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Energetic Adaptations Persist after Bariatric Surgery in Severely Obese Adolescents

Nancy F. Butte[1], **Mary L. Brandt**[2], **William W. Wong**[1], **Yan Liu**[1], **Nitesh R. Mehta**[1], **Theresa A. Wilson**[1], **Anne L. Adolph**[1], **Maurice R. Puyau**[1], **Firoz A. Vohra**[1], **Roman J. Shypailo**[1], and **Issa F. Zakeri**[3]

[1]USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030

[2]Department of Surgery, Baylor College of Medicine, Houston, Texas 77030

[3]Department of Epidemiology and Biostatistics, Drexel University, Philadelphia, PA 19120

Abstract

Objective—Energetic adaptations induced by bariatric surgery have not been studied in adolescents or for extended periods post-surgery. Energetic, metabolic and neuroendocrine responses to Roux-en-Y gastric bypass surgery (RYGB) were investigated in extremely obese adolescents.

Design and Methods—At baseline and at 1.5, 6 and 12 months post-baseline, 24-h room calorimetry, body composition and fasting blood biochemistries were measured in eleven obese adolescents relative to five matched controls.

Results—In RYGB group, mean weight loss was 44±19 kg at 12 months. Total energy expenditure (TEE), activity EE, basal metabolic rate (BMR), sleep EE and walking EE significantly declined by 1.5 months (p=0.001) and remained suppressed at 6 and 12 months. Adjusted for age, sex, FFM and FM, EE was still lower than baseline (p=0.001). Decreases in serum insulin, leptin, and T3, gut hormones, and urinary norepinephrine (NE) paralleled the decline in EE. Adjusted changes in TEE, BMR and/or sleep EE were associated with decreases in insulin, HOMA, leptin, TSH, total T3, PYY3–36, GLP2 and urinary NE and epinephrine (p=0.001–0.05).

Conclusions—Energetic adaptations in response to RYGB-induced weight loss are associated with changes in insulin, adipokines, thyroid hormones, gut hormones and sympathetic nervous system activity, and persist 12 months post-surgery.

Keywords

bariatric surgery; basal metabolic rate; total energy expenditure; calorimetry

Address all correspondence to: Nancy F. Butte, Ph.D., Children's Nutrition Research Center, Baylor College of Medicine, 1100 Bates Street, Houston, TX 77030, Telephone: 713-798-7179, FAX: 713-798-7187,nbutte@bcm.edu.

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Introduction

Bariatric surgery induces massive reductions in body weight that are associated with energetic adaptations that favor weight regain (1). These adaptations involve multiple signals including regulatory hormones from the gastrointestinal tract and pancreas impacting glucose homeostasis, adipokines affecting inflammation and insulin resistance, and the hypothalamic-pituitary axis (HPA) regulating energy balance in part through thyroid, autonomic nervous system, and adrenal mediators (2, 3).

The metabolic changes induced by bariatric surgery result in resolution or improvement in obesity-related comorbidities including type 2 diabetes, hyperlipidemia, liver disease, obstructive sleep apnea, pseudotumor cerebri, hypertension, and psychological disorders (3). Inevitably, bariatric surgery induces some loss of fat-free mass (FFM) which is undesirable since FFM is responsible for the majority of basal metabolism, regulation of core body temperature, cardiopulmonary function, skeletal integrity and mobility.

For extremely obese adolescents who have been unable to achieve a healthy weight with conventional treatment, Roux-en-Y gastric bypass surgery (RYGB) is an option (4). RYGB is a diversionary procedure which creates a very small gastric pouch considerably restricting meal size and promoting early satiety. A surgical anastomosis connects the gastric pouch to the mid-jejunum using a 125–150 cm Roux limb, diverting ingested macro- and micronutrients from the duodenum, decreasing the efficiency of micronutrient absorption (5).

Dietary energy restriction and weight loss elicit energetic adaptations or compensatory changes in energy expenditure that are greater than that accounted for by the residual active tissue mass (9). Decreased sympathetic nervous system (SNS) tone and circulating concentrations of leptin, and thyroid hormones act coordinately to favor weight regain. Energetic adaptations to bariatric surgery have been documented in adults mainly using portable respiration calorimeters (6), but also room respiration calorimetry (7) and doubly labeled water (8).

Persistence of energetic adaptations beyond the period of active weight loss by conventional means (9, 10) or bariatric surgery remains controversial (6). Studies demonstrate prolonged reduction in EE (9, 11, 12), while others show no persistence (13, 14). Whether energetic adaptations occur and persist in maturing adolescents is critical to understanding mechanisms of weight loss maintenance, and in particular, recidivism after RYGB.

The primary study objective was to investigate energetic, metabolic and neuroendocrine responses to RYGB in extremely obese adolescents at 1.5, 6 and 12 months after surgery. Specific aims were to: 1) monitor changes in weight and body composition using a multi-compartment model, 2) measure changes in neuroendocrine factors, 3) measure 24-h EE and substrate utilization using room respiration calorimetry, and 4) identify neuroendocrine factors associated with the changes in EE and substrate utilization.

Methods

Human subjects

A 12-month prospective study design was used to investigate energetic, metabolic and neuroendocrine responses to RYGB (n=11) in extremely obese adolescents. A control group (n=5) matched for initial weight, body mass index (BMI) and body composition was used to ascertain effects due to extreme obesity itself or protocol procedures. Anthropometry, body composition, 24-h room respiration calorimetry, and 12-h fasting blood and 24-h urine samples for neuroendocrine biochemistries were measured at baseline, and at 1.5, 6 and 12 months post-baseline to represent the following pre-surgical (baseline) and post-surgical phases: rapid weight loss (1.5 months after surgery), moderate weight loss (6 months after surgery), and minimal weight loss or weight maintenance (12 months after surgery). Controls were studied at baseline, and at 1.5, 6 and 12 months post-baseline.

Subjects were recruited from the Texas Children's Hospital (TCH) Adolescent Bariatric Surgery Program. Adolescents electing surgery (RYGB group) or declining surgery and not enrolled in conventional weight loss programs (controls) were asked to participate. Inclusion criteria were Tanner stage IV or V and BMI≥50 kg/m^2 or BMI≥40 kg/m^2 with comorbidities. Exclusion criteria included a positive urine pregnancy test, and serious psychiatric or cognitive disorders.

Study participation did not interfere with the routine clinical care of the RYGB patients. Following bariatric surgery, regular and frequent follow-up visits assessed weight loss and monitored for postoperative complications, dietary progression, and adequacy of physical activity. Immediately postoperative until day 2, the patients ingested only clear liquids. Thereafter, patients were slowly advanced from a sugar-free full liquid diet to a soft diet, and finally to a regular diet. By six months post-surgery, the diet prescription was a regular diet consisting of 3 meals and 2 snacks per day, with an emphasis on high protein sources. A multivitamin mineral supplement with iron and supplemental calcium were prescribed.

Anthropometry

Body weight to the nearest 0.1 kg was measured with a digital scale (Tanita Corporation, model TBF-410, Arlington Heights, IL) and height to the nearest 1 mm was measured with a stadiometer (Seca, model 226l Chino, CA). Waist circumference was measured using a non-extensible metal tape measure.

Body Composition

Body composition was estimated using the Fuller three-compartment model based on total body water (TBW) and body volume (15). TBW was measured by the ^2H isotope dilution following an oral dose (0.04 g/kg body weight) of deuterium oxide (^2H_2O). ^2H abundances of baseline, 4- and 6-h post-dose urine samples were measured by gas-isotope-ratio mass spectrometry (16, 17). Body volume and body density were measured by air-displacement plethysmography (ADP) utilizing the BodPod (Life Measurements, Inc. Concord, CA).

Blood Chemistries

Serum glucose (Analox Instruments, Lundeburg, MA) and nonesterified fatty acids (NEFA) were measured by enzymatic-colorimetric techniques (Wako Diagnostics, Richmond, VA). Enzyme-linked-immunosorbent assays (ELISA) were used to measure serum insulin, resistin, adiponectin and glucagon-like peptide-2 (GLP2) (Millipore, Billerica, MD) and C-reactive protein (CRP) (Alpco Diagnostics, Salem, NH). Homeostatic model assessment (HOMA) was used to quantify insulin resistance (18). Radioimmunoassays (RIA) were used to measure serum leptin, peptide YY3–36 (PYY3–36), glucagon-like peptide-1(GLP1) (EMD Millipore, Billerica, MA), and thyroid stimulating hormone (TSH), total and free thyroxine (T4) and triiodothyronine (T3) and reverse T3 (Siemens, Deerfield, IL).

ELISAs were used to quantify urinary norepinephrine (NE) and epinephrine (E) (Rocky Mountain Diagnostics, Colorado Springs, CO). Urinary nitrogen concentrations were determined by Kjeldahl digestion (Kjeltec Auto Analyzer 1030; Tecator, Hoganas, Sweden) and a phenol-hypochlorite colorimetric reaction (19).

Room Respiration Calorimetry Protocol

Energy expenditure was measured for 24 hours in one of the two large 34-m^3) calorimeters. The design, instrumentation and performance of the calorimeters have been published (20). During the 24-h calorimetry, subjects adhered to a schedule of physical activity (treadmill walking), feeding and sleeping. Heart rate and physical activity were recorded using Actiheart (CamNtech, Cambridge, UK). From the VO_2, VCO_2, and urinary nitrogen excretion, TEE, nonprotein energy expenditure (NPEE), respiratory quotient (RQ), and net substrate utilization (21).

During 24-h calorimetry, the diet prescribed for the RYGB patients was served to both the RYGB and control groups. Food intake was provided as three meals and two snacks with a macronutrient composition consisting of 30% protein, 25% fat and 45% carbohydrate. Food intake was offered at 1.2 times BMR predicted for obese adolescents at baseline, and at 600, 1100 and 1400 kcal/d at 1.5, 6 and 12 months post-baseline, respectively.

BMR was measured after a 12-h fast upon awakening for 30 minutes. Sleeping EE was measured for the entire night sleep period, confirmed by heart rate and motion sensors. Activity energy expenditure (AEE) was computed as TEE-BMR-0.1TEE assuming diet-induced thermogenesis to be 10% of TEE. Physical activity level (PAL) was defined as TEE/BMR. Energy cost of walking was measured while walking at 2.5 mph for 15 minutes on a treadmill (Vision Fitness T9600)(22). The energy economy of walking ($kcal \cdot kg^{-1} \cdot km^{-1}$) was calculated as the ratio of the net EE standardized by weight per minute ($kcal \cdot kg^{-1} \cdot min^{-1}$) divided by speed (km/min).

Statistical Methods

Statistical analysis was performed using STATA (version 13.0, Statacorp, College Station, TX) and SAS (SAS Institute Inc., Cary, NC). Independent t tests for continuous variables and chi-square tests for categorical variables were used for descriptive analyses. A nonlinear

regression with an exponential decay model was used to fit the weight data of the RYGB group (GraphPad Software, Inc., La Jolla, CA).

A linear mixed effects regression model for repeated measures was used where subjects were treated as random effects and group assignment (RYGB or control), measurement time from baseline, and potential interactions between group and time as fixed effects. As necessary, natural logarithms were used to transform data to better satisfy the linearity and distributional assumptions. Post-hoc comparisons using Tukey-Kramer for multiple comparisons with two-tailed statistical tests between time points were performed.

Results

A total of 11 adolescents (3M/8F) electing RYGB and 5 controls (3M/2F) participated. Mean age at enrollment was 16.5 ± 0.8 y in the RYGB and 14.8 ±1.2 y in controls (p=0.03). At baseline, weight, height, BMI, waist circumference, body volume, FFM, FM and percent FM did not differ between RYGB and controls.

Anthropometry and body composition of the RYGB and controls are summarized in Table 1. Adjusted for age and sex, significant group X time interactions were observed for all parameters (p=0.000–0.019). Highly significant (p=0.001) time effects for weight, BMI, waist circumference, and the body composition parameters were seen for the RYGB group only.

In the RYGB group, mean total weight lost was 44 ± 19 kg or 30 ± 11% of initial body weight at 12 months. Mean weight loss was −16, −18 and −10 kg from baseline to 1.5 months, 1.5 to 6 months and 6 to12 months, equivalent to 11, 14 and 9% of initial body weight, respectively. Substantial variation was seen in the rate of weight loss (299 ± 120 g/d during the first 1.5 months, 110 ± 62 g/d between 1.5 to 6 months, and 48 ± 45 g/d between 6 and 12 months). Based on multiple clinical weights, individual patterns of weight loss in the RYGB group were described by a negative exponential function (mean r^2=0.98) (Figure 1). By 12 months, weight loss had reached a plateau in all (−5 ± 5 g/d) but two RYGB participants (−51 g/d and −77 g/d). No change in height was observed over the period of study in either group.

Body composition changed significantly in the RYGB group (p<0.001), but not in the controls. TBW and FFM loss occurred primarily in the first 1.5 months after surgery, with only minor (non-significant) changes thereafter. Hydration of FFM averaged 73.4% and did not differ by group or time. Total FFM loss averaged 8.3 ± 3.7 kg or 12 ± 5% of initial FFM. In contrast, FM decreased steadily over the 12 months post-surgery; total FM loss was 36 ± 20 kg or 47 ± 22% of initial FM.

Fasting blood chemistries and 24-h urinary catecholamines are presented in Table 2. Adjusted for age and sex, significant group X time interactions were seen for all parameters (p=0.0012–0.048). Further analysis revealed significant time effects for the RYGB group only. NEFA increased significantly in the RYGB group 1.5 months after surgery and then declined (p=0.001). Glucose was significantly lower than baseline at 1.5, 6 and 12 months post-surgery (p=0.001). Insulin and consequently HOMA were significantly lower after

surgery (p=0.001). Adiponectin steadily increased and leptin decreased post-surgery (p=0.001), but resistin did not change. The inflammation marker CRP declined post-surgery (p=0.01). Thyroid status was altered by RYGB: fasting serum TSH (p=0.03) and total T3 (p=0.003) decreased post-surgery. Significant changes were not seen in total T4, reverse T3 or free T3 or T4. Fasting levels of PPY3–36 and GLP2 declined (p=0.001), but GLP1 did not change. Urinary excretion of norepinephrine, but not epinephrine, decreased after surgery (p=0.01).

Total energy expenditure and its components measured by 24-h calorimetry are summarized in Table 3. Adjusted for age and sex, significant group X time interactions were seen for TEE and its components (p=0.001–0.01); significant time effects were observed in the RYGB group, but not controls. TEE, BMR, sleep EE declined by 24, 19, and 24% at 1.5 months, and then remained at the suppressed level at 6 and 12 months after surgery. Adjusted for age, sex, FFM and FM, post-surgical TEE (kcal/d), BMR (kcal/min) and sleep EE (kcal/min) were still significantly lower than baseline (p=0.001). TEE, BMR and sleep EE as a function of FFM are graphically displayed in Figure 2; the downward shift in TEE, BMR and sleep EE occurred in the initial 1.5 months post-surgery and then persisted. Similar to the pattern in EE, heart rate throughout the 24-h decreased significantly at 1.5 months after surgery (p=0.001), and remained at the lower level at 6 months (p=0.001) and 12 months (p=0.002).

In addition to changes in basal energy requirements, the energy expended in physical activity also fell. AEE declined by 41% and the energy cost of walking dropped by 28% at 1.5 months after surgery (p=0.001). Adjusted for age, sex, FFM and FM, post-surgical AEE (kcal/d) and walking EE (kcal/min) were still significantly lower than baseline (p=0.001–0.0001) (Figure 2). The energy economy of walking ($kcal \cdot kg^{-1} \cdot km^{-1}$) also decreased at 1.5 months post-surgery (p=0.001) and persisted at the lower level at 6 and 12 months post-surgery.

Substrate utilization was significantly altered in the RYGB, but not controls (Table 4). At 1.5 months post-surgery, 24-h RQ and NPRQ declined sharply, reflective of increased fat utilization and decreased carbohydrate utilization (p=0.001). Thereafter, the changes in fat and carbohydrate utilization reversed, approaching baseline values. At 1.5 months post-surgery, protein utilization dropped significantly (p=0.001), but was restored at 6 and 12 months. Adjusted for age, sex, FFM, FM and energy balance, the time effects for substrate utilization were still significant (p=0.001–0.05).

Mixed-effects linear regression models adjusted for age, sex, FFM and FM were used to explore neuroendocrine mechanisms associated with suppressed EE following RYGB (Table 5; Figure 3). Changes in TEE, BMR and/or sleep EE were associated with changes in insulin, HOMA, adiponectin, leptin, TSH, total T3, PYY3–36, GLP2, and urinary NE and E. Substrate utilization was not associated with neuroendocrine alterations; however, fat utilization was positively associated with fasting serum NEFA.

Discussion

Here within, we demonstrate that energetic adaptations in response to RYGB in severely obese adolescents 1) are not totally explained by weight, FFM or FM loss; 2) are associated with changes in insulin, leptin, adiponectin, T3, gut hormones, and SNS activity; and 3) persist 12 months after surgery despite a diminishing rate of weight loss.

RYGB-induced energetic adaptations were observed in TEE and its components after surgery. The majority of the adaptive thermogenesis occurred by 1.5 months after surgery, coincident with the decline in FFM and biochemical changes. TEE, AEE, BMR, sleep EE and walking EE declined by 24, 41, 19, 24, and 28% at 1.5 months, and then remained at the suppressed level at 6 and 12 months after surgery. Heart rate paralleled the decline in EE, probably driven by the autonomic nervous system (23). Despite the significant slowing of weight loss by 12 months post-surgery, the pre-surgical relationship between EE and weight or FFM was not restored. Lower energy economy of walking post-surgically also indicated energy conservation. Within the confines of the calorimeter, AEE and PAL declined in both groups, possibly due to habituation to the room calorimeter at follow-up.

As expected on very low calorie diets, negative energy balance caused a shift towards increased fat oxidation. At 1.5 months after surgery, mean 24-h RQ was 0.76, and fat utilization had increased markedly to 77% of EE, a finding likely explained best by a shift from use of exogenous (dietary) energy intake to use of endogenous fat stores for fuel during the rapid weight loss phase associated with hypocaloric dietary intake early postoperatively. The measurements at 6 and 12 months demonstrated a decrease in fat utilization and an increase in carbohydrate utilization, despite continued fat mass loss (utilization).

As first observed in the Minnesota Experiment by Keys et al. (24), caloric restriction resulted in a reduction in basal metabolic rate (BMR) that was greater than that accounted for by the loss in weight and FFM. In these adolescents, RYGB resulted in substantial reductions in weight (30% of initial weight), as in other studies (25), and FM (47% of initial FM) at 12 months post-surgery, but FFM (12% of initial FFM) appeared to be relatively conserved. FFM loss occurred primarily in the first 1.5 months after surgery, and plateaued thereafter. In these adolescents, the proportion of total weight loss was 22% as FFM, and 78% as FM at 12 months post-surgery. In adults, the proportion of weight loss was 31% as FFM with RYGB (26).

The neuroendocrine mechanisms underlying the energetic responses to weight loss induced by RYGB are not well elucidated but may involve insulin, adipokines, thyroid hormones, gut hormones, and SNS activity. Our data demonstrates that decreases in fasting serum insulin, leptin, and T3, and gut hormones, and 24-h urinary excretion of NE parallel the fall in TEE, BMR and sleep EE, and that the effects on EE are statistically independent of FFM and FM losses.

After RYGB, there was a rapid improvement in insulin sensitivity associated with changes in total T3, leptin and adiponectin. The fall in insulin (27) and leptin with weight loss (29) acts to decrease SNS activity (30), thereby lowering BMR independently of changes in weight. Changes in NE likely contribute to the suppressed EE through direct effects on

skeletal muscle and indirect effects on thyroid hormones (28). Adipokines (leptin, adiponectin, resistin) interact both centrally and peripherally to regulate energy intake and EE (29). Leptin can reduce FM centrally through inhibition of appetite, stimulation of thermogenesis and fat oxidation. In these adolescents, leptin correlated closely with FM loss. Leptin was a strong predictor of the adaptations in TEE, BMR and sleep EE. We did not observe a significant effect of leptin on substrate utilization.

Thyroid hormones, specifically TSH and T3, decreased after RYGB-induced weight loss in these adolescents. Elevated TSH and T3 levels in obese individuals have been shown to normalize with substantial weight loss (30). The changes in T3 were associated with adaptations in TEE, BMR and sleep EE, confirming the role of thyroid hormones in the regulation of energy metabolism. A reduction in thyroid activity acts to decrease oxygen consumption, slow cellular metabolism and conserve energy stores (31). In conventional weight loss, plasma T3 fell in conjunction with 24-h TEE (32).

Changes in gut hormones after RYGB have been hypothesized to mediate enhanced satiety, while effects on EE are uncertain. In humans, the effects of GLP1 and PYY on EE are emerging but inconsistent (6). PYY was positively correlated with resting EE (33) and negatively correlated in another study (34). Infusion of PYY3–36 tended to reduce EE in lean and obese adults (35). In our study, fasting PYY3–36 and GLP2 declined after RYGB, and were positively associated with TEE, BMR and sleep EE.

A series of studies explored whether energetic adaptations were a result of caloric restriction during active weight loss or maintenance of a reduced weight after conventional weight loss (9, 23,28, 36, 37). Maintenance of reduced weight was accompanied by increased skeletal muscle work efficiency, decreased serum T3 and urinary norepinephrine excretion (28). Our results corroborate these findings in that energetic adaptations were not observed in controls subjected to acute caloric restriction during 24-h calorimetry, and TEE and its components remained suppressed after RYGB-induced weight loss plateaued at 12 months.

Controversy exists over the persistence of energetic adaptations after weight loss (6, 10, 36, 38). The suppression of TEE, BMR, sleep EE, AEE and walking EE observed in these adolescents after RYGB clearly persisted, despite the fact that weight loss had plateaued in most cases. In 12 adults undergoing RYGB, TEE and sleep EE were reduced at 6 months and persisted at 12 months (7). In another study, patients who regained weight two years after RYGB had lower resting EE (39). After conventional weight loss, a disproportionate reduction in EE persisted in individuals who maintained a body weight reduction of ≥10% for greater than one year (9).

RYGB, when used for appropriate patients, clearly can afford substantial health benefits for extremely obese adolescents. This study demonstrated that RYGB improved insulin sensitivity, decreased heart rate and reduced inflammation, but also induced persistent energetic, metabolic and endocrine adaptations that favor weight regain. Elucidating the adaptations induced by weight loss after RYGB will be instrumental in guiding the clinical management of these patients to prevent recidivism and future research into alternate surgical and non-surgical treatments for morbid obesity.

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What is already known about this subject?

- Energetic adaptations occur after conventional weight loss and Roux-en-Y gastric bypass surgery (RYGB) in adults
- Energy adaptations following conventional weight loss and semi-starvation involve changes in autonomic nervous system, thyroid hormones, insulin, adiposity-derived hormones and gut hormones
- Weight loss and regain after RYGB are highly variable in adolescents, yet the underlying mechanisms are unclear

What does this study add?

- Energetic adaptations involving all components of energy expenditure (basal, activity, sleep and walking) occur in adolescents following RYGB
- Energy adaptations are possibly mediated by insulin, leptin, T3, gut hormones and norepinephrine in weight-reduced adolescents.
- Energy adaptations persist up to 12 months in adolescents after RYGB

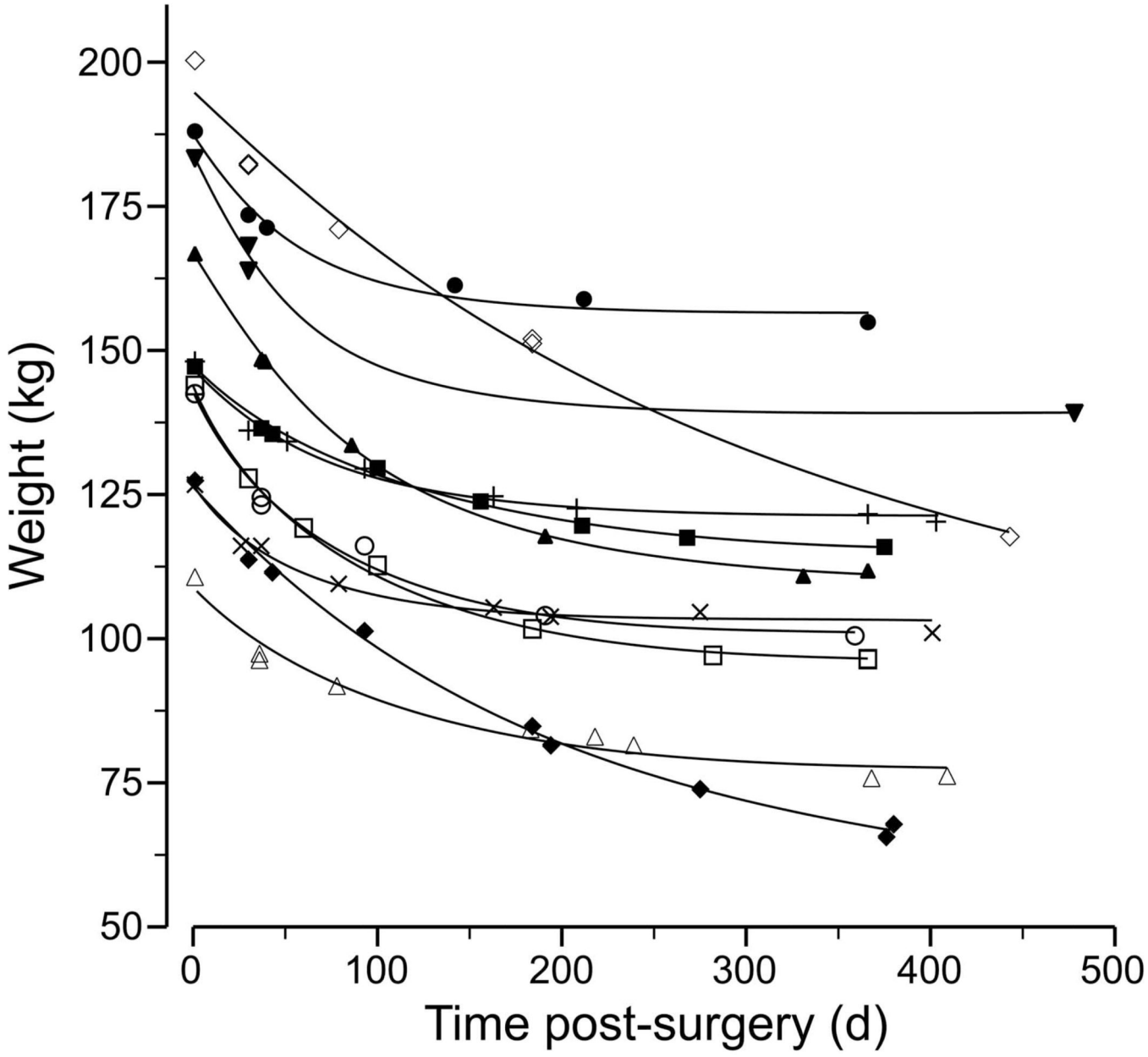

Figure 1.
Patterns of weight loss in adolescents undergoing RYGB surgery described by a negative exponential function

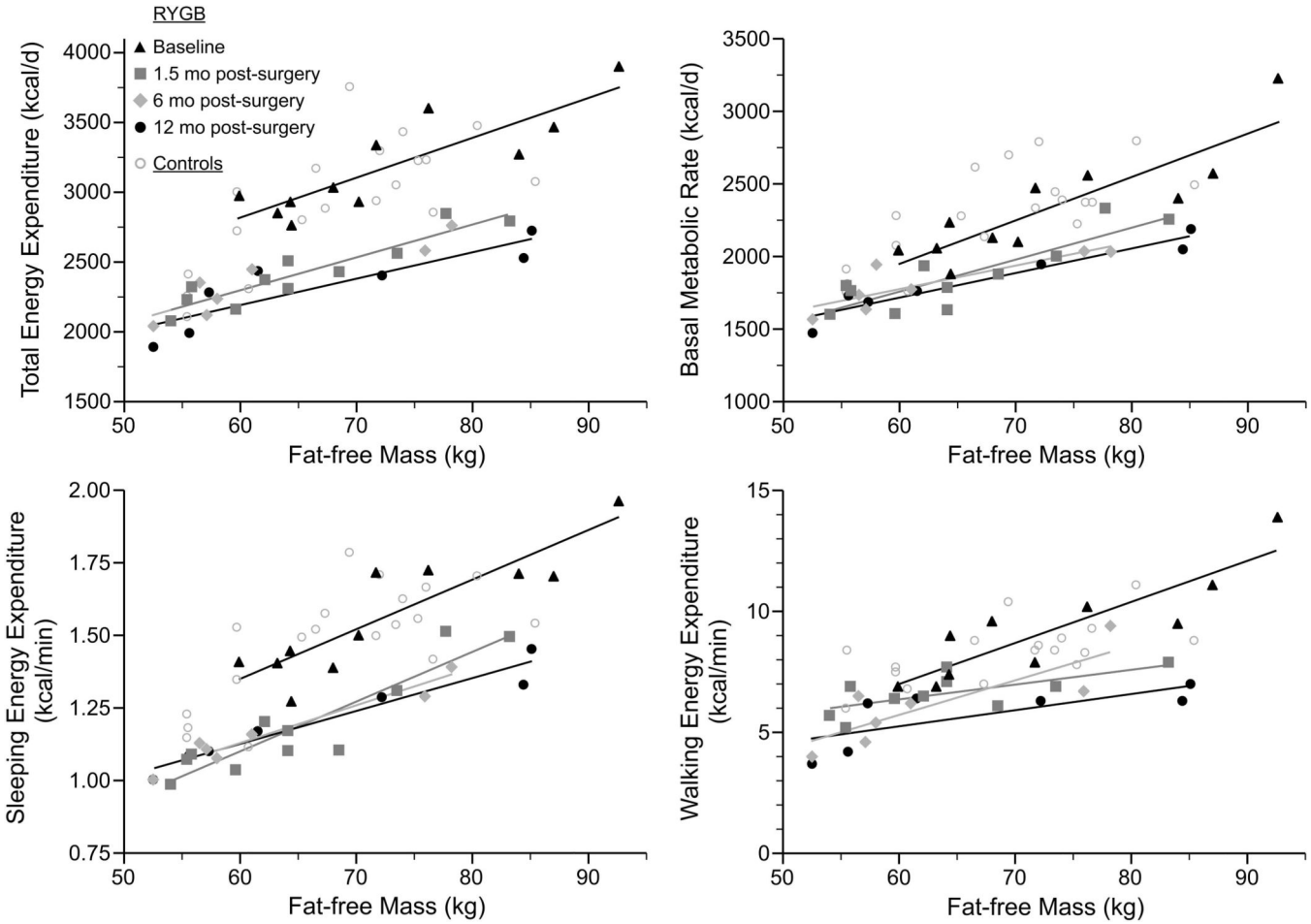

Figure 2.

Relationship between total, basal, sleeping and walking energy expenditure and fat-free mass in RYGB and control groups at baseline and 1.5, 6 and 12 months post-baseline

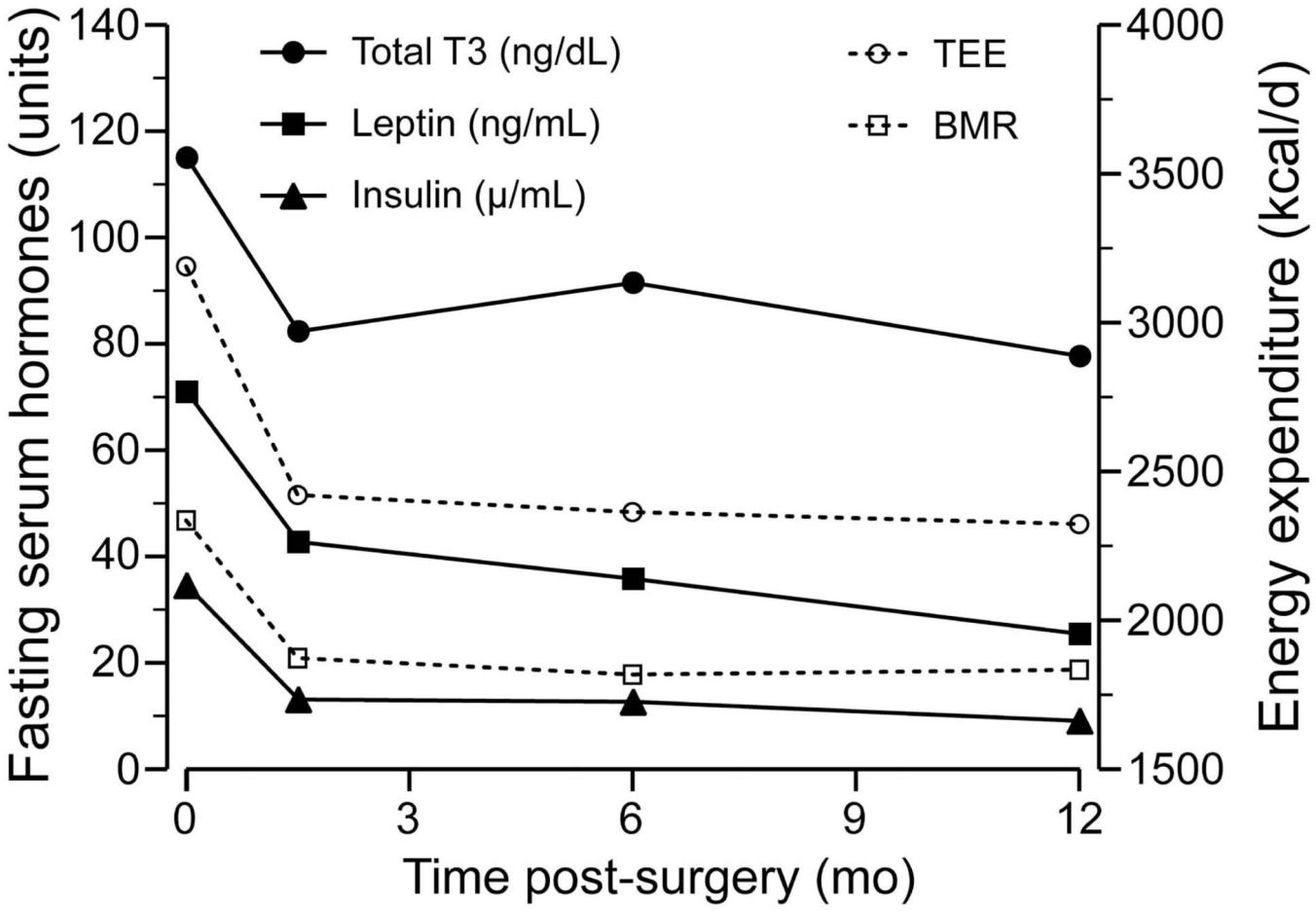

Figure 3.
Changes in total energy expenditure (TEE), basal metabolic rate (BMR), and fasting serum hormones in adolescents at baseline and 1.5, 6 and 12 months post-surgery

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Table 1

Anthropometric and body composition of the RYGB (n=11) and control (n=5) groups

		Post-baseline				
	Baseline	**1.5 mo**	**6 mo**	**12 mo**	**Time effect within group**	**Post-hoc test[1]**
Weight (kg)					(p-value)	
RYGB	153.1 ± 28.7*	136.9 ± 27.5	117.3 ± 30.6	106.6 ± 26.3	<0.0001	ab, ac, ad, bd
Control	133.2 ± 24.9	133.0 ± 27.4	134.7 ± 31.6	131.4 ± 30.7	0.929	
Height (m)						
RYGB	1.64 ± 0.07	1.64 ± 0.07	1.64 ± 0.05	1.64 ± 0.07	0.197	NS
Control	1.65 ± 0.06	1.66 ± 0.06	1.67 ± 0.06	1.68 ± 0.06	0.800	
BMI (kg/m^2)						
RYGB	57.0 ± 10.5	50.9 ± 10.4	45.3 ± 11.2	40.1 ± 10.7	<0.0001	ab, ac, ad, bc, bd
Control	48.0 ± 8.7	48.3 ± 9.2	47.9 ± 10.3	46.0 ± 9.1	0.809	
Waist circumference (cm)						
RYGB	133.7 ± 16.2	126.9 ± 21.3	115.9 ± 18.6	110.8 ± 18.0	0.016	ac, ad, bc, bd
Control	122.9 ± 16.0	127.2 ± 19.2	119.5 ± 19.4	119.2 ± 21.4	0.229	
Body volume (L)						
RYGB	146.5 ± 24.6	139.3 ± 29.4	117.9 ± 32.6	105.3 ± 28.3	<0.0001	ab, ac, ad, bc, bd
Control	131.4 ± 28.7	134.0 ± 29.3	127.0 ± 31.4	131.3 ± 31.1	0.889	
TBW (kg)						
RYGB	54.1 ± 8.7	48.3 ± 7.8	46.2 ± 8.6	47.3 ± 10.3	0.001	ab, ac, ad
Control	49.4 ± 6.3	49.3 ± 5.8	50.2 ± 7.31	51.9 ± 8.70	0.441	
FFM (kg)						
RYGB	72.9 ± 10.8	65.3 ± 9.6	62.8 ± 10.1	65.0 ± 12.6	0.001	ab, ac, ad
Control	66.0 ± 8.0	67.9 ± 8.1	68.3 ± 8.1	72.1 ± 13.5	0.352	
FM (kg)						
RYGB	80.3 ± 20.9	71.6 ± 21.0	54.6 ± 21.9	41.5 ± 22.2	<0.0001	ab, ac, ad, bc, bd, cd
Control	67.1 ± 17.0	65.1 ± 21.1	66.4 ± 23.7	59.3 ± 17.8	0.882	
FM (%weight)						
RYGB	51.8 ± 5.2	51.6 ± 6.0	44.9 ± 8.6	37.0 ± 12.9	0.002	ac, ad, bc, bd
Control	49.8 ± 4.1	47.8 ± 7.8	47.8 ± 7.9	44.4 ± 4.70.738		

[*] Data are shown as mean ± SD.

[1] Post-hoc estimation using Tukey-Kramer for multiple comparisons with $p<0.05$; letters refer to statistically significant differences between time points baseline (a),1.5 months (b), 6 months (c) and 12 months (d).

TBW, total body water; FFM, fat free mass; FM, fat mass.

Table 2

Fasting blood chemistries and 24-h urinary catecholamines of the RYGB (n=11) and control (n=5) groups

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
NEFA (mEq/L)					(p-value)	
RYGB	0.72 ± 0.26*	0.92 ± 0.23	0.61 ± 0.17	0.49 ± 0.17	0.014	ab, bc
Control	0.60 ± 0.11	0.70 ± 0.21	0.68 ± 0.17	0.70 ± 0.26	0.704	
Glucose (mg/dL)						
RYGB	102.3 ± 21.4	91.6 ± 7.7	85.9 ± 7.1	86.8 ± 8.5	0.037	ab, ac, ad
Control	95.1 ± 6.0	98.2 ± 11.4	99.0 ± 7.3	98.9 ± 7.1	0.547	
Insulin (μu/mL)						
RYGB	34.5 ± 24.0	13.1 ± 8.8	12.7 ± 7.1	9.1 ± 5.4	0.006	ab, ac, ad
Control	29.0 ± 10.4	23.1 ± 8.5	21.6 ± 11.6	22.8 ± 13.9	0.472	
HOMA						
RYGB	8.1 ± 4.8	2.9 ± 1.7	2.6 ± 1.3	1.9 ± 1.1	0.001	ab, ac, ad
Control	6.7 ± 2.1	5.5 ± 1.7	5.2 ± 2.7	5.5 ± 3.3	0.600	
Adiponectin (ng/mL)						
RYGB	6474 ± 2540	8422 ± 2688	8634 ± 3620	10900 ± 4820	0.002	ab, ac, ad, bd, cd
Control	6873 ± 4331	6686 ± 4229	7088 ± 4936	7690 ± 6502	0.909	
Resistin (ng/mL)						
RYGB	11.79 ± 2.82	12.11 ± 4.46	12.47 ± 3.03	12.55 ± 3.88	0.931	NS
Control	9.44 ± 3.30	10.49 ± 2.76	10.90 ± 6.16	7.96 ± 2.45	0.714	
Leptin (ng/mL)						
RYGB	71.0 ± 36.6	42.7 ± 24.5	35.8 ± 21.9	25.4 ± 24.1	0.001	ab, ac, ad
Control	66.2 ± 22.5	52.8 ± 19.1	60.0 ± 25.0	43.0 ± 14.9	0.238	
CRP (ng/mL)						
RYGB	11360 ± 9801	4546 ± 3455	6945 ± 5986	3160 ± 4795	0.016	
Control	6433 ± 5537	6172 ± 3487	7252 ± 3557	5500 ± 4400	0.666	
TSH (μIU/mL)						
RYGB	3.05 ± 1.36	2.10 ± 0.80	1.47 ± 0.51	1.65 ± 0.94	0.031	ab, ac, ad
Control	1.77 ± 0.97	1.66 ± 0.69	1.77 ± 1.01	1.58 ± 1.21	0.768	

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
Total T3 (ng/dL)						
RYGB	115.0 ± 30.7	82.3 ± 23.8	91.5 ± 26.8	77.7 ± 17.9	0.003	ab, ad
Control	111.9 ± 37.2	104.1 ± 32.4	104.7 ± 32.6	97.1 ± 13.5	0.233	
Total T4 (μg/dL)						
RYGB	7.77 ± 1.65	7.14 ± 1.64	7.82 ± 3.18	7.32 ± 1.23	0.480	NS
Control	6.18 ± 1.49	6.39 ± 0.97	6.20 ± 1.29	6.10 ± 2.47	0.027	
Free T3 (pg/mL)						
RYGB	3.34 ± 0.49	2.82 ± 0.60	2.72 ± 0.57	2.59 ± 0.51	0.203	
Control	3.52 ± 0.70	3.27 ± 1.10	3.08 ± 0.93	3.14 ± 0.44	0.554	
Free T4 (ng/dL)						
RYGB	1.31 ± 0.18	1.19 ± 0.22	1.29 ± 0.30	1.26 ± 0.25	0.525	NS
Control	1.10 ± 0.18	1.22 ± 0.16	1.15 ± 0.18	1.18 ± 0.43	0.541	
Reverse T3 (ng/mL)						
RYGB	0.33 ± 0.08	0.34 ± 0.09	0.32 ± 0.08	0.27 ± 0.04	0.120	bd
Control	0.24 ± 0.08	0.27 ± 0.05	0.22 ± 0.06	0.20 ± 0.08	0.026	
PYY3–36 (pg/mL)						
RYGB	105.2 ± 24.6	68.1 ± 20.8	89.5 ± 14.5	77.8 ± 28.4	0.001	ab, ad, bc
Control	77.0 ± 23.5	58.4 ± 22.4	72.1 ± 32.6	84.2 ± 17.0	0.240	
GLP1 (pM)						
RYGB	16.1 ± 6.0	17.2 ± 10.3	15.6 ± 8.1	13.0 ± 6.6	0.903	
Control	13.1 ± 3.7	13.5 ± 7.2	8.6 ± 4.8	15.8 ± 10.1	0.365	
GLP2 (ng/mL)						
RYGB	8.63 ± 1.83	5.38 ± 2.07	5.97 ± 0.65	6.23 ± 1.87	0.001	ab, ac
Control	5.58 ± 2.35	5.33 ± 2.03	6.64 ± 1.45	6.25 ± 2.55	0.341	
Urinary NE (nmol/d)						
RYGB	326 ± 166	232 ± 168	250 ± 92	205 ± 91	0.014	
Control	296 ± 62	218 ± 86	300 ± 175	311 ± 105	0.632	
Urinary E (nmol/d)						
RYGB	49.1 ± 14.8	42.5 ± 41.5	53.0 ± 19.1	43.3 ± 14.1	0.604	
Control	47.3 ± 9.1	48.2 ± 17.2	45.7 ± 32.1	57.8 ± 29.1	0.643	

[*] Data are shown as mean ± SD. Models adjusted for age and sex; significant group X time interactions for all parameters (p=0.001–0.05)

[1] Post-hoc estimation using Tukey-Kramer for multiple comparisons with p<0.05; letters refer to statistically significant differences between time points baseline (a),1.5 months (b), 6 months (c) and 12 months (d).

NEFA, nonesterified fatty acids; HOMA, homeostatic model assessment; CRP, C-reactive protein; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; PYY3–36, peptide YY3–36; GLP1, glucagon-like peptide-1; GLP2, glucagon-like peptide-2; NE, norepinephrine; E, epinephrine.

Table 3

Energy expenditure, heart rate and physical activity during 24-h calorimetry of the RYGB (n=11) and control (n=5) groups

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
TEE (kcal/d)					(p-value)	
RYGB	3189 ± 358*	2421 ± 243	2363 ± 256	2323 ± 294	0.001	ab, ac, ad
Control	3110 ± 512	2859 ± 374	2927 ± 421	2887 ± 575	0.072	
PAL						
RYGB	1.39 ± 0.07	1.30 ± 0.12	1.32 ± 0.08	1.24 ± 0.12	0.001	ab, ad, cd
Control	1.36 ± 0.07	1.29 ± 0.07	1.27 ± 0.11	1.27 ± 0.07	0.212	
AEE (kcal/d)						
RYGB	535 ± 111	306 ± 115	309 ± 130	257 ± 118	0.001	ab, ac, ad
Control	495 ± 183	332 ± 133	304 ± 221	303 ± 132	0.160	
HR (bpm)						
RYGB	85.8 ± 6.1	71.6 ± 9.5	72.6 ± 3.6	70.5 ± 7.6	0.002	ab, ac, ad
Control	84.0 ± 11.6	79.3 ± 12.7	80.1 ± 9.4	77.5 ± 13.1	0.484	
Actiheart (counts/d)						
RYGB	24202 ± 4082	20619 ± 8099	22716 ± 7356	19839 ± 5419	0.326	NS
Control	29088 ± 8200	27650 ± 5211	27187 ± 13405	22836 ± 13178	0.977	
BMR (kcal/d)						
RYGB	2335 ± 374	1909 ± 333	1818 ± 189	1877 ± 305	0.001	ab, ac, ad
Control	2304 ± 319	2241 ± 329	2331 ± 321	2296 ± 450	0.150	
BMR HR (bpm)						
RYGB	76.6 ± 7.7	64.4 ± 10.3	62.5 ± 5.0	64.9 ± 6.7	0.001	ab, ac, ad
Control	73.9 ± 8.1	75.6 ± 8.5	72.3 ± 10.5	71.7 ± 13.0	0.874	
Sleep EE (kcal/min)						
RYGB	1.57 ± 0.21	1.19 ± 0.18	1.17 ± 0.13	1.20 ± 0.16	<0.0001	ab, ac, ad
Control	1.52 ± 0.22	1.41 ± 0.20	1.51 ± 0.17	1.49 ± 0.24	0.085	
Sleep HR (bpm)						
RYGB	75.7 ± 7.3	62.0 ± 10.2	61.0 ± 4.6	63.8 ± 7.0	0.002	ab, ac
Control	72.2 ± 10.8	71.0 ± 13.4	72.5 ± 9.6	69.8 ± 12.6	0.816	

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
Walking EE at 2.5 mph (kcal/min)						
RYGB	9.2 ± 2.2	6.6 ± 0.8	6.1 ± 1.8	5.7 ± 1.3	<0.0001	ab, ac, ad
Control	8.7 ± 1.1	8.2 ± 1.0	7.7 ± 1.2	9.0 ± 2.0	0.597	
Walking HR at 2.5 mph (bpm)						
RYGB	143 ± 14.0	128 ± 12.3	121 ± 9.7	112 ± 11.1	0.003	ab, ac, ad
Control	146 ± 7.0	135 ± 14.3	124 ± 8.6	141 ± 7.7	0.019	ac
Energy economy of walking (kcal·kg^{-1}·km^{-1})						
RYGB	0.013 ± 0.002	0.010 ± 0.001	0.010 ± 0.001	0.010 ± 0.001	0.001	ab, ad
Control	0.013 ± 0.003	0.013 ± 0.002	0.012 ± 0.002	0.012 ± 0.002	0.847	

[*] Data are shown as mean ± SD. Models adjusted for age and sex; significant group X time interactions for all parameters (p=0.001–0.01)

[1] Post-hoc estimation using Tukey-Kramer for multiple comparisons with p<0.05; letters refer to statistically significant differences between time points baseline (a),1.5 months (b), 6 months (c) and 12 months (d).

TEE, total energy expenditure; PAL, physical activity level; AEE, activity energy expenditure; HR, heart rate; BMR, basal metabolic rate.

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Table 4

Substrate Utilization during 24-h calorimetry of the RYGB (n=11) and control (n=5) groups

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
RQ					(p-value)	
RYGB	0.85 ± 0.03*	0.76 ± 0.02	0.81 ± 0.03	0.82 ± 0.03	<0.0001	ab, bc, bd
Control	0.83 ± 0.02	0.82 ± 0.03	0.81 ± 0.05	0.84 ± 0.04	0.385	
Protein utilization (g/d)						
RYGB	97 ± 43	34 ± 12	70 ± 20	77 ± 12	<0.0001	ab, bc, bd
Control	101 ± 21	80 ± 23	70 ± 31	95 ± 28	0.208	
Carbohydrate utilization (g/d)						
RYGB	331 ± 72	94 ± 46	169 ± 48	172 ± 54	<0.0001	ab, ac, ad
Control	293 ± 94	222 ± 76	227 ± 144	282 ± 130	0.567	
Fat utilization (g/d)						
RYGB	142 ± 40	197 ± 30	140 ± 35	131 ± 38	0.001	ab, bc, bd, cd
Control	149 ± 19	164 ± 44	174 ± 39	133 ± 33	0.352	
Protein utilization (%EE)						
RYGB	14.2 ± 5.3	6.5 ± 2.2	14.2 ± 4.6	16.0 ± 3.6	<0.0001	ab, bd
Control	15.5 ± 3.2	13.2 ± 4.0	11.4 ± 5.0	15.5 ± 3.5	0.424	
Carbohydrate utilization (%EE)						
RYGB	43.9 ± 9.9	16.3 ± 8.2	30.0 ± 8.7	31.3 ± 10.2	<.0001	ab, bc, bd
Control	38.6 ± 6.5	32.5 ± 10.4	31.2 ± 17.1	39.8 ± 12.3	0.333	
Fat utilization (%EE)						
RYGB	41.7 ± 9.0	76.8 ± 8.6	55.6 ± 10.9	52.5 ± 11.0	<0.0001	ab, bc, bd
Control	45.7 ± 6.5	54.1 ± 12.2	57.1 ± 14.6	44.5 ± 11.8	0.375	
NPRQ						
RYGB	0.85 ± 0.03	0.76 ± 0.02	0.81 ± 0.03	0.81 ± 0.03	<.0001	ab, bc, bd
Control	0.84 ± 0.02	0.81 ± 0.04	0.81 ± 0.05	0.84 ± 0.04	0.375	
Carbohydrate utilization (%NPEE)						
RYGB	51.2 ± 10.9	17.5 ± 8.8	35.3 ± 11.4	37.4 ± 12.2	<0.0001	ab, bc, bd
Control	45.7 ± 7.3	37.8 ± 13.1	34.9 ± 17.3	47.2 ± 14.1	0.466	

	Baseline	Post-baseline 1.5 mo	Post-baseline 6 mo	Post-baseline 12 mo	Time effect within group	Post-hoc test[1]
Fat utilization (%NPEE)						
RYGB	48.8 ± 10.9	82.5 ± 8.8	64.7 ± 11.4	62.6 ± 12.2	<0.0001	ab, bc, bd
Control	54.3 ± 7.3	62.2 ± 13.1	65.1 ± 17.3	52.8 ± 14.1	0.456	

*Data are shown as mean ± SD. Models adjusted for age and sex; significant program by time interactions for all parameters (p=0.000–0.04)

[1]Post-hoc estimation using Tukey-Kramer for multiple comparisons with p<0.05; letters refer to statistically significant differences between time points baseline (a),1.5 months (b), 6 months (c) and 12 months (d).

RQ, respiratory quotient; EE, energy expenditure; NPRQ, nonprotein RQ; NPEE, nonprotein EE.

Table 5

Associations between energy expenditure and fasting serum hormones and urinary catecholamine excretion in RYGB group (n=11)

	TEE		BMR		Sleep EE		HR	
	β (se)	p-value	β (se)	p-value	β (se)	p-value	β (se)	p-value
Independent variables								
Insulin (μu/mL)*	328 (71)	**0.001**	204 (68)	**0.008**	0.14 (0.04)	**0.001**	7.68 (2.58)	**0.008**
HOMA*	338 (57)	**0.0001**	210 (59	**0.002**	0.17 (0.03)	**0.001**	7.88 (2.27)	**0.003**
Adiponectin (ng/mL)*	372 (149)	**0.023**	219 (129)	0.108	−0.18 (0.08)	**0.042**	−8.2 (5.0)	0.117
Resistin (ng/mL)	18.4 (15.6)	0.253	7.91 (11.4)	0.495	0.01 (0.01)	0.333	0.27 (0.53)	0.615
Leptin (ng/mL)	367 (94)	**0.001**	127 (80.6)	0.132	0.12 (0.05)	**0.043**	2.93 (3.17)	0.366
CRP (ng/mL)*	63.5 (39.8)	0.128	28.8 (29.3)	0.338	0.02 (0.02)	0.265	3.61 (0.99)	**0.002**
TSH (μIU/mL)*	266 (110)	**0.027**	166 (83)	0.062	0.12 (0.06)	0.056	5.07 (3.80)	0.200
Total T3 (ng/dL)	624 (143)	**0.001**	497 (119)	**0.001**	0.33 (0.08)	**0.001**	13.28 (4.94)	**0.015**
Total T4 (ng/dL)	189 (248)	0.455	11.1 (179)	0.951	0.08 (0.12)	0.542	11.13 (6.77)	0.118
Free T3 (pg/mL)	188 (99)	0.075	120 (74)	0.124	0.10 (0.05)	0.053	5.5 (2.26)	**0.026**
Free T4 (ng/dL)	184 (228)	0.431	60.5 (170)	0.726	0.09 (0.12)	0.443	8.92 (4.81)	0.081
Reverse T3 (ng/mL)	−1298 (719)	0.091	772 (530)	0.165	−0.61 (0.36)	0.109	−8.48 (23.54)	0.724
PYY3–36 (pg/mL)	5.68 (1.33)	**0.001**	2.94 (1.38)	**0.049**	0.002 (0.0007)	**0.004**	0.16 (0.05)	**0.007**
GLP1 (pM)	−1.79 (2.37)	0.460	2.04 (1.72)	0.252	−0.0008 (0.001)	0.307	0.12 (0.05)	**0.023**
GLP2 (ng/mL)	68.5 (16.5)	**0.001**	60.2 (15.5)	**0.001**	0.04 (0.01)	**0.003**	2.24 (0.51)	**0.001**
Urinary NE (nmol/d)	181.4 (56.5)	**0.005**	135 (60)	**0.037**	0.10 (0.03)	**0.004**	5.74 (1.94)	**0.009**
Urinary E (nmol/d)	167.4 (54.1)	**0.006**	116 (70)	0.114	0.07 (0.05)	0.151	2.83 (2.14)	0.201

*Natural logarithm transformed. Models adjusted for age, sex, FFM and FM.

NEFA, nonesterified fatty acids; HOMA, homeostatic model assessment; CRP, C-reactive protein; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; PYY3–36, peptide YY3–36; GLP1, glucagon-like peptide-1; GLP2, glucagon-like peptide-2; NE, norepinephrine; E, epinephrine.