Caloric Restriction and Weight Loss Are Primary Factors in the Early Tissue-Specific Metabolic Changes After Bariatric Surgery

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OBJECTIVE

To evaluate changes in insulin sensitivity, hormone secretion, and hepatic steatosis immediately after caloric restriction, vertical sleeve gastrectomy (VSG), and Roux-en-Y gastric bypass (RYGB).

RESEARCH DESIGN AND METHODS

Obese subjects were assessed for *1*) insulin sensitivity with hyperinsulinemic-euglycemic clamp with glucose tracer infusion, *2*) adipokine concentrations with serum and subcutaneous adipose interstitial fluid sampling, and *3*) hepatic fat content with MRI before and 7–10 days after VSG, RYGB, or supervised caloric restriction.

RESULTS

Each group exhibited an ∼5% total body weight loss, accompanied by similar improvements in hepatic glucose production and hepatic, skeletal muscle, and adipose tissue insulin sensitivity. Leptin concentrations in plasma and adipose interstitial fluid were equally decreased, and reductions in hepatic fat were similar.

CONCLUSIONS

The improvements in insulin sensitivity and adipokine secretion observed early after bariatric surgery are replicated by equivalent caloric restriction and weight loss.

Bariatric surgeries including Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) cause substantial and sustained weight loss in obese patients and are superior in the reversal of type 2 diabetes (T2D) compared with medical treatment (1). Improvements in T2D and insulin sensitivity are observed in the initial days and weeks after bariatric surgery (2,3) while weight loss is minimal (4), giving rise to the hypothesis that weight loss–independent mechanisms contribute to the metabolic improvements after bariatric surgery. A recent study contrasting outcomes from RYGB after 16 weeks and from caloric restriction at 23 weeks showed that after an equivalent 18% body weight reduction the rates of glucose disposal and metabolic variables were similarly improved (5). We tested the hypothesis that improvements in insulin resistance observed early after bariatric surgery are due to caloric restriction–dependent weight loss.

RESEARCH DESIGN AND METHODS

Participants in the RYGB and VSG groups were recruited from the Vanderbilt Center for Surgical Weight Loss and studied after informed, written consent was obtained. Participants in the diet group were recruited from the local community. Exclusion criteria included age <18 years or >65 years; smoking; pregnancy or breastfeeding;

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significant renal, hepatic, or cardiovascular disease; recent history of cancer; and previous malabsorptive or restrictive gastrointestinal surgery. This study was approved by the Vanderbilt Institutional Review Board and registered with ClinicalTrials.gov (NCT01474785).

Bariatric surgery participants completed study visits 2–3 before and ~1–2 weeks after surgery. Participants in the diet group completed study visits before and 7–9 days after a post–bariatric surgery diet without bariatric surgery. Each study visit consisted of a hyperinsulinemic-euglycemic clamp, adipose tissue microdialysis, and a body composition measurement. Details of the study methods can be found in Supplementary Material. A subset of subjects underwent hepatic MRI (6). T2D was identified according to prior medical diagnosis or fasting plasma glucose ≥126 mg/dL during the baseline study. Subjects on oral antidiabetes medications discontinued usage 5 days prior to study.

RESULTS

Weight loss occurred in all three groups, with a significant difference among the groups. Mean ± SD weight loss for each group was 4.7 ± 1.4 kg for diet, 7.0 ± 3 kg for RYGB, and 7.2 ± 2.4 kg for VSG (P = 0.013). Subjects in the diet group lost significantly less weight compared with the surgery groups ($P \leq 0.049$). Percent total body weight loss was 5.2 ± 1.5 for RYGB, 5.6 ± 1.7 for VSG, and 3.9 ± 0.9 for diet (P = 0.007) and only significantly different between the VSG and diet groups (P = 0.006). The postintervention study was 8 ± 1 days after diet, 10 ± 3 days after RYGB, and 11 ± 2 days after VSG ($P \geq 0.161$); differences were related to scheduling.

Fasting plasma glucose, insulin, free fatty acid concentrations, and basal endogenous glucose production (EGP) were reduced significantly by equivalent amounts among the groups (Supplementary Table 1). Hepatic insulin sensitivity also improved after RYGB, VSG, and diet ($P < 0.0001$) with no differences among groups (P = 0.730) (Fig. 1*A*). EGP was on average suppressed by ~80% during insulin infusion and improved slightly in all groups. Insulin-stimulated glucose disposal (M) did not significantly change over time or among groups. During the clamp procedure, mean ± SD plasma insulin concentrations were 193 ± 39 μU/mL at the baseline visit and significantly decreased to 170 ± 30 μU/mL at the postintervention study visit with no differences among the groups, corresponding with an increased clearance rate of insulin (MCR-I) (Supplementary Table 1). When M values were normalized to steady-state plasma insulin concentrations (M/I), values were significantly increased over time but not different among groups. Insulin-stimulated glucose uptake over basal was significantly increased over time without a group-by-time interaction (Fig. 1*B*). Adipose tissue insulin sensitivity also equally improved after each intervention (Fig. 1*C*).

In all three groups, plasma leptin levels significantly decreased and were associated with significant increases in IL-8 and TNFα over time (Supplementary Table 2). There were no significant changes after RYGB, VSG, or diet intervention in plasma concentrations of adiponectin, resistin, MCP-1, PAI-1, IL-6, or IL-1β over time. Plasma concentrations of acyl ghrelin decreased after RYGB and VSG but were not significantly different after 1 week of diet. Desacyl ghrelin concentrations only decreased after VSG. The acyl–to–desacyl ghrelin ratio decreased over time, with no differences among groups. The changes in adipose tissue interstitial fluid levels were more apparent, with demonstrated significant decreases over time in leptin, adiponectin, and PAI-1 that were not detected in the plasma (Supplementary Table 3).

A subset of subjects underwent abdominal MRI/MRS for quantification of hepatic fat (Supplementary Fig. 1*A*). In a combined analysis, mean ± SD hepatic fat content significantly decreased after surgical or dietary intervention by 19.0 ± 17.3%, from 12.9 ± 11.4% fat content at baseline (range 2.7–38.9) to 10.8 ± 10.2% after intervention (2.5–32.5) (P = 0.0071) (Supplementary Fig. 1*B*). At baseline, 9 of the 20 subjects had ≤5% hepatic fat; the decrease in steatosis remained significant after exclusion of these subjects (20.4 ± 10.3% vs. 17.19 ± 9.8%, P = 0.022). At baseline, percent hepatic fat positively correlated with fasting glucose and insulin, negatively correlated with hepatic insulin sensitivity and M, and did not correlate with weight, BMI, body fat, MCR-I, or EGP. The change in hepatic fat after intervention did not correlate with changes in any of these parameters.

CONCLUSIONS

Immediately after bariatric surgery, patients are instructed to consume a significantly restricted caloric diet within the range of 500–800 kcal/day. Numerous studies have implicated this reduction in caloric intake in the postoperative improvements in overall insulin sensitivity

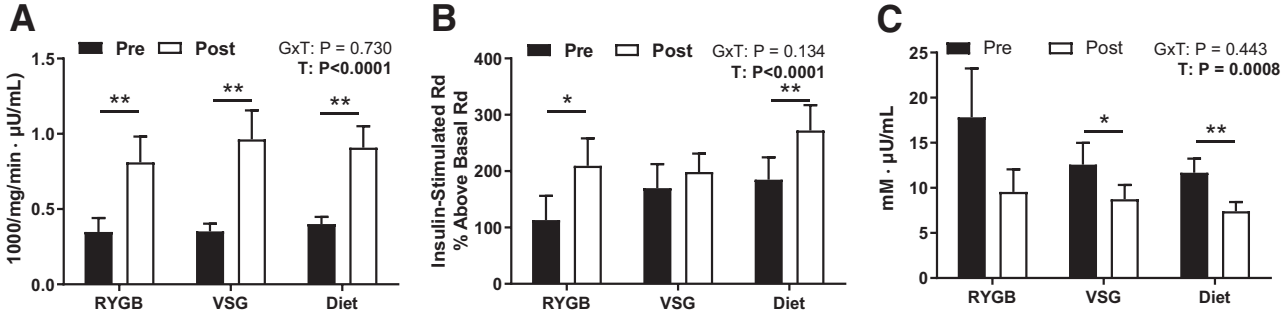

Figure 1—Insulin sensitivity before (Pre) and after (Post) RYGB, VSG, or diet. *A*: Hepatic insulin sensitivity index. *B*: Skeletal muscle insulin sensitivity. *C*: Adipose tissue insulin resistance index. Data are means ± SEM for n = 11 RYGB and n = 15 VSG (*A*–*C*), n = 14 diet (*A*), and n = 13 diet (*B* and *C*). GxT, group-by-time interaction; T, time.

observed following bariatric procedures, especially RYGB (2,7–13). Except for one (8), findings of studies are in agreement that bariatric surgery is associated with decreased EGP and increased hepatic insulin sensitivity but variable improvements in peripheral insulin sensitivity (2,9,11,13). Our data support an improvement in insulin-stimulated glucose disposal at 1 week after RYGB and VSG, attributed to significant increases in insulin clearance rates. Effects of VSG on glucose disposal were less robust than those of RYGB and may be due to the greater preoperative adiposity in the VSG group or to body water/hydration status.

Improvements in hepatic insulin sensitivity after bariatric surgery are commonly reported to be secondary to reductions in hepatic fat. Previous studies demonstrated hepatic fat reductions were not observed at 4 weeks postoperative (14). Similarly, decrements in hepatic fat content (~4%) were not observed 2 weeks after a low-calorie diet (800–1,100 kcal/day) (15). In this study, improvements in hepatic insulin sensitivity were similar among groups, with a 2% average reduction in hepatic fat. Our data suggest that early improvements (within 12 days) in hepatic insulin sensitivity after bariatric surgery or caloric restriction are due to factors beyond changes in hepatic fat, suggesting additional signaling pathways as drivers of metabolic improvement. We observed significant increases in plasma leptin and decreases in IL-8 and TNFα, while in adipose interstitial fluid levels of leptin, adiponectin, and PAI-1 were decreased. Whether changes in levels of interstitial fluid adipokines reflect altered function or are secondary to altered adipose tissue blood flow is unclear.

In summary, weight loss and the associated improvements in insulin sensitivity observed early after bariatric surgery can be replicated by equivalent, short-term caloric restriction. The observed metabolic improvements are characterized by overall improved hepatic and peripheral insulin sensitivities and consistent with a resolution of adipose tissue inflammation unique to bariatric procedures.

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References

1. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med 2017;376:641–651

2. Bojsen-Møller KN, Dirksen C, Jørgensen NB, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes 2014;63:1725–1737

3. Wickremesekera K, Miller G, Naotunne TD, Knowles G, Stubbs RS. Loss of insulin resistance after Roux-en-Y gastric bypass surgery: a time course study. Obes Surg 2005;15:474–481

4. Patriti A, Facchiano E, Annetti C, et al. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. Obes Surg 2005;15:1258–1264

5. Yoshino M, Kayser BD, Yoshino J, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. N Engl J Med 2020;383:721–732

6. Gifford A, Towse TF, Walker RC, Avison MJ, Welch EB. Characterizing active and inactive brown adipose tissue in adult humans using PET-CT and MR imaging. Am J Physiol Endocrinol Metab 2016;311:E95–E104

7. Plum L, Ahmed L, Febres G, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. Obesity (Silver Spring) 2011;19:2149–2157

8. Camastra S, Gastaldelli A, Mari A, et al. Early and longer term effects of gastric bypass surgery on tissue-specific insulin sensitivity and beta cell function in morbidly obese patients with and without type 2 diabetes. Diabetologia 2011;54:2093–2102

9. Gastaldelli A, Iaconelli A, Gaggini M, et al. Short-term effects of laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass. Diabetes Care 2016;39:1925–1931

10. Campos GM, Rabl C, Peeva S, et al. Improvement in peripheral glucose uptake after gastric bypass surgery is observed only after substantial weight loss has occurred and correlates with the magnitude of weight lost. J Gastrointest Surg 2010;14:15–23

11. Dunn JP, Abumrad NN, Breitman I, et al. Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. Diabetes Care 2012;35:137–142

12. Lima MM, Pareja JC, Alegre SM, et al. Acute effect of roux-en-y gastric bypass on whole-body insulin sensitivity: a study with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab 2010;95:3871–3875

13. Vetter ML, Wadden TA, Teff KL, et al. GLP-1 plays a limited role in improved glycemia shortly after Roux-en-Y gastric bypass: a comparison with intensive lifestyle modification. Diabetes 2015;64:434–446

14. Johansson L, Roos M, Kullberg J, et al. Lipid mobilization following Roux-en-Y gastric bypass examined by magnetic resonance imaging and spectroscopy. Obes Surg 2008;18:1297–1304

15. Edholm D, Kullberg J, Karlsson FA, Haenni A, Ahlström H, Sundbom M. Changes in liver volume and body composition during 4 weeks of low calorie diet before laparoscopic gastric bypass. Surg Obes Relat Dis 2015;11:602–606