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RYGB produces more sustained body weight loss and improvement of glycemic control compared with VSG in the diet-induced obese mouse model

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Abstract

Objective—To compare the effects of murine models of vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) surgery on body weight, body composition, food intake, energy expenditure, and glycemic control.

Background—Weight regain and type-2 diabetes relapse has been reported in a significant proportion of VSG patients in some studies, but definitive conclusions regarding the long-term comparative effectiveness of VSG and RYGB are lacking both in humans and rodent models.

Methods—VSG, RYGB, and sham surgery was performed in high-fat diet-induced obese mice and the effects on body weight and glycemic control were observed for a period of 12 weeks.

Results—After the initial weight loss, VSG mice regained significant amounts of body weight and fat mass that were only marginally lower than in sham-operated mice. In contrast, RYGB produced sustained loss of body weight and fat mass up to 12 weeks, and drastically improved fasting insulin and HOMA-IR compared with sham-operated mice. Using weight-matched control groups we also found that the adaptive hypometabolic response to weight loss was blunted by both VSG and RYGB, and that despite large weight/fat regain, fasting insulin and HOMA-IR were markedly improved, but not reversed, in VSG mice.

Conclusions—VSG is less effective to lastingly suppress body weight and improve glycemic control compared with RYGB in mice. Given similar observations in many human studies, the run towards replacing RYGB with VSG is premature and should await carefully controlled randomized long term trials with VSG and RYGB.

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Conflict of Interest Statement

None of the authors has any conflict of interest.

Statement of Animal Rights

Animal care and experimentation was approved by the Pennington Biomedical Research Center Institutional Animal Care and Use Committee and strictly followed rules and guidelines provided by the American Physiological Society and NIH.

Keywords

Bariatric surgery; body composition; food intake; fasting insulin; weight regain; energy expenditure; metabolic adaptation

Introduction

Bariatric surgeries produce substantial and sustained body weight loss and improve glycemic control in patients with obesity and type 2 diabetes. [1–3]. Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) are currently the most commonly performed bariatric surgeries with the latter rapidly gaining in popularity (for example [4, 5]).

Direct comparisons of these two surgeries show that RYGB is slightly more effective in reducing body weight and improving glycemic control than VSG, but that both surgeries are clearly superior to intensive medical treatment or behavioral lifestyle interventions [6, 7]. However, a common problem with such studies, particularly VSG, is that they are relatively short-term, rarely looking beyond 3 years after surgery [7–15].

With surgeries performed in increasingly younger patients, follow-up for much longer periods is imperative. In a recent longer-term study with predominantly male patients, weight loss at 4 years after RYGB surgery was significantly greater than after VSG (27.5 vs. 17.8%) [16]. Furthermore, only about half of 53 obese patients undergoing VSG had a significantly sustained total weight loss at 10 years, while roughly the other half had significant weight regain of more than 15kg from nadir at 1–3 years. About a third of the patients were converted into RYGB after 3 years due to significant weight regain [17].

Although it is unclear what causes weight regain after bariatric surgery, some of the outcome variability may be related to differences in psychological and dietary counseling and actual dietary habits after surgery. On the one hand, the effects of counselling and the resulting changes in eating behavior could be a major driver of metabolic improvements, independent of surgery [18]. On the other hand, non-compliance with behavioral and dietary instructions could be driving weight regain. Because of these confounding influences on the overall outcome of bariatric surgeries in humans, modeling in rodents and other animals has become an important tool.

While RYGB in diet-induced mice generally produces the same sustained decrease in body weight from pre-surgical obese levels [19–22], VSG in mice reduces body weight only initially, which then climbs back to pre-surgical levels and above within 6–14 weeks [23–25]. Although, body weight after VSG is significantly lower than in sham-operated mice, it is not lower than before surgery. These differences between RYGB and VSG outcome could be due to different experimental conditions and procedures in different laboratories, and there have been no direct comparisons in the same laboratory.

The goal of this study was to directly compare RYGB and VSG in their ability to produce long-term changes in body weight, body composition, food intake, energy expenditure, and glycemic control in mice under the same experimental conditions in the same laboratory.

Methods

Animals

Male high-fat diet-induced obese and regular chow-fed control C57BL6J mice were purchased from Jackson Laboratories at the age of 14–16 weeks. Upon arrival at the Pennington Biomedical Research Center, they were continued on either a two-choice diet consisting of high-fat diet (60% fat, Research Diets #D12492) and regular chow (13% fat; Purina 5001) or regular chow throughout the duration of the study. All mice were initially group housed in shoe box cages with corn cob bedding. Ten days before surgery, they were single-housed on grid floors for the measurement of food intake. Animals were kept under standard laboratory conditions with a room temperature of 21–23°C and a 12h light-dark cycle (lights on at 7:00).

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Experimental Overview

A total of 52 diet-induced obese mice and 8 chow-fed lean mice were used in 3 separate cohorts. After 12–14 weeks on high-fat diet (HFD), at an age of 20–21 weeks, obese mice were assigned to one of 6 groups, VSG ($n = 12$), VSG weight matched ($n = 8$), RYGB ($n = 11$), RYGB weight matched ($n = 9$), and sham surgery (Sham, $n = 12$) based on their body weight and fat mass. The weight matched groups were calorically restricted to match the average body weight of either VSG or RYGB animals and did not undergo any surgical procedures. The sham surgery consisted of anesthesia, laparotomy, and re-closing. All groups were fed a two-choice diet consisting of HFD (60% fat) and regular chow (13% fat) pellets for the duration of the study, except for the time in the metabolic chambers (days 10–24 and 54–69 after surgery) during which they received only HFD. An additional age-matched control group ($n = 8$) was fed only regular chow and was not subjected to any surgery. Except for the time in the metabolic chambers, no other tests or invasive procedures that could perturb body weight were conducted. At the end of the observation period, blood plasma and tissues were harvested for biochemical and histological analyses.

Surgery

VSG: Mice were anesthetized with inhalation anesthesia (1% isoflurane) and midline laparotomy was performed. The stomach was freed by cutting the perigastric ligaments (Fig. S1 A). All of the branches of the gastroepiploic vessels were carefully ligated and cut close to the greater curvature of stomach (Fig. S1 B). An incision was made on the greater curvature and all stomach content was removed. A custom stainless steel clamp was applied from the fundus to below the pylorus to outline the gastric sleeve (Fig. S1 C). A second clamp was applied immediately below the first one to create a free margin for suturing. The stomach was transected below the second clamp and about 80% of the stomach was removed (Fig. S1 D). The second clamp was removed and the edge was closed using whole layer interrupted 11-0 nylon suture (Fig. S1 E, F). The first clamp was then removed, and the first suture layer was inverted into the stomach lumen. A second layer of 11-0 nylon suture was

then made using an interrupted seromuscular pattern (Fig. S1 G, H), completing the gastric sleeve. The abdominal wall was closed using interrupted 11-0 nylon suture for the muscular layer and 5-0 for the skin. Animals promptly emerged from anesthesia and were returned to their home cage, which was placed on a regulated heating blanket for the first night. Additional analgesia was given as necessary, and all animals were placed back on ad-lib two-choice diet the following morning. The optimal size of the sleeve that would not lead to obstruction and complications was determined in pilot experiments.

RYGB: Details of our RYGB surgical procedure were reported previously [26]. Briefly, it consisted of a very small gastric pouch, a 5–6 cm long Roux-limb, a 4–5 cm long biliopancreatic limb, and a 10–12 cm long common limb.

Measurement of food intake and choice

Food intake was measured to the nearest 0.1 g daily between 10:00 and 12:00 h, throughout the duration of the study, by subtracting the amount of high-fat and chow diet recovered from the amount weighed in, corrected for spillage found under the grid floor (distinguishable by the blue color of high-fat crumbs). Metabolizable energy was calculated as 5.24 kcal/g for high-fat and 2.91 kcal/g for chow. Chow preference was calculated as the percentage of total caloric intake obtained from chow diet. Animals in the weight matched groups were given 93–97% of total restricted calories as high-fat and 3–7% as regular chow, based on the observed preference of mice from the paired surgical group.

Measurement of body weight and body composition

Body weight was measured daily between 10:00 and 12:00 h to the nearest 0.1 g throughout the duration of the study. Body composition was measured to the nearest 0.1 g with whole body MRI (Minispec LF 50 and LF 110, Bruker, The Woodlands, TX) on average 1 week before, and 2, 4, 8, and 12 weeks (± 5 days) after surgery. The adiposity index was calculated by dividing fat mass by lean mass.

Measurement of energy expenditure in the metabolic cages

VO_2 , VCO_2 , RER, locomotor activity, food and water intake were measured in metabolic chambers (Phenomaster/Lab Master, TSE Systems, Germany) at the end of the rapid weight loss period (10–24 days after surgery) and during the stable weight or weight regain phase (54–69 days after surgery). After 5 days with training lids on their home cages to facilitate learning to eat from hanging wire baskets, mice were transferred to special metabolic chambers. Mice were kept at 23°C, and after an adaptation period of 24 hours, all parameters were sampled at a frequency of 40 min and averaged over 2 consecutive days and nights. At 12 weeks, after collecting data at 23°C, chamber temperature was increased to 29°C (near thermoneutrality) to minimize the potential masking effect of cold-induced thermogenesis. After another 24 hours of adaptation to the new temperature, all parameters were again sampled over 2 consecutive days and nights.

Energy expenditure in kcal was calculated on the basis of VO_2 and VCO_2 by company supplied software and expressed a) per mouse, b) per kg body weight, and c) per kg lean body mass. For lean mass the average of measurements before and after the metabolic

chamber period was used. Locomotor activity is defined as the total number of laser beam breaks in both the X and Y plane (7mm spatial resolution, 10ms temporal resolution) over a given time period.

Plasma glucose and hormone assays

At 12 weeks post-surgery all mice were overnight fasted and euthanized by decapitation. 500 μ l of trunk blood was collected in microtubes containing 83.5 μ l EDTA (Sigma, St. Louis, MO) and 15 μ l of a protease inhibitor cocktail (5 μ l of each of the following: Protease inhibitor, Sigma, St. Louis, MO; DPP-IV inhibitor, EMD Millipore, St. Charles, MO; Pefabloc SC, Roche, Indianapolis, IN) and immediately centrifuged at 4° C and 3000 RPM for 10 minutes to separate the plasma from the whole blood. Plasma aliquots were frozen in liquid nitrogen, and stored at –80° C prior to processing. Plasma was subjected to ELISA for measurement of insulin and leptin concentrations (MMHMAG-44K Milliplex map mouse metabolic hormone magnetic bead panel – metabolism multiplex assay, EMD Millipore, St. Charles, MO). One drop of unprocessed tail vein blood was used for baseline glucose measurement (Onetouch Ultra Glucometer, LifeScan INC, Milpitas, CA; Onetouch Ultra Strips, LifeScan INC, Milpitas, CA). One drop of unprocessed trunk blood was used for baseline glucose measurement (Onetouch Ultra Glucometer, LifeScan INC, Milpitas, CA; Onetouch Ultra Strips, LifeScan INC, Milpitas, CA).

Measurement of sleeve size

Following euthanasia, the gastrointestinal tract was carefully dissected and the portion of the gastric sleeve was laid flat and photographed at a fixed magnification. The surface area of the gastric sleeve from the gastroesophageal junction to the pylorus was measured with ImageJ software (NIH, Bethesda, MD). The stomach area was then plotted against body weight loss, body weight change, body weight regain, and fat mass regain. Correlations were determined using linear regression analysis.

Statistical analysis

One way ANOVA was used to analyze body weight change, body composition, TSE measurements, and plasma hormone assays. All ANOVAs were followed by a Bonferroni-corrected multiple comparison post-test. Sleeve size analysis was done using linear regression. Significance was accepted at the $p < 0.05$ level. All data are expressed as the mean $\pm$ SEM.

Results

Body weight

Before surgery, body weight was not significantly different between the groups made obese on a HFD, but was about 60% higher than age-matched chow-fed controls (Fig. 1A). After surgery, body weight initially decreased similarly with VSG and RYGB (Fig. 1A, C), but while it remained lower after RYGB for the remainder of the study, body weight returned to pre-surgical levels by 6 weeks after VSG (Fig. 1A,D). Sham surgery produced only minor initial weight loss that was rapidly regained by about 3 weeks after surgery. At 12 weeks after surgery, RYGB mice lost 21.8% of their initial body weight, while VSG mice gained

14.4% (Fig. 1B). Compared to sham surgery, VSG mice weighed only about 5% less, while RYGB mice weighed 38% less at the end of the study. Compared to chow controls without surgery, VSG mice weighed 80% more, while RYGB mice weighed 17% more at 12 weeks after surgery.

Body composition

Fat mass and the adiposity index followed more or less the changes in total body mass, with relatively minor changes in lean mass (Fig. 2A–C). Fat mass and adiposity index were only transiently reduced after VSG and surpassed pre-surgical levels at 12 weeks after surgery, although both measures were still significantly lower than in sham-operated controls. In contrast, fat mass and adiposity index were drastically and lastingly reduced by RYGB (Fig. 2A,C). Weight-matching to RYGB through calorie restriction was slightly but significantly less effective in reducing fat mass and adiposity index. Generally, lean mass did not change much in the surgical groups except for a transient decrease at 2 weeks after surgery (Fig. 2B).

Food intake, feed efficiency, and food choice

In the first 8 days following surgery there was a significant suppression of food intake in both the VSG and RYGB groups when compared to sham surgery (Fig 3 A, B). However, from day 9 onwards the food intake in RYGB mice had recovered and by day 26 onwards neither RYGB nor VSG mice were significantly different from the sham-operated mice. Even though the VSG, RYGB, and sham surgical groups had similar food intake after day 25, only RYGB mice failed to gain weight during this period. While the amount of calories required to match body weight of VSG mice was not significantly different (–7%) from the actual calorie intake of VSG mice, it was significantly lower (–36%) to match body weight of RYGB mice compared with the actual intake of RYGB mice (Fig. 3A,B). Neither VSG nor RYGB mice had significantly altered feed efficiency when compared to their respective weight matched controls. However, when compared to the sham group, the surgeries followed opposite trends with VSG leading to slightly increased feed efficiency, and RYGB leading to dramatically reduced feed efficiency, not significantly different from chow fed, non-surgical controls (Fig. 3C).

Before surgery, all mice on a 2-choice diet showed an overwhelming preference for high-fat (Fig 3D). Except for the first week, VSG did not appreciably change this preference, while RYGB produced a small but significant downward shift in high-fat preference. During postsurgical week 6 onwards, fat preference was significantly different between VSG and RYGB mice.

Energy expenditure, RER, and locomotor activity

Data for all metabolic chamber parameters was collected over 2–4 days of continuous measurement following 24 hours of adaptation at a given temperature. At 2 weeks after surgery, VSG mice had significantly less total energy expenditure (EE) when compared to the sham group, but this difference disappeared when adjusting for total body mass or lean mass (Fig 4A). At 8 weeks, EE of VSG mice was no longer different than the sham group, but became significantly higher when adjusted for body weight or lean mass. Compared to

mice weight matched to VSG without surgery, energy expenditure of VSG mice at 23°C was generally slightly but significantly higher, except when corrected for lean mass. EE corrected for body weight or lean mass at 23° C and at both time points was significantly lower after RYGB compared with sham-operated mice.

To unmask non-thermogenic EE, we also tested mice near thermoneutrality at 29°C at 8 weeks after surgery. Independent of correction, EE of VSG mice was slightly but significantly lower than in sham-operated mice, although this effect disappeared when corrected for total body mass or lean mass. RYGB mice expended significantly more energy than sham-operated and VSG mice when not corrected or when corrected for lean mass. Importantly, however, compared to their respective weight-matched group, both VSG and RYGB mice had significantly increased energy expenditure at 29°C and 8 weeks after surgery, suggesting weight loss-independent effects on energy expenditure of both surgeries (Figs. 4A,B; Supplementary Table 1).

RER and locomotor activity

As expected, the respiratory exchange ratio (RER) of chow mice was significantly higher than all other groups at all temperatures and time points due to the higher carbohydrate intake (Fig 4C). At two weeks after surgery, RER was significantly reduced in the VSG group when compared to both the sham and RYGB groups, but no difference was observed between the sham and RYGB groups. At 8 weeks, the RYGB mice had a significantly higher RER when compared to both the sham and VSG groups, which may be explained by the higher chow preference of the RYGB mice. Interestingly, though, at 29° C the RER of VSG mice rose and was no longer significantly different than that of the RYGB mice.

At 2 weeks after surgery, locomotor activity was not significantly different between any of the groups (Fig 4D). At 8 weeks, the sham and VSG weight matched groups showed slightly lower activity levels when compared to the chow fed and RYGB weight matched groups. At 29° C, the VSG group also began to show reduced locomotor activity when compared to the chow fed group, however at this temperature there was no longer any differences between any of the high-fat fed groups.

Fasting plasma glucose and hormones and HOMA insulin resistance

At 12 weeks after surgery, fasting blood glucose in VSG mice was slightly but not significantly higher than in sham operated controls (Fig. 5A). In contrast, fasting blood glucose in RYGB mice was significantly lower than both VSG and sham animals, and was not significantly different than in lean chow fed controls. Interestingly, even though blood glucose levels were similarly high in the VSG and sham mice, plasma insulin was drastically reduced after VSG, almost down to the levels of RYGB and chow mice (Fig. 5B). As expected with low plasma insulin levels, HOMA-IR in VSG mice was also significantly reduced when compared to sham mice, and only slightly higher than in RYGB and chow-fed control mice (Fig. 5C).

Sleeve size in VSG mice

Gastric sleeve surface area varied from about 25–60 mm² (Fig. 6A,B), with evidence for incomplete elimination of the fundic part of the stomach in 3 mice (VSG 7, 11, and 12, Fig. 6A). To illuminate possible effects of sleeve size on weight loss and regain, we carried out two separate analyses, one using subgroups of mice and one correlative. First, body weight and fat mass curves for the 3 potentially incomplete sleeves were not significantly different from the rest of the mice. Also, final body weight and weight regain were not significantly different for mice with a sleeve surface area <40 mm² (n = 7) compared with >40 mm² (n = 6) (not shown). Second, there were no significant negative correlations between weight loss or fat mass loss at 2 weeks and sleeve size and no positive correlations between body weight or fat mass regain from nadir and sleeve size (Fig. 6B).

Discussion

Given the trend to replace RYGB with VSG surgery in patients with obesity [27], the goal of our study was to directly compare the outcomes of these two bariatric surgeries in mouse models carried out under the same conditions and by the same laboratory. Somewhat unexpectedly, the study clearly shows the superiority of RYGB over VSG to produce sustained body weight loss in mice. In contrast to RYGB, weight loss after VSG was only transient with significant weight and fat mass regain after reaching a nadir at about 10 days post-surgery. Insufficient gastrectomy and adaptation (ballooning) of the remaining sleeve was not the reason for this lack of sustained weight loss and weight regain, as post mortem analysis of gastric sleeve size did not find any correlations between sleeve size and weight loss or weight regain.

Comparing our observations with previous studies in mice, the modest effect of VSG on weight loss is not too surprising, as considerable weight regain after the initial nadir has been unanimously demonstrated [23–25, 28–30]. The time to reach pre-surgical levels varied between 5 weeks [30] and approximately 18 weeks [28]. It is clear that some of this weight regain is a normal reaction to at least some restriction of calorie intake during the first 3–10 days after surgery practiced in most laboratories, and to the normal growth of mice, particularly if surgery was performed at an early age. The fact that the mice in our study were not food restricted for the first days after surgery may have contributed to the relatively rapid weight regain.

Comparing our observations with clinical studies, the modest effect of VSG on weight loss is more surprising. Numerous clinical studies have concluded that VSG is not or is only marginally less effective in producing weight loss, at least in the short term [7–15] and this was an important factor to spur the present preference for VSG as the bariatric surgery of choice. Only a few clinical studies have found VSG to be significantly less efficient in producing sustained body weight loss. In one such study, patients undergoing VSG lost about 10% less of their baseline weight than patients with RYGB at 4 years after surgery [16]. In another study with a 10 year follow-up period, about half of the patients with VSG suffered from significant weight regain and many of these were converted to RYGB after only about 3 years [17]. Furthermore, in a five year follow-up study, long-term relapse after initial remission of type 2 diabetes occurred in over 40% of patients [31].

Translating relative lifespans between mice and humans, 12 mouse weeks equates to approximately 7 human years, but most available data from VSG in humans covers only 1–3 years [7–15]. Thus, more long-term data with observation periods of up to 20 years are needed to make informed conclusions about the efficiency of VSG in patients with obesity.

What causes weight regain after VSG: increased food intake or decreased energy expenditure? In our mouse model, total food intake is similar after VSG, RYGB, and sham surgery. However, it should be noted that there is some fecal energy loss after RYGB, amounting to 1–3 kcal/day, as reported earlier in mouse models of RYGB yielding similar body weight outcomes [20, 21]. Assuming that there is no fecal energy loss after VSG, this difference in metabolizable energy intake of approximately 10–15% could thus be responsible for the weight regain after VSG but not RYGB.

In humans, it is generally suspected that increased food intake after relaxing of postsurgical dietary and behavioral counselling is the main reason for weight regain. This explanation has not been directly tested, but it was reported that greater weight loss was associated with decreased hunger sensations [32]. Mechanistic reasons for increased food intake and weight regain are not clear. In humans it could be the fading inhibitory control of food intake. Alternatively it could be related to sleeve dilatation. Two recent studies using gastric volumetry with either 3D gastric computed tomography or radiology concluded that some degree of sleeve dilatation occurred in a majority of patients, but that the degree of dilatation was not correlated with food intake and percent weight loss [33, 34]. Interestingly, this is also what we find in our mouse model – no correlation of two-dimensional sleeve surface area with weight loss and weight regain. Therefore simple anatomical adaptation does not explain the variability in body weight outcome after VSG.

Another possible reason for weight regain after VSG is decreased (or lack of increased) energy expenditure. In murine models of RYGB it is generally agreed that energy expenditure as measured in metabolic chambers is increased after RYGB, particularly if compared with mice that are weight-matched to RYGB by calorie restriction [19, 20, 22]. It appears from these studies that conservation of energy, a normal biological adaptation to starvation, is blunted or prevented by RYGB. We found a similar protective effect after VSG, with about 15% higher energy expenditure at 8 weeks after VSG compared with weight-matched, non-surgical mice. However, in spite of this relatively higher energy expenditure, our VSG mice regained massive amounts of weight and fat. The outcome of clinical studies is controversial, with blunting [35, 36] or without blunting of the adaptive response [37, 38].

One mechanism proposed for weight loss after VSG is rapid gastric emptying, quickly pushing nutrients to more distal portions of the small intestine, and subsequent changes in gut hormone secretion [39], or perhaps changes in bile acid reabsorption and signaling [25]. It could thus be hypothesized that this pathway is less affected or recovers faster in cases with weight regain after VSG, such as in our mouse model or in many patients with VSG. To test this possibility, we need to investigate gastric emptying and bile acid signaling in our mouse model of VSG.

Improvement of glycemic control is another beneficial effect of bariatric surgeries. In our terminal assessment 12 weeks after surgery, fasting levels of glucose were improved by RYGB, but not by VSG. Similarly, fasting insulin levels and HOMA-IR were higher in VSG vs. RYGB mice. However, in spite of the massive weight regain after VSG and nearly indistinguishable body weight and adiposity with sham surgery, both fasting insulin and HOMA-IR were significantly and markedly lower after VSG compared with sham surgery, supporting the notion that failed surgical weight loss does not necessarily mean failed metabolic effects [40]. However, our assessment of insulin sensitivity is only rudimentary and clamp methodology will be necessary to shed further light on this issue. In general, long-term metabolic improvements, and in particular improvements in glycemic control, are to a large extent dependent on weight loss with both RYGB and VSG [41], and in this respect RYGB is superior to VSG [14], as confirmed in our mouse model.

Conclusions

Directly comparing VSG and RYGB in HFD-induced obese mice in the same laboratory shows the superiority of RYGB to produce sustained weight loss and improvement in glycemic control. After an initially substantial weight loss, mice with VSG regained large amounts of body weight and fat mass, with only modest differences to sham-operated mice at the end of the 12 week follow-up, equivalent to about 7 human years. However, our results also suggest that even without lasting weight loss, VSG can significantly improve long-term insulin sensitivity in mice. Given the paucity of long-term follow-up studies in patients with VSG and the considerable weight recidivism and rate of type 2 diabetes relapse in longer-term studies, our findings suggest that the trend towards VSG is premature and should await the outcome of longer-term randomized controlled trials. However, our results also suggest that even without lasting weight loss, VSG can significantly improve long-term insulin sensitivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Effect of VSG (n = 12) and RYGB (n = 11) on food intake, feed efficiency, and food choice in high-fat diet-induced obese mice. Controls include sham surgery (Sham, n = 12) and never obese, regular chow-fed mice (Chow, n = 8). **A:** Absolute body weight over the course of the study. **B:** Percent change in body weight from the day of surgery. **C:** Absolute and percent weight loss at 2 weeks post surgery. **D:** Absolute and percent weight regain from week 2 to week 11 post surgery. Bars that do not share a letter are significantly different from each other ($p < 0.05$, based on ANOVA followed by Bonferroni-corrected multiple comparison).

Fig. 2.

Effect of VSG (n = 12) and RYGB (n = 11) on food intake, feed efficiency, and food choice in high-fat diet-induced obese mice. Controls include sham surgery (Sham, n = 10), high-fat caloric restriction to match body weight of VSG (VSG/WM, n = 8) and RYGB (RYGB/WM, n = 9) and mice, and never obese chow fed mice (Chow, n = 8). **A,B:** Fat mass and lean mass as determined by whole body NMR spectroscopy. **C:** Adiposity index calculated as the ratio of fat mass to lean mass. * p < 0.05, VSG vs. Sham; ^ p < 0.05, RYGB vs. Sham; # p < 0.05, VSG vs. RYGB; + p < 0.05, RYGB vs. RYGB/WM. **D:** Plasma leptin levels measured at 12 weeks after surgery. Bars that do not share the same letters are significantly different from each other (p < 0.05, based on ANOVA followed by Bonferroni-corrected multiple comparisons).

Fig 3.

Effect of VSG ($n = 12$) and RYGB ($n = 11$) on food intake, feed efficiency, and food choice in high-fat diet-induced obese mice. Controls include sham surgery (Sham, $n = 12$), high-fat caloric restriction to match body weight of VSG (VSG/WM, $n = 8$) and RYGB (RYGB/WM, $n = 9$) mice, and never obese chow fed mice (Chow, $n = 8$). **A**: Total food intake over the course of the study, with periods inside metabolic chambers indicated by gray bars. **B**: Average daily food intake for four phases of the study. **C**: Feed efficiency for days 26–76 after surgery. Bars that do not share a letter are significantly different from each other ($p < 0.05$, based on ANOVA followed by Bonferroni-corrected multiple comparison). **D**: Preference for chow over high-fat diet for RYGB, VSG, and sham mice. * $p < 0.05$, VSG vs. RYGB; # $p < 0.05$, RYGB vs. Sham.

Fig 4.

Effect of VSG ($n = 12$) and RYGB ($n = 11$) on energy expenditure, respiratory exchange ratio, and locomotor activity in high-fat diet-induced obese mice at 2–3 weeks and 8 weeks post-surgery, and at 23 and 29 °C. Controls include sham surgery (Sham, $n = 12$), high-fat caloric restriction to match body weight of VSG (VSG/WM, $n = 8$) and RYGB (RYGB/WM, $n = 9$) mice, and never obese chow fed mice (Chow, $n = 8$, or $n = 2$ at 2–3 weeks and 29 °C). **A:** Total energy expenditure per day (top row), or normalized to total body weight (BW; middle row) or lean mass (LM; bottom row). **B:** Linear regression curves showing total energy expenditure per day as a function of lean mass. Bars that do not share a

letter are significantly different from each other ($p < 0.05$, based on ANOVA followed by Bonferroni-corrected multiple comparison. **(C)** Respiratory exchange ratio (RER). **(D)** Locomotor activity as measured by beam breaks in the metabolic cages. Bars that do not share a letter are significantly different from each other ($p < 0.05$, based on ANOVA followed by Bonferroni-corrected multiple comparison.

Fig 5.

Effect of VSG (n = 12) and RYGB (n = 9) on fasting plasma glucose (**A**), insulin (**B**), and HOMA-IR (**C**) at 12 weeks after surgery. Controls include sham surgery (Sham, n = 10), high-fat caloric restriction to match body weight of VSG (VSG/WM, n = 8) and RYGB (RYGB/WM, n = 7), as well as never obese chow fed mice (Chow, n = 7). Bars that do not share a letter are significantly different from each other ($p < 0.05$, based on ANOVA followed by Bonferroni-corrected multiple comparison).

Fig 6.

Sleeve size has no effect on weight loss, weight regain, or fat mass regain following VSG (n = 12). **A:** Pictures of ventral views of sleeves at twelve weeks post-surgery. **B:** Absence of correlations between ventral view sleeve areas and body weight loss, body weight change, body weight regain, and fat mass regain.