of time after surgery.

The benefits of protein supplementation are illustrated by studies of patients undergoing bariatric surgery who do not reach the minimum recommended protein intake at any point during the postoperative period [28–30, 49]. Insufficient protein intake might be due to restricted overall food consumption imposed by the surgical procedure itself and characterized by intolerance or difficulty in consuming dairy products, fish, and red meat, even years after surgery [29, 30, 50]. In our study, energy and protein intake were similar for all groups, except for absolute protein intake of the PRO group, which was higher than that of the CON group after 12 weeks of intervention; this finding can be explained by an increased tolerance to protein, resulting from the intake of whey protein.

A protein intake of 60 g/day or 1.0–1.1 g/kg of ideal weight/day was associated with greater weight loss, lower BF, and better preservation of FFM after bariatric surgery in previous reports [26–28]. When associated with low energy intake, the consumption of approximately 1.5 g of protein/kg of ideal body weight can attenuate FFM loss, according to clinical practice guidelines [9]. Gomes et al. [51] evaluated the effect of whey protein supplementation at a dose similar to that used in the current investigation combined with a low-calorie diet on the weight loss and body composition of women with weight regain in the late postoperative period of RYGB. The authors observed that the intervention group demonstrated greater weight and FM losses than the control group, thus indicating the preservation of FFM. Therefore, optimal protein intake in the postoperative period of bariatric surgery until the moment defined by the consumption of approximately 1.5 g of protein/kg of ideal body weight should be encouraged because it can improve the evolution of patients' body composition.

There is no currently established physical training protocol for the different follow-up stages after bariatric surgery. Training protocols differ in the type, volume, and duration of intervention, thus resulting in the heterogeneity of evidence included in systematic reviews [11, 14, 52]. The efficacy of our RT protocol was indicated by the improvements in isokinetic muscle strength observed in the exercise groups. Daniels et al. [21] and Huck et al. [22] applied RT protocols similar to those used in the present study; however, they did not find differences in FFM because they evaluated patients during the first postoperative year, which is a period marked by rapid and massive weight loss. Nevertheless, they found improvements in muscle strength and quality, thus demonstrating that RT has positive effects that go beyond body composition.

A metaanalysis of the effect of whey protein supplementation alone or combined with RT on body composition of adult individuals who had not undergone surgery has been reported [53]. Despite between-study heterogeneity, the authors concluded that the use of supplements for improving body composition is evidence-based and that the impact of supplements is greater when their use is combined with RT [53]. This finding might explain why the best FFM results were observed in the RTP+PRO group in the present study. Morton et al. [54] conducted a metaanalysis on the effect of protein supplementation on RT-induced gains in muscle parameters.

Table 2 Usual energy, carbohydrate, and protein intake during the study of individuals in the late postoperative period of Roux-en-Y gastric bypass

Energy, carbohydrate, and protein intake during follow-up	Groups				*p* value [1]
	CON (*n* = 17)	PRO (*n* = 18)	RTP (*n* = 13)	RTP + PRO (*n* = 15)	
Food intake baseline					
kcal/day	1564 ± 296	1669 ± 306	1548 ± 234	1556 ± 393	0.647
kcal/kg of current weight	21.0 ± 4.6	21.1 ± 4.9	19.7 ± 4.1	20.1 ± 4.3	0.799
g carbohydrate/day	194.7 ± 43.7	205.9 ± 44.6	189.1 ± 34.5	197.6 ± 54.2	0.769
g protein/day	72.7 ± 4.3	72.7 ± 4.0	72.8 ± 4.0	70.1 ± 4.8	0.250
g protein/kg of current weight	0.98 ± 0.14	0.92 ± 0.14	0.94 ± 0.21	0.93 ± 0.18	0.710
g protein/kg of the ideal weight	1.14 ± 0.09	1.08 ± 0.09	1.10 ± 0.13	1.08 ± 0.12	0.404
Food intake after 6 week					
kcal/day	1354 ± 268	1678 ± 400 [a]	1505 ± 337	1626 ± 329	0.049
kcal/kg of current weight	17.9 ± 3.6	20.9 ± 5.1	18.9 ± 5.0	20.9 ± 5.1	0.230
g carbohydrate/day	162.3 ± 35.1	196.4 ± 44.0	180.2 ± 53.1	180.4 ± 44.2	0.203
g protein/day	62.1 ± 15.5	70.9 ± 23.3	63.9 ± 13.0	73.5 ± 22.0	0.316
g protein/kg of current weight	0.82 ± 0.21	0.88 ± 0.28	0.80 ± 0.20	0.96 ± 0.39	0.448
g protein/kg of the ideal weight	0.97 ± 0.24	1.06 ± 0.33	0.95 ± 0.14	1.14 ± 0.38	0.327
Food intake after 12 week					
kcal/day	1427 ± 408	1729 ± 428	1632 ± 511	1721 ± 517	0.209
kcal/kg of current weight	19.5 ± 7.0	21.5 ± 6.4	20.4 ± 7.3	21.5 ± 4.9	0.760
g carbohydrate/day	185.9 ± 53.5	193.0 ± 45.7	201.7 ± 60.9	204.0 ± 73.4	0.812
g protein/day	59.4 ± 14.2	81.0 ± 27.8 [a]	64.7 ± 18.6	75.5 ± 25.9	0.029
g protein/kg of current weight	0.80 ± 0.21	1.00 ± 0.38	0.81 ± 0.26	0.95 ± 0.32	0.159
g protein/kg of the ideal weight	0.92 ± 0.21	1.20 ± 0.40	0.97 ± 0.26	1.16 ± 0.42	0.050
Food intake + whey protein supplementation or placebo [3]					
kcal/day	1474 ± 259	1799 ± 412	1640 ± 345	1745 ± 360	0.063
kcal/kg of current weight	19.6 ± 3.7	22.5 ± 5.4	20.6 ± 5.2	22.4 ± 5.4	0.307
g carbohydrate/day	190.3 ± 34.0	198.7 ± 44.2	214.0 ± 54.5	185.2 ± 50.7	0.386
g protein/day	63.8 ± 17.4	94.9 ± 26.6 [a,b]	63.9 ± 13.0	95.0 ± 26.2 [a,b]	< 0.001
g protein/kg of current weight	0.85 ± 0.23	1.19 ± 0.35 [a,b]	0.80 ± 0.20	1.22 ± 0.44 [a,b]	< 0.001
g protein/kg of the ideal weight	1.00 ± 0.27	1.41 ± 0.36 [a,b]	0.96 ± 0.14	1.46 ± 0.44 [a,b]	< 0.001
Whey protein supplementation intake [4]					
g/day	NA	30.9 ± 2.8	NA	30.4 ± 6.0	0.740 [2]

[1] One-way ANOVA with Tukey's post hoc test; [2] Student's *t* test for independent samples; [3] Analyzed during intervention at 6-week follow-up; [4] Mean of whey protein supplementation intake during intervention. [a] $p < 0.05$ when compared to CON group; [b] $p < 0.05$ when compared to RTP group. *CON* Control; *PRO* whey protein supplementation; *RTP* resistance training program

Although the sample included healthy rather than energy-restricted individuals, the authors demonstrated RT combined with protein supplementation was associated with an additional increase in FFM, compared with isolated RT. Nevertheless, protein intake beyond approximately 1.6 g/kg/day did not provide additional benefits.

RT promotes muscle mass gain [54] and has a potent effect on the mammalian target of rapamycin (mTOR) signaling [55]. This pathway is responsible for stimulating muscle protein synthesis and downregulation of catabolic processes through phosphorylation and activation of target proteins [33]. In addition, skeletal muscle adaptation can increase when RT is combined with protein supplementation [56], since its rapid digestibility promotes hyperaminoacidemia and high plasma bioavailability of essential amino acids, in particular, leucine in muscle tissue [31–33], inducing muscle hypertrophy.

To date, only one clinical trial has evaluated the effect of RT combined with protein supplementation on body composition and physical fitness in women after RYGB [35]. In this trial, RT started 6 weeks after surgery, lasted 18 weeks, and the dose of whey protein used was 48 g/day for all patients. The authors noted no between-group differences regarding FFM, but the group that received combined interventions showed an increase in the relative muscular strength of the lower limbs compared to the remaining groups.

Table 3 Effect of resistance training and protein supplementation, isolated or combined, on blood parameters of individuals in the late postoperative period of Roux-en-Y gastric bypass

Variables	Time (weeks)	Groups				p value [1]
		CON (n = 14)	PRO (n = 14)	RTP (n = 10)	RTP + PRO (n = 11)	
Glucose (mg/dL)	0	83.3 ± 7.0	85.7 ± 6.3	82.4 ± 5.1	84.1 ± 7.8	0.625
	12	81.4 ± 6.3	84.9 ± 6.8	81.4 ± 4.7	85.8 ± 4.0	
	Δ	− 1.92 ± 8.18	− 0.86 ± 5.46	− 1.00 ± 5.19	1.70 ± 7.02	
Insulin (μUI/mL)	0	6.3 ± 2.9	7.0 ± 3.1	7.8 ± 3.1	6.0 ± 3.0	0.086
	12	7.3 ± 3.2	7.4 ± 3.1	6.6 ± 1.7	7.4 ± 3.5	
	Δ	1.05 ± 3.10	0.37 ± 2.15	− 1.18 ± 2.09	1.45 ± 2.10	
HOMA-IR	0	1.28 ± 0.57	1.49 ± 0.76	1.58 ± 0.65	1.24 ± 0.59	0.092
	12	1.50 ± 0.77	1.58 ± 0.71	1.33 ± 0.38	1.58 ± 0.78	
	Δ	0.23 ± 0.72	0.09 ± 0.45	− 0.25 ± 0.48	0.34 ± 0.45	
HOMA-β	0	125.4 ± 82.3	116.2 ± 38.4	140.1 ± 67.1	114.6 ± 63.4	0.588
	12	144.3 ± 41.8	125.4 ± 39.8	126.4 ± 33.7	116.0 ± 47.8	
	Δ	18.83 ± 63.09	9.24 ± 48.04	− 13.7 ± 58.11	1.41 ± 49.28	
Total cholesterol (mg/dL)	0	163.8 ± 26.3	168.5 ± 29.4	157.8 ± 22.3	160.6 ± 23.1	0.064
	12	171.5 ± 34.8	164.4 ± 26.0	154.6 ± 25.3	172.4 ± 19.5	
	Δ	7.71 ± 18.22	− 4.14 ± 15.13	− 3.20 ± 16.80	11.73 ± 17.77	
HDL-c (mg/dL)	0	59.4 ± 9.3	61.5 ± 8.7	61.7 ± 13.9	60.0 ± 14.8	0.366
	12	61.3 ± 10.4	62.3 ± 7.2	59.2 ± 12.2	60.3 ± 11.0	
	Δ	1.93 ± 5.53	0.79 ± 5.54	− 2.50 ± 4.79	0.27 ± 8.01	
LDL-c (mg/dL)	0	88.6 ± 21.3	89.3 ± 27.7	82.7 ± 19.3	87.0 ± 22.9	0.057
	12	95.7 ± 28.4	84.6 ± 23.6	81.1 ± 23.3	95.9 ± 20.7	
	Δ	7.07 ± 14.97	− 4.64 ± 14.84	− 1.60 ± 12.68	8.91 ± 13.50	
Triglycerides (mg/dL)	0	77.4 ± 29.3	90.3 ± 48.2	65.1 ± 10.8	97.2 ± 58.3	0.920
	12	82.1 ± 27.7	89.9 ± 30.2	68.6 ± 16.9	98.1 ± 55.4	
	Δ	4.79 ± 19.18	− 0.43 ± 27.18	3.50 ± 18.02	0.91 ± 18.16	
Creatinine (mg/dL)	0	0.68 ± 0.08	0.75 ± 0.19	0.67 ± 0.12	0.67 ± 0.09	0.196
	12	0.68 ± 0.08	0.77 ± 0.28	0.73 ± 0.15	0.67 ± 0.10	
	Δ	0.00 ± 0.03	0.03 ± 0.11	0.06 ± 0.07	0.00 ± 0.04	
Albumin (g/dL)	0	4.24 ± 0.22	4.09 ± 0.25	4.14 ± 0.35	4.15 ± 0.17	0.127
	12	4.12 ± 0.21	4.07 ± 0.20	4.11 ± 0.30	4.23 ± 0.21	
	Δ	− 0.11 ± 0.25	− 0.01 ± 0.15	− 0.03 ± 0.16	0.07 ± 0.17	

[1] Two-way mixed ANOVA test with repeated measures for the time/group interaction. Data presented as mean ±SD. *CON* Control; *PRO* whey protein supplementation; *RTP* resistance training program; *HOMA-IR* homeostatic model assessment for insulin resistance; *HOMA-β* homeostatic model assessment for beta cell function; *HDL-c* high density lipoprotein; *LDL-c* low density lipoprotein

Studies that have evaluated the effect of physical exercise, protein supplementation, or both on energy expenditure after bariatric surgery are scarce, and results are controversial. In the present clinical trial, no significant changes were observed in REE among the groups, which might be due to patients undergoing RYGB maintaining a greater mass of trunk organs with a high metabolic rate, such as heart, kidneys, and liver, even in the late postoperative period [18]. Although FM influences REE, FFM corresponds to the most metabolically active body component for organs with a high metabolic rate [57, 58] and, to a lesser extent, for SMM [59, 60]. As such, the increase in FFM, mostly due to the increase in SMM, observed in the RTP+PRO group was probably not enough to cause changes in absolute or relative REE. An intervention of a longer duration comparing different types and intensities of training might be required to investigate the impact of body composition changes on REE in this population. RQ values outside the range of 0.67–1.30 suggest flaws in the indirect calorimetry test, such as air leakage in the respiratory circuit, agitation, or severe pain [61, 62]. The obtained RQ values demonstrated that the test was adequate for determining REE.

Blood parameters did not change significantly in any of the groups over 12 weeks, although the RTP group showed a marginally significant improvement to insulin levels and HOMA-IR. Physical exercise improves insulin sensitivity and could provide additional improvements to the effects of

Table 4 Effect of resistance training and protein supplementation, isolated or combined, on anthropometric parameters, body composition, strength, and resting energy expenditure of individuals in the late postoperative period of Roux-en-Y gastric bypass

Variables	Time (weeks)	Groups				*p* value [1]
		CON (*n* = 17)	PRO (*n* = 18)	RTP (*n* = 13)	RTP + PRO (*n* = 15)	
BW (kg)	0	75.7 ± 12.0	81.0 ± 11.3	81.7 ± 21.6	79.1 ± 22.4	0.015
	12	75.7 ± 12.2	81.9 ± 10.5	83.3 ± 21.8	81.1 ± 22.5	
	Δ	− 0.06 ± 2.40	0.94 ± 2.07	1.61 ± 1.38	2.07 ± 1.30 [a]	
Body mass index (kg/m^2)	0	29.3 ± 4.4	30.1 ± 5.4	29.8 ± 6.1	29.4 ± 5.6	0.016
	12	29.3 ± 4.5	30.5 ± 5.6	30.4 ± 6.2	30.2 ± 5.4	
	Δ	− 0.03 ± 0.96	0.36 ± 0.74	0.59 ± 0.50	0.78 ± 0.49 [a]	
FFM (kg)	0	46.6 ± 4.3	50.3 ± 5.7	49.3 ± 10.6	48.5 ± 12.0	0.009
	12	46.3 ± 4.9	50.7 ± 5.3	50.1 ± 10.7	50.0 ± 12.4	
	Δ	− 0.24 ± 1.64	0.32 ± 1.57	0.83 ± 1.19	1.46 ± 1.02 [a]	
Skeletal muscle mass (kg)	0	25.3 ± 2.6	27.5 ± 3.4	26.9 ± 6.4	26.6 ± 7.1	0.009
	12	25.2 ± 2.9	27.7 ± 3.2	27.5 ± 6.3	27.5 ± 7.4	
	Δ	− 0.08 ± 0.96	0.22 ± 0.95	0.58 ± 0.67	0.91 ± 0.64 [a]	
Fat mass (kg)	0	29.2 ± 9.2	30.7 ± 11.1	32.4 ± 13.9	30.6 ± 11.8	0.689
	12	29.3 ± 9.2	31.3 ± 10.8	33.3 ± 13.8	31.2 ± 11.9	
	Δ	0.17 ± 1.80	0.62 ± 1.32	0.80 ± 1.21	0.61 ± 1.61	
Body fat (%)	0	37.7 ± 6.7	37.1 ± 8.9	38.4 ± 8.2	38.1 ± 5.6	0.741
	12	38.0 ± 6.6	37.4 ± 8.7	38.7 ± 7.5	37.9 ± 5.8	
	Δ	0.32 ± 1.68	0.36 ± 1.30	0.28 ± 1.47	− 0.18 ± 1.63	
Knee extensors isokinetic PT 60°/s (Nm)	0	124.2 ± 23.8	136.0 ± 41.5	153.2 ± 52.1	147.6 ± 52.6	< 0.001
	12	122.3 ± 23.0	133.7 ± 42.9	164.8 ± 54.4	155.2 ± 50.7	
	Δ	− 2.05 ± 4.93	− 2.33 ± 5.16	11.66 ± 13.53 [a,b]	7.61 ± 7.69 [a,b]	
REE (kcal/day)	0	1401 ± 194	1504 ± 147	1477 ± 214	1503 ± 304	0.343
	12	1377 ± 153	1440 ± 139	1488 ± 197	1489 ± 319	
	Δ	− 24.1 ± 96.9	− 64.4 ± 109.6	11.0 ± 104.9	− 14.3 ± 150.9	
REE/BW (kcal/kg)	0	18.6 ± 1.5	18.8 ± 2.4	18.7 ± 3.2	19.4 ± 2.7	0.294
	12	18.4 ± 1.9	17.7 ± 2.2	18.6 ± 3.6	18.7 ± 2.7	
	Δ	− 0.20 ± 1.36	− 1.05 ± 1.26	− 0.14 ± 1.32	− 0.75 ± 2.22	
REE/FFM (kcal/kg)	0	30.1 ± 3.0	30.0 ± 2.7	30.3 ± 2.3	31.5 ± 4.2	0.359
	12	29.8 ± 2.7	28.6 ± 2.6	30.0 ± 3.7	30.1 ± 3.5	
	Δ	− 0.26 ± 2.32	− 1.48 ± 2.03	− 0.27 ± 2.69	− 1.40 ± 3.22	
Respiratory quotient	0	0.83 ± 0.03	0.82 ± 0.04	0.82 ± 0.03	0.83 ± 0.06	0.778
	12	0.84 ± 0.05	0.83 ± 0.05	0.83 ± 0.03	0.83 ± 0.04	
	Δ	0.015 ± 0.057	0.009 ± 0.055	0.015 ± 0.030	− 0.001 ± 0.051	

[1] Two-way mixed ANOVA test with repeated measures for the time/group interaction. Data presented as mean ±SD. [a] $p < 0.05$ when compared to CON group; [b] $p < 0.05$ when compared to PRO group. *CON* Control; *PRO* whey protein supplementation; *RTP* resistance training program; *BW* body weight; *FFM* fat-free mass; *PT* peak torque; *REE* resting energy expenditure

RYGB [63–65] by increasing mitochondrial oxidative capacity and reducing the levels of lipid types that impair adequate insulin signaling [63]. It should be noted that present participant biochemical and metabolic profile at baseline showed values within the reference range, which may explain why the observed effects were small.

This study contributes to the development of feasible interventions related to clinical care practice in the late postoperative period of bariatric surgery, a period characterized by frequent discontinuity of follow-up.

Strengths and Limitations

This study has several strengths and limitations. RT was closely supervised, and the whey protein supplement was administered at individualized doses. The evidence presented here extends the knowledge regarding exercise and nutritional interventions in individuals undergoing long-term bariatric surgery, a population for which not enough data exist. However, whether the participants retained their baseline physical activity levels were not evaluated in the nonexercising groups, and this could affect our findings. Owing to logistic and scheduling reasons, participants in both RT groups were not allocated in a randomized manner. The relatively large loss to follow-up observed in this study, which arose from intervention dropouts and noncompliance with the postblood tests and other phases of the protocol, should be noted. Sample losses reduce the statistical power of the tests and may have prevented the detection of the other effects of the intervention. These losses in clinical trials emerge from multiple transportation requirements for the assessment and training visits, along with the daily difficulties experienced by the volunteers. However, despite the sample loss, the methodological attention employed and the statistical treatment applied for the remaining sample support the validity of our results.

Conclusion

RT combined with whey protein supplementation for 12 weeks increase FFM and SMM in patients 2–7 years postRYGB. Although RT alone elicited mean absolute improvements, these results were not statistically significant. Concurrently, RT with or without whey protein supplementation did not promote alterations in REE and blood parameters. These findings support the use of RT combined with protein supplementation in the long-term outpatient care of patients after bariatric surgery as an effective strategy for improving SMM, which is known to decline as a result of RYGB. Of note, the development of muscle-related phenotypes potentially leads to augmented functional performance and enhances patients' ability to perform activities of daily living.

Acknowledgments We are particularly thankful to Isabela Rios and Gabriela Sousa de Oliveira for participating in data collection, Gustavo Neves de Souza Gomes for conducting the supervised resistance training program applied to the participants of this study, and the Nucleus of Support on Research from Sabin Institute and Sabin Diagnostic medicine for partial funding and support for blood tests.

Authors' Contributions The study was coordinated by Kênia Mara Baiocchi de Carvalho. Kênia Mara Baiocchi de Carvalho, Eliane Said Dutra, Nathalia Pizato, Teresa Helena Macedo da Costa, Ricardo Moreno Lima, and Fernando Lamarca wrote the study protocol and designed the study. Fernando Lamarca and Flávio Teixeira Vieira realized literature searches, data collection, and performed manuscript preparation. Eduardo Yoshio Nakano and Fernando Lamarca performed data analysis. All authors contributed to data analysis, figures, and tables conception, reviewed the manuscript, and approved the version to be submitted.

Funding This study was funded by Foundation for Research Support of the Federal District (FAPDF; grant number 0193.001.462/2016), Brazilian National Technological and Scientific Development Council and Ministry of Health (CNPq/MS; grant number 408340/2017-7).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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