Metabolic Adaptation Following Massive Weight Loss is Related to the Degree of Energy Imbalance and Changes in Circulating Leptin

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Objective: To measure changes in resting metabolic rate (RMR) and body composition in obese subjects following massive weight loss achieved via bariatric surgery or calorie restriction plus vigorous exercise.
Methods: Body composition and RMR were measured in 13 pairs of obese subjects retrospectively matched for sex, body mass index, weight, and age who underwent either Roux-en-Y gastric bypass surgery (RYGB) or participated in "The Biggest Loser" weight loss competition (BLC).
Results: Both groups had similar final weight loss (RYGB: 40.2 ± 12.7 kg, BLC: 48.8 ± 14.9 kg; $P = 0.14$); however, RYGB lost a larger proportion of their weight as fat-free mass (FFM) (RYGB: $30 \pm 12\%$, BLC: $16 \pm 8\%$ [$P < 0.01$]). In both groups, RMR decreased significantly more than expected based on measured body composition changes. The magnitude of this metabolic adaptation was correlated with the degree of energy imbalance ($r = 0.55$, $P = 0.004$) and the decrease in circulating leptin ($r = 0.47$, $P = 0.02$).
Conclusions: Calorie restriction along with vigorous exercise in BLC participants resulted in preservation of FFM and greater metabolic adaption compared to RYGB subjects despite comparable weight loss. Metabolic adaptation was related to the degree of energy imbalance and the changes in circulating leptin.

Introduction

The prevalence of Class III obesity (i.e., body mass index > 40 kg/m^2) is increasing rapidly (1) along with the risk of cardiovascular disease, diabetes, some forms of cancer, and several other chronic diseases (2). Bariatric surgery is an increasingly popular and effective treatment (3) that results in massive weight loss leading to marked improvements in insulin sensitivity, cardio-metabolic health, and reduced mortality (4-7). However, bariatric surgery patients often experience a disproportionate loss of fat-free mass (FFM) (8-10) which may lead to functional deficits, especially with advancing age (11,12). Disproportionate reduction of FFM may also suppress resting metabolic rate (RMR) as FFM comprises the metabolically active tissues of the body (13) and may thereby predispose to weight regain (14).

Few lifestyle interventions can match the degree of weight loss that is achieved through bariatric surgery. This fact makes it difficult to

assess the effects of bariatric surgery on energy metabolism and body composition in comparison to a group with similar weight loss achieved via lifestyle intervention alone. The current study aims to investigate changes in body composition, RMR, and cardio-metabolic health in class III obese subjects following massive weight loss achieved with vigorous exercise and self-selected diet restriction as part of "The Biggest Loser" competition (BLC) (15) compared to retrospectively pair-matched subjects following Roux-en-Y gastric bypass surgery (RYGB) (10).

We hypothesized that the BLC intervention would lead to a relative preservation of FFM compared to RYGB participants because of the vigorous exercise of the BLC group. We further hypothesized that both groups would experience a metabolic adaptation, with RMR decreasing greater than expected based on the observed body composition changes and that the magnitude of metabolic adaptation

would be related to the degree of energy imbalance and changes in circulating leptin and thyroid hormones.

Methods

Bariatric surgery

As previously described (10), RYGB patients were admitted to the Vanderbilt Clinical Research Center on three separate occasions: pre-operatively, 6 months postoperatively, and 12 months postoperatively. Patients were under no dietary restrictions prior to the pre-operative study visit, but following surgery they were counseled to transition from a liquid diet to a balanced diet of 900-1000 kcal/d containing 70 g of protein and were encouraged to exercise. The study was approved by the Vanderbilt University Institutional Review Board (#040572).

Biggest loser intervention

As previously described (15), BLC participants were housed on a ranch near Los Angeles, CA, where they engaged in 90 minutes per day (6 d/wk) of directly supervised vigorous circuit training and/or aerobic training and were encouraged to exercise up to an additional 3 h/d. Participants prepared their own food and were free to eat as desired, but were advised to avoid fats, sugars, and processed grains and consume a calorie restricted diet consisting of low-fat sources of protein and dairy, fresh fruits, and vegetables. Participants were instructed to aim for a calorie ratio of protein:carbohydrate:fat of 30:45:25 and advised to consume greater than 70% of their estimated baseline RMR (16). The study was approved by the Institutional Review Board of Cedars Sinai Medical Center (#8967) and the Pennington Biomedical Research Center.

Measurements

Body composition was determined by dual energy x-ray absorptiometry (iDXA; GE Lunar, Madison, WI) and FFM and fat mass (FM) were calculated from weight and whole-body percent fat using the thick scan mode. All participants' supine body width exceeded the dimensions of the scan window and were analyzed using the iDXA MirrorImage^{TM} application (17). RMR was measured using indirect calorimetry (BLC: Max II metabolic cart, AEI Technologies, Naperville, FL; RYGB: Medgraphics Ultima metabolic cart, Medical Graphics Corporation, St. Paul, MN and TrueOne metabolic cart, ParvoMedics, Sandy, UT). Following a 12-h fast, participants rested supine in a quiet, darkened room for 30 minutes before measurements of VO_2 and VCO_2 for 20 minutes with the last 15 minutes used to determine RMR. Body composition and RMR were also measured in nine of the RYGB patients at 6 months postoperatively.

Biochemical assays

Blood samples from overnight fasted BLC participants were analyzed by a commercial laboratory (West Coast Clinical Laboratories, Van Nuys, CA). The chemistry panel was measured on a Beckman Synchron CX5CE or CX9PRO. Insulin was determined by radioimmunoassay, and leptin and adiponectin concentrations were measured using a commercially available kit (Millipore, St. Charles, MO). Analysis of overnight fasted blood samples from RYGB subjects was performed at Vanderbilt University Medical Center. Glucose was measured at the bedside using the glucose oxidase method

(Beckman Glucose Analyzer, Fullerton, CA). Insulin and leptin were determined by radioimmunoassay and adiponectin by multiplex immunoassay (Millipore, St. Charles, MO). Triglycerides, total HDL and LDL cholesterol were assayed with ACE reagents and instrumentation (Alfa Wassermann, Caldwell, NJ). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) using fasting measurements of glucose and insulin (18). In both BLC and RYGB samples, thyroid panel (T3, T4, TSH) was measured by immunoassay with chemiluminescent detection (Millipore Corporation, Billerica, MA). Samples from only nine of the 13 pairs were available for analysis because of a lack of sufficient sample for 4 RGYB participants.

Statistical analysis

Data are expressed as mean ± SD. Analyses were performed using Intercooled Stata version 10.0 (Stata Corp, LP, College Station, TX). BLC and RYGB subjects were retrospectively matched on the basis of sex, baseline body weight, BMI, and age using the statistical software command "optmatch2" which creates sets of subjects with the smallest possible dissimilarities. Linear regression analysis was used to generate an equation for RMR using baseline data from all BLC ($n = 16$) and RYGB ($n = 26$) subjects. The independent variables for the regression analysis were FFM, FM, age, and group. The group term was included because different metabolic carts were used at each site resulting in an environment consistent within groups but different between groups.

At follow-up, differences between the measured and predicted RMR defined the magnitude of metabolic adaptation which was considered to be present if the RMR residuals were significantly different from zero (15). Associations between the degree of metabolic adaptation, energy imbalance, percent change in leptin, average rate of weight loss, and thyroid hormones were examined and the Bonferroni correction was used to adjust for multiple comparisons. The average degree of energy imbalance was calculated from the measured rates of change of FM and FFM along with their respective energy densities of 9.4 and 1.2 kcal/g (19). Statistical analysis of 6-month RYGB data in comparison to baseline and 12 months was limited to data from the same nine RYGB patients at all time points.

Results

Study participants

Twenty-two female and four male RYGB patients had complete data at baseline and 12 months with an age range of 27-58 years (43 ± 10 y), a mean BMI of 46.9 ± 7.1 kg/m^2 and a mean body weight of 130.6 ± 23.6 kg, half of which was fat (50 ± 5 %). The BLC participants were nine women and seven men ranging in age from 20 to 56 years (33 ± 10 y) and, similar to the RYGB cohort, they were Class III obese at baseline with a mean BMI of 49.4 ± 9.4 kg/m^2 and body weight of 149.2 ± 38.0 kg, of which nearly half was fat (49 ± 5 %). Software-aided matching of the two cohorts for sex, body weight, BMI, and age resulted in 13 pairs of subjects (nine women, four men) with similar baseline body weight (BLC: 140 ± 36 kg, RYGB: 135 ± 28 kg, $P = 0.68$), BMI (BLC: 47.6 ± 9.5 kg/m^2, RYGB: 47.0 ± 7.6 kg/m^2, $P = 0.87$), and age (BLC: 32 ± 11 y, RYGB: 39 ± 9 y, $P = 0.14$) (Table 1). There were no significant differences in body weight, BMI, or age, at baseline between RYGB subjects with or without 6 month data (18 with/8 without).

TABLE 1 Anthropometric and energy metabolism measurements in 13 pair-matched BLC and RYGB subjects

	BLC		RYGB		
	Baseline $n = 13$	7 months $n = 13$	Baseline $n = 13$	6 months[a] $n = 9$	12 months $n = 13$
Age (y)	32 ± 11		39 ± 9		
Body weight (kg)	139.6 ± 35.6	90.8 ± 25.4[c]	135.0 ± 28.0	106.6 ± 25.3[c]	94.9 ± 21.6[c, i]
Body weight change (kg)		−48.8 ± 14.9		−35.6 ± 8.7[e]	−40.2 ± 12.7[i]
Percent weight change		−35.0% ± 7.1%		−25.2% ± 4.6%[e]	−29.6% ± 7.0%[i]
BMI (kg/m^2)	47.6 ± 9.5	30.9 ± 6.8[c]	47.0 ± 7.6	36.3 ± 7.3[c]	33.0 ± 6.4[c, i]
Fat-free mass (kg)	70.4 ± 18.6	62.4 ± 15.9[c]	69.8 ± 16.5	63.8 ± 16.9[c]	58.3 ± 15.6[c, i]
Fat mass (kg)	69.2 ± 20.9	28.5 ± 14.4[c]	65.3 ± 17.1	42.8 ± 15.2[c, f]	36.6 ± 12.6[c, i]
Percent body fat	49.5% ± 5.6%	30.4% ± 9.5%[c]	48.3% ± 6.6%	39.9% ± 9.6%[c, f]	38.4% ± 9.7%[c, f, i]
Weight loss proportion:					
Fat-free mass		16.4% ± 8.1%		29.2% ± 13.5%[f]	29.6% ± 11.9%[e]
Fat mass		83.6% ± 8.1%		70.8% ± 13.5%[f]	70.4% ± 11.9%[e]
Average energy imbalance (kcal/d)		−1848 ± 584		−1382 ± 436[f]	−779 ± 285[e, i]
RMR measured (kcal/d)	2474 ± 477	1857 ± 463[c]	2128 ± 291[g]	1754 ± 377[c]	1832 ± 196[c]
RMR predicted (kcal/d)[b]	2564 ± 408	2275 ± 330[c]	2142 ± 353[g]	1955 ± 351[c]	1824 ± 320[c, e, i]
Metabolic adaptation (kcal/d)		−419 ± 169[h]		−201 ± 182[f, h]	8 ± 191[f]

Data are presented as mean ± SD.
[a]Statistical analysis of 6-month RYGB data in comparison to baseline or 12-month RYGB data are limited to same nine subjects at all time points; statistical analysis of 6-month RYGB data in comparison to 7-month BLC data are limited to within the nine pairs.
[b]Predicted RMR was calculated from the best-fit linear regression to baseline data ($R^2 = 0.80$):
RMR$_{predict}$= 1026 kcal/d + FFM×19.8 kcal/kg/d + FM×3.1 kcal/kg/d − age×2.3 kcal/y/d - group×381 kcal/d.
[c]Denotes a significant difference from the within-group baseline, $P < 0.01$.
[d]Denotes a significant difference from the within-group baseline, $P < 0.05$.
[e]Denotes a significant difference from BLC 7-month, $P < 0.01$.
[f]Denotes a significant difference from BLC 7-month, $P < 0.05$.
[g]Denotes a significant difference from BLC baseline, $P < 0.05$.
[h]Denotes a metabolic adaptation significantly different from zero, $P < 0.01$.
[i]Denotes a significant difference from RYGB 6-month, $P < 0.01$.

Body weight and composition

BLC participants lost weight more rapidly than RYGB patients. At 7 months, BLC participants lost an average of 48.8 ± 14.9 kg whereas RYGB patients did not achieve a similar amount of weight loss until 12 months after surgery (40.2 ± 12.7 kg, $P = 0.14$). At 6 months RYGB patients lost 35.6 ± 8.7 kg, of which 29.2 ± 13.5 % was from loss of FFM. For RYGB patients with data at both 6 and 12 months, weight loss at 6 months was significantly less than at 12 months (35.6 ± 8.7 kg vs. 44.3 ± 11.7 kg, $P < 0.005$). Despite similar weight loss at 7 months for BLC compared with 12 months for RYGB, the BLC subjects demonstrated a relative preservation of FFM with only 16.4 ± 8.1% of their weight loss from FFM. In contrast, the FFM proportion of weight loss in the RYGB patients at 12 months was 29.6 ± 11.9% and was significantly greater than BLC participants ($P < 0.01$) (Table 1 and Figure 1).

Resting metabolic rate

At the end of the study, metabolic rate was suppressed to a greater degree in BLC participants compared to RYGB patients despite similar amounts of weight loss. In BLC, measured RMR was reduced by over 600 kcal/d ($P < 0.001$), whereas it decreased by ∼300 kcal/d ($P < 0.001$) in RYGB patients (Table 1). In RYGB patients with 6 and 12 month data, average RMR decreased significantly from baseline to 6 months (2194 ± 307 kcal/d to 1754 ± 377 kcal/d,

$P < 0.005$), and was maintained at 12 months despite continued weight loss (1872 ± 211 kcal/d, $P = 0.12$).

To investigate how much of the observed suppression in metabolic rate could be accounted for by body composition change, we used
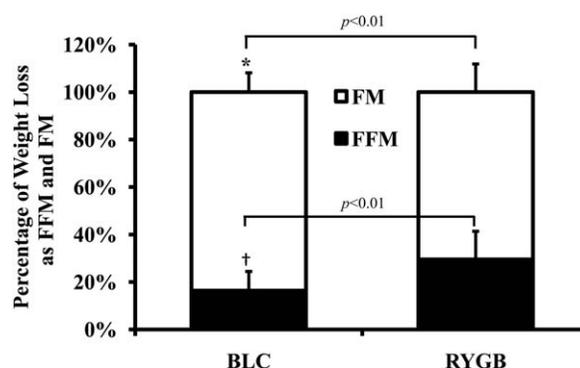
Figure 1 Percentage of total weight loss from fat mass (FM) and fat-free mass (FFM) in 13 pair-matched BLC and RYGB participants (mean ± SD). *$P < 0.01$, BLC percentage of total weight loss from FM significantly different from RYGB. †$P < 0.01$, BLC percentage of total weight loss from FFM significantly different from RYGB.
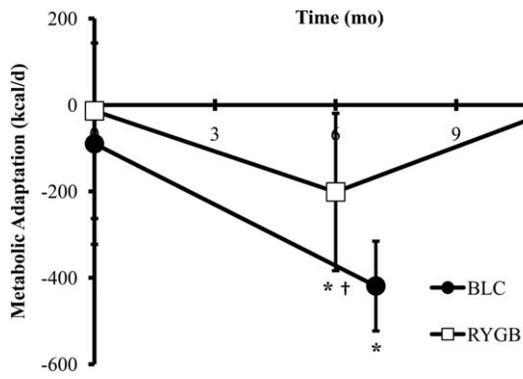
Figure 2 Metabolic adaptation (measured minus predicted RMR) in BLC (•) at baseline and 7 months; and in RYGB (□) at baseline ($n = 13$), 6 months ($n = 9$), and 12 months ($n = 13$) (mean ± SD). *$P < 0.01$, metabolic adaptation significantly different from zero. †$P < 0.05$, compared with BLC 7 month.

the baseline RMR data to generate a prediction equation as a function of FFM, FM, age, and group (Table 1). The residual between the measured and predicted RMR defined the degree of metabolic adaptation. The predicted average RMR in BLC participants at 7 months was 2275 ± 330 kcal/d which was 419 ± 169 kcal/d more than measured ($P < 0.001$), indicating that significant metabolic adaptation was present at the end of the weight loss period. In RYGB patients, there was a greater than expected decrease in RMR of 201 ± 182 kcal/d ($P < 0.05$) at 6 months; however, at 12 months there was no significant difference between measured and predicted RMR (8 ± 191 kcal/d, $P = 0.89$). Therefore, metabolic adaptation had dissipated in the RYGB patients at 12 months despite a similar amount of weight loss compared with BLC participants at 7 months (Figure 2).

The average energy imbalance was significantly greater in BLC compared to RYGB (Table 1) and was positively associated with the degree of metabolic adaptation in combined BLC and RYGB at the end of the study ($r = 0.64$, $P = 0.003$). The degree of metabolic adaptation also correlated with the average rate of weight loss ($r = 0.61$, $P = 0.006$). Furthermore, the percent change in circulating leptin at the end of the study was found to be positively associated with metabolic adaptation ($r = 0.61$, $P = 0.006$). While the observed changes in leptin may have been greater than expected based on the observed body composition changes, we found no evidence that the residual leptin changes were correlated with metabolic adaptation (data not shown). The correlations between metabolic adaptation and energy imbalance ($r = 0.55$, $P = 0.004$ (Figure 3A), rate of weight loss ($r = 0.53$, $P = 0.007$), and change in leptin ($r = 0.47$, $P = 0.03$) (Figure 3B) persisted when including RYGB data at 6 months.

Cardio-metabolic profile

Both interventions resulted in similar improvements in insulin sensitivity and cardio-metabolic profile despite some differences at baseline (Table 2). Fasting glucose concentration was similar between BLC and RYGB at baseline, but fasting insulin concentration was lower in the BLC group. Together, this resulted in a significantly lower calculated HOMA-IR in BLC compared to RYGB, indicating that BLC participants were more insulin sensitive at baseline. Fast-

ing glucose and insulin decreased with weight loss to within the normal range in both BLC and RYGB, although the final mean concentrations were lower in BLC than in RYGB (Table 2). As a consequence, both BLC and RYGB demonstrated improved insulin sensitivity as HOMA-IR decreased by over 50% in both groups. Blood pressure was similar between BLC and RYGB at baseline and significantly decreased with weight loss in BLC, with a trend towards improved systolic pressure in RYGB ($P = 0.08$).

Triglycerides, adiponectin, and C-peptide concentrations were lower in BLC than RYGB at baseline; however, cholesterol, HDL, LDL, and leptin were similar (Table 2). While circulating triglycerides decreased significantly with weight loss in both groups, total cholesterol tended to increase in BLC and consisted of increases in both HDL and LDL components. In RYGB, total cholesterol decreased mainly as a result of lower LDL. As expected with weight loss, leptin decreased significantly in both BLC and RYGB, but the decrease was greater in BLC with the final leptin concentration being 80% lower in BLC compared to RYGB despite similar FM. Thyroid profile was measured in nine pairs of subjects and was similar at baseline between BLC and RYGB. Triiodothyronine (T3) significantly decreased in BLC after weight loss but not in RYGB. The change in T_3 concentration after weight loss in the combined group was positively associated with the average negative energy balance ($r = 0.84$, $P < 0.001$) and rate of weight loss ($r = 0.78$, $P < 0.01$), but in contrast to our hypothesis there was no significant association between changes in T_3 and metabolic adaptation ($r = 0.58$, $P = 0.41$). No
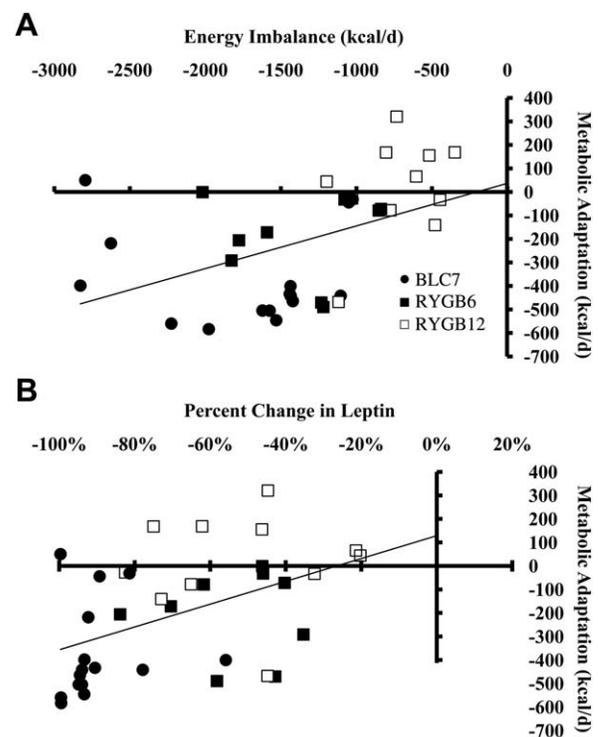
Figure 3 Correlation between metabolic adaptation and (**A**) average energy imbalance ($r = 0.55$, $P = 0.004$) and (**B**) percent decrease in circulating leptin ($r = 0.47$, $P = 0.02$) in BLC at 7 months (•) and RYGB at 6 months (■) and 12 months (□). Linear correlations were calculated for all data combined.

TABLE 2 Biochemical and blood pressure measurements in 13 pair-matched BLC and RYGB participants

	BLC ($n = 13$)		RYGB ($n = 13$)	
	Baseline	7 Months	Baseline	12 Months
Glucose (mg/dL)	97 ± 17	78 ± 5[b]	113 ± 42	88 ± 9[c, c]
Insulin (μU/mL)	8.0 ± 7.5	4.2 ± 1.9	25.5 ± 11.9[a]	9.2 ± 3.9[b, c]
HOMA-IR	2.0 ± 2.1	0.8 ± 0.3	8.1 ± 8.6[b]	2.0 ± 1.0[c, c]
Leptin (ng/mL)	45.2 ± 18.4	3.2 ± 2.4[b]	36.8 ± 13.4	16.4 ± 10.5[b, c]
Adiponectin (μg/mL)	2.9 ± 1.1	4.8 ± 1.7[b]	8.1 ± 5.5[a]	14.7 ± 8.0[b, c]
C-Peptide (ng/mL)	2.5 ± 1.3	1.4 ± 1.0[c]	4.2 ± 1.1[a]	2.0 ± 0.3
Triglyceride (mg/dL)	116 ± 82	58 ± 24[b]	175 ± 59[b]	96 ± 36[b, d]
Cholesterol (mg/dL)	168 ± 40	192 ± 48	192 ± 29[b]	155 ± 23[b, d]
HDL (mg/dL)	44 ± 18	53 ± 14[c]	44 ± 11	47 ± 9
LDL (mg/dL)	100 ± 28	127 ± 41	113 ± 26	89 ± 20[c, d]
Thyroid profile ($n = 9$ pairs)				
Triiodothyronine (T3; nmol/L)	1.30 ± 0.29	0.74 ± 0.16[b]	1.64 ± 0.41	1.53 ± 0.23[c]
Thyroxin (T4; nmol/L)	90.6 ± 18.5	82.3 ± 17.5	81.4 ± 9.4	82.2 ± 9.0
Thyroid stimulating hormone (TSH; mIU/L)	1.3 ± 1.0	1.1 ± 0.8	0.7 ± 0.5	0.7 ± 0.7
Systolic BP (mm Hg)	132 ± 8	118 ± 11[b]	132 ± 18	122 ± 13
Diastolic BP (mm Hg)	82 ± 8	72 ± 10[b]	78 ± 13	75 ± 12

Data are presented as mean ± SD.
[a]$P < 0.01$, $P < 0.05$—denotes significant difference from BLC baseline.
[b]$P < 0.01$, $P < 0.05$—denotes significant difference from respective baseline.
[c]$p < 0.01$, $p < 0.05$—denotes significant difference from BLC 7 month.
HOMA-IR: homeostatic model assessment-estimated insulin resistance.

significant changes occurred in thyroxin and thyroid stimulating hormone in BLC or RYGB after weight loss.

Discussion

We observed similarly massive weight loss in both BLC participants and RYGB patients over 7 and 12 months, respectively. On average, both groups lost in excess of 30% of their initial weight with a corresponding resolution of their Class III obesity and significant improvements in cardio-metabolic profile. Insulin sensitivity doubled, circulating triglycerides were cut in half, and blood pressure tended to decrease in both groups.

An important objective during weight loss is to reduce body fat while minimizing loss of FFM to maintain optimal metabolic and physical functioning. Limited data suggest that adding exercise to a weight loss program may help spare FFM, but most previous studies have investigated only modest weight loss (20-22). Here, we demonstrated that in the context of rapid and massive weight loss, BLC participants preserved their FFM with only 16% of total weight loss from FFM compared with 30% in matched RYGB patients who lost a similar amount of weight. The BLC participants were advised to consume a diet comprising 30% of energy from protein, and, given their energy intake of ∼1600 kcal/d over the course of the intervention (23), they may have consumed more protein than was recommended to the RYGB group (about 120 vs. 70 g/d, respectively). Therefore, increased dietary protein may have contributed to the relative maintenance of FFM in BLC vs. RYGB. Furthermore, the BLC participants were more insulin sensitive at baseline which may have played a role in preserving FFM. However, the vigorous exercise program likely played a predominant role in preserving FFM in BLC participants because of skeletal muscle hypertrophy (24). Thus, substantial losses of FFM are not a necessary consequence of rapid massive weight loss. Whether incorporating a resistance exercise program or an increase in dietary protein following gastric bypass would result in similar preservation of FFM is a subject worthy of future investigation.

Since FFM comprises the metabolically active lean tissues of the body (13), its relative preservation in BLC participants would be expected to result in better maintenance of RMR compared with RYGB patients (22). However, despite the substantial differences in FFM loss between the groups, RMR decreased to a greater degree in BLC versus RYGB. Furthermore, both groups exhibited a reduction in RMR out of proportion to the decrease in FFM and FM indicating significant metabolic adaptation to weight loss, although metabolic adaptation in RYGB patients only occurred at month 6 during active weight loss.

The mechanisms underlying metabolic adaptation are not clear, but it has been speculated to involve decreases in circulating leptin and thyroid hormones in association with blunted activity of the sympathetic nervous system (25-30). In support of this concept, we found that the degree of metabolic adaptation was correlated with the change in leptin as well as the degree of average energy deficit in our subjects. Note that the observed FM changes were included within the RMR prediction model. Therefore, the relationship between changes in leptin and metabolic adaptation was beyond the expected effect of FM loss on RMR. Emerging data suggests that replacement of circulating leptin to pre-weight loss levels reverses metabolic adaptation, perhaps through alterations in mitochondrial

content and/or coupling (31,32), and maintenance of thyroid hormone concentrations (28,33).

Another possible explanation for the increased metabolic adaptation in BLC participants may be because of the nature of the weight loss competition with significantly decreased energy intake and increased exercise in the days leading up to the final measurements. Such an acute negative energy balance may have led to transient additional suppression of circulating leptin, sympathetic drive, and thyroid function (27,29,34). Some evidence of this possibility includes the larger decrease in leptin in comparison to RYGB and the rise in circulating cholesterol which has been observed following acute starvation (35,36). In contrast, it is likely that RYGB subjects may have been in a state of approximate energy balance at 12 months when metabolic adaptation had dissipated.

Limitations of this study include the differing rates of weight loss in the BLC and RYGB groups and the lack of a weight loss maintenance phase to investigate the subjects in a state of energy balance. Furthermore, the physical activity status of RYGB subjects was not measured, but we believe that their exercise levels were likely substantially lower than BLC subjects. While persistent weight loss is a hallmark of bariatric surgery, significant weight regain is sometimes observed following gastric bypass (37) which has been related to reduced RMR (14). Metabolic adaptation may therefore predispose individuals to weight regain, and BLC participants exhibited a greater metabolic adaptation at 7 months compared to RYGB subjects at 12 months despite similar weight loss. However, the magnitude of the energy deficit is likely a main driver of metabolic adaptation, as predicted by mathematical models of human metabolism (23,38). Therefore, the metabolic adaptation in BLC participants would be expected to be greatly attenuated during a weight loss maintenance phase when energy balance is achieved. Indeed, we found that RYGB subjects had no metabolic adaptation at 12 months when their energy imbalance was greatly reduced in comparison to 6 months after surgery.

Despite our attempts to retrospectively match subjects, there were significant differences in several baseline circulating hormones, biochemical, and metabolic measurements, possibly because of different assays and equipment used, which may have confounded our interpretation of the differences between the groups. While it would be highly desirable to prospectively match subjects undergoing RYGB and BLC interventions, the opportunistic nature of studying the latter intervention makes this difficult.

An advantage of the intensive lifestyle intervention is that BLC participants had greatly improved physical fitness and were fully capable of maintaining the levels of physical activity characteristic of successful weight loss maintenance (23,39). In contrast, success in achieving a sustained reduction in energy intake and thereby maintaining weight loss in RYGB is likely the result of alterations in appetite, satiety, and food reward systems (40).

In conclusion, we found that an intensive lifestyle intervention consisting of daily vigorous exercise plus self-selected dietary restriction resulted in massive weight loss of similar magnitude to a matched group of subjects following gastric bypass surgery. Both groups showed significant improvements in cardio-metabolic profile and a resolution of Class III obesity. Unlike RYGB patients who lost a substantial amount of FFM, BLC participants partially preserved FFM despite rapid weight loss. However, FFM preservation

did not attenuate the reduction of metabolic rate and both groups demonstrated a significant metabolic adaptation to weight loss that was correlated with the energy deficit and changes in leptin. O

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