The threshold shift paradigm of obesity: evidence from surgically induced weight loss1–3

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ABSTRACT
Background: The high prevalence of obesity has called attention to the near-intractable problem of sustained weight reduction and its underlying mechanisms. With diet-induced weight loss, achieved body weight is closely related to initial body weight. Objective: The objective was to compare the relation between initial and achieved body mass index (BMI) in patients treated with diet-induced weight loss or bariatric surgery. Design: We analyzed data from a cohort of 223 healthy individuals who lost a mean (±SD) of 5 ± 3 kg body weight over 3 y by diet (diet group) and data from 182 obese individuals [BMI (in kg/m²) ≥5] who had lost an average of 47 ± 17 kg 1 y after Roux-en-Y gastric bypass (a restrictive procedure; n = 71) or biliopancreatic diversion (a malabsorptive procedure; n = 111) (surgery group). Results: In the diet group, final BMI was strongly related to initial BMI (r = 0.96, P < 0.0001). By multivariate analysis, the decrease in BMI at 3 y was age independent and was predicted only by initial BMI and sex (both P < 0.0001). Strikingly, final BMI was also strongly related to initial BMI (r = 0.67, P < 0.0001) in the surgery group, irrespective of the type of operation. The surgically induced decrease in BMI was predicted by age (P = 0.0002) and initial BMI (P < 0.0001). In 110 surgery patients, serum leptin concentrations decreased from 39 ± 16 to 10 ± 5 mg/mL after surgery (P < 0.0001) and were correlated with BMI both before and after surgery, but the slope of the relation was significantly (P < 0.01) flatter after surgery. Conclusion: The strong predictivity of initial BMI for achieved BMI observed even when voluntary control of energy intake is interfered with through diverse anatomical rearrangements of the gastrointestinal tract supports the concept of a weight “threshold” paradigm: in the obese, anabolic responses are triggered by adiposity-related signals at a higher threshold, which leads to defense of a higher body weight. Am J Clin Nutr 2014;100:996–1002.

INTRODUCTION
The current increase in prevalence of obesity has focused attention on the near-intractable problem of sustained weight reduction. Most obese or overweight people can lose weight by restricting caloric intake, but the great majority of them regain the lost weight in the longer term (typically, 12–24 mo later) (1–3). In this context, weight cycling is common (4). A growing body of evidence supports the existence of physiologic mechanisms that defend body fat and subvert efforts to maintain a reduced body weight (5–12). More specifically, attempts to sustain weight loss result in a persistent hypometabolic and hyperphagic state (8), thus creating optimal circumstances for weight regain. The hypometabolic state is characterized by declines in resting energy expenditure (EE)4 and activity EE (due to increased contractile efficiency of skeletal muscle) and is augmented by decreased activity of the hypothalamic-pituitary-thyroid axis, decreased sympathetic nervous system tone, and increased parasympathetic tone. The hyperphagia is characterized by delayed satiation, decreased activity in the prefrontal cortex and brain areas involved in food restraint, and increased activity in the orbitofrontal cortex and brain areas involved in food reward (9). Weight-reduced mice will eat more in response to stress than nonweight reduced animals (11).

Subjects undergoing bariatric surgery provide a unique opportunity for further investigation of the physiologic mechanisms that favor regain of lost weight by virtue of the increased likelihood of sustaining some degree of weight loss and the greater reduction in obesity-related comorbidities compared with nonsurgically weight-reduced subjects (13). There are improvements in diabetes (13), cardiovascular disease (14), and mortality (15, 16) associated with surgically induced major weight reduction, which exceed the benefits of diet-induced weight loss (17, 18). Bariatric surgical procedures differ substantially from one another, ranging from predominantly restrictive (eg, gastric bypass) to primarily malabsorptive (eg, biliopancreatic diversion) (19). In somewhat different ways, these operations mitigate volition to

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4 Abbreviations used: BPD, biliopancreatic diversion; EE; energy expenditure; EEFFM, energy expenditure of fat-free mass; EEFM, energy expenditure of fat mass; FFM, fat-free mass; FM, fat mass; FMEn, energy content of fat mass; RISC, Relation Between Insulin Sensitivity and Cardiovascular Disease; RYGB, Roux-en-Y gastric bypass; TDEE, total daily energy expenditure.

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a substantial extent, thereby offering the opportunity to test whether they abrogate defense of attained weight.

In the current study, we took advantage of data obtained in obese patients losing weight by 2 different kinds of bariatric surgery: Roux-en-Y gastric bypass (RYGB) and bilipancreatic diversion (BPD). We hypothesized that the attendant changes in the quality and quantity of available nutrients, gut microbiome, and/or gut anatomy make it easier to sustain weight loss by physically limiting the capacity for hyperphagia and/or the molecular drive to eat (20) and/or by raising the metabolic rate (21) compared with individuals who have undergone spontaneous (dietary) weight loss. We therefore examined cohorts of subjects before and after diet- and surgically induced weight reduction to test whether the method of weight loss (surgical compared with dietary) affects the level of defended body weight.

SUBJECTS AND METHODS

Subjects

We examined 2 cohorts. The first cohort included participants in the Relation Between Insulin Sensitivity and Cardiovascular Disease (RISC) study (22), which is a longitudinal, observational investigation of incident diabetes in healthy subjects of European descent started in 2002. A subgroup of individuals from the RISC study [n = 223: 91 with a BMI (in kg/m²) ≤ 25, 98 with a BMI between 25 and 30, and 34 with a BMI > 30] was selected on the basis of having lost weight over a 3-y follow-up period (mean ± SD: 6 ± 4% of initial body weight); this cutoff was defined as a change in BMI between baseline and 3 y within the lowest quintile of the distribution of BMI changes for the entire RISC cohort (n = 1048) (23). This group is hereafter referred to as the diet group, on the likely assumption that the weight loss was mostly attributable to intentional reductions in caloric intake; weight had been stable for the 8–12 wk preceding the follow-up visit at 3 y. None of these subjects was receiving chronic treatment with drugs, such as β-blockers, which are known to affect EE.

The second cohort included 182 subjects with a BMI ≥ 35, who were referred to the Metabolic Research Center of the Department of Medicine at the University of Pisa for severe obesity and underwent bariatric surgery starting in 2006; these individuals were studied before surgery (baseline) and again at 1 y after surgery. Of these patients, 71 underwent RYGB—a bariatric procedure that combines a large reduction in stomach volume (to ~30 mL) with a bypass of food transit around the duodenum and the proximal jejunum. The other 111 patients underwent BPD—a procedure that combines modest gastric resection with the diversion of bilipancreatic juices from the duodenum into the terminal portion of the ileum (50 cm from the ileocecal valve) (24, 25). This cohort, collectively referred to as the surgery group, consumed an ad libitum diet after surgery and body weight had been stable for the preceding 6–8 wk at the 1-y visit. Those patients with type 2 diabetes before surgery were no longer receiving oral hypoglycemic agents 1 y after surgery, and none was on chronic treatment with drugs known to affect EE.

Measurements and estimates

In the diet group, fat-free mass (FFM) was measured at baseline by electrical bioimpedance on a Tanita scale (22); these measurements correlated very well (r = 0.95, P < 0.0001) with estimates derived from Hall’s model of metabolic adaptation to weight perturbations (see below) in the same subjects. Although electrical bioimpedance has been shown to perform satisfactorily in severe obesity (26), it was not used in our surgery group. For consistency, we therefore employed Hall’s model (27–30) to estimate body composition and EE in both the diet and surgery groups. Hall’s model uses Jackson’s formula (31) to estimate percentage body fat and predictive equations by Mifflin et al (32) to estimate resting EE; the FFM-fat mass (FM) Forbes relation used by the dynamic model was validated from data sets that included nonobese and obese subjects and individuals with surgically induced weight loss (33).

Using the Body Weight Simulator (http://bwsimulator.niddk.nih.gov), for each subject we entered sex, age, height, and estimated physical activity level. In the diet group, physical activity level at baseline and follow-up were estimated with the use of the International Physical Activity Questionnaire, as previously described (34). In the surgery group, physical activity was assumed to be low because morbidly obese individuals typically are sedentary. The simulator generates percentage FM and total daily EE (TDEE; in kcal/d). FMF (in kg) was calculated as the arithmetic difference between whole-body weight and FM. The energy content of FM (FMEFm; in kcal/g) was calculated as FFM × 9.4, and the energy content of FFM (FMEFM) as FFM × 1.8 (27). Whole-body energy content is the sum of FMEFM and FMEf. Tissue-specific EE of FM (EEFM) and FFM (EEFFM) were assumed to be 6.45 and 27.7 kcal · kg⁻¹ · d⁻¹, respectively (30). The sum of EEFM and EEFFM approximates resting EE based on body composition alone. Serum leptin measurements (by radioimmunoassay; Millipore Corporation) obtained at baseline and follow-up were available for 110 patients in the surgery group.

Statistical analysis

Data are reported as means ± SDs or medians (IQRs) for variables with a normal or skewed distribution, respectively. Group comparisons were performed by using the Mann-Whitney U test and Wilcoxon signed-rank test for unpaired and paired data, respectively. Associations were tested by using the Pearson or Spearman method (for normal and skewed distributions, respectively) and were expressed as the r (or ρ) coefficient; multiple regression analysis was carried out by using standard methods. A P value ≤ 0.05 was considered statistically significant; all analyses were carried out by using JMP 7.0 (SAS Institute).

RESULTS

Baseline

The surgery group had a higher proportion of females, was significantly younger, and had significantly higher values for all indexes of body weight and body fatness compared with the diet group (Table 1). In lean subjects in the diet group (BMI ≤ 25, n = 85), the FM-to-FFM ratio was 0.42 ± 0.06 in women and 0.25 ± 0.04 in men. In the surgery group, the FM-to-FFM ratio was higher than in the diet group for both women and men (P < 0.0001); as a consequence, the surgery group had 3 times more calculated energy stored in fat (FMEf) but only ~8% more energy stored in lean tissues (FMEFM) than did the diet group.
Follow-up

Weight loss in the surgery group 1 y after the operation was ~10-fold that in the diet group 3 y after the initial visit (46 ± 17 compared with 5 ± 3 kg) (Table 1). In both groups, absolute and fractional weight loss increased progressively across tertiles of initial BMI—the trend being more pronounced in the surgery group than in the diet group (Figure 1).

In both study groups, plots of final BMI compared with initial BMI were linear (Figure 2). In the diet group, the correlation coefficient of the regression (r) was 0.96 for all subjects, and the intercept and slope were similar in men and women. In the surgery group, the coefficient was lower (r = 0.67) but was still highly statistically significant and similar between the RYGB and BPD groups. Likewise, final body weight correlated with initial body weight in both the diet (r = 0.98, P < 0.0001) and surgery (r = 0.72, P < 0.0001) groups. For BMI, both the intercept and slope of the regression lines were significantly different between the diet and surgery groups (P < 0.0001 for both). For example, an initial BMI of 40 predicted a final BMI of 37.2 in the diet group and 27.5 in the surgery group (Figure 3). In the diet group, in a multivariate regression including baseline BMI, sex, and age as independent predictor variables, the decrease in BMI at follow-up was independent of age and significantly greater in women than in men (by 0.35 ± 0.06, P < 0.0001). In the surgery group, the same multivariate model indicated that the decrease in BMI was negatively related to age (by 1.10 ± 0.30 for every 10 y, P = 0.0002); the effect was comparable in women and men.

Serum leptin concentrations (in the subgroup of surgery patients in whom it was measured) decreased from 39 ± 16 ng/mL before surgery to 10 ± 5 ng/mL after surgery (P < 0.0001). Leptin concentrations correlated with BMI both before and after surgery, but the slope of the relation was significantly (P < 0.01) lower after surgery (Figure 3).

**DISCUSSION**

The major finding of this study was that achieved BMI was strongly related to initial BMI, both in healthy subjects who lost modest amounts of weight (~5 kg) spontaneously and in morbidly obese patients who lost large amounts of weight (~45 kg) after bariatric operations. This was true regardless of whether BMI or other measures of body fatness (body weight, FM, percentage FM) were used.
In the diet group at the 3-y follow-up, heavier individuals had lost more weight than leaner individuals (Figure 1), consistent with data reported in weight-reduction trials (35–39) or observational studies of spontaneous weight loss (40). However, so far as we are aware, previous work has focused attention on changes in body composition and EE, possibly overlooking the simple, model-independent relation of achieved BMI to initial BMI (Figure 2). This close relation enables high predictability of initial body weight for weight loss in subjects under free-living conditions (outperforming more complex predictive models). The well-known underlying principle is that, after imposition of an absolute initial negative energy balance, weight loss will cease when this reduced energy intake equals the EE of the reduced metabolic mass. In other words, subjects losing weight will descend along the TDEE/body weight relation (see Supplemental Figure under “Supplemental data” in the online issue), although resting EE during dynamic weight loss by caloric restriction is lower than the resting EE during weight maintenance at the same weight (10). Here, however, we used this relation to support the notion of defense of attained weight. In fact, whereas precise quantity and time course of the caloric deficit in our diet group were undetermined, it is remarkable that the subjects did not lose more weight than their initial body weight predicted (according to the relation shown elsewhere; see Supplemental Figure under “Supplemental data” in the online issue), such as would have occurred if they had applied further restrictions of caloric intake—in addition to the initial caloric restriction—as the weight was being lost. Instead, for the entire cohort, final body weight was proportional to initial body weight within a very narrow range. Thus, in the longer run (measurements of diet-induced metabolic changes have rarely extended beyond 6–12 mo), the diet group resisted normalization of body weight (eg, a BMI of \( \approx 25 \)). For example, obese diet participants (BMI \( \geq 30 \), \( n = 34 \)) lost 6.4 \( \pm \) 4.3 kg (\( P < 0.0001 \) compared with the 4.3 \( \pm \) 2.6 kg of the nonobese), but none of them reached a BMI of 25 (final BMI was 30.8 \( \pm \) 3.2).

One year after surgery, the surgery group had lost more absolute and fractional amounts of weight than did the diet group. Nonetheless, the significant correlation of achieved BMI to initial BMI, although less tight than in the diet group (Figure 2), was preserved regardless of the type of bariatric operation. This result is particularly impressive if one considers the main mechanism by which a caloric deficit is realized with RYGB compared with that with BPD. With RYGB, caloric intake is estimated to be as low as 600–800 kcal/d early after the operation and to increase to \( \approx 1300 \) kcal/d over the following weeks (41–43). Obviously, if this quantity remained unchanged, all patients would eventually reach approximately the same postoperative lean body mass. Adaptation of feeding behavior occurs in these patients, who with time learn—or are forced by virtue of nausea, abdominal distress, etc—to eat smaller meals more frequently (41–43). Such adaptive responses vary considerably among individuals and do not predict achieved weight (40). Moreover, diet-induced

**FIGURE 1.** Absolute and fractional weight loss by tertile of baseline BMI, from lowest (BMI\(_1\)) to highest (BMI\(_3\)) in the diet and surgery groups. *Significantly different from BMI\(_1\), \( P \leq 0.05 \). Boxes identify medians, 25th and 75th percentiles, and 95% CIs.

**FIGURE 2.** Relation between final and initial BMIs in the diet group (blue line) and in the RYGB or BPD surgery group (red line). The equation of the blue regression line is \( y = 0.68 + 0.91x \) (\( r = 0.96 \)) and that of the red regression line is \( y = 7.22 + 0.51x \) (\( r = 0.67 \)). The dotted lines represent 95% CIs of the slope. BPD, biliopancreatic diversion; RYGB, Roux-en-Y gastric bypass.
weight loss is associated with some metabolic slowing, despite preservation of fat-free mass (44). There appears to be similar metabolic slowing after RYGB (45, 46) and increased postprandial thermogenesis (47, 48). It is therefore all the more impressive that achieved body weight remains directly related to initial body weight.

With BPD, the absorptive limb—where biliopancreatic juices and intestinal contents mix—is the same length in all subjects (50 cm) and would therefore allow absorption of what has been estimated to be a maximum of 1250 kcal/d in every subject (49). Here again, however, adaptation in dietary habits, such as avoidance of fatty foods to prevent steatorrhea (50), hypertrophy of ileal mucosa (51), and other less well-defined mechanisms (52–54), coordinately raise net caloric absorption to a value that ends up being largely a function of the initial degree of obesity (as depicted in Figure 2). Thus, even when voluntary control of energy intake is bypassed through diverse anatomical rearrangements of food transit and digestion, achieved body weight remains proportional to initial body weight.

In the diet group, reversion toward an initial body weight that had been established and maintained for a relatively long period of time could have been due to the persistence of environmental factors compounded by a degree of metabolic slowing (44). In the surgery group, the imposed changes in gut anatomy and physiology and variable increments in EE through physical activity (21) might have blunted the relation between final and initial body weights. However, the persisting dependence of attained weight on starting weight under such diverse conditions as spontaneous dieting and surgical intervention bespeaks a fundamental weight on starting weight under such diverse conditions as spontaneous dieting and surgical intervention bespeaks a fundamental physiologic phenomenon. As previously suggested (12), a “threshold” model of weight regulation fits these observations. In this formulation (Figure 4), weight loss generates adiposity-related signals (eg, leptin, insulin, other hormones, and neurotransmitters) (55) that trigger an anabolic response (eg, increased appetite and reduced EE). However, the relation of such signals to anabolic response is asymmetrical: when signal intensity falls below the threshold (a lower “set point” for adiposity), the anabolic response increases sharply, whereas suppression of the anabolic response induced by weight gain is weaker. In chronic overweight/obesity, the threshold is progressively shifted to the right, causing the steep phase of the anabolic response to weight loss to be triggered at higher signal (adiposity) levels (56). Consistent with this formulation, circulating leptin concentrations during the phase of active weight loss are lower than predicted by the loss of adipose mass, thereby predisposing to weight regain (9). That is, hypometabolism and hyperphagia may be induced very early during weight loss, partially as a result of a precipitous drop in circulating leptin concentrations. In our surgery group, 1 y after surgery, serum leptin was lower than predicted by their new body weight/adiposity (Figure 3), which suggests that they were still in negative energy balance. This model is consistent with the minimal response of obese or nonobese individuals to high doses of leptin (57), which had no effect on body weight in women 18 mo after gastric bypass (58) but may be helpful in maintaining reduced weight in postobese individuals (59). The brain pathways involved in the general process of defense of achieved body weight (60–62) may involve a gut-brain link activated by bariatric surgery.

In summary, the finding of a direct, linear dependence of attained body weight on initial body weight in a large number of patients subjected to dietary and surgical interventions that alter caloric availability in different ways supports the notion that the energy homeostasis system is inherently biased toward maintenance of achieved body weight.

The authors’ responsibilities were as follows—EF: designed and conducted the research; and EF, MR, and RLL: analyzed the data and wrote the manuscript. All authors read and approved the final manuscript. None of the authors had any duality of interest to disclose.

REFERENCES


