Vertical sleeve gastrectomy and semaglutide have distinct effects on skeletal health and heart function in obese male mice

Caroline de Carvalho Picoli,

Sergey Tsibulnikov,

Mavy Ho,

Victoria DeMambro,

Tiange Feng,

May Eltahir,

Phuong T. Le,

Carolyn Chlebek,

Clifford J. Rosen,

Sergey Ryzhov,

Ziru Li

Center for Molecular Medicine, MaineHealth Institute for Research, Scarborough, Maine, United States

Abstract

Obesity is a global health challenge associated with significant metabolic and cardiovascular risks. Bariatric surgery and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are effective interventions for weight loss and metabolic improvement, yet their comparative effects on systemic metabolism—particularly energy metabolism, bone health, and heart function—remain unclear. In this study, obese male mice underwent vertical sleeve gastrectomy (VSG), 6 wk of GLP-1RA (semaglutide) treatment, or sham procedure with saline injection as controls. Dynamic changes in body weight, food intake, fat mass, lean mass, and bone mineral density were monitored. Energy metabolism was assessed using indirect calorimetry. Bone parameters and heart function were evaluated by microcomputed tomography or echocardiography, respectively. Compared with obese controls, VSG and semaglutide treatment comparably reduced body weight and improved glucose metabolism. However, VSG decreased energy expenditure, whereas both treatments similarly promoted lipid utilization. Semaglutide treatment increased ambulatory activity during nighttime. VSG led to significant bone loss, although 6 wk of semaglutide treatment had no significant effects on the skeleton. Cardiovascular outcomes also differed: VSG

Author Manuscript

increased stroke volume without altering heart mass, whereas semaglutide reduced heart mass and transiently elevated heart rate. These findings underscore the importance of carefully weighing the benefits and potential risks of different weight loss treatments when addressing obesity and its systemic complications.

NEW&NOTEWORTHY: Comparative studies of surgical and pharmaceutical approaches to weight loss offer critical insights that can guide clinical decision-making for managing obesity. VSG and semaglutide exhibit comparable efficacy in promoting weight reduction and improving glucose metabolism. VSG reduces energy expenditure, whereas semaglutide increases animal activity during nighttime. VSG leads to significant bone loss, whereas semaglutide preserves bone mass independent of weight loss. VSG improves cardiac outcomes, whereas semaglutide transiently affects heart function.

Keywords

bone loss; heart function; semaglutide; vertical sleeve gastrectomy; weight loss

INTRODUCTION

Obesity represents a significant public health challenge, with its prevalence sharply increasing worldwide, contributing to numerous comorbidities, including cardiovascular diseases, type 2 diabetes (T2D), and various types of cancers (1–4). The economic burden is substantial; in 2019, the estimated costs of managing overweight and obesity accounted for an average of 2.19% of the global gross domestic product (GDP) across 161 countries (5). If current trends continue, the estimated costs are projected to rise to 3.29% of global GDP by 2060. Therefore, the development of efficient and safe weight-loss strategies has been gaining notoriety.

Bariatric surgery is widely recognized for its effectiveness in managing obesity and T2D (6–10), providing significant improvements in glucose homeostasis, lipid profiles, and insulin sensitivity. One of the mechanisms underlying the benefits of bariatric surgery is the increased secretion of glucagon-like peptide-1 (GLP-1), a gut-derived incretin hormone that enhances insulin release and inhibits glucagon secretion in a glucose-dependent manner (11). The most popular bariatric surgery procedures, such as vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass, significantly boost postprandial GLP-1 levels (12, 13). Thus, the development of GLP-1 receptor agonists (GLP-1RAs), such as semaglutide and liraglutide, has been gaining popularity in managing hyperglycemia and overweight/obesity (13–19).

Beyond the metabolic benefits of VSG and GLP-1RAs, it is worth noting that their side effects are becoming more apparent, especially as more clinical and preclinical data become available. For instance, bariatric surgery has been shown to reduce bone mineral density (BMD) and increase the risk of fractures over time (20–23). VSG-induced bone loss goes beyond calcium and vitamin D deficiency, mechanical unloading, diet preferences, orsex differences (12). Many other factors, such as gut hormones, bile acids, microbiota, and sympathetic drive, may also contribute to VSG-induced bone loss. However, clinical studies

with GLP-1RAs have shown inconsistent conclusions on skeleton health showing either beneficial (24), deteriorative (25), or nonsignificant effects (26).

Obesity increases cardiovascular risks (27) and causes adverse cardiac remodeling (28). Bariatric surgery has demonstrated substantial benefits in cardiovascular events; resolving hypertension in 61.7% of patients, and improving hyperlipidemia in 70% of patients (29). With the significant reduction in body weight and cardiac workload, it is not surprising to find that bariatric surgery positively impacts cardiac geometry and function, which is linked to decreased left ventricular (LV) mass, reduced left atrial diameter, and increased LV ejection fraction (LVEF) (30). In a similar scenario, GLP-1RAs generally reduce the risk for major adverse cardiovascular events (31) and improve outcomes in pre-existing heart diseases (32). However, Neves et al. (33) found that GLP-1RA may increase the risk of heart failure in patients with LVEF < 40%. Moreover, long-acting GLP-1RAs, such as liraglutide and albiglutide, have been associated with pronounced increases in heart rate with 6–10 beats/min higher than placebo (34). A mechanistic study in pigs revealed that GLP-1 has direct chronotropic effects on the heart by regulating PKA-dependent phosphorylation of calcium-cycling proteins in the sinus node (35).

Overall, bariatric surgery improves heart function in subjects with pre-existing heart disease but negatively affects bone health, whereas the effects of GLP-1RA treatment remain less clear and warrant further investigation. Comparative studies between these interventions are critical to understanding their benefits and risks. In this study, we directly compared metabolic, skeletal, and cardiac outcomes following VSG, semaglutide treatment, or sham with saline injection. VSG and semaglutide treatment had comparable effects on metabolic improvement. Bone mass was reduced with VSG, but not changed after 6 wk of semaglutide treatment. VSG and semaglutide demonstrated different effects on the heart. VSG increased the left ventricular dimensions, which resulted in the enhanced stroke volume. Semaglutide decreased heart mass while inducing a transient increase in the heart rate.

MATERIALS AND METHODS

Vertical Sleeve Gastrectomy

After 8 wk of high-fat diet (HFD; 60% kcal% fat; Research Diets D12492; New Brunswick, NJ) feeding (more details are available in Supplemental Methods), obese male mice underwent either sham or VSG procedures. Under isoflurane anesthesia, a small laparotomy was performed, and 80% of the stomach (along the greater curvature and fundus) was excised in the VSG group using microvessel clips, followed by hand-sewn sutures. Sham surgeries involved applying pressure to the stomach with a microvessel clip for 15 s. Postsurgical care included a single dose of buprenorphine (0.08 mg/kg, sc) and warm saline (1 mL), with daily carprofen (5 mg/kg, sc) injections for 3 days. Mice received a high-energy gel diet (DietGel Boost; ClearH$_2$O, Westbrook, ME) 1 day before surgery and 3 days postsurgery, followed by reintroduction of HFD on *day 4*. Body weights were monitored daily for the first week postsurgery and weekly thereafter. Body composition was assessed using dual-energy X-ray absorptiometry (DEXA) at baseline (*day 0*), and *day 21* and *day 42* postsurgery.

Semaglutide Treatment

A third group of obese male mice received semaglutide (Ozempic; 400 μg/kg sc; Novo Nordisk, Plainsboro, NJ) injections daily for 6 wk (36). The treatment was initiated with a dose escalation (100 μg/kg on *day* 1, 200 μg/kg on *day* 2) before reaching 400 μg/kg for the remainder of the study. Sham mice received daily saline injections (2.5 mL/kg sc) and were used as controls. All injections were administered at 10:00 AM.

Indirect Calorimetry

A subset of mice from each group was housed in Promethion Metabolic Cage System (Sable Systems, Las Vegas, NV) 4 wk after treatment for 24-h acclimation followed by 72-h data collection. Parameters, such as energy expenditure, respiratory exchange ratio (RER), and ambulatory activity, were monitored as previously described (37). Data acquisition and analysis were performed using Promethion Live (v23.0.08) and Macro Interpreter (v24.5.6) software (Sable Systems International) with detailed scripts for all aspects of data transformation.

Dual-Energy X-Ray Absorptiometry

DEXA was performed at baseline (*day 0*) and on *day 21* and *day 42* post-treatment using a Hologic Faxitron UltraFocus DXA system (Tucson, AZ). The Faxitron was calibrated with bone and fat phantoms from the manufacturer before each scanning session. Measurements included whole body (excluding the head) bone mineral density (BMD), lean mass, and fat mass, as well as regional BMD for femora, tibiae, lumbar vertebrae (L4), and caudal (tail) vertebra 4.

Echocardiography

Cardiac function was assessed by echocardiography (ECHO) in vivo on unsedated mice using a Vevo F2 Imaging System (VisualSonics, Inc., Toronto, ON, Canada). M-mode images were obtained from the parasternal short-axis view at the papillary muscles level and analyzed with Vevo LAB 5.8.1. software by another investigator in a blinded manner.

Microcomputed Tomography Analysis

Tibiae were fixed in 10% formalin for 24 h at 4°C and stored in Sorenson's buffer. Scans were performed using a high-resolution desktop microtomographic vivaCT 40 system (Scanco Medical AG, Brüttisellen, Switzerland). Scans were acquired using a 10.5 μm^3 isotropic voxel size, 70 kVp peak X-ray tube intensity, 114 mA X-ray tube current, 250 ms integration time, and were subjected to Gaussian filtration and segmentation. Trabecular bone was analyzed at the metaphysis for bone volume fraction (Tb.BV/TV, %), trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, mm^{-1}), trabecular separation (Tb.Sp, mm), and trabecular bone mineral density (Tb.BMD, mg HA/cm^3). Cortical bone was analyzed at the midshaft for bone area fraction (Ct.Ar/Tt.Ar, %), cortical thickness (Ct.Th, mm), and cortical tissue mineral density (Ct.TMD, mg HA/cm^3). All analyses were performed using the Scanco software (Medical AG, version 4.05).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism (version 10). Data normality was determined using the Shapiro–Wilk test. Differences between groups were assessed using either one-way ANOVA or two-way repeated-measures ANOVA with appropriate post hoc tests. One-way ANOVA was used to determine significant differences between independent groups, with a post hoc Tukey test or Dunnett's test. Two-way repeated-measures ANOVA analysis was used when both time and treatment are considered as factors, evaluating the individual effect of each factor and their interaction. A P-value of < 0.05 was considered statistically significant. Data are presented as means ± SD.

To distinguish VSG and semaglutide as independent treatment factors, the statistical analyses for Fig. 2 were performed using R software (version 4.4.1). A two-way ANOVA was applied to evaluate the main effects of therapy (sham, VSG, and semaglutide) and time (day and night) on the dependent variable, as well as their interaction effects. Post hoc pairwise comparisons between therapy groups were conducted using Tukey's honest significant difference (HSD) test to control for the family-wise error rate associated with multiple comparisons (R code is available in Supplemental Methods). P values for each pairwise comparison (sham vs. VSG, sham vs. semaglutide, and VSG vs. semaglutide) were extracted from the Tukey HSD results and reported to indicate statistical significance.

To determine the effects of the variation in lean mass between treatment groups on indirect caloric measurements, including total energy expenditure (EE), resting EE (REE), active EE (AEE), oxygen consumption (VO_2) and carbon dioxide production (VCO_2), analysis of covariance (ANCOVA) was performed using JMP statistical software. Lean mass was found to be a significant covariate ($P < 0.05$) with all energy expenditure parameters. Data reported here are shown as per mouse and adjusted means when this covariation was accounted for (38).

RESULTS

VSG and Semaglutide Have Comparable Effects on Weight Reduction and Glucose Improvement

Male C57BL/6J mice were fed with an HFD for 8 wk before undergoing sham, VSG, or semaglutide treatments. Both VSG and semaglutide treatment caused a sharp initial weight loss (~20%) within the first 14 days; this weight reduction persisted and further decreased to 22%–27% by *day 42* (Fig. 1A). This weight reduction was partially attributed to decreased food intake post-treatment (Fig. 1, B and C). Of note, VSG mice had a transient reduction in food intake during postsurgical recovery phase, which normalized after 2 wk, whereas semaglutide treatment consistently inhibited food intake throughout the experiment. This suggests that the sustained weight loss following VSG may extend beyond mere food intake restriction. DEXA scanning revealed a significant reduction in fat mass with both treatments: 60% and 58% reductions by *day 21* for VSG and semaglutide, respectively, and 58% and 63% by *day 42* (Fig. 1D). Although VSG maintained lean mass, semaglutide showed a trend toward reduced lean mass compared with the sham group ($P = 0.08$ at *day 21* and $P = 0.11$ at *day 42*) (Fig. 1E). Consistent with prior studies (39–42), both VSG and

semaglutide greatly improved glucose tolerance (Fig. 1, F and G) and reduced circulating insulin concentrations to a similar extent (Fig. 1H). Histological analysis of pancreatic islets indicated no significant differences between sham and VSG mice, whereas semaglutide-treated mice had a higher proportion (55%) of smaller islets ($<25,000$ μm^2), indicating different mechanisms for glucose metabolic improvement between the two treatments (Fig. 1, I and M). Compared with sham mice, lipid deposition in the liver was markedly alleviated following VSG and semaglutide treatment, with semaglutide resulting in significantly smaller liver sizes (Fig. 1, J and M). Both treatments greatly decreased epididymal white adipose tissue (eWAT) and subcutaneous white adipose tissue (sWAT) weights and adipocyte size in each depot (Fig. 1, K–M). These results confirm that both VSG and semaglutide treatments effectively reduced body weight, primarily through fat mass reduction, and improved glucose metabolism, albeit via potentially different mechanisms.

To investigate metabolic changes induced by VSG and semaglutide treatments, a subgroup of mice was analyzed in metabolic cages. No statistical differences in total energy expenditure (EE) were identified during the day or night cycles, except for a reduction in daytime EE observed with semaglutide treatment (Fig. 2A). Neither VSG nor semaglutide caused significant changes in resting EE (Fig. 2B). Interestingly, VSG significantly reduced the active EE, and semaglutide treatment showed a similar trend without reaching statistical significance (Fig. 2C). However, when analyzing the overall effects across daytime and nighttime (Supplemental Table S1), both VSG and semaglutide treatments significantly reduced total EE and active EE, with no difference between the two treatments (Supplemental Table S1). Of note, since semaglutide treatment reduced lean mass at *weeks 3* and *4*—when metabolic cage analysis was conducted—it is essential to normalize EE to lean mass. VSG consistently decreased total EE in both day and night cycles when the covariation between lean mass and EE parameters was taken into account via ANCOVA (Fig. 2D). Interestingly, no significant effects of semaglutide treatment on total EE were noted. Analysis of resting EE and active EE revealed similar patterns of significance (Fig. 2, E and F). No significant changes in oxygen consumption ($\dot{V}O_2$) were detected, whereas carbon dioxide production ($\dot{V}CO_2$) decreased significantly with both treatments during the daytime and nighttime (Fig. 2, G and H). Compared with the sham group, the respiratory exchange ratio (RER) also dropped significantly during the daytime for both treatment groups, indicating a shift toward higher lipid utilization for energy production (Fig. 2I). When the effects across daytime and nighttime were combined, both treatments significantly influenced $\dot{V}O_2$, $\dot{V}CO_2$, and RER compared with the sham group; however, no differences were observed between VSG and semaglutide treatments (Supplemental Table S1). Intriguingly, normalizing $\dot{V}O_2$ and $\dot{V}cO_2$ to lean mass revealed significant reductions only in the VSG group, whereas semaglutide treatment preserved these values at levels comparable to the sham group, except lower $\dot{V}cO_2$ at daytime (Fig. 2, J and K). In terms of activity, only semaglutide-treated mice exhibited increased *x*-ambulatory, *y*-ambulatory activity, and pedestrian locomotion (PedMeters) during the night cycle (Fig. 2, L–N). Together, our results suggest that VSG and semaglutide treatments exert differential effects on energy metabolism, especially when lean mass is considered as a covariation, and in their impact on activity patterns. Understanding how these weight-loss strategies influence energy

balance and physical activity could have implications for optimizing long-term efficacy and sustainability of these interventions.

VSG Causes Bone Loss, While Semaglutide Treatment Maintains Bone Mass

Consistent with previous studies demonstrating bone loss following VSG in humans (22) and rodents (12), our VSG group exhibited a significant reduction in total body BMD 42 days postsurgery, as determined by DEXA scanning (Fig. 3A). Site-specific analysis revealed significant decreases in femoral, tibial, tail vertebral, and lumbar vertebral (L4) BMD starting from *day 21* (Fig. 3, B–E). Despite the striking weight loss following semaglutide treatment, no significant effects on total body or site-specific BMD were observed throughout the 6-wk treatment period (Fig. 3, A–E) except for L4 BMD.

Aligning with the observations determined by DEXA, microCT analysis of mouse tibiae showed significant reductions in trabecular bone volume fraction (Tb.BV/TV) and BMD in VSG mice compared with sham or semaglutide-treated mice (Fig. 3, F–H). The trabecular bone reduction was reflected by the dramatic changes in the microstructure, including decreased trabecular bone number (Tb.N) and increased separation between trabeculae (Tb.Sp) following VSG, without significant changes in trabecular bone thickness (Tb.Th) (Fig. 3, I–K). Similar reductions in cortical bone were determined by significant lower cortical bone area fraction (Ct.Ar/Tt.Ar), cortical thickness (Ct.Th), and total mineral density (Ct.TMD) in VSG mice compared with sham or semaglutide-treated mice (Fig. 3, L–O). Of note, none of the parameters in trabecular and cortical bone morphology was changed by 6 wk of semaglutide treatment, compared with sham mice. Further analysis revealed increased levels of bone turnover markers in VSG mice compared with sham, including both the bone resorption marker C-terminal telopeptide of type I collagen (CTX-1) and the bone formation marker procollagen type I N-terminal propeptide (P1NP). This suggests that VSG induces a state of high bone turnover, potentially contributing to the observed bone loss. In contrast, compared with sham mice, semaglutide-treated mice showed no significant changes in either marker, suggesting stable bone turnover and preservation of bone mass. Understanding these differences could guide clinical decision-making, particularly for patients at risk of osteoporosis or fractures.

Bone marrow adipose tissue (BMAT), a significant component of the bone marrow niche, can either positively or negatively influence bone homeostasis, depending on the metabolic conditions (43). Our previous study found that VSG induces both BMAT depletion and bone loss in parallel (12). Consistent with this notion, VSG depleted the majority of proximal tibial BMAT, with a marked decrease in both the number and size of bone marrow adipocytes (BMAds) (Fig. 3, R–T). Semaglutide treatment showed a trend towards BMAd reduction, but the effect was not statistically significant. Size distribution analysis revealed a clear shift towards smaller BMAds (250 and 500 μm^2) following VSG, whereas semaglutide treatment increased the proportion of small BMAds at 500 μm^2 while reducing the prevalence of larger BMAds at 1,750 μm^2 compared with sham mice (Fig. 3U). Overall, semaglutide appeared to cause less BMAT loss than VSG. This observation is intriguing, as BMAT is well-known to expand upon caloric restriction (44). However, this was not the case with semaglutide treatment, despite its marked reduction in food intake (Fig. 1, B and C).

This finding suggests that semaglutide's effects on the bone marrow niche extend beyond those of food restriction alone.

VSG and Semaglutide Have Different Effects on Cardiac Function

Since heart size correlates with the body size (45, 46), it is not a surprise to see that semaglutide-treated mice, with reduced body mass, had smaller hearts compared with control mice (Fig. 4A). Interestingly, this correlation was absent following VSG because the heart mass in VSG-treated mice remained similar to control, leading to a significantly higher heart-to-body weight ratio in this group (Fig. 4B). Consistent with this notion, echocardiography (ECHO) exam showed increases in left ventricular internal diameter in systole (LVIDs) and diastole (LVIDd) in VSG group compared with groups of sham and semaglutide-treated mice (Fig. 4, D and E). In addition, the stroke volume was significantly elevated in the VSG group by *day 42*, whereas semaglutide-treated mice displayed levels comparable to sham controls (Fig. 4F). To examine if increased LV dimensions are associated with the hypertrophic remodeling, we collected hearts from another independent cohort after confirming the consistent changes in heart function by ECHO. No differences were found in cardiomyocyte size (Fig. 4, K and L), and Mason's trichrome staining revealed no fibrosis in VSG-treated hearts (Fig. 4, M and N). These results indicate that larger and stronger hearts observed in VSG mice likely reflect physiological, not pathological, adaptations. Of note, both VSG and semaglutide reduced left ventricular anterior wall thickness in diastole (LVAWd) compared with sham mice starting at *day 21*, indicating improvements in both treatment groups (Fig. 4G). In contrast to VSG, semaglutide temporarily increased heart rate and ejection fraction at *day 21* (Fig. 4, H–J), suggesting potential adaptive changes to the treatment during the early phase, which normalized by *day 42*. Overall, these findings suggest that VSG and semaglutide treatment led to improved heart function and structural adaptations without adverse remodeling, most likely using different molecular mechanisms. Understanding these distinct cardiovascular effects can help tailor weight-loss strategies for patients with pre-existing cardiac conditions.

DISCUSSION

Using a male DIO mouse model, we conducted a parallel comparison between different weight loss approaches, including VSG and semaglutide treatments, to evaluate their metabolic, skeletal, and cardiac outcomes. Our findings revealed comparable efficacy of VSG and semaglutide in reducing body weight and improving glucose metabolism, with different effects on energy metabolism and animal ambulatory activity. It is worth highlighting the distinct effects of VSG and semaglutide treatments on bone health and heart function.

The reductions in body weight and fat mass observed in both VSG and semaglutide treatments align with previous studies in humans and animal models (10, 12, 13, 17), confirming their efficacy in managing obesity and related metabolic disorders. VSG induces weight loss through mechanisms beyond mechanical restriction, malabsorption, and secretion of satiety gut hormones such as GLP-1 and PYY, with growing evidence supporting the gut microbiome as a significant contributor, such as elevated bile acid

signaling and the antimicrobial peptide *Reg3g* expression (47–49). Additional mechanisms such as shifts in food preference and changes in energy expenditure also contribute to weight reduction but in a more complex manner (50). Semaglutide, a GLP-1RA, exerts its effects through GLP-1 signaling, which plays a pivotal role in regulating food intake, glucose homeostasis, and energy metabolism (17). GLP-1 receptors are widely expressed in tissues, such as the pancreas (51–53), gastrointestinal tract (54, 55), kidney (16, 56), brain (57, 58), and adipose tissue (59), supporting the diverse physiological benefits of semaglutide (17). These include promoting insulin production, suppressing glucagon secretion, reducing hepatic glucose out-put, inhibiting lipid accumulation (60, 61), reducing energy intake (62), and offering neuroprotective and cardiovascular benefits (63).

Bariatric surgery decreases total EE, primarily due to reduced active EE, indicating the body's adaptation to significant reductions in fat mass and fat-free mass (64–66). This metabolic adaptation poses challenges for maintaining long-term weight loss. There is limited information about the effects of GLP-1RA treatment on active EE, although reports on resting EE remain inconclusive, with studies showing increases (67), decreases (68), or no change (69, 70). Our indirect calorimetry studies revealed similar trends of reductions in total EE and active EE with both VSG and semaglutide treatment. However, after normalizing to lean mass, semaglutide treatment has no significant effects on EE. Both treatments decreased the RER compared with sham mice, particularly during the daytime, suggesting a shift toward greater lipid utilization. Of note, semaglutide treatment particularly increased ambulatory activity and pedestrian locomotion during the nighttime, suggesting behavioral changes. These differences may have implications for the sustainability of weight loss and warrant further investigation in long-term studies, particularly as it relates to potential effects on the central nervous system (71–73).

Although the effectiveness of VSG and semaglutide treatment for weight loss and metabolic improvements are high-lighted in both clinical and animal studies, it is worth noting that side effects of each treatment should be fully weighed against the benefits, particularly for individuals with pre-existing health issues. For instance, VSG causes anemia, ulcers, hernias, vomiting, dumping syndrome (74, 75), depression (76, 77), and bone loss, evidenced by reductions in BMD at femoral neck, total hip, and lumbar spine (78). Longitudinal human studies confirmed that bariatric surgery is associated with an increased risk of osteoporotic fracture (79, 80). Mechanistically, bariatric surgery-induced bone loss is linked to elevated bone turnover, as shown by increased levels of bone resorption (CTX-I) and formation (P1NP) markers, consistent with human studies following VSG (81, 82).

GLP-1 receptors are also expressed in bone cells, including bone marrow skeletal stem cells, osteoblasts, and osteoclasts (83, 84). In vitro studies have shown that liraglutide treatment promoted osteoblastogenesis (85) and suppressed osteoclastogenesis (86). In vivo studies of GLP-1RA like liraglutide showed variable results, potentially due to differences in compounds, doses, and duration of treatment, as well as the disease conditions. Ovariectomized mice treated with liraglutide or exenatide demonstrated positive effects on trabecular bone without significant changes in cortical bone (84). Treatment of streptozotocin-induced diabetic mice with liraglutide was inefficient to prevent trabecular or cortical bone loss (87). In human studies, a 52-wk semaglutide regimen did not affect

P1NP levels but increased bone resorption marker CTx, leading to significant reductions in lumbar spine and total hip BMD (88). These data differ slightly from bariatric surgery, where sustained bone loss is a major concern, suggesting semaglutide treatment may be a safer option for patients at risk of osteoporosis.

Bariatric surgery has protective effects against heart failure, coronary artery disease, myocardial infarction, and cardiovascular mortality (89). These benefits are achieved through several mechanisms. VSG reduces circulating lipids and mitigates hyperglycemia, which in turn alleviates their detrimental effects on the heart. In addition, bariatric surgery decreases systemic inflammation, reduces oxidative stress, and restores endothelial function, resulting in lower risks of atherosclerosis, arrhythmia, and hypertension (90–92). These changes collectively enhance cardiovascular health, as evidenced by improved left ventricular function, reduced cardiac workload, and diminished fat infiltration in the myocardium, ultimately leading to enhanced cardiac performance (93, 94). Our study in male mice confirmed the improvement of heart function, showing an increase in stroke volume and left ventricular dimensions following VSG. Importantly, histological analysis revealed no significant fibrosis or structural damage, suggesting that the cardiac improvements observed with VSG are likely adaptive rather than pathological.

GLP-1RAs application in clinical studies demonstrated overall beneficial effects on heart function. For example, semaglutide has been shown to reduce cardiovascular mortality in patients with pre-existing cardiovascular disease and obesity in the absence of diabetes (32). However, an observational study demonstrated that semaglutide increased the cumulative hazards to congestive heart failure when compared with bariatric surgery (94). Our study highlighted transient increases in heart rate and ejection fraction with semaglutide, which may reflect compensatory mechanisms or stress on the heart. However, the potential long-term cardiac implications of semaglutide treatment remain unclear and warrant further investigation. This is particularly relevant in clinical settings where dose escalation is often used, raising the need for further research to clarify the safety and efficacy of prolonged treatment.

Although both VSG and semaglutide provide significant cardiovascular benefits, bariatric surgery appears to offer more robust and sustained improvements in cardiac function and structure in patients with pre-existing cardiac disease. Semaglutide, though effective for cardiovascular risk reduction in high-risk populations, requires further evaluation to clarify its long-term effects and optimal use. Our study demonstrated that VSG and semaglutide mediated their cardioprotective effects, most likely via independent molecular mechanisms as the pattern and dynamics of those changes were significantly different. Personalized treatment strategies based on patient-specific risk factors and goals remain essential for maximizing cardiovascular outcomes.

In summary, both VSG and semaglutide treatment provide significant benefits for weight loss and metabolic health, but their distinct effects on bone health and cardiac function highlight the importance of tailoring weight-loss strategies based on individual health profiles. The negative effects of VSG on bone morphology and turnover were not observed with semaglutide treatment, potentially making GLP-1RAs a preferable option for

populations with pre-existing skeletal fragilities. The improvements in cardiac performance of VSG mice might be more beneficial for patients with pre-existent heart conditions. Comparative studies in clinical populations will be essential to refine our understanding of these treatments and guide their application in obesity and metabolic disease management.

LIMITATIONS

There are some limitations to this study, despite the valuable insights provided into the comparative effects of VSG and semaglutide treatment. This work is primarily descriptive, lacking deeper mechanistic exploration, which restricts a comprehensive understanding of the pathways underlying the observed outcomes. The mouse model, while informative, may not fully replicate human physiology, necessitating future studies to confirm these findings in human populations. This includes exploring the molecular mechanisms driving the observed differences and evaluating the prolonged safety and efficacy of VSG and semaglutide in clinical settings. Our study characterized overall metabolic changes and functional parameters related to bone and heart health, but future investigations should expand to include additional tissues and organs, such as the pancreas, liver, and brain. Moreover, a more detailed analysis of hormonal and microbiota regulation could yield valuable insights into how these treatments can be optimized and tailored to individual patient needs. We only included male mice in the current study, future studies using female mice are necessary to determine potential sexual dimorphism in response to semaglutide treatment, as women lose more weight in response to semaglutide (95). In addition, the influence of sex on tissue weight loss, such as the proportion of fat versus lean mass, as well as cardiac function, needs further investigation, including comparisons between rodents and humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

GRANTS

DATA AVAILABILITY

Data will be made available upon reasonable request.

REFERENCES

1. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol 9: 13–27, 2013. doi:10.1038/nrendo.2012.199. [PubMed: 23165161]

2. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 10, Suppl 3: 97S–104S, 2002. doi:10.1038/oby.2002.202. [PubMed: 12490658]

3. Evans M, de Courcy J, de Laguiche E, Faurby M, Haase CL, Matthiessen KS, Moore A, Pearson-Stuttard J. Obesity-related complications, healthcare resource use and weight loss strategies in six

European countries: the RESOURCE survey. Int J Obes (Lond) 47: 750–757, 2023. doi:10.1038/s41366-023-01325-1. [PubMed: 37258646]

4. Valenzuela PL, Carrera-Bastos P, Castillo-Garcia A, Lieberman DE, Santos-Lozano A, Lucia A. Obesity and the risk of cardiometabolic diseases. Nat Rev Cardiol 20: 475–494, 2023. doi:10.1038/s41569-023-00847-5. [PubMed: 36927772]

5. Okunogbe A, Nugent R, Spencer G, Powis J, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for 161 countries. BMJ Glob Health 7: e009773, 2022. doi:10.1136/bmjgh-2022-009773.

6. Shen Y, Zhang B, Hu X, Zhang N, Huang Y, Han T, Sun X, Xiang X, Bi Y, Tang W, Feng W. Metabolic surgery results in greater metabolic benefits in patients who achieve healthy weight. Surg Obes Relat Dis 20: 925–934, 2024. doi:10.1016/j.soard.2024.04.013. [PubMed: 38749782]

7. Konttinen H, Sjoholm K, Carlsson LMS, Peltonen M, Svensson PA. Fifteen-year changes in health-related quality of life after bariatric surgery and non-surgical obesity treatment. Int J Obes (Lond) 48: 1447–1456, 2024. doi:10.1038/s41366-024-01572-w. [PubMed: 38902388]

8. Rizzello M, Abbatini F, Casella G, Alessandri G, Fantini A, Leonetti F, Basso N. Early postoperative insulin-resistance changes after sleeve gastrectomy. Obes Surg 20: 50–55, 2010. doi:10.1007/s11695-009-0017-2. [PubMed: 19916040]

9. Benaiges D, Flores Le-Roux JA, Pedro-Botet J, Chillaron JJ, Renard M, Parri A, Ramon JM, Pera M, Goday A. Sleeve gastrectomy and Roux-en-Y gastric bypass are equally effective in correcting insulin resistance. Int J Surg 11: 309–313, 2013. doi:10.1016/j.ijsu.2013.02.007. [PubMed: 23462580]

10. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: state of the art. Nat Rev Gastroenterol Hepatol 14: 160–169, 2017. doi:10.1038/nrgastro.2016.170. [PubMed: 27899816]

11. Cavin JB, Bado A, Le Gall M. Intestinal adaptations after bariatric surgery: consequences on glucose homeostasis. Trends Endocrinol Metab 28: 354–364, 2017. doi:10.1016/j.tem.2017.01.002. [PubMed: 28209316]

12. Li Z, Hardij J, Evers SS, Hutch CR, Choi SM, Shao Y, Learman BS, Lewis KT, Schill RL, Mori H, Bagchi DP, Romanelli SM, Kim KS, Bowers E, Griffin C, Seeley RJ, Singer K, Sandoval DA, Rosen CJ, MacDougald OA. G-CSF partially mediates effects of sleeve gastrectomy on the bone marrow niche. J Clin Invest 129: 2404–2416, 2019. doi:10.1172/JCI126173. [PubMed: 31063988]

13. Hutch CR, Sandoval D. The role of GLP-1 in the metabolic success of bariatric surgery. Endocrinology 158: 4139–4151, 2017 [Erratum in Endocrinology 165: bqae042, 2024]. doi:10.1210/en.2017-00564. [PubMed: 29040429]

14. Çalık Ba aran N, Dotan I, Dicker D. Post metabolic bariatric surgery weight regain: the importance of GLP-1 levels (Preprint). Int J Obes (Lond), 2024. doi:10.1038/s41366-024-01461-2.

15. Lin K, Mehrotra A, Tsai TC. Metabolic bariatric surgery in the era of GLP-1 receptor agonists for obesity management. JAMA Netw Open 7: e2441380, 2024 [Erratum in JAMA Netw Open 8: e251603, 2025]. doi:10.1001/jamanetworkopen.2024.41380. [PubMed: 39453660]

16. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, Joles JA, van Raalte DH. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol 13: 605–628, 2017. doi:10.1038/nrneph.2017.123. [PubMed: 28869249]

17. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C, Gao J. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther 9: 234, 2024. doi:10.1038/s41392-024-01931-z. [PubMed: 39289339]

18. Reardon S. How 'miracle' weight-loss drugs will change the world. Nature 635: 22–24, 2024. doi:10.1038/d41586-024-03589-7. [PubMed: 39501120]

19. Wong ND, Karthikeyan H, Fan W. US population eligibility and estimated impact of semaglutide treatment on obesity prevalence and cardiovascular disease events. Cardiovasc Drugs Ther 39: 75–84, 2025. doi:10.1007/s10557-023-07488-3. [PubMed: 37578663]

20. Kim J, Nimeri A, Khorgami Z, El Chaar M, Lima AG, Vosburg RW; American Society for Metabolic and Bariatric Surgery (ASMBS) Clinical Issues Committee. Metabolic bone changes after bariatric surgery: 2020 update, American Society for Metabolic and Bariatric Surgery

Clinical Issues Committee position statement. Surg Obes Relat Dis 17: 1–8, 2021. doi:10.1016/j.soard.2020.09.031. [PubMed: 33162343]

21. Corbeels K, Verlinden L, Lannoo M, Simoens C, Matthys C, Verstuyf A, Meulemans A, Carmeliet G, Van der Schueren B. Thin bones: vitamin D and calcium handling after bariatric surgery. Bone Rep 8: 57–63, 2018. doi:10.1016/j.bonr.2018.02.002. [PubMed: 29955623]

22. Gagnon C, Schafer AL. Bone health after bariatric surgery. JBMR Plus 2: 121–133, 2018. doi:10.1002/jbm4.10048. [PubMed: 30283897]

23. Stein EM, Silverberg SJ. Bone loss after bariatric surgery: causes, consequences, and management. Lancet Diabetes Endocrinol 2: 165–174, 2014. doi:10.1016/S2213-8587(13)70183-9. [PubMed: 24622720]

24. Iepsen EW, Lundgren JR, Hartmann B, Pedersen O, Hansen T, Jorgensen NR, Jensen JE, Holst JJ, Madsbad S, Torekov SS. GLP-1 receptor agonist treatment increases bone formation and prevents bone loss in weight-reduced obese women. J Clin Endocrinol Metab 100: 2909–2917, 2015. doi:10.1210/jc.2015-1176. [PubMed: 26043228]

25. Jensen SBK, Sørensen V, Sandsdal RM, Lehmann EW, Lundgren JR, Juhl CR, Janus C, Ternhamar T, Stallknecht BM, Holst JJ, Jørgensen NR, Jensen JB, Madsbad S, Torekov SS. Bone health after exercise alone, GLP-1 receptor agonist treatment, or combination treatment: a secondary analysis of a randomized clinical trial. JAMA Netw Open 7: e2416775, 2024. doi:10.1001/jamanetworkopen.2024.16775. [PubMed: 38916894]

26. Hygum K, Harslof T, Jorgensen NR, Rungby J, Pedersen SB, Langdahl BL. Bone resorption is unchanged by liraglutide in type 2 diabetes patients: a randomised controlled trial. Bone 132: 115197, 2020. doi:10.1016/j.bone.2019.115197. [PubMed: 31870634]

27. Neeland IJ, Ross R, Déspres JP, Matsuzawa Y, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB, Griffin B, Zambon A, Barter P, Fruchart JC, Eckel RH; International Atherosclerosis Society; International Chair on Cardiometabolic Risk Working Group on Visceral Obesity. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol 7: 715–725, 2019. doi:10.1016/S2213-8587(19)30084–1. [PubMed: 31301983]

28. Abbasi SA, Hundley WG, Bluemke DA, Jerosch-Herold M, Blankstein R, Petersen SE, Rider OJ, Lima JA, Allison MA, Murthy VL, Shah RV. Visceral adiposity and left ventricular remodeling: the Multi-Ethnic Study of Atherosclerosis. Nutr Metab Cardiovasc Dis 25: 667–676, 2015. doi:10.1016/j.numecd.2015.03.016. [PubMed: 26033394]

29. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA 292: 1724–1737, 2004 [Erratum in JAMA. 293: 1728, 2005]. doi:10.1001/jama.292.14.1724. [PubMed: 15479938]

30. Doumouras AG, Wong JA, Paterson JM, Lee Y, Sivapathasundaram B, Tarride JE, Thabane L, Hong D, Yusuf S, Anvari M. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease: a population-based retrospective cohort study. Circulation 143: 1468–1480, 2021. doi:10.1161/CIRCULATIONAHA.120.052386. [PubMed: 33813836]

31. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, Rosenstock J, Gerstein HC. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 9: 653–662, 2021. doi:10.1016/S2213-8587(21)00203–5. [PubMed: 34425083]

32. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 389: 2221–2232, 2023. doi:10.1056/NEJMoa2307563. [PubMed: 37952131]

33. Neves JS, Packer M, Ferreira JP. Increased risk of heart failure hospitalization with GLP-1 receptor agonists in patients with reduced ejection fraction: a meta-analysis of the EXSCEL and FIGHT trials. J Card Fail 29: 1107–1109, 2023. doi:10.1016/j.cardfail.2023.03.017. [PubMed: 37028749]

34. Lorenz M, Lawson F, Owens D, Raccah D, Roy-Duval C, Lehmann A, Perfetti R, Blonde L. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. Cardiovasc Diabetol 16: 6, 2017. doi:10.1186/s12933-016-0490-6. [PubMed: 28086882]

35. Lubberding AF, Veedfald S, Achter JS, Nissen SD, Soattin L, Sorrentino A, Vega ET, Linz B, Eggertsen CHE, Mulvey J, Torang S, Larsen SA, Nissen A, Petersen LG, Bilir SE, Bentzen BH, Rosenkilde MM, Hartmann B, Lilleor TNB, Qazi S, Moller CH, Tfelt-Hansen J, Sattler SM, Jespersen T, Holst JJ, Lundby A. Glucagon-like peptide-1 increases heart rate by a direct action on the sinus node. Cardiovasc Res 120: 1427–1441, 2024. doi:10.1093/cvr/cvae120. [PubMed: 38832935]

36. Bozadjieva-Kramer N, Shin JH, Blok NB, Jain C, Das NK, Polex-Wolf J, Knudsen LB, Shah YM, Seeley RJ. Liraglutide impacts iron homeostasis in a murine model of hereditary hemochromatosis. Endocrinology 165: bqae090, 2024. doi:10.1210/endocr/bqae090. [PubMed: 39045670]

37. DeMambro VE, Le PT, Guntur AR, Maridas DE, Canalis E, Nagano K, Baron R, Clemmons DR, Rosen CJ. Igfbp2 deletion in ovariectomized mice enhances energy expenditure but accelerates bone loss. Endocrinology 156: 4129–4140, 2015. doi:10.1210/en.2014-1452. [PubMed: 26230658]

38. Maridas DE, Rendina-Ruedy E, Helderman RC, DeMambro VE, Brooks D, Guntur AR, Lanske B, Bouxsein ML, Rosen CJ. Progenitor recruitment and adipogenic lipolysis contribute to the anabolic actions of parathyroid hormone on the skeleton. FASEB J 33: 2885–2898, 2019. doi:10.1096/fj.201800948RR. [PubMed: 30354669]

39. Dahl K, Brooks A, Almazedi F, Hoff ST, Boschini C, Baekdal TA. Oral semaglutide improves postprandial glucose and lipid metabolism, and delays gastric emptying, in subjects with type 2 diabetes. Diabetes Obes Metab 23: 1594–1603, 2021. doi:10.1111/dom.14373. [PubMed: 33710717]

40. Hjerpsted JB, Flint A, Brooks A, Axelsen MB, Kvist T, Blundell J. Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity. Diabetes Obes Metab 20: 610–619, 2018. doi:10.1111/dom.13120. [PubMed: 28941314]

41. Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes. Gastroenterology 143: 897–912, 2012. doi:10.1053/j.gastro.2012.07.114. [PubMed: 22885332]

42. Xia J, He Q, He M, Xu G, Tang Y, Ren Y. Residual gastric dilatation interferes with metabolic improvements following sleeve gastrectomy by upregulating the expression of sodium-glucose cotransporter-1. Obes Surg 29: 3324–3333, 2019. doi:10.1007/s11695-019-03997-z. [PubMed: 31201691]

43. Li Z, Rosen CJ. The multifaceted roles of bone marrow adipocytes in bone and hematopoietic homeostasis. J Clin Endocrinol Metab 108: e1465–e1472, 2023. doi:10.1210/clinem/dgad355. [PubMed: 37315208]

44. Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, Baron R, Rosen CJ, Bouxsein ML. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. J Bone Miner Res 25: 2078–2088, 2010. doi:10.1002/jbmr.82. [PubMed: 20229598]

45. Iglesias-Garriz I, Alonso D, Garrote C, Casares V, Vara J, De la Torre JM, Rodriguez MA, Fernandez-Vazquez F. Scaling echocardiographic cardiac dimensions to body size: a bayesian analysis in healthy men and women. J Cardiovasc Imaging 28: 10–17, 2020. doi:10.4250/jcvi.2019.0056. [PubMed: 31805619]

46. Seo JS, Lee SY, Won KJ, Kim DJ, Sohn DS, Yang KM, Cho SH, Park JD, Lee KH, Kim HD. Relationship between normal heart size and body indices in Korean. J Korean Med Sci 15: 641–646, 2000. doi:10.3346/jkms.2000.15.6.641. [PubMed: 11194190]

47. Arble DM, Sandoval DA, Seeley RJ. Mechanisms underlying weight loss and metabolic improvements in rodent models of bariatric surgery. Diabetologia 58: 211–220, 2015. doi:10.1007/s00125-014-3433-3. [PubMed: 25374275]

48. Albaugh VL, He Y, Münzberg H, Morrison CD, Yu S, Berthoud HR. Regulation of body weight: lessons learned from bariatric surgery. Mol Metab 68: 101517, 2023. doi:10.1016/j.molmet.2022.101517. [PubMed: 35644477]

49. Shin JH, Bozadjieva-Kramer N, Shao Y, Lyons-Abbott S, Rupp AC, Sandoval DA, Seeley RJ. The gut peptide Reg3g links the small intestine microbiome to the regulation of energy balance, glucose levels, and gut function. Cell Metab 34: 1765–1778.e6, 2022. doi:10.1016/j.cmet.2022.09.024. [PubMed: 36240758]

50. Akalestou E, Miras AD, Rutter GA, Le Roux CW. Mechanisms of weight loss after obesity surgery. Endocr Rev 43: 19–34, 2022. doi:10.1210/endrev/bnab022. [PubMed: 34363458]

51. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol 28: 391–402, 2015. doi:10.1038/modpathol.2014.113. [PubMed: 25216224]

52. Nakashima K, Kaneto H, Shimoda M, Kimura T, Kaku K. Pancreatic alpha cells in diabetic rats express active GLP-1 receptor: endosomal co-localization of GLP-1/GLP-1R complex functioning through intraislet paracrine mechanism. Sci Rep 8: 3725, 2018. doi:10.1038/s41598-018-21751-w. [PubMed: 29487355]

53. Marchetti P, Lupi R, Bugliani M, Kirkpatrick CL, Sebastiani G, Grieco FA, Del Guerra S, D'Aleo V, Piro S, Marselli L, Boggi U, Filipponi F, Tinti L, Salvini L, Wollheim CB, Purrello F, Dotta F. A local glucagon-like peptide 1 (GLP-1) system in human pancreatic islets. Diabetologia 55: 3262–3272, 2012. doi:10.1007/s00125-012-2716-9. [PubMed: 22965295]

54. Fujinaga A, Ohta M, Endo Y, Nakanuma H, Kawamura M, Hirashita Y, Kawasaki T, Masuda T, Hirashita T, Gotoh K, Inomata M. Changes of short-chain fatty acids and their receptors in an obese rat model after sleeve gastrectomy. Obes Surg 32: 2649–2657, 2022. doi:10.1007/s11695-022-06130-9. [PubMed: 35648365]

55. Cao N, Merchant W, Gautron L. Limited evidence for anatomical contacts between intestinal GLP-1 cells and vagal neurons in male mice. Sci Rep 14: 23666, 2024. doi:10.1038/s41598-024-74000-8. [PubMed: 39390033]

56. Hviid AVR, Sørensen CM. Glucagon-like peptide-1 receptors in the kidney: impact on renal autoregulation. Am J Physiol Renal Physiol 318: F443–F454, 2020. doi:10.1152/ajprenal.00280.2019. [PubMed: 31841385]

57. Fu Z, Gong L, Liu J, Wu J, Barrett EJ, Aylor KW, Liu Z. Brain endothelial cells regulate glucagon-like peptide 1 entry into the brain via a receptor-mediated process. Front Physiol 11: 555, 2020. doi:10.3389/fphys.2020.00555. [PubMed: 32547420]

58. Ruze R, Xu Q, Liu G, Li Y, Chen W, Cheng Z, Xiong Y, Liu S, Zhang G, Hu S, Yan Z. Central GLP-1 contributes to improved cognitive function and brain glucose uptake after duodenum-jejunum bypass on obese and diabetic rats. Am J Physiol Endocrinol Physiol 321: E392–E409, 2021. doi:10.1152/ajpendo.00126.2021.

59. Vendrell J, El Bekay R, Peral B, García-Fuentes E, Megia A, Macias-Gonzalez M, Fernández Real J, Jimenez-Gomez Y, Escoté X, Pachón G, Simó R, Selva DM, Malagón MM, Tinahones FJ. Study of the potential association of adipose tissue GLP-1 receptor with obesity and insulin resistance. Endocrinology 152: 4072–4079, 2011. doi:10.1210/en.2011-1070. [PubMed: 21862620]

60. MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 51, Suppl 2: S434–S442, 2002. doi:10.2337/diabetes.51.2007.s434. [PubMed: 12475787]

61. Bu T, Sun Z, Pan Y, Deng X, Yuan G. Glucagon-like peptide-1: new regulator in lipid metabolism. Diabetes Metab J 48: 354–372, 2024. doi:10.4093/dmj.2023.0277. [PubMed: 38650100]

62. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes Obes Metab 23: 754–762, 2021. doi:10.1111/dom.14280. [PubMed: 33269530]

63. Drucker DJ. The biology of incretin hormones. Cell Metab 3: 153–165, 2006. doi:10.1016/j.cmet.2006.01.004. [PubMed: 16517403]

64. Fidilio E, Comas M, Giribes M, Cardenas G, Vilallonga R, Palma F, Pelaez RB, Simo R, Ciudin A. Evaluation of resting energy expenditure in subjects with severe obesity and its evolution after bariatric surgery. Obes Surg 31: 4347–4355, 2021. doi:10.1007/s11695-021-05578-5. [PubMed: 34345955]

65. Mirahmadian M, Hasani M, Taheri E, Qorbani M, Hosseini S. Influence of gastric bypass surgery on resting energy expenditure, body composition, physical activity, and thyroid hormones in morbidly obese patients. Diabetes Metab Syndr Obes 11: 667–672, 2018. doi:10.2147/DMSO.S172028. [PubMed: 30425544]

66. Thivel D, Brakonieki K, Duche P, Morio B, Boirie Y, Laferrere B. Surgical weight loss: impact on energy expenditure. Obes Surg 23: 255–266, 2013 [Erratum in Obes Surg 23: 734, 2013]. doi:10.1007/s11695-012-0839-1. [PubMed: 23224568]

67. Tan TM, Field BC, McCullough KA, Troke RC, Chambers ES, Salem V, Gonzalez Maffe J, Baynes KC, De Silva A, Viardot A, Alsafi A, Frost GS, Ghatei MA, Bloom SR. Coadministration of glucagon-like peptide-1 during glucagon infusion in humans results in increased energy expenditure and amelioration of hyperglycemia. Diabetes 62: 1131–1138, 2013. doi:10.2337/db12-0797. [PubMed: 23248172]

68. van Eyk HJ, Paiman EHM, Bizino MB, IJzermans SL, Kleiburg F, Boers TGW, Rappel EJ, Burakiewicz J, Kan HE, Smit JWA, Lamb HJ, Jazet IM, Rensen PCN. Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 30: 616–624, 2020. doi:10.1016/j.numecd.2019.12.005. [PubMed: 32127340]

69. Maciel MG, Beserra BTS, Oliveira FCB, Ribeiro CM, Coelho MS, Neves FAR, Amato AA. The effect of glucagon-like peptide 1 and glucagon-like peptide 1 receptor agonists on energy expenditure: a systematic review and meta-analysis. Diabetes Res Clin Pract 142: 222–235, 2018. doi:10.1016/j.diabres.2018.05.034. [PubMed: 29857094]

70. Bergmann NC, Lund A, Gasbjerg LS, Meessen ECE, Andersen MM, Bergmann S, Hartmann B, Holst JJ, Jessen L, Christensen MB, Vilsboll T, Knop FK. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. Diabetologia 62: 665–675, 2019. doi:10.1007/s00125-018-4810-0. [PubMed: 30683945]

71. Tipa RO, Balan DG, Georgescu MT, Ignat LA, Vacaroiu IA, Georgescu DE, Raducu L, Mihai DA, Chiperi LV, Balcangiu-Stroescu AE. A systematic review of semaglutide's influence on cognitive function in preclinical animal models and cell-line studies. Int J Mol Sci 25: 4972, 2024. doi:10.3390/ijms25094972. [PubMed: 38732190]

72. Trapp S, Brierley DI. Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. Br J Pharmacol 179: 557–570, 2022. doi:10.1111/bph.15638. [PubMed: 34323288]

73. Poupon-Bejuit L, Hughes MP, Liu W, Geard A, Faour-Slika N, Whaler S, Massaro G, Rahim AA. A GLP1 receptor agonist diabetes drug ameliorates neurodegeneration in a mouse model of infantile neurometabolic disease. Sci Rep 12: 13825, 2022. doi:10.1038/s41598-022-17338-1. [PubMed: 35970890]

74. Auge M, Menahem B, Savey V, Lee Bion A, Alves A. Long-term complications after gastric bypass and sleeve gastrectomy: what information to give to patients and practitioners, and why? J Visc Surg 159: 298–308, 2022. doi:10.1016/j.jviscsurg.2022.02.004. [PubMed: 35304081]

75. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults: a review. JAMA 324: 879–887, 2020. doi:10.1001/jama.2020.12567. [PubMed: 32870301]

76. Law S, Dong S, Zhou F, Zheng D, Wang C, Dong Z. Bariatric surgery and mental health outcomes: an umbrella review. Front Endocrinol (Lausanne) 14: 1283621, 2023. doi:10.3389/fendo.2023.1283621. [PubMed: 38027159]

77. Alyahya RA, Alnujaidi MA. Prevalence and outcomes of depression after bariatric surgery: a systematic review and meta-analysis. Cureus 14: e25651, 2022. doi:10.7759/cureus.25651. [PubMed: 35784972]

78. Hofsø D, Hillestad TOW, Halvorsen E, Fatima F, Johnson LK, Lindberg M, Svanevik M, Sandbu R, Hjelmesæth J. Bone mineral density and turnover after sleeve gastrectomy and gastric bypass: a Randomized Controlled Trial (Oseberg). J Clin Endocrinol Metab 106: 501–511, 2021. doi:10.1210/clinem/dgaa808. [PubMed: 33150385]

79. Beavers KM, Greene KA, Yu EW. Management of endocrine disease: bone complications of bariatric surgery: updates on sleeve gastrectomy, fractures, and interventions. Eur J Endocrinol 183: R119–R132, 2020. doi:10.1530/EJE-20-0548. [PubMed: 32869608]

80. Yu EW, Lee MP, Landon JE, Lindeman KG, Kim SC. Fracture risk after bariatric surgery: Roux-en-Y gastric bypass versus adjustable gastric banding. J Bone Miner Res 32: 1229–1236, 2017. doi:10.1002/jbmr.3101. [PubMed: 28251687]

81. Farup PG. Changes in bone turnover markers 6–12 months after bariatric surgery. Sci Rep 14: 14844, 2024. doi:10.1038/s41598-024-65952-y. [PubMed: 38937532]

82. Schafer AL, Kazakia GJ, Vittinghoff E, Stewart L, Rogers SJ, Kim TY, Carter JT, Posselt AM, Pasco C, Shoback DM, Black DM. Effects of gastric bypass surgery on bone mass and microarchitecture occur early and particularly impact postmenopausal women. J Bone Miner Res 33: 975–986, 2018. doi:10.1002/jbmr.3371. [PubMed: 29281126]

83. Pacheco-Pantoja EL, Ranganath LR, Gallagher JA, Wilson PJ, Fraser WD. Receptors and effects of gut hormones in three osteoblastic cell lines. BMC Physiol 11: 12, 2011. doi:10.1186/1472-6793-11-12. [PubMed: 21801348]

84. Pereira M, Jeyabalan J, Jorgensen CS, Hopkinson M, Al-Jazzar A, Roux JP, Chavassieux P, Orriss IR, Cleasby ME, Chenu C. Chronic administration of glucagon-like peptide-1 receptor agonists improves trabecular bone mass and architecture in ovariectomised mice. Bone 81: 459–467, 2015. doi:10.1016/j.bone.2015.08.006. [PubMed: 26314515]

85. Wu X, Li S, Xue P, Li Y. Liraglutide, a glucagon-like peptide-1 receptor agonist, facilitates osteogenic proliferation and differentiation in MC3T3-E1 cells through phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), extracellular signal-related kinase (ERK)1/2, and cAMP/protein kinase A (PKA) signaling pathways involving beta-catenin. Exp Cell Res 360: 281–291, 2017. doi:10.1016/j.yexcr.2017.09.018. [PubMed: 28919123]

86. Li Z, Li S, Wang N, Xue P, Li Y. Liraglutide, a glucagon-like peptide-1 receptor agonist, suppresses osteoclastogenesis through the inhibition of NF-kappaB and MAPK pathways via GLP-1R. Biomed Pharmacother 130: 110523, 2020. doi:10.1016/j.biopha.2020.110523. [PubMed: 32702632]

87. Mansur SA, Mieczkowska A, Bouvard B, Flatt PR, Chappard D, Irwin N, Mabilleau G. Stable incretin mimetics counter rapid deterioration of bone quality in type 1 diabetes mellitus. J Cell Physiol 230: 3009–3018, 2015. doi:10.1002/jcp.25033. [PubMed: 26016732]

88. Hansen MS, Wölfel EM, Jeromdesella S, Moller JK, Ejersted C, Jorgensen NR, Eastell R, Hansen SG, Frost M. Once-weekly semaglutide versus placebo in adults with increased fracture risk: a randomised, double-blinded, two-centre, phase 2 trial. EClinicalMedicine 72: 102624, 2024. doi:10.1016/j.eclinm.2024.102624. [PubMed: 38737002]

89. Chandrakumar H, Khatun N, Gupta T, Graham-Hill S, Zhyvotovska A, McFarlane SI. The effects of bariatric surgery on cardiovascular outcomes and cardiovascular mortality: a systematic review and meta-analysis. Cureus 15: e34723, 2023. doi:10.7759/cureus.34723. [PubMed: 36909063]

90. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol 26: 968–976, 2006. doi:10.1161/01.ATV.0000216787.85457.f3. [PubMed: 16627822]

91. Nijhuis J, van Dielen FM, Fouraschen SM, van den Broek MA, Rensen SS, Buurman WA, Greve JW. Endothelial activation markers and their key regulators after restrictive bariatric surgery. Obesity (Silver Spring) 15: 1395–1399, 2007. doi:10.1038/oby.2007.167. [PubMed: 17557976]

92. Lin LY, Lee WJ, Shen HN, Yang WS, Pai NH, Su TC, Liau CS. Nitric oxide production is paradoxically decreased after weight reduction surgery in morbid obesity patients. Atherosclerosis 190: 436–442, 2007. doi:10.1016/j.atherosclerosis.2006.02.033. [PubMed: 16546195]

93. Ashrafian H, le Roux CW, Darzi A, Athanasiou T. Effects of bariatric surgery on cardiovascular function. Circulation 118: 2091–2102, 2008. doi:10.1161/CIRCULATIONAHA.107.721027. [PubMed: 19001033]

94. Bariatric metabolic surgery is associated with a lower risk for heart failure versus GLP-1RAs. Nat Med 30: 2417–2418, 2024. doi:10.1038/s41591-024-03120-5. [PubMed: 39009781]

95. Ryan DH, Lingvay I, Deanfield J, Kahn SE, Barros E, Burguera B, Colhoun HM, Cercato C, Dicker D, Horn DB, Hovingh GK, Jeppesen OK, Kokkinos A, Lincoff AM, Meyhöfer SM, Oral TK, Plutzky J, van Beek AP, Wilding JPH, Kushner RF. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. Nat Med 30: 2049–2057, 2024. doi:10.1038/s41591-024-02996-7. [PubMed: 38740993]
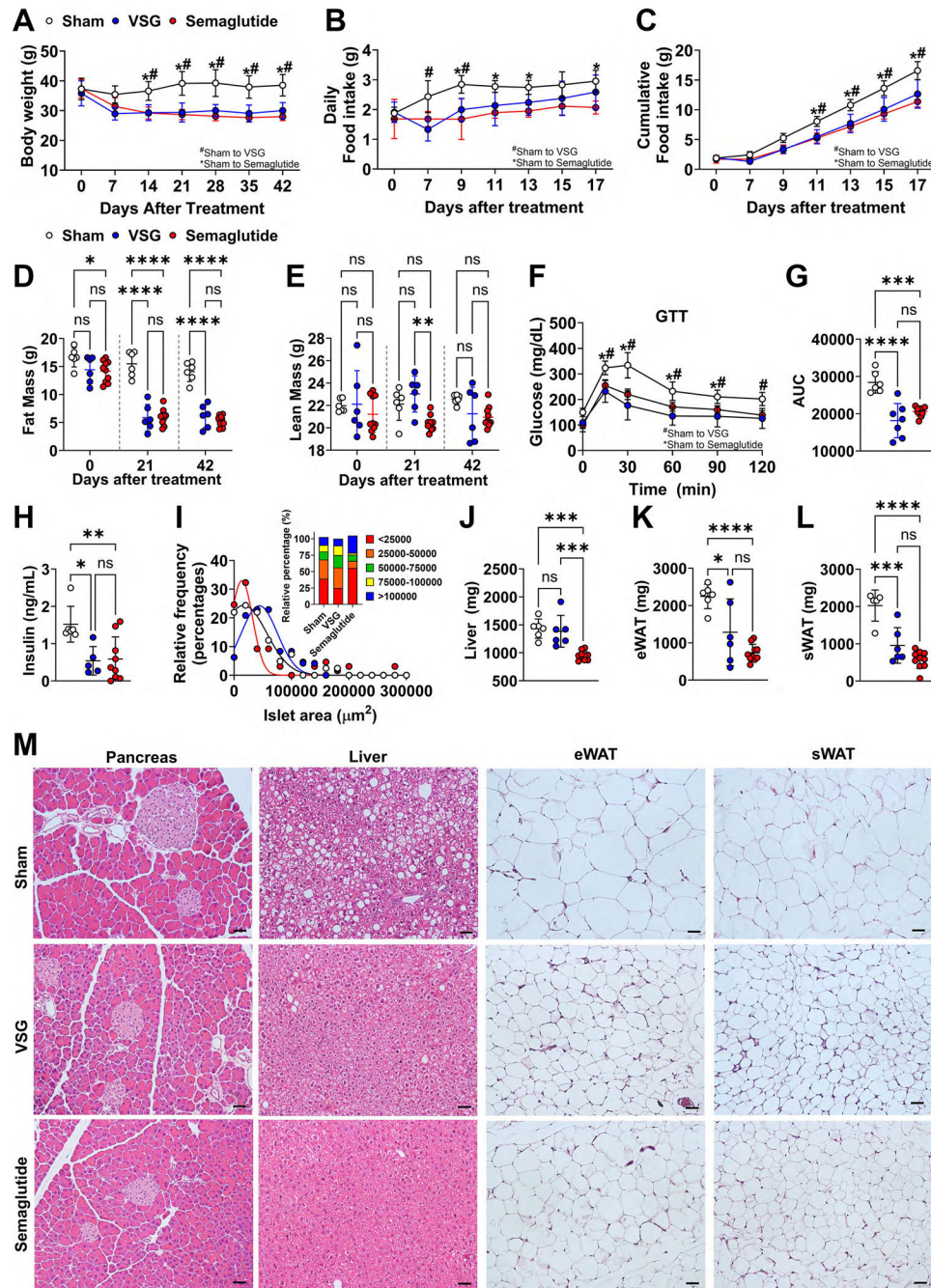
Figure 1.

Semaglutide and VSG reduce body weight and improve glucose metabolism in diet-induced obese (DIO) mice. Male C57BL/6J mice were fed an HFD starting from 6 wk old and lasted for 8 wk before vertical sleeve gastrectomy (VSG) or semaglutide treatment. Mice were euthanized 6 wk after treatments. Body weight was monitored weekly (*A*); daily food intake (*B*) and cumulative food intake (*C*) were measured every 2 days from *day 0* to *day 17*. Fat mass (*D*) and lean mass (*E*) were measured by DEXA at *days 0, 21,* and *42*. *F*: intraperitoneal glucose tolerance test (IPGTT; Supplemental Methods) was performed

at *week 4* after treatments. *G*: area under the curve (AUC) was calculated. *H*: circulating insulin concentrations were measured by ELISA. *I*: pancreatic islet sizes were quantified by ImageJ and relative frequency of size distribution was calculated by GraphPad Prism. Soft tissue, including liver (*J*), eWAT (*K*), and sWAT (*L*), weights were measured at the end of study. *M*: representative images of pancreas, liver, eWAT, and sWAT were taken under light microscope at ×20 following paraffin section and H&E staining (Supplemental Methods). Scale bar: 50 lm. Data are expressed as means ± SD. * or #$P < 0.05$; **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$ with a two-way ANOVA (*A–F*) and one-way ANOVA test (*G, H,* and *J–L*). DEXA, dual-energy X-ray absorptiometry; eWAT, epididymal white adipose tissue; H&E, hematoxylin-eosin; sWAT, subcutaneous white adipose tissue.
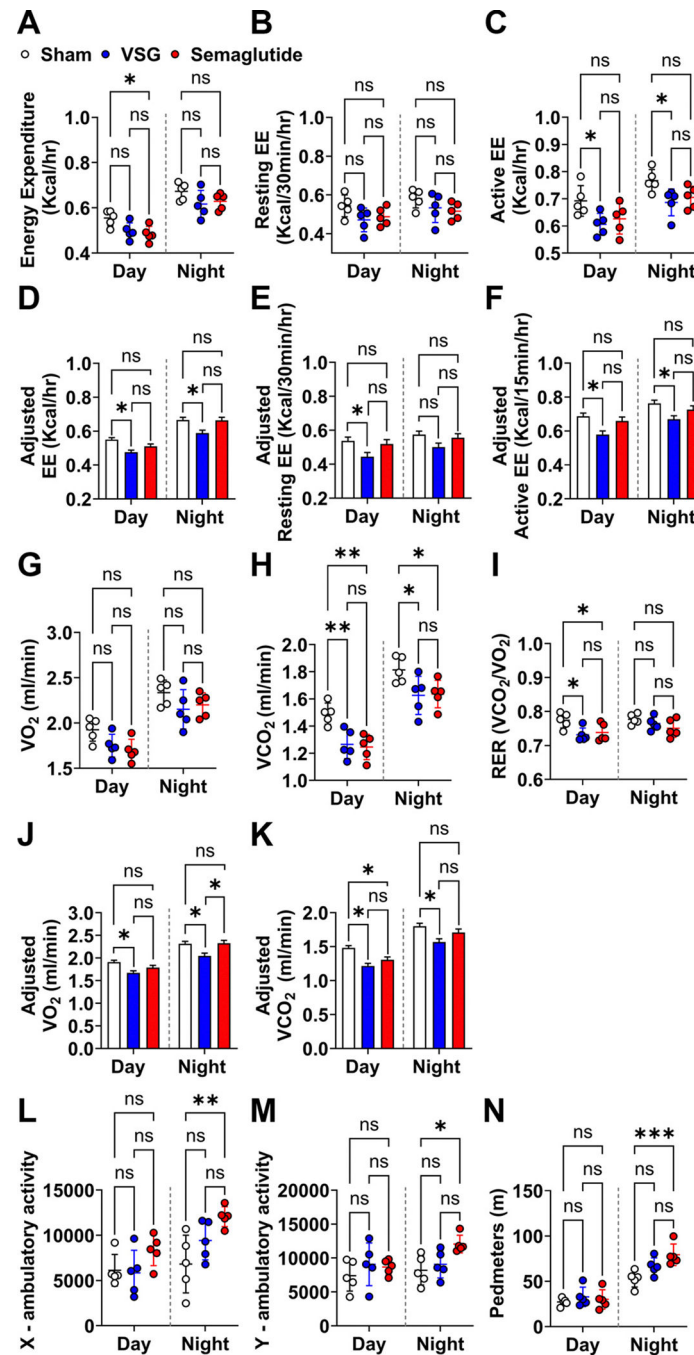
Figure 2.
Metabolic cages. A subgroup of mice from each treatment was placed into metabolic cages at 5 wk after treatment for 72 h. Total energy expenditure (EE; *A*), resting EE (*B*), and active EE (*C*) were measured and adjusted to lean mass, which are shown as adjusted EE (*D*), adjusted resting EE (*E*), and adjusted active EE (*F*). Oxygen consumption ($\dot{V}O_2$; *G*, CO_2 production ($\dot{V}CO_2$; H), and respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$; *I*) were measured, and $\dot{V}O_2$ and $\dot{V}CO_2$ were adjusted to lean mass, which are shown as adjusted $\dot{V}O_2$ (*J*) and adjusted $\dot{V}CO_2$ (*K*). X-ambulatory activity (*L*), Y-ambulatory activity (*M*), and pedestrian

locomotion (PedMeters; N) were determined. Data are expressed as means ± SD. *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$ with two-way ANOVA.
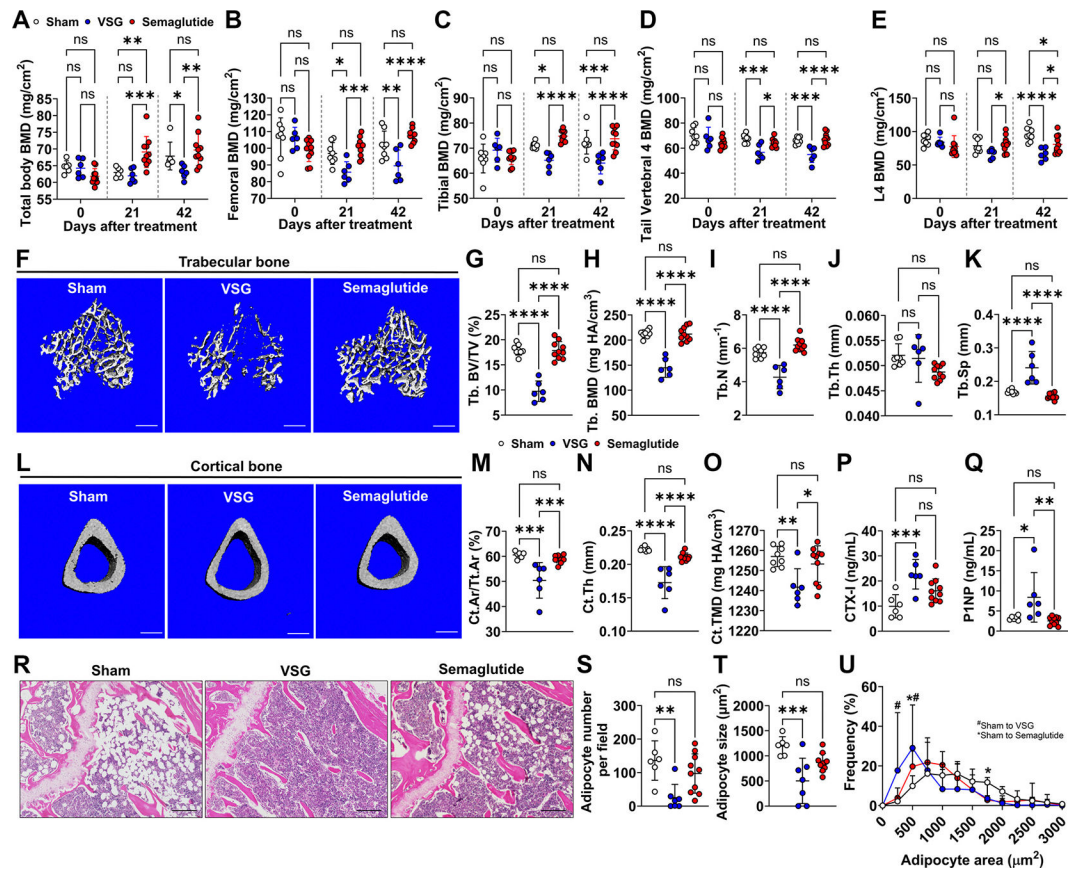
Figure 3.

VSG reduces bone mass while semaglutide preserves the bone. Bone mineral density (BMD) for total body (*A*), femur (*B*), tibia (*C*), tail vertebral 4 (*D*), and lumbar vertebral 4 (L4; *E*) were measured by DEXA at baseline (*day 0*), *day 21*, and *day 42* after treatments. *F*: representative 3-D images of trabecular bone in proximal tibiae. Scale bar: 500 μm. Trabecular bone volume fraction (Tb.BV/TV; *G*), BMD (*H*), number (Tb.N; *I*), thickness (Tb.Th; *J*), and separation (Tb.Sp; *K*) were measured by lCT. *L*: representative 3-D images of cortical bone in midshaft tibiae. Scale bar: 500 μm. Cortical bone area fraction (Ct.Ar/Tt.Ar; *M*), thickness (Ct.Th; *N*), and tissue mineral density (Ct.TMD; *O*) were determined by μCT. Circulating CTX-I (*P*) and P1NP (*Q*) were measured by ELISA assay (Supplemental Methods). *R*: representative images of tibiae were taken under light microscope at ×10 following paraffin section and H&E staining. Scale bar: 200 μm. Adipocyte number per field (*S*), average adipocyte size (μm^2; *T*), and adipocyte size frequency distribution (%; *U*) were quantified. Data are expressed as means ± SD. * or #$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ****$P < 0.0001$ with a two-way ANOVA (*A–E*, and *U*) or one-way ANOVA test (*G–K*, *M–Q*, *S,* and *T*). 3-D, three-dimensional; DEXA, dual-energy X-ray absorptiometry; H&E, hematoxylin-eosin; μCT, microcomputed tomography; VSG, vertical sleeve gastrectomy.
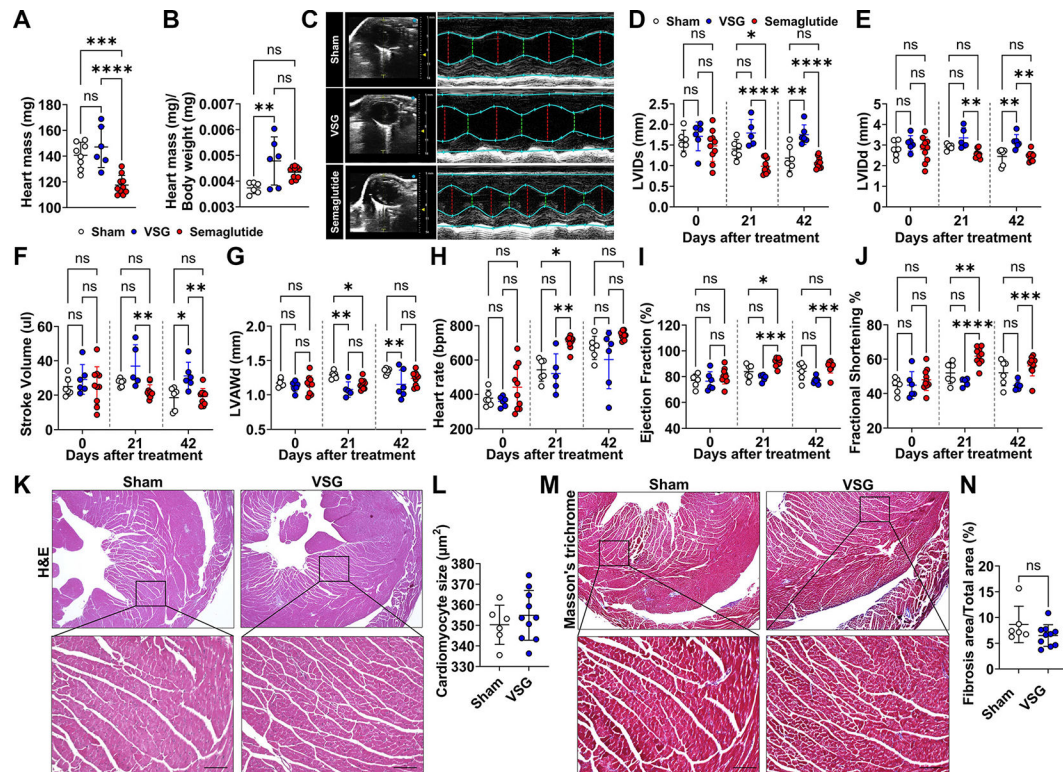
Figure 4.
VSG improves heart function while semaglutide has a transient effect. *A*: heart mass (mg) was determined by the end of study. *B*: ratio of heart mass (mg)/body weight (mg) was calculated. *C*: representative echocardiography (ECHO) images of the left ventricle (LV) display dimensions of the ventricular walls, LV cavity, and cardiac function measurements. LV internal diameters in end-systole (LVIDs; *D*) and end-diastole (LVIDd; *E*), stroke volume (µL; *F*), LV anterior wall in diastole (LVAWd; *G*), heart rate (beats/min; *H*), ejection fraction (%; *I*), and fractional shortening (%; *J*) were determined. *K–N*: another independent cohort with only sham and VSG mice was used to perform the histological analysis. *K* and *L*: H&E staining was used to quantify cardiomyocyte size. *M* and *N*: Masson's trichrome staining was used to highlight collagen fibers and quantify the relative proportion of fibrosis area/total area (%). Scale bar: 100 µm. Data are expressed as means ± SD. *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001 with a one-way ANOVA (*A* and *B*), two-way ANOVA test (*D–J*), or Student's *t* test (*L* and *N*). H&E, hematoxylin-eosin; VSG, vertical sleeve gastrectomy.