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Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy

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Physiological changes after Roux-en-Y gastric bypass and sleeve gastrectomy*

*Compared with unoperated control subjects. All groups matched on sex, age BMI and post-operative weight loss
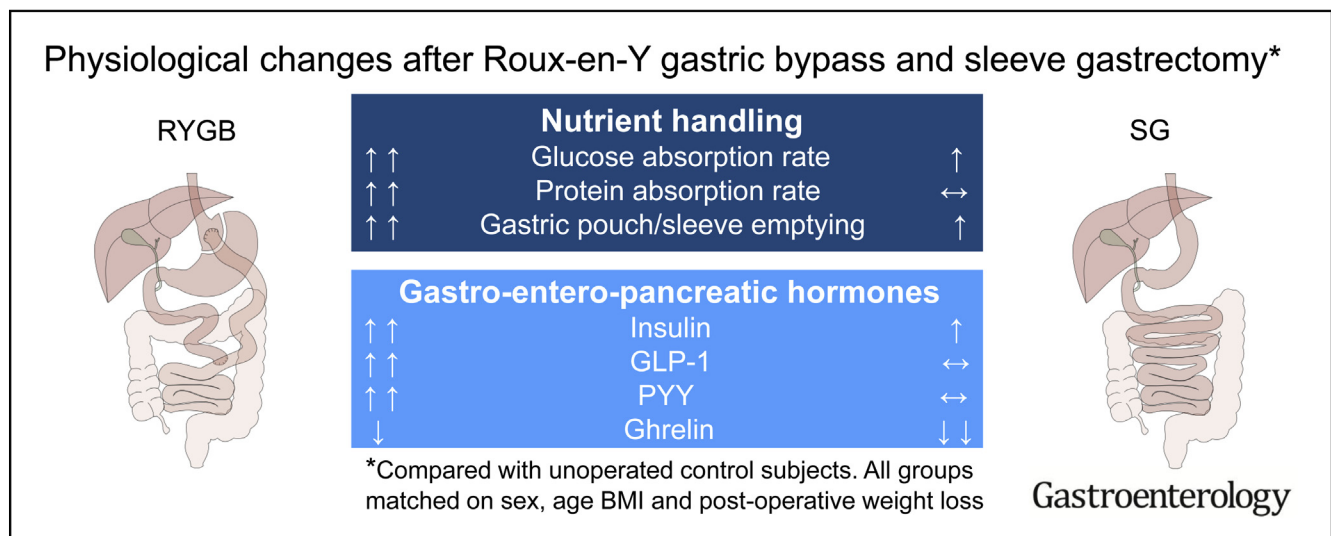
BACKGROUND & AIMS: Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) induce substantial weight loss and improve glycemic control in patients with type 2 diabetes, but it is not clear whether these occur via the same mechanisms. We compared absorption rates of glucose and protein, as well as profiles of gastro-entero-pancreatic hormones, in patients who had undergone SG or RYGB vs controls. **METHODS:** We performed a cross-sectional study of 12 patients who had undergone sleeve gastrectomy, 12 patients who had undergone RYGB, and 12 individuals who had undergone neither surgery (controls), all in Denmark. Study participants were matched for body mass index, age, sex, and postoperative weight loss, and all had stable weights. They received continuous infusions of stable isotopes of glucose, glycerol, phenylalanine, tyrosine, and urea before and during a mixed meal containing labeled glucose and intrinsically phenylalanine-labeled caseinate. Blood samples were collected for 6 hours, at 10- to 60-minute intervals, and analyzed. **RESULTS:** The systemic appearance of ingested glucose was faster after RYGB and SG vs controls; the peak glucose appearance rate was 64% higher after RYGB, and 23% higher after SG (both $P < .05$); the peak phenylalanine appearance rate from ingested casein was 118% higher after RYGB ($P < .01$), but similar between patients who had undergone SG and controls. Larger, but more transient increases in levels of plasma glucose and amino acids were accompanied by higher secretion of insulin, glucagon-like peptide 1, peptide YY, and cholecystokinin after RYGB, whereas levels of ghrelin were lower after SG, compared with RYGB and controls. Total 6-hour oral recovery of ingested glucose and protein was comparable among groups. **CONCLUSIONS:** Postprandial glucose and protein absorption and gastro-entero-pancreatic hormone secretions differ after SG and RYGB. RYGB was characterized by accelerated absorption of glucose and amino acids, whereas protein metabolism after SG did not differ significantly from controls, suggesting that different mechanisms explain improved glycemic control and weight loss after these surgical procedures. ClinicalTrials.gov ID NCT03046186.

CLINICAL AT

R oux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) both induce major weight loss and recovery from obesity-associated comorbidities, including type 2 diabetes.[1,2] A recent randomized controlled trial showed comparable weight loss after SG and RYGB,[3] while another study demonstrated only slightly larger weight loss after RYGB, below the prespecified threshold for clinical significance, at 5 years after surgery.[4] Also improvements in glycemic control have been suggested to be comparable between the 2 procedures,[2] or only slightly better after RYGB.[5] The physiological mechanisms behind weight loss and improved glycemic control after SG are studied less than those after RYGB. The comparable clinical outcomes may seem surprising, given the marked post-surgical anatomical differences between the procedures. After SG, the only change is a longitudinal excision of the major curvature of the stomach, leaving a narrow tube for nutrient passage; importantly, the pyloric sphincter is preserved after SG. By contrast, after RYGB, there is an extensive rearrangement of the upper gastrointestinal tract, including the creation of a small gastric pouch and bypass of the stomach and upper small intestine, resulting in unimpeded pouch emptying and accelerated entry of nutrients into the small intestine. The latter has important consequences. A greatly enhanced absorption of glucose and protein is seen,[6–9] which is accompanied by exaggerated meal-related release of several gut hormones involved in appetite regulation and glucose homeostasis, including the anorexigenic glucagon-like peptide 1 (GLP-1), peptide YY (PYY), cholecystokinin (CCK), and oxyntomodulin, whereas secretion of the orexigenic ghrelin is reported to be attenuated, increased, or unchanged after RYGB.[10–12] The sum of these hormonal alterations are thought to be important for the decreased appetite and weight loss seen after RYGB.[13] The improved glycemic control arises from a combination of factors, including increased hepatic and peripheral insulin sensitivity,[14] and improved meal-induced insulin secretion, facilitated by exaggerated GLP-1 secretion.[15]

Accelerated gastric emptying and enhanced glucose absorption are also reported after SG,[9,16] and an increased secretion of GLP-1, comparable to that seen after RYGB, has been reported in some,[17–19] but not all,[20–22] studies. Using the GLP-1 receptor antagonist, exendin 9-39, it has been demonstrated that GLP-1 affects β-cell function and glucose tolerance after both RYGB and SG.[15,23] However, both SG and RYGB remain effective in GLP-1 receptor knockout mice,[24,25] suggesting that additional mechanisms are involved. Both ghrelin and bile acids have been proposed to play a role for weight loss and improved glucose metabolism after RYGB and SG,[19,26,27] but the role remains unclear in humans.

Thus, the physiological changes after SG and RYGB are not fully clarified. Modified nutrient delivery to the

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Sleeve gastrectomy and gastric bypass induce substantial weight loss and improved glycemic control, but it is unknown whether the mechanisms via which these procedures act are similar.

NEW FINDINGS

Absorption of glucose and protein was greatly accelerated after gastric bypass and only modestly accelerated after sleeve gastrectomy. Insulin, GLP-1, PYY, and CCK secretion also differed markedly between the procedures.

LIMITATIONS

The study was performed as a cross-sectional study. However, this design was chosen to examine the surgical patients in the weight-stable phase following a matched weight loss.

IMPACT

Different mechanism may underlie the beneficial effects of the two surgical procedures.

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intestine and accelerated absorption and metabolism of nutrients, as well as altered gut hormone secretion, could be critically important for the post-bariatric changes. We performed a detailed analysis of the postprandial absorption and metabolism of glucose and protein after SG and RYGB using a variety of stable, isotopically labeled metabolites in connection with a mixed meal containing intrinsically labeled protein and glucose tracers. Furthermore, gastro-entero-pancreatic hormonal secretion was assessed.

Previously published studies have investigated SG- and RYGB-operated individuals separately,[6,7,28,29] have been performed early postoperatively during an ongoing weight loss,[6,7,9] or lacked a proper control group.

Therefore, we chose to study SG- and RYGB-operated subjects who were individually matched in terms of postoperative weight loss and were in the weight-stable phase, as well as to compare these patients with a group of unoperated body mass index (BMI)–matched control subjects. We hypothesized that glucose and protein absorption rates would be increased after SG compared with unoperated controls.

Materials and Methods

Subjects

Twelve subjects who had undergone uncomplicated SG more than 12 months before inclusion were recruited from the Bariatric Surgery Program at Copenhagen University Hospital Hvidovre (Hvidovre, Denmark). For each SG subject, 1 subject who had undergone uncomplicated RYGB more than 12 months earlier was recruited based on individual matching in terms of current BMI, age, sex, and preoperative BMI. In addition, 12 unoperated control subjects also individually matched in terms of BMI, age, and sex were recruited through local advertisement. All subjects were weight-stable (±3 kg during the last month) and had normal glucose tolerance (fasting plasma glucose <6.1 mmol/L and hemoglobin A1c <48 mmol/mol), and none of the operated subjects had a history of diabetes before surgery. The exclusion criteria were inadequately treated thyroid disease, serious heart or respiratory illness, hemoglobin <6.5 mmol/L, pregnancy, and breastfeeding.

Surgical Techniques

Using standard laparoscopic procedures, SG and RYGB were performed at the Department of Surgical Gastroenterology at Copenhagen University Hospital at Hvidovre (Hvidovre, Denmark) by experienced surgeons. RYGB was created via the formation of a 4×6.5 cm gastric pouch with a 75-cm biliopancreatic limb and a 125-cm Roux limb. SG was performed using a standard laparoscopic technique, with division of the greater curvature of the stomach via the use of a linear stapler 4 cm from the pylorus to the angle of His along a 40-Ch orally inserted gastric tube.

Ethics

The study was approved by the Regional Ethical Committee of the Capital Region (Protocol number: H-15009263) and by the Danish Data Protection Agency. It was performed in accordance with the Helsinki declaration and was registered at ClinicalTrials.gov (NCT03046186). Written informed consent was obtained from all participants before inclusion. All co-authors had access to the study data and have reviewed and approved the final manuscript.

Study Design

Dual-energy x-ray absorptiometry was used to assess fat-free mass (FFM). Subjects were instructed to avoid strenuous physical activity for 2 days before the experimental day and to follow their normal dietary habits. On the experimental day, patients arrived after an overnight fast (10–12 hours) and were weighed and placed in a hospital bed in a reclined position. No physical activity was allowed throughout the day. Intravenous catheters were inserted into antecubital veins: in one arm for tracer infusion and in the other, which was kept warm in a heating pad to "arterialize" the blood, for blood sampling. Three fasting blood samples were drawn (time –130 to –120) to determine the abundance of natural occurring isotopes. A priming bolus of L-[ring-D$_4$] tyrosine (0.46 μmol/kg FFM) was injected, and a primed-continuous infusion of [6,6-D$_2$] glucose (prime 17.6 μmol/kg FFM, continuous 0.4 μmol/kg FFM/min), [1,1,2,3,3-D$_5$] glycerol (prime 1.5 μmol/kg FFM, continuous 0.1 μmol/kg FFM/min), L-[ring-D$_5$] phenylalanine (prime 3 μmol/kg FFM, continuous 0.07 μmol/kg FFM/min), L-[ring-3,5-D$_2$] tyrosine (prime 2.3 μmol/kg FFM, continuous 0.04 μmol/kg FFM/min), and [^{15}N$_2$] urea (prime 84 μmol/kg FFM, continuous 0.15 μmol/kg FFM/min) was provided with a volumetric infusion pump (mVP5000; Arcomed Ag, Kloten, Switzerland) for a total of 8 hours. The actual concentrations of the tracers were measured in the infused solution and used in the subsequent calculations. Stable isotopes for the intravenous infusions (from Cambridge Isotope Laboratories, Andover, MA) were prepared under sterile conditions by the Capital Region Pharmacy (Herlev, Denmark).

After 1.5 hours of basal tracer infusion, basal blood samples were drawn (time –30, –15, and 0) for the determination of basal steady-state tracer enrichments and hormone concentrations. At time = 0, a liquid mixed meal (200 mL, 400 kcal, carbohydrate 50 E%, protein 15 E%, and fat 35 E%) was provided. It was composed of glucose (47.8 g dextrose monohydrate + 2.7 g [U-^{13}C$_6$]glucose), rapeseed oil (14.1 g), and caseinate that was intrinsically labeled (16.7 g) with 11.8% [^{15}N]phenylalanine enrichment of the phenylalanine and flavored with 1 g of raspberry aroma. Intrinsically labeled caseinate was produced via an infusion of [^{15}N]-phenylalanine into one lactating cow to obtain [^{15}N]-phenylalanine-enriched milk, from which the caseinate fraction was obtained at Arla Foods (Nørre Vium, Denmark) following a previously described procedure.[30] One gram of paracetamol (Pamol; Nycomed, Roskilde, Denmark) was added to the first 2 cl of the meal to estimate gastric emptying, and the rest of the meal was consumed evenly over 20 minutes under supervision. Blood sampling was continued frequently for 6 hours relative to start of the test meal (at 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, and 360 minutes).

Sample Collection and Laboratory Analyses

Blood was collected into chilled EDTA tubes containing a specific DPP-4 inhibitor (valine-pyrrolidide, final concentration of 0.01 mM; a gift from Novo Nordisk, Bagsværd, Denmark) for the analysis of GLP-1, glucose-dependent insulinotropic polypeptide (GIP), glucagon, PYY, and ghrelin. The storage of samples and immunoassays for total GLP-1, GIP, and glucagon in EDTA plasma were carried out as described previously.[31] Total PYY and total ghrelin were measured in EDTA plasma, and active ghrelin was measured in EDTA plasma treated with 1 N hydrochloric acid (5 μL/mL plasma) and phenylmethylsulfonyl fluoride (20 μL/mL plasma) using a Millipore RIA kit (cat. no. PYYT-66HK, GHRT-89HK and GHRT-88HK; Millipore, Billerica, MA). CCK was measured in EDTA plasma as reported previously.[32] Serum insulin, C-peptide, and fatty acid concentrations were determined via Immulite 2000 analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY). Metabolite concentrations and enrichments were analyzed with a liquid chromatography triple mass spectrometer. Liquid chromatography triple mass spectrometry analysis of glucose and glycerol (Accela + Surveyer pumps; TSQ Vantage, ThermoFisher Scientific, San Jose, CA) and amino acids (AA) (Double Pump Ultimate3000, TSQ Quantiva, ThermoFisher Scientific) was performed as described previously.[33,34]

Calculations

Basal concentrations were calculated as the mean of 3 basal samples. The area under the curve (AUC) was calculated using the trapezoidal rule and incremental AUC (iAUC) with subtracted basal values. Total metabolite rate of appearance (Ra) and rate of disappearance (Rd) were estimated via standard Steele non–steady-state equations. Equations and detailed descriptions of calculations can be found in the Supplementary Material. In short, oral Ra glucose (Ra_{glu}) was calculated from the $[U-^{13}C_6]$ glucose enrichment multiplied with the total Ra_{glu}. Endogenous Ra_{glu} (endogenous glucose production [EGP]) was calculated by subtracting oral Ra_{glu} from total Ra_{glu}. The oral Ra of phenylalanine (Ra_{phe}) and endogenous Ra_{phe} were calculated likewise using enrichment of $[^{15}N]$-phenylalanine. The oral recovery of glucose and phenylalanine represents the total systemic appearance over 6 hours. This is calculated from the AUC of the oral Ra and is expressed as a percentage of the amount of ingested glucose or phenylalanine in the meal.

To estimate whole-body protein kinetics, endogenous Ra_{phe} was used as an index of whole-body protein breakdown. The rate of phenylalanine-to-tyrosine hydroxylation (calculated as the product of total Ra_{tyr} and D_4-tyrosine/D_5-phenylalanine-ratio) is the rate-limiting step in phenylalanine oxidation and was used as an estimate of oxidative loss; hence, whole-body protein synthesis was calculated as Rd_{phe} minus the rate of phenylalanine-to-tyrosine hydroxylation. Net protein synthesis was calculated as whole-body protein synthesis minus whole-body protein breakdown. Ra_{urea} represents irreversible loss of nitrogen from hepatic AA degradation and was used as an estimate of net whole-body protein catabolism.

Prehepatic insulin secretion rates (ISRs) were derived via deconvolution of peripheral C-peptide concentrations, as described previously.[35] β-Cell glucose sensitivity was calculated as the slope of the linear relation between ISR and the corresponding plasma glucose value for each individual.[13] These slopes were calculated separately for increasing and decreasing values of plasma glucose. Insulin sensitivity was estimated as 1/Homeostatic Model Assessment of Insulin Resistance, and the Hepatic Insulin Sensitivity Index was calculated as the product of EGP and basal C-peptide.[14] β-Cell function was evaluated using the disposition index, calculated as the products of 1/Homeostatic Model Assessment of Insulin Resistance and β-cell glucose-sensitivity for the upslope and downslope of the glucose concentration curve separately.

Suppression of EGP, free fatty acids, and glycerol in the postprandial phase was calculated as the difference between nadir and basal levels and expressed as a percentage of the basal level. Excess BMI loss was calculated as (preoperative BMI – current BMI) / (preoperative BMI – 25) × 100%.

Gastric/pouch emptying was estimated using time to peak of paracetamol concentrations (T_{max} pcm). We validated this measure of gastric/pouch emptying in a separate study with comparable groups of SG- and RYGB-operated and unoperated controls.[36] In this study, a fatty liquid meal (558 kcal carbohydrate 10 E%, protein 7 E%, and fat 83 E%) thoroughly mixed with 1 g of paracetamol (Pamol; Nycomed) and a radiolabeled tracer ^{111}In-DTPA (4 MBq) was ingested uniformly over 10 minutes. Scintigraphy (Symbia Intevo, Siemens Healthineers, Erlangen, Germany) and blood sampling were frequently performed for 300 minutes to estimate T_{max} pcm and gastric/pouch mean emptying time, an integrated measure of the entire emptying process[37] calculated as the area under the gastric retention (fraction) × time curve.

Statistical Analysis

Sample size was calculated to n = 8 in each group to detect a significant difference in the primary outcome, peak Ra of oral glucose, between SG and controls with 80% power and a 2-sided α-error of .05, assuming that the changes after SG would be 50% of the changes after RYGB.[6] However, because our power calculation was based on a study involving only data from RYGB-operated subjects (as these were the only data available), we chose to include 12 in each group.

The postprandial time courses of glucose, glycerol, phenylalanine, tyrosine, and urea kinetics were analyzed in repeated-measurement linear mixed-effects models using time, group, time × group interaction, and an additional match variable (specifying the pairing of the individually matched subjects) as categorical fixed effects and individual subjects as a random effect. The analysis of variance (ANOVA) for time × group interaction was reported as the primary readout. Logarithmic transformation was used in the case of a skewed distribution for optimal model fit, and a Shapiro-Wilk test was used to test for normal distribution of residuals. Non-repeated data (basal and peak concentrations and AUCs) were analyzed via two-way ANOVA, with group and match variable treated as fixed effects, followed by a post-hoc Tukey's test for multiple comparisons to determine differences between the groups. Statistical analysis was performed in R, version 3.2.3 (www.R-project.org), with the "nlme" package for linear mixed-effects models. A P value <.05 was considered significant. All values are mean ± SEM unless otherwise stated.

Results

Characteristics of Subjects

Twelve SG-operated, 12 RYGB-operated, and 12 unoperated control subjects were included. The groups were matched 1:1:1 in terms of age (SG: 42.8 ± 3.3 years, RYGB: 43.0 ± 2.1 years, controls: 44.9 ± 3.4 years; ANOVA P = .86), sex (9 women in each group), and BMI (SG: 33.4 ± 2.4 kg/m², RYGB: 33.5 ± 2.1 kg/m², controls: 33.4 ± 1.7 kg/m²; P = .99). In addition, the surgical groups were matched in terms of preoperative BMI (SG: 44.0 ± 2.0 kg/m² vs RYGB 44.1 ± 2.4 kg/m²; P = .96) and, accordingly, postoperative excess BMI loss was comparable (SG: 60% ± 8% vs RYGB: 61% ± 7%; P = .94). FFM did not differ between groups (SG: 61 ± 4 kg, RYGB: 64 ± 5 kg, controls: 60 ± 4 kg; P = .85) and neither did the trunk-to-leg fat percent ratio. Time from surgery was slightly higher in the RYGB group vs SG (median, 2.1 [IQR, 0.3] years vs median, 1.8 [IQR, 0.6]; P = .04).

Glucose Kinetics

Basal concentrations of plasma glucose were similar in the 2 surgical groups and were lower compared with controls (P < .02 vs RYGB, P = .13 vs SG). Postprandial glucose excursions differed significantly between the 3 groups, with higher peak (P < .01 vs controls, P = .13 vs SG) and lower nadir (P < .01 vs controls, P =.07 vs SG)

after RYGB, whereas the iAUCs of plasma glucose were comparable between all groups (ANOVA $P = .43$) (Figure 1, Table 1).

The appearance of oral glucose in the systemic circulation was faster and had a higher peak oral Ra_{glu} in the 2 surgical groups compared with controls, but the appearance of glucose also differed between SG and RYGB, with a 33% higher peak oral Ra_{glu} after RYGB ($P = .002$ vs SG). As for the iAUC of plasma glucose, the overall 6-hour recoveries of the meal-derived glucose in the systemic circulation during the entire test period were similar between groups, but the recovery within the first postprandial hour was 31% ± 1% in the RYGB group, compared with 23% ± 1% and 14% ± 1% of ingested glucose in the SG and control groups (both $P < .001$ vs RYGB).

Basal EGP was comparable between groups, whereas the postprandial time course differed (time × group interaction ANOVA $P < .001$), with less suppression and earlier post-suppression rise in the RYGB group resulting in slightly higher EGP at the end of the study day compared with both the SG and control group (both $P < .05$, Figure 1). The postprandial curves for total Ra_{glu} were significantly different between groups ($P < .01$ for all comparisons), with highest peak value being seen after RYGB, followed by SG, and lowest being seen in the control group. Also, a faster decline after the peak was seen in the 2 surgical groups. Total Rd_{glu} was slightly delayed compared with total Ra but followed the same group kinetics.

Postprandial lactate followed plasma glucose excursions and differed between all groups, with highest lactate formation after RYGB (Table 1, Figure 1).

Insulin and Insulin Secretion Rates

Insulin and C-peptide concentrations were lower in the fasting state after RYGB compared with controls. Peak values for both insulin and ISR were greatly exaggerated after RYGB, whereas neither basal nor peak values differed between SG and controls (Table 1, Figure 2). However, the iAUC of insulin and ISR values were comparable between the groups.

Insulin Sensitivity, Clearance, and β-Cell Function

Insulin sensitivity, evaluated by 1/Homeostatic Model Assessment of Insulin Resistance, was higher in the surgical groups ($P = .03$ for RYGB vs controls, $P = .07$ for SG vs controls), whereas Hepatic Insulin Sensitivity Index, which mainly reflects hepatic insulin sensitivity, was significantly higher only after RYGB, with no difference between SG and controls ($P = .67$). β-Cell glucose sensitivity did not differ between groups either on the upslope or the downslope of the glucose concentration curves. However, when evaluated as the disposition index, β-cell function was comparable in the surgical groups and was numerically higher compared with controls, although only the difference between RYGB and controls reached statistical significance on the downslope of the glucose concentration (Table 1).

Oral Protein Absorption and Amino Acid Concentration Kinetics

Basal plasma phenylalanine was comparable in all groups. After the meal, a more pronounced rise in phenylalanine concentrations was seen in RYGB subjects, as demonstrated by a higher peak concentration than in both SG and controls (Figure 3). In the SG group, the peak phenylalanine concentration was comparable to that in controls ($P = .99$), but the peak was reached faster after meal intake. Phenylalanine AUCs were comparable between groups. Total Ra_{phe} kinetics showed the same pattern as phenylalanine concentrations, with a greatly exaggerated peak in total Ra_{phe} only after RYGB.

The systemic appearance rates of phenylalanine from the ingested caseinate (oral Ra_{phe}) differed significantly between the groups, with 118% and 61% higher peak oral Ra_{phe} after RYGB compared with controls and SG, respectively (both $P < .01$). The peak oral Ra_{phe} in the SG-operated subjects was reached more quickly but was only numerically higher compared with controls ($P = .22$). The oral 6 hours recovery of the ingested protein was comparable between the groups during the entire postprandial period, with 60% ± 4%, 55% ± 4%, and 54% ± 4% of ingested phenylalanine appearing in the systemic circulation in RYGB, SG, and controls, respectively. However, the systemic appearance of the ingested phenylalanine was greatly accelerated after RYGB, with significantly enhanced oral recovery within the first postprandial hour (Table 2).

The concentrations of total AA did not differ between groups in the fasting state but increased more postprandially after RYGB than after SG and in controls (both $P < .01$ for peak concentrations); essential AA and alanine followed the same pattern. In contrast, branched-chain AAs were lower in the fasting state after both RYGB and SG, but the peak was higher after RYGB. Glutamate and glutamine concentrations did not differ between groups (Figure 4).

Whole-Body Protein Metabolism

Whole-body protein breakdown and synthesis in the basal state were comparable between groups. After meal intake, whole-body protein breakdown increased slightly after RYGB. Likewise, the phenylalanine-to-tyrosine oxidation rate was higher in the early postprandial period after RYGB, but was comparable between groups when calculated as percentage of total Ra_{phe} (ANOVA >0.45 for all between-group differences in postprandial trajectories, Figure 3). Concomitantly, protein synthesis was even more increased, resulting in a greatly increased positive net protein balance after RYGB during the first 3 postprandial hours (AUC_{0-180} of net protein balance: RYGB: +190 g protein/d, SG: +110, controls: +30, $P < .01$ RYGB vs controls, $P = .13$ RYGB vs SG), whereas no difference was found in the AUC of net protein balance between groups during the entire postprandial period (ANOVA $P = .60$). However, it should be noted that the postprandial anabolic phase (positive net protein balance) was approximately 2.5 hours in these RYGB-operated subjects compared with approximately 4 hours for SG and controls.
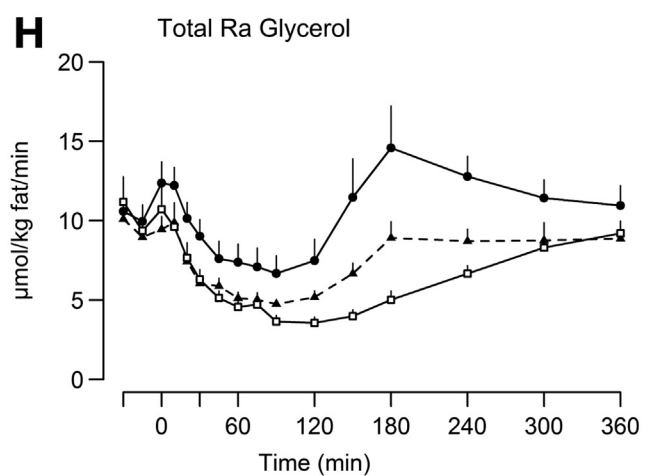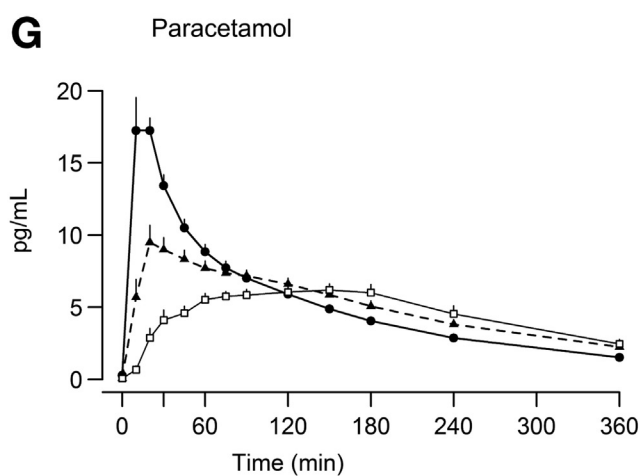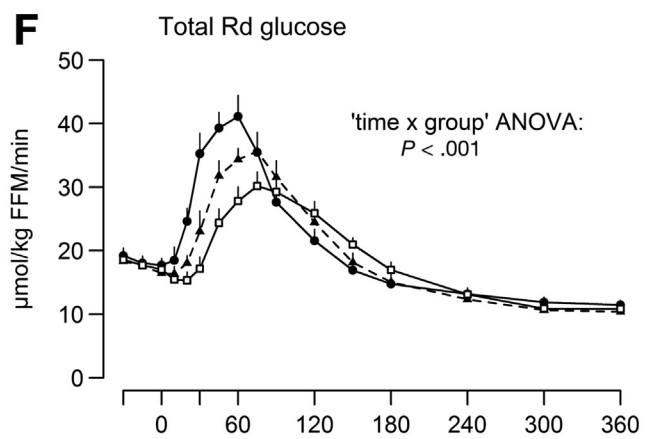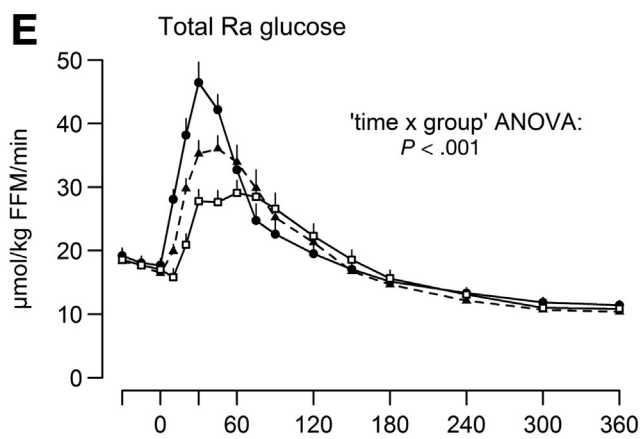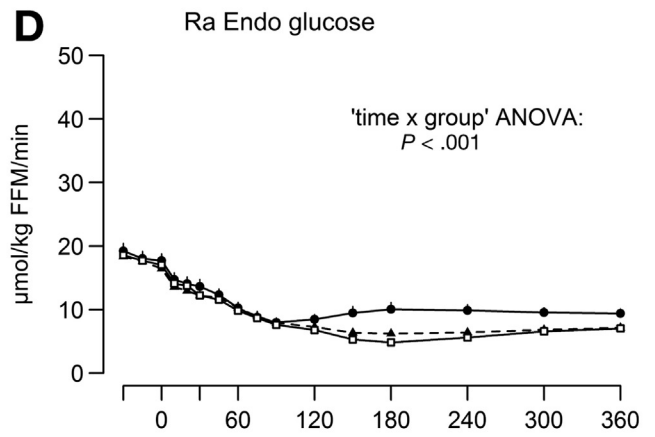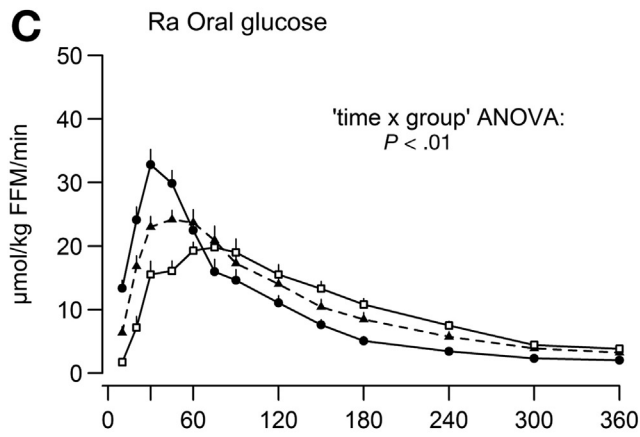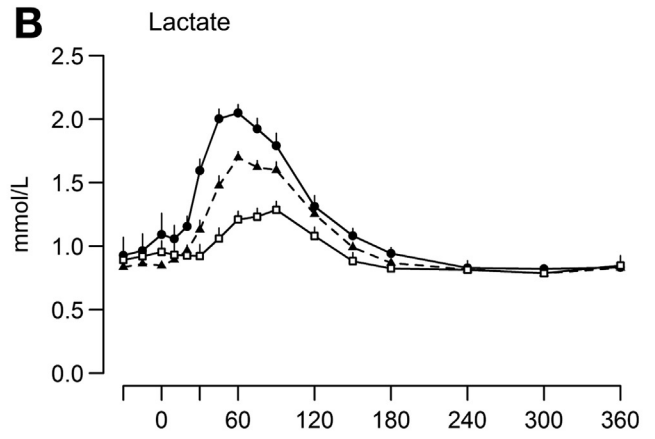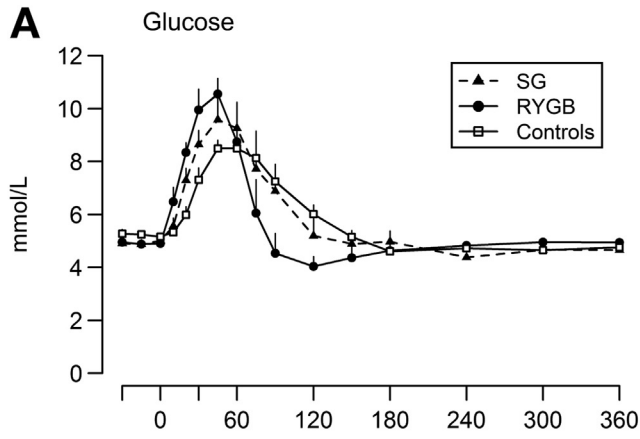
Table 1. Fasting and Incremental Area Under the Curve for Plasma Glucose, Lactate, Insulin, Insulin Secretion Rates, and Paracetamol, and Indices of Insulin Clearance (Fasting C-Peptide/Insulin), Insulin Sensitivity (Homeostatic Model Assessment of Insulin Resistance and Hepatic Insulin Sensitivity Index), and β-Cell Function (β-Cell Glucose Sensitivity and Disposition Index, Calculated Separately for the Upslope, Downslope, and Full Plasma Glucose Curve)

Variable	RYGB, mean ± SEM	SG, mean ± SEM	Controls, mean ± SEM	P value (ANOVA)	RYGB vs controls	SG vs controls	SG vs RYGB
Hemoglobin A1c, mmol/mol	32 ± 0.9	34 ± 1.4	36 ± 1.1	.13	.11	.45	.64
Fasting PG, mmol/L	4.9 ± 0.1	5.0 ± 0.1	5.3 ± 0.1	.019	.02	.13	.58
Peak PG, mmol/L	10.9 ± 0.4	9.9 ± 0.4	8.8 ± 0.4	<.01	<.01	.09	.13
Nadir PG, mmol/L	3.8 ± 0.2	4.3 ± 0.1	4.4 ± 0.1	.01	.01	.69	.07
$\Delta PG_{max-min}$, mmol/L	7.2 ± 1.6	5.6 ± 1.5	4.3 ± 0.4	<.01	<.01	.10	.05
iAUC PG, mmol/L * min	275 ± 109	212 ± 29	153 ± 37	.43	.39	.80	.77
Fasting lactate, mmol/L	1.0 ± 0.1	0.8 ± 0.02	0.9 ± 0.1	.73	.89	.93	.70
Peak lactate, mmol/L	2.1 ± 0.1	1.8 ± 0.1	1.4 ± 0.1	<.01	<.01	<.01	.02
AUC lactate, mmol/L * min	416 ± 15	372 ± 9	333 ± 21	<.01	<.01	.24	.16
Fasting insulin, pmol/L	25 ± 3.5	34 ± 12	54 ± 9.4	.06	.049	.22	.70
Peak insulin, pmol/L	1516 ± 290	669 ± 104	614 ± 137	<.01	<.01	.72	.04
iAUC insulin, nmol/L * min	76.7 ± 14.2	57.7 ± 11.1	52.6 ± 9.6	.43	.37	.87	.65
Fasting C-peptide, pmol/L	460 ± 45	592 ± 83	671 ± 67	.05	.04	.59	.25
Fasting ISR, pmol/kg/min	1.3 ± 0.1	1.6 ± 0.2	1.8 ± 0.1	.05	.04	.59	.27
Peak ISR, pmol/kg/min	23 ± 3.5	16 ± 1.0	13 ± 1.4	.02	.01	.33	.21
iAUC ISR, pmol/kg	1834 ± 224	2025 ± 184	1947 ± 163	.67	1.00	.71	.72
HOMA-IR	0.8 ± 0.1	1.1 ± 0.4	1.8 ± 0.3	.03	.03	.07	.90
HISI	1.5 ± 0.2	1.1 ± 0.1	1.0 ± 0.2	.04	.04	.67	.21
Fasting C-peptide/insulin	20 ± 1	23 ± 2	17 ± 3	.04	.20	.04	.64
Insulinogenic Index	197 ± 40	132 ± 15	141 ± 22	.71	.74	1.00	.78
β-GS$_{up}$	3.8 ± 0.7	3.0 ± 0.4	3.8 ± 0.4	.43	.69	.40	.87
β-GS$_{down}$	3.3 ± 0.5	2.8 ± 0.4	2.9 ±0.2	.76	1.00	.82	.77
DI: β-GS$_{up}$ * 1/HOMA-IR	5.5 ± 1.3	4.8 ± 1.1	3.1 ± 0.7	.16	.14	.47	.72
DI: β-GS$_{down}$*1/HOMA-IR	4.8 ± 0.9	4.3 ± 1.0	2.4 ± 0.5	.01	.01	.09	.59
Time to peak paracetamol, min	15 ± 2	36 ± 6	105 ± 19	<.01	<.01	<.01	<.01

β-GS, β-cell glucose sensitivity; DI, Disposition Index; HISI, Hepatic Insulin Sensitivity Index; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; PG, plasma glucose.

Net protein catabolism, as estimated by the rate of urea synthesis, was equal between groups both in the basal state and after meal intake (Supplementary Figure 1).

Free Fatty Acids and Glycerol

Free fatty acids and glycerol concentrations were equally suppressed in all groups (Figure 1, Supplementary Figure 2). However, the subsequent return toward basal levels occurred earlier after RYGB. The Ra of glycerol was comparable between groups in the basal state but less suppressed after RYGB (47%) compared with the greater (66%) and more prolonged suppression seen in controls. In contrast, no difference was found between the Ra of glycerol between the 2 surgical groups. The Rd of glycerol followed the same pattern as the Ra.

Gastrointestinal Hormones

Basal concentrations of GLP-1, GIP, and glucagon did not differ between the groups. Postprandial GLP-1 concentrations differed significantly between the groups, with larger peaks and iAUCs after RYGB as compared with controls, as well as >2-fold greater iAUC and peak concentrations after RYGB vs SG (P < .001, Figure 2, Table 3). The iAUC of GLP-1 was greater in the early postprandial period after SG as compared with controls (P = .03 for AUC$_{0-60}$), whereas the iAUCs for the total postprandial period were comparable. PYY followed GLP-1 concentrations, with higher peak and iAUC in RYGB compared with both SG and controls, between which no difference was seen.

Peak GIP did not differ between groups, but the duration of GIP secretion was longer and iAUCs were higher in SG and controls as compared with RYGB. Peak and iAUC of CCK differed between groups and was highest after RYGB (Table 3).

The peak and total AUC of glucagon concentrations did not differ between groups; however, the timing of glucagon release differed markedly (significant time × group interaction), with higher glucagon release within the first 2 hours in RYGB (P < .05 vs SG and controls).

The concentrations of total and acylated ghrelin were lower in the basal state after SG as compared with RYGB and

Figure 1. Plasma glucose concentrations, glucose and glycerol metabolism, and paracetamol concentrations during fasting and in response to a mixed-meal in 12 SG-operated (*solid triangle, dotted line*), 12 RYGB-operated (*solid circled, solid line*), and 12 control subjects (*white squares, solid line*).

Figure 2. (*A*) ISRs, (*B*) insulin, (*C*) glucagon, (*D*) GLP-1, (*E*) CCK, (*F*) GIP, (*G*) PYY, (*H*) acyl-ghrelin, and (*I*) total ghrelin in response to a mixed-meal in SG-operated (*solid triangle, dotted line*), RYGB-operated (*solid circled, solid line*), and control subjects (*white squares, solid line*).
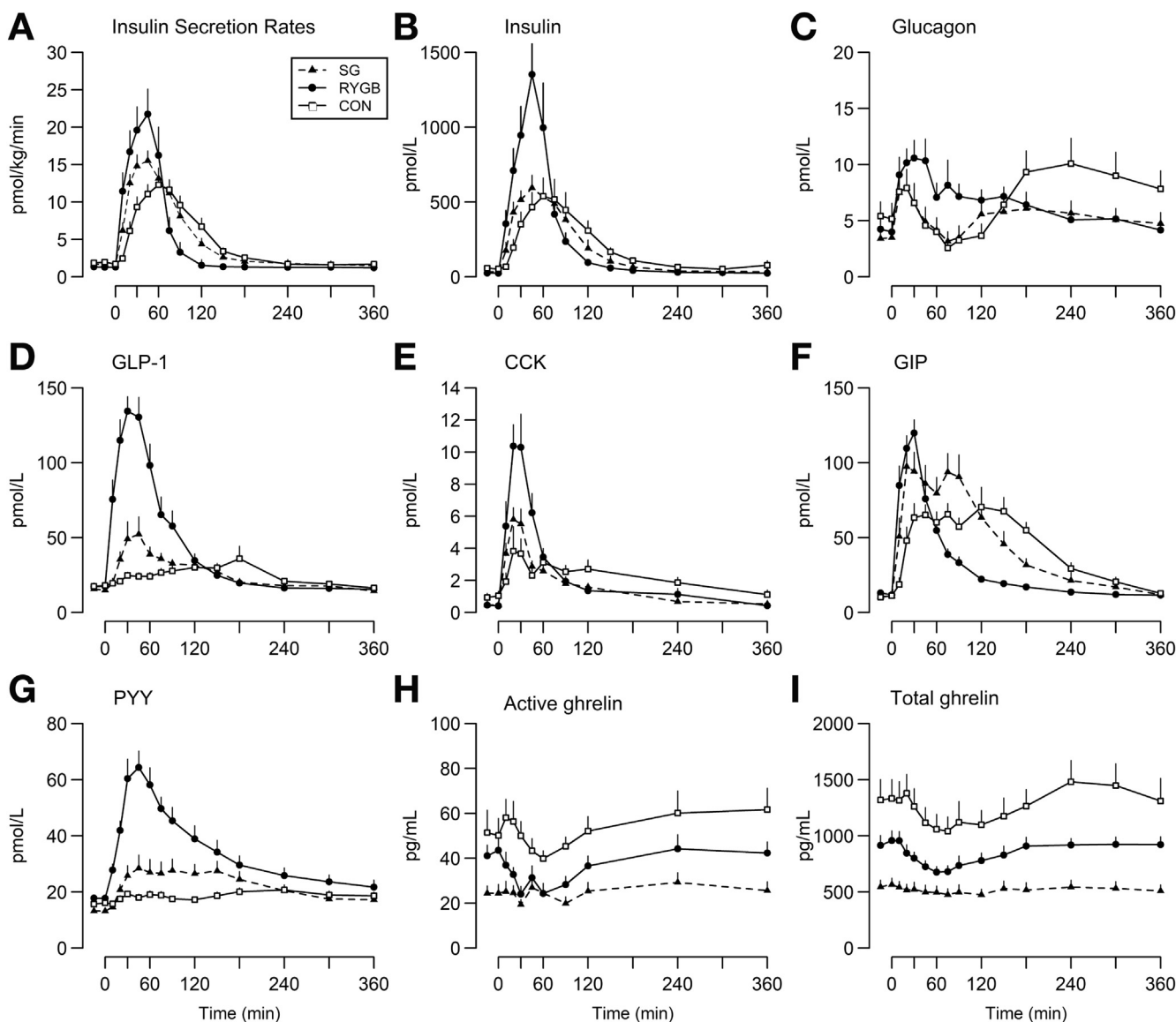
controls and remained low throughout the postprandial period after SG. In addition, total ghrelin was lower after RYGB as compared with controls, whereas the difference in acylated ghrelin between RYGB and controls did not reach statistically significance.

Gastric/Pouch Emptying

Paracetamol absorption was faster in both surgical groups compared with controls, with shorter times to peak for plasma paracetamol (T_{max} pcm, both $P < .01$ vs controls), but the kinetics also differed between RYGB and SG, with significantly shorter T_{max} pcm after RYGB ($P < .01$) (Table 1, Figure 1).

The scintigraphy study included 10 SG-operated, 10 RYGB-operated, and 10 control subjects matched on age (SG: 41.8 ± 2.8 years, RYGB: 46.2 ± 2.9 years, controls: 45.2 ± 2.9 years; ANOVA $P = .54$), BMI (SG: 31.8 ± 2.0 kg/m^2,

RYGB: 29.7 ± 1.0 kg/m^2, controls: 29.1 ± 1.3 kg/m^2; $P = .44$) and sex (7 women in each group). T_{max} pcm (RYGB 32 ± 5 minutes, SG 108 ± 17 minutes, controls 165 ± 18 minutes; $P = .03$ for SG vs controls and $P < .01$ for RYGB vs both SG and controls) and gastric/pouch mean emptying time (RYGB 11 ± 2 minutes; SG 56 ± 11 minutes; controls 113 ± 8 minutes; $P < .01$ for all comparisons) differed between all 3 groups and, importantly, were significantly correlated (Spearman's $\rho = .79$, $P < .01$).

Discussion

In this study, we compared glucose and protein absorption and metabolism and gastro-entero-pancreatic hormone secretion between SG- and RYGB-operated subjects, as well as with unoperated matched controls. The systemic appearances of meal-derived glucose, AA, and
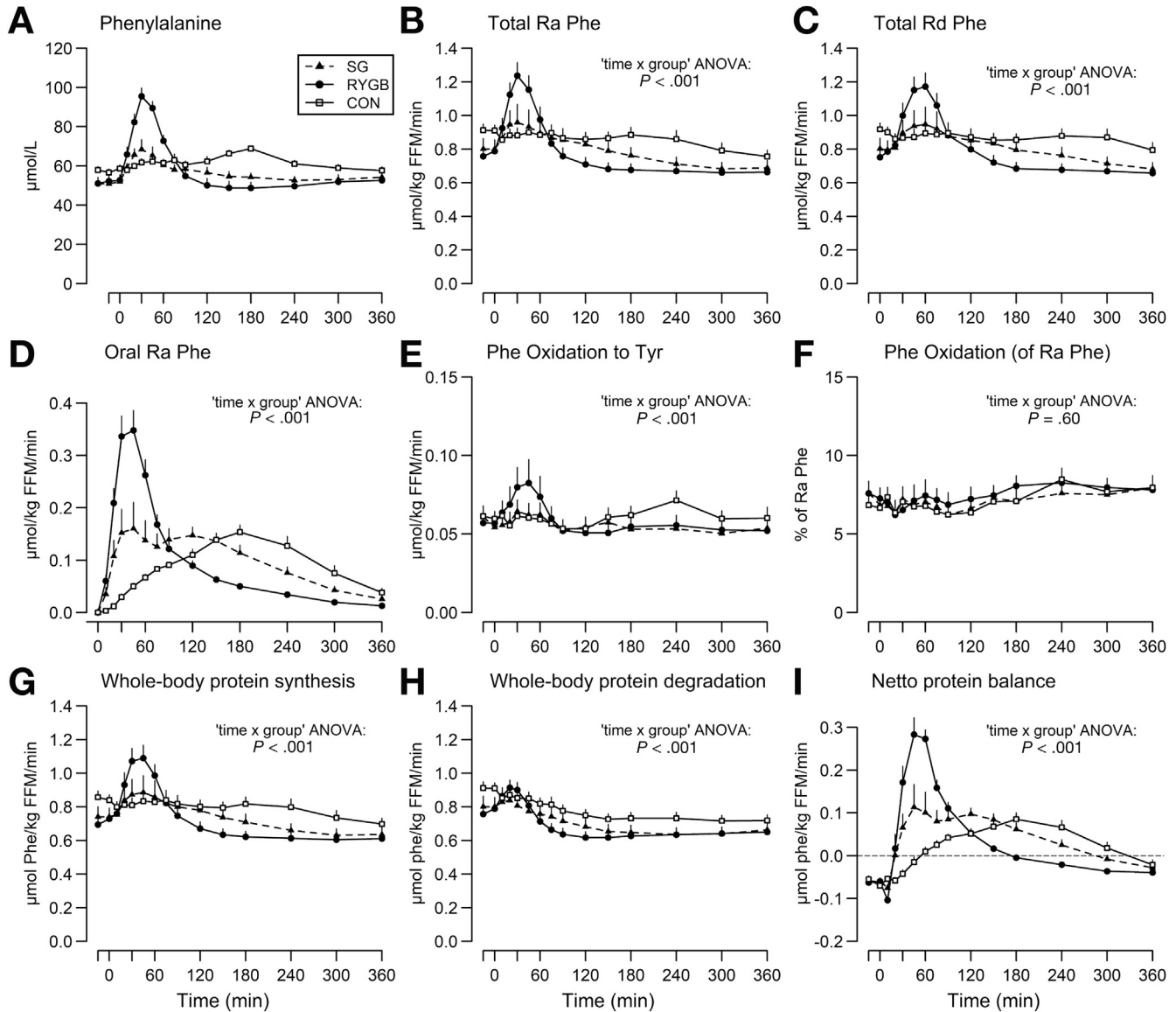
Figure 3. Protein absorption and metabolism. Phe, phenylalanine; Tyr, tyrosine. Data are means ± SEM.

gastrointestinal hormone profiles differed significantly between the surgical procedures, with greatly accelerated digestion and absorption after RYGB. Surprisingly, the postprandial metabolite kinetics after SG differed markedly from those observed after RYGB and were only modestly different from those of the controls. Similarly, gastric/pouch emptying, evaluated by both scintigraphy and paracetamol absorption, was greatly accelerated after RYGB compared with controls, but less so after SG. Together the accelerated nutrient appearance rates and paracetamol absorption after RYGB point to a very rapid intestinal nutrient entry after RYGB confirming data from studies using both tracers[6,7] and scintigraphic techniques.[38] Also, postprandial concentrations of insulin, GLP-1, PYY, and CCK were particularly enhanced after RYGB, likely related to the accelerated entry of nutrients into the small intestine. Accelerated gastric emptying has been demonstrated in some[39,40] but not all[41] previous studies

after SG as well, but the 2 procedures have not been compared directly. We found a marked difference in both gastric/pouch emptying and nutrient appearance rates between the 2 surgical procedures. Thus, diverging rates of intestinal nutrient entry likely explain much of the differences in the systemic appearance rates of glucose and AAs, but also in the secretion of insulin, GLP-1, PYY, and CCK although the direct delivery to the distal gut after RYGB, but not after SG, may also contribute. The importance of rate and site of nutrient entry for hormone secretion is supported by studies in which feeding after reversal of RYGB or through gastrostomy tubes reversed both GLP-1 and insulin hypersecretion.[42,43] Hyperplasia of gut epithelium may result in increased numbers of glucose transporters and higher entry rates, and higher density of incretin-producing cells have also been reported, primarily after RYGB and not after SG, which could contribute to the observed differences.[44]

Table 2. Glucose and Amino Acid Absorption and Metabolism And Lipolysis

Variable	RYGB, mean ± SEM	SG, mean ± SEM	Controls, mean ± SEM	P value (ANOVA)	RYGB vs controls	SG vs controls	SG vs RYGB
Glucose Metabolism							
Basal EGP, *μmol/kg FFM/min*	18 ± 1	17 ± 1	18 ± 1	.86	.93	.98	.85
EGP suppression, *% from basal*	60 ± 2	67 ± 2	74 ± 1	<.001	<.01	.05	.04
Peak Ra oral glucose, *μmol/kg FFM/min*	36 ± 2	27 ± 1	22 ± 2	<.001	<.01	.04	<.01
Time to peak Ra oral glucose, *min*	39 ± 3	41 ± 5	74 ± 9	.002	.007	<.01	1.00
Oral recovery 360 min, *% of ingested glucose in systemic circulation*	72 ± 4	79 ± 5	78 ± 4	.61	.66	1.00	.67
Basal total Ra glucose, *μmol/kg FFM/min*	18.3 ± 1.1	17.5 ± 1.0	17.8 ± 1.3	.86	.93	.98	.85
Peak total Ra glucose, *μmol/kg FFM/min*	49.2 ± 3.0	38.2 ± 2.0	32.1 ± 2.0	<.001	<.01	.03	<.01
Basal Rd glucose, *μmol/kg FFM/min*	18.3 ± 1.1	17.5 ± 1.0	17.8 ± 1.3	.86	.93	.98	.85
Peak Rd glucose, *μmol/kg FFM/min*	44.8 ± 2.8	38.1 ± 2.5	31.2 ± 2.2	.002	.001	.11	.12
Lipolysis							
Suppression of FFA, *% from basal*	72 ± 6	72 ± 2	69 ± 5	.74	.81	.76	.99
Basal Ra glycerol, *μmol/kg fat/min*	11.0 ± 1.0	9.5 ± 0.8	10.4 ± 1.1	0.54	—	—	—
Suppression Ra glycerol, *% from basal*	47 ± 4	58 ± 3	66 ± 3	.007	.005	.29	.15
Protein metabolism							
Fasting Phe, *μmol/L*	52 ±2.9	51 ± 1.8	58 ±1.7	.11	.11	.09	.99
Peak Phe, *μmol/L*	97 ± 3.8	73 ± 4.3	72 ± 1.2	<.001	<.01	.99	<.01
AUC Phe, *mmol/L × min*	20 ± 1.1	20 ± 0.6	22 ± 0.5	.09	.14	.14	1.00
Peak Ra oral Phe, *μmol/kg FFM/min*	0.37 ± 0.04	0.23 ± 0.04	0.17 ± 0.01	<.001	<.01	.22	<.01
Time to peak Ra or Phe, *min*	38 ± 2	93 ± 13	176 ± 14	<.001	<.01	<.01	<.01
Oral recovery 60 min, *% of ingested phe*	30 ± 2.2	13 ± 3.3	4 ± 0.5	<.001	<.01	.01	<.01
Oral recovery 360 min, *% of ingested phe*	67 ± 3	70 ± 4	67 ± 4	.64	1.00	.70	.68
Basal total Ra Phe, *μmol/kg FFM/min*	0.77 ± 0.04	0.80 ± 0.06	0.91 ± 0.03	.02	.02	.07	.82
Peak total Ra Phe, *μmol/kg FFM/min*	1.25 ± 0.08	1.0 ± 0.10	0.98 ± 0.04	.001	.009	.88	.03
AUC total Ra Phe, *μmol/kg FFM*	272 ± 16	281 ± 19	306 ± 14	.14	.15	.27	.93
Basal whole-body protein synthesis, *μmol/kg FFM/min*	0.71 ± 0.04	0.74 ± 0.06	0.84 ± 0.03	.02	.02	.08	.82
Peak whole-body protein synthesis, *μmol/kg FFM/min*	1.11 ± 0.08	0.93 ± 0.10	0.91 ± 0.04	.07	.09	.96	.15
AUC whole-body protein synthesis, *μmol/kg FFM*	252 ± 15	261 ± 19	284 ± 14	.16	.15	.35	.87
Basal whole-body protein degradation (Ra endogenous Phe), *μmol/kg FFM/min*	0.77 ± 0.04	0.80 ± 0.06	0.91 ± 0.03	.02	.02	.07	.82
AUC whole-body protein degradation (AUC Ra endogenous Phe), *μmol/kg FFM*	241 ± 13	246 ± 16	272 ± 12	.08	.08	.16	.92
Basal net protein balance, *g protein/d*	–0.9 ± 0.1	–0.8 ± 0.1	–1.0 ± 0.1	.96	.99	.95	.99
AUC net protein balance, *g protein/d*	154 ± 30	184 ± 36	138 ± 44	.67	1.00	.70	.74
Basal Ra urea, *μmol/kg FFM/min*	5.1 ± 0.3	4.0 ± 0.5	5.1 ± 0.5	.24	.99	.30	.32
AUC total Ra urea, *μmol/kg FFM*	1768 ± 101	1334 ± 166	1634 ± 146	.11	.92	.26	.12

Phe, phenylalanine.

The glucose kinetics differed between unoperated controls and both surgical groups, but we also found a marked difference between RYGB and SG. The peak oral Ra of glucose was 64% higher after RYGB and 21% higher after SG compared with controls, and a larger proportion of ingested glucose appeared in the systemic circulation during the first postprandial hour after RYGB. Also, elevated lactate formation was found, especially after RYGB, probably reflecting glucose fluxes.[45] In contrast, the oral recovery of glucose did not differ between groups during the full study day—a finding that does not support enhanced splanchnic glucose disposal as a major contributor to improved glycemic control after RYGB, as proposed by others.[44] In a previous study,[9] comparable improvements in insulin sensitivity were observed after an approximately 20% weight loss induced by RYGB or SG, and differences between the groups for peak Ra oral glucose appeared to exist with numerically higher values after RYGB[9] in agreement with our findings.

The enhanced GLP-1 secretion after RYGB is in line with numerous previous reports, but surprisingly, the iAUC of GLP-1 in SG-operated subjects did not differ from that of controls, although a slightly enhanced response was observed just after meal intake. This is in agreement with a few previously published reports,[20–22] but it is in direct contrast to other studies reporting equally enhanced GLP-1 after SG and RYGB.[17–19] Peak CCK concentration was also considerably higher after RYGB compared with SG and controls, whereas peak GIP concentrations were comparable after both surgical procedures, although the duration of the GIP response was significant longer in the SG-operated subjects than in RYGB.
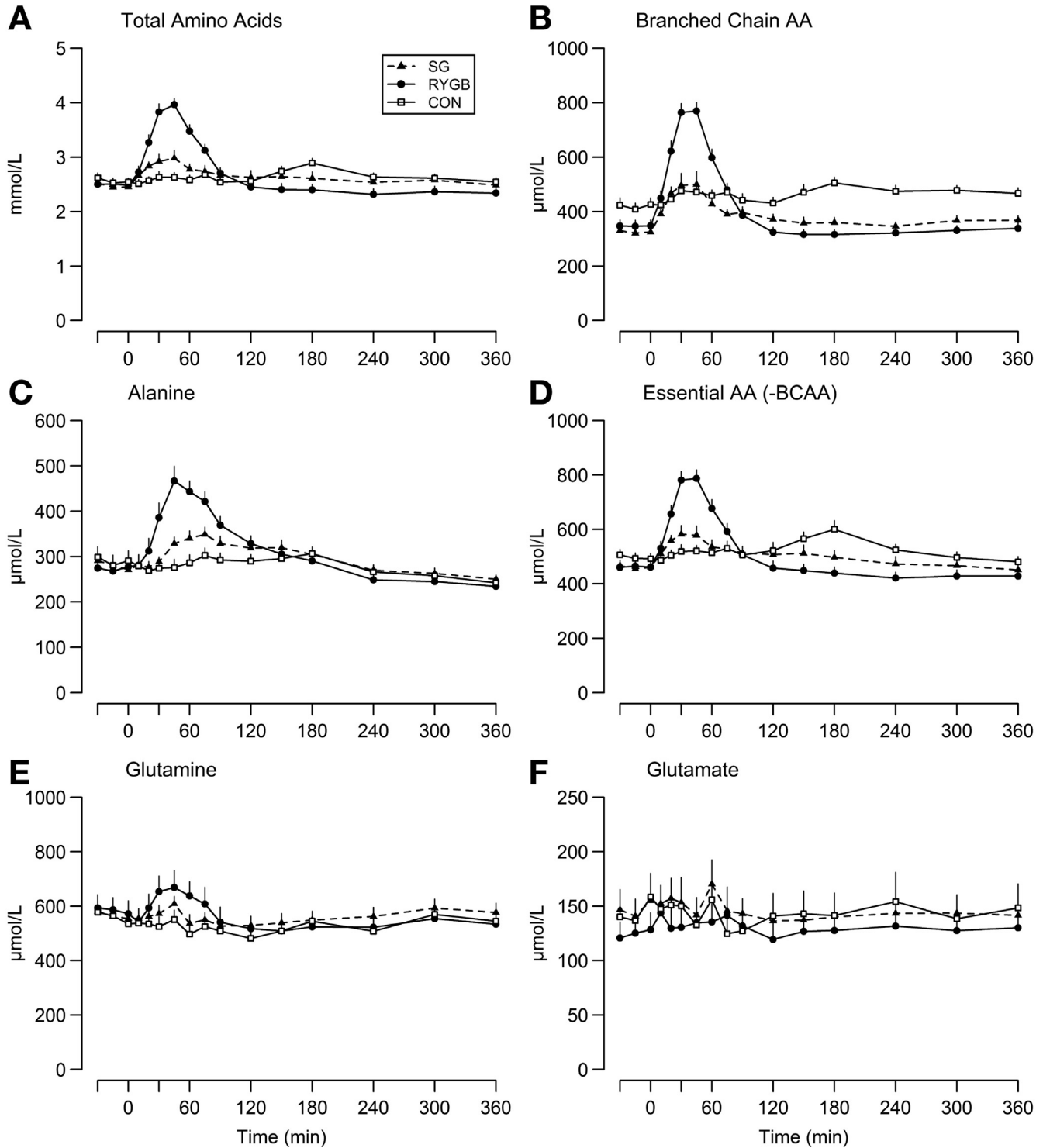
A Total Amino Acids

B Branched Chain AA

C Alanine

D Essential AA (-BCAA)

E Glutamine

F Glutamate

Figure 4. Selected plasma AAs concentrations. Data are means ± SEM.

The lack of difference especially in GLP-1 secretion between RYGB and SG in other studies can be attributed to various factors: differences in surgical techniques with different limb lengths,[18,19] small group sizes,[18,19] and the timing of blood sampling because frequent postprandial blood sampling is essential in detecting the peaks of rapidly degradable hormones.[18,19,46] Inaccuracy of certain commercial assays can also be a matter of concern and,

furthermore, the type and texture of ingested nutrients affect the responses seen.

In this study, glucagon concentrations followed the AA absorption and plasma AA concentrations closely, with an early increase after RYGB and a later increase in controls, in agreement with a previously proposed feedback loop.[47] Confirming previous findings, ghrelin was lower after SG,[19] which, combined with slightly higher levels of PYY,

Table 3. Gastrointestinal Hormones

Variable	RYGB, mean ± SEM	SG, mean ± SEM	Controls, mean ± SEM	P value (ANOVA)	RYGB vs controls	SG vs controls	SG vs RYGB
Fasting GLP-1, *pmol/L*	17 ± 3	15 ± 1	18 ± 1	.51	.98	.54	.62
Peak GLP-1, *pmol/L*	147 ± 9	63 ± 10	42 ± 8	<.001	<.01	.05	<.01
iAUC GLP-1, *nmol/L * min*	8.192 ± 0.847	3.622 ± 0.730	2.444 ± 0.408	<.001	<.01	.48	<.01
Fasting GIP, *pmol/L*	12 ± 2	11 ± 1	11 ± 1	.92	.98	.97	.91
Peak GIP, *pmol/L*	128 ± 8	120 ± 13	95 ± 11	.09	.08	.33	.68
iAUC GIP, *nmol/L * min*	6.2 ± 0.5	12.1 ± 1.9	11.8 ± 1.3	.004	.03	.98	.02
Fasting PYY, *pmol/L*	18 ± 1.1	13 ± 1.0	16 ± 1.3	.01	.37	.14	.01
Peak PYY, *pmol/L*	70 ± 6.4	32 ± 4.3	23 ± 1.5	<.001	<.01	.16	<.01
iAUC PYY, *pmol/L * min*	5821 ± 949	3311 ± 751	1017 ± 420	<.001	<.01	.08	.05
Fasting glucagon, *pmol/L*	4 ± 1	3 ± 1	5 ± 1	.18	.70	.16	.52
Peak glucagon, *pmol/L*	16 ± 2	10 ± 1	12 ± 2	.10	.18	.98	.12
AUC glucagon, *pmol/L * min*	2339 ± 283	1917 ± 354	2606 ± 555	.29	.97	.42	.31
Fasting CCK, *pmol/L*	0.4 ± 0.3	0.5 ± 0.2	1.0 ± 0.9	0.03	.01	.06	.45
Peak CCK, *pmol/L*	12.8 ± 7	7.0 ± 3	5.0 ± 5	<.001	<.01	.02	<.01
iAUC CCK, *pmol/L * min*	623 ± 317	383 ± 181	426 ± 195	.046	.09	.40	.02
Fasting acylated ghrelin, *pg/mL*	42 ± 5	24 ± 3	51 ± 9	.006	.82	.007	.03
AUC acylated ghrelin, *ng/mL*	15 ± 1	9 ± 1	20 ± 3	<.001	.13	<.001	.05
Fasting total ghrelin, *pg/mL*	936 ± 86	555 ± 55	1325 ± 175	<.001	.049	<.001	<.01
AUC total ghrelin, *ng/mL*	473 ± 34	281 ± 32	716 ± 93	<.001	.01	<.001	<.01

AUC, area under the curve.

GLP-1, and CCK, might explain some of the weight-reducing effects of SG. This is in contrast to RYGB, in which exaggerated concentrations of L-cell hormones seem important.[13] Accordingly, different combinations of hormonal changes could hypothetically contribute to the appetite-regulating effects of the 2 procedures. The role of ghrelin needs further investigation because mice lacking ghrelin signaling and their wild-type counterparts had comparable weight losses after SG.[48]

Notably, all participants were glucose-tolerant before the procedures. Therefore, differences in β-cell glucose sensitivity between the groups were not expected.[14,46] Nevertheless, when relating β-cell glucose sensitivity to ambient insulin sensitivity, the surgical groups displayed increased β-cell function (ie, disposition index) compared with controls. Although GLP-1 was excessively higher after RYGB, SG-operated subjects also demonstrated enhanced GLP-1 and GIP early postprandially, which, in combination with a steeper increase in glucose concentrations, would be expected to elicit augmented insulin secretion. Furthermore, GIP responses were considerably prolonged in SG compared with RYGB. Importantly, the dose–response relationship between the endogenously secreted incretins and the potentiation of glucose-stimulated insulin secretion remains unknown in these groups of individuals.

Postprandial AA kinetics have not been assessed after SG previously, and although it occurred earlier, the peak oral Ra of phenylalanine was not elevated after SG compared with controls. This indicates unaltered protein digestion and absorption after SG, in contrast to the accelerated absorption of protein (with a 118% larger peak rate) seen after RYGB in this study and in our previous study.[7]

This study adds substantial new knowledge about protein metabolism after RYGB and SG[7] via the estimation of whole-body protein balance. We observed a fast and transient rise in total AA concentration, and a correlated rise in the systemic appearance of meal-derived AAs after RYGB. This confirms that the postprandial increase in AAs originates from ingested food and not from increased protein degradation,[7] and suggests that the accelerated protein digestion and absorption rates persist years after RYGB, when patients are weight-stable. Protein kinetics differed markedly between RYGB and SG, and SG-operated subjects did not differ from the control group in this respect. Nevertheless, the 6-hour postprandial oral recovery of ingested protein was comparable between all groups, which indicates that no differences in splanchnic extraction of AAs or protein malabsorption exist in either surgical group.

The hydroxylation of phenylalanine to tyrosine is an index of phenylalanine oxidative loss and paralleled the accelerated appearance of orally ingested phenylalanine. Likewise, protein synthesis was greatly stimulated in the early postprandial period only after RYGB, followed by later suppression. Because of these 2 opposing processes, net protein synthesis ended up being similar in all groups. In other words, the proportion of ingested phenylalanine targeted to protein synthesis and to oxidative loss, respectively, was similar in the 3 groups during the entire postprandial period. However, the net-positive protein balance lasted only 2.5 hours after RYGB, compared with 4 hours after SG and in controls, and the consequences of this more pronounced but shorter anabolic phase require further investigation. Taken together, our findings support effective digestion and absorption of protein after RYGB and early stimulation of protein synthesis. Obviously, inadequate protein intake can still lead to a negative nitrogen balance. Loss of muscle mass is a natural adaptation to major weight loss,[49] but the present study does not support any specific

protein-wasting side effects of RYGB. This is supported by studies demonstrating higher FFM percentages after both RYGB and SG compared with unoperated controls, inconsistent with major FFM depletion after surgery.[50] Instead, the loss of FFM seems comparable to what is expected due to the weight loss itself.[51]

The cross-sectional design of our study has the advantage that we were able to examine patients in the weight-stable phase and to obtain matching for both pre- and postoperative BMI to minimize the confounding effect of differing postoperative weight losses. Hence, our findings represent the late metabolic effects of surgery, which might differ significantly from the acute effects within the first postoperative year when weight loss is still ongoing. This cross-sectional design poses some limitations because the findings are associations and not causal relationships. Accordingly, these hypothesis-generating findings need to be confirmed in future prospective or interventional studies. The magnitudes of the weight losses after SG and RYGB are debated. Some studies report similar weight losses,[3,21] while others report a smaller weight loss after SG.[2,5,52] If we assume that SG-operated patients have similar or slightly less weight loss, then, if anything, our selection of patients would underestimate differences between SG and RYGB, making the observed differences a conservative estimate. Only participants without prior diabetes were included, which should be considered when assessing potential mechanisms related to diabetes remission. Finally, the use of a liquid meal in our study meal could have influenced the results and future studies comparing the surgical procedures in patients with diabetes and the use of meals also consisting of solid components would be of interest.

Conclusions

Postprandial glucose and protein absorption and metabolism, as well as patterns of gastro-entero-pancreatic hormone secretion differed markedly between RYGB- and SG-operated subjects matched in terms of postoperative weight loss. We have shown enhanced systemic glucose appearance and more exaggerated glucose excursions after RYGB. Also, accelerated protein digestion, absorption, and whole-body protein synthesis were seen after RYGB. In contrast, protein metabolism after SG largely resembled that of unoperated subjects. The differences between the procedures may be explained by the greatly accelerated pouch emptying and more distal nutrient delivery after RYGB. Both procedures altered postprandial gastrointestinal hormone secretions, with exaggerated secretion of GLP-1, PYY, and CCK, especially after RYGB, whereas ghrelin was lower and GIP responses more prolonges after SG. These observations may be important for our understanding of the clinical effects of the 2 surgical procedures.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www. gastrojournal.org, and at https://doi.org/10.1053/j.gastro. 2019.01.262.

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Supplementary Material

Tracer Calculations and Equations

Total Ra and Rd of glucose, phenylalanine, and tyrosine were estimated using non–steady-state equations using enrichments of [6,6-D_2] glucose, L-[ring-$^2D_5$] phenylalanine and L-[ring 3,5-D_2]tyrosine, respectively:

$$Total\ Ra\ =\ \frac{F - Vd\ x\ C(t)\ x\ \frac{\Delta Eiv}{\Delta t}}{Eiv(t)}$$

$$Total\ Rd\ =\ Total\ Ra - Vd\ x\ \frac{\Delta C}{\Delta t}$$

F is the infusion rate of the intravenous tracer,

Vd is the distribution volume (set to 0.07),

$C(t)$ is the mean plasma concentrations of glucose, phenylalanine or tyrosine between two time points,

$\frac{\Delta Eiv}{\Delta t}$ is the time-dependent variation in plasma enrichments (tracer-to-tracee ratio) derived from the intravenous tracers,

$Eiv(t)$ is the mean of plasma enrichments derived from the intravenous tracers between 2 time consecutive time points, and

$\frac{\Delta C}{\Delta t}$ is the time-dependent variation in plasma concentrations of glucose, phenylalanine or tyrosine.

Oral appearance rate of phenylalanine (oral Ra$_{phe}$) was calculated from plasma [15N Phe]-enrichments (tracer-to-tracee ratios) multiplied with Total Ra Phe and was corrected for time-dependent variations in plasma [15N Phe]-enrichments:

$$Oral\ Ra\ Phe\ =\ \frac{Total\ Ra\ Phe\ x\ Eoral(t) + Vd\ x\ \frac{\Delta Eoral}{\Delta t}}{Eprotein}$$
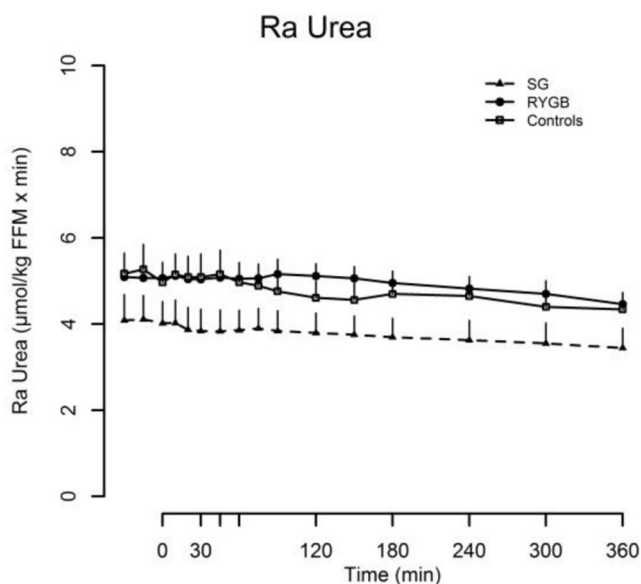
$Eoral(t)$ is the mean plasma enrichment of the oral [15N Phe] tracer,

$\frac{\Delta Eoral}{\Delta t}$ is the time-dependent variation in plasma enrichments derived from the oral[15N Phe] tracer, and
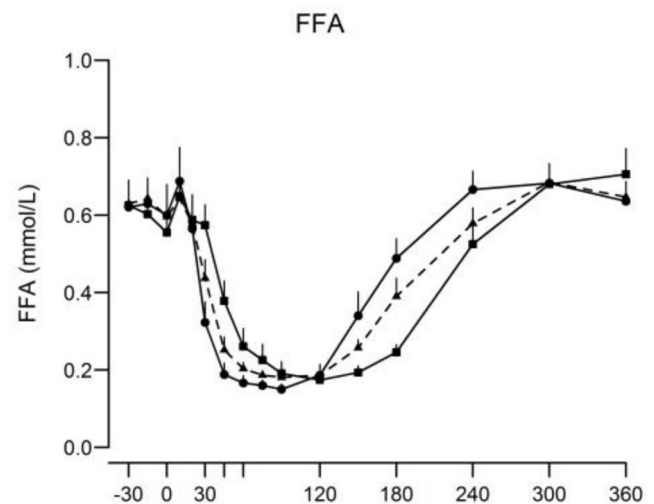
$Eprotein$ is the [15N Phe] enrichment in the ingested protein ($\sim$0.12).

Endogenous Ra was calculated as:

$Endo\ Ra = Total\ Ra - Oral\ Ra.$

Supplementary Figure 1. Ra of urea in 12 SG-operated subjects (*solid triangle, dotted line*), 12 RYGB-operated subjects (*solid circled, solid line*), and 12 control subjects (*white squares, solid line*).

Supplementary Figure 2. Plasma concentrations of FFA in the basal state and after ingestion of a liquid mixed meal at time = 0 in 12 SG-operated subjects (*solid triangle, dotted line*), 12 RYGB-operated subjects (*solid circled, solid line*), and 12 unoperated control subjects (*solid squares, solid line*).