Magnitude and Variability of the Glucagon-Like Peptide-1 Response in Patients With Type 2 Diabetes up to 2 Years Following Gastric Bypass Surgery

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OBJECTIVE—To characterize the magnitude and variance of the change of glucose and glucagon-like peptide-1 (GLP-1) concentrations, and to identify determinants of glucose control up to 2 years after gastric bypass (GBP).

RESEARCH DESIGN AND METHODS—Glucose and GLP-1 concentrations were measured during an oral glucose challenge before and 1, 12, and 24 months after GBP in 15 severely obese patients with type 2 diabetes.

RESULTS—Glucose area under the curve from 0 to 180 min ($AUC_{0–180}$) started decreasing in magnitude ($P < 0.05$) 1 month after surgery. GLP-1 $AUC_{0–180}$ increased in magnitude 1 month after GBP ($P < 0.05$), with increased variance only after 1 year ($P_{\sigma}{}^2 \leq 0.001$). GLP-1 $AUC_{0–180}$ was positively associated with insulin $AUC_{0–180}$ ($P = 0.025$).

CONCLUSIONS—The increase in variance of GLP-1 at 1 and 2 years after GBP suggests mechanisms other than proximal gut bypass to explain the enhancement of GLP-1 secretion. The association between GLP-1 and insulin concentrations supports the idea that the incretins are involved in glucose control after GBP.

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The enhanced glucagon-like peptide-1 (GLP-1) levels and incretin effect on insulin secretion, with weight loss, explain improved diabetes control after gastric bypass (GBP) surgery (1–3). However, the long-term clinical outcome after GBP differs greatly between patients, with diabetes relapse in up to 30% (4,5). This study aimed to assess the changes in magnitude and variance of GLP-1 and glucose concentrations in response to an oral glucose challenge (OGTT) in patients with type 2 diabetes and to identify determinants of glucose control up to 2 years after GBP.

RESEARCH DESIGN AND METHODS

Fifteen obese patients (1 man, 14 women) known to have type 2 diabetes for 2.5 ± 2.5 years, HbA_{1c} 7.1 ± 1.1%, BMI 43.7 ± 4.9 kg/m^2, age 47.5 ± 9.1 years, were studied before and 1, 12, and 24 months after GBP. Before GBP, seven participants took metformin and/or sulfonylureas, which were discontinued 3 days before testing. Participants, after signing an informed consent, underwent a 50-g 3-h OGTT, followed by an isoglycemic intravenous glucose challenge (isoG IVGT) to measure the incretin effect (6). Plasma samples were collected and analyzed as described previously (1,2). Total areas under the curve (AUCs) for 0 to 180 min ($AUC_{0–180}$) were calculated using the trapezoidal method. The homeostasis model assessment of insulin resistance (HOMA-IR) and the insulin sensitivity index (ISI) composite were calculated, as previously described (7). HOMA-B was used to assess β-cell function (8). Data are expressed as mean ± SD.

General linear models were used to analyze changes over time. Pitman tests were used to compare correlated variances (square of the SD [σ^2]) to quantify changes in variability over time. A level of significance of 0.05 identified changes between intervals. To identify determinants of glucose control, a mixed-model approach was used. Outcomes were glucose and insulin $AUC_{0–180}$, with GLP-1 $AUC_{0–180}$, weight loss, HOMA-IR, HOMA-B, incretin effect, and ISI as covariates. Data were ln-transformed, and the mean was centered if necessary. An $\alpha = 0.10$ level of significance identified a covariate as a determinant.

RESULTS

All 15 patients completed the study. Because of difficult intravenous access, one patient had no isoIVGT. After GBP, all patients discontinued diabetes medications. Changes in magnitude and variance are shown in Fig. 1. The pattern of change after GBP for all outcome variables given hereafter was similar in the male and female patients. Weight, glucose $AUC_{0–180}$, ISI, and HOMA-IR all decreased significantly up to 1 year after GBP, with no further decrease between 1 and 2 years. The decrease in insulin $AUC_{0–180}$ became significant at 2 years. HOMA-B levels showed an increasing trend that was not statistically significant at any post-GBP interval. Insulin $AUC_{0–30}$, GLP-1 $AUC_{0–180}$, and incretin effect on insulin secretion increased significantly 1 month after GBP with no further changes at 1 and 2 years.

Variance of glucose $AUC_{0–180}$ decreased starting 1 year after GBP. Variances decreased starting at 1 month after GBP for HOMA-IR and at 2 years for HOMA-B (Fig. 1*A*). Variances of weight and incretin effect on insulin showed a decreasing trend (Fig. 1*B*). The variance of insulin $AUC_{0–30}$ and GLP-1 $AUC_{0–180}$ increased after GBP starting at 1 month and

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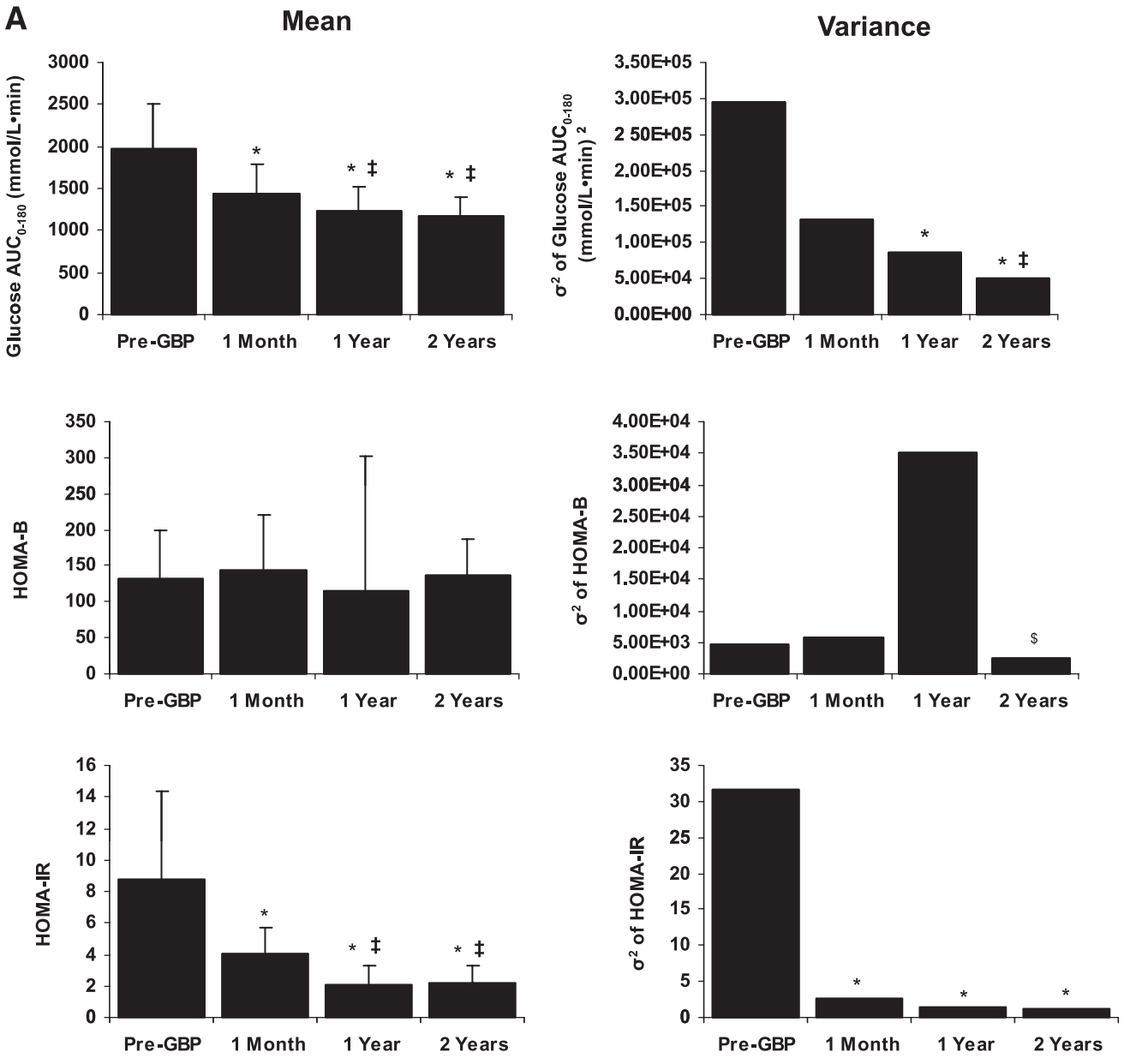

Figure 1—A: *Variables for which variance decreased over time after GBP*. Left: *Mean ± SD for glucose $AUC_{0–180}$, HOMA-B, and HOMA-IR*. Right: *Variance of glucose $AUC_{0–180}$, HOMA-B, and HOMA-IR*. B: *Variables for which variance tends to decrease over time after GBP*. Left: *Mean ± SD for weight and incretin effect on insulin*. Right: *Variance of weight and incretin effect on insulin*. C: *Variables for which variance increased over time after GBP*. Left: *Mean ± SD for GLP-1 $AUC_{0–180}$ and insulin $AUC_{0–30}$*. Right: *Variance for GLP-1 $AUC_{0–180}$ and insulin $AUC_{0–30}$*. D: *Variables for which variance did not change after GBP*. Left: *Mean ± SD for insulin $AUC_{0–180}$ and ISI composite*. Right: *Variance of and ISI composite insulin $AUC_{0–180}$*. *P < *0.05 vs. baseline*, ‡P < *0.05 vs. 1 month*, $P < *0.05 vs. 1 year*. N = *15 (except for incretin effect,* n = *14)*.

1 year, respectively (Fig. 1*C*). The variances of insulin $AUC_{0–180}$ and ISI composite did not change (Fig. 1*D*).

Changes in glucose $AUC_{0–180}$ over time were positively associated in univariate analyses with weight loss ($P = 0.059$) and negatively associated with HOMA-B ($P < 0.001$) and ISI composite ($P = 0.026$). In the multivariate analysis, weight loss ($P = 0.061$), HOMA-B ($P = 0.004$), and ISI ($P < 0.001$) were determinants of glucose $AUC_{0–180}$. GLP-1 $AUC_{0–180}$ was positively related to $AUC_{0–180}$ insulin ($P = 0.025$).

CONCLUSIONS—The assessment of changes in the variances of glucose, insulin, and GLP-1 concentrations over time provides more information than solely assessing the mean change of their concentrations. For glucose, an overall decrease in intersubject variability is observed after GBP, which may be explained by the normalization of glucose homeostasis, with a further decrease in glucose levels being halted by a "floor-effect." The normalization of glucose levels in all patients thus results in less intersubject variability. In contrast, the variance of the GLP-1 response to oral glucose increases, but only 1 to 2 years after the surgical procedure. Thus, although the mean postprandial GLP-1 concentrations increase immediately after GBP, the intersubject variability of the GLP-1 release only increases later. This suggests that something other than

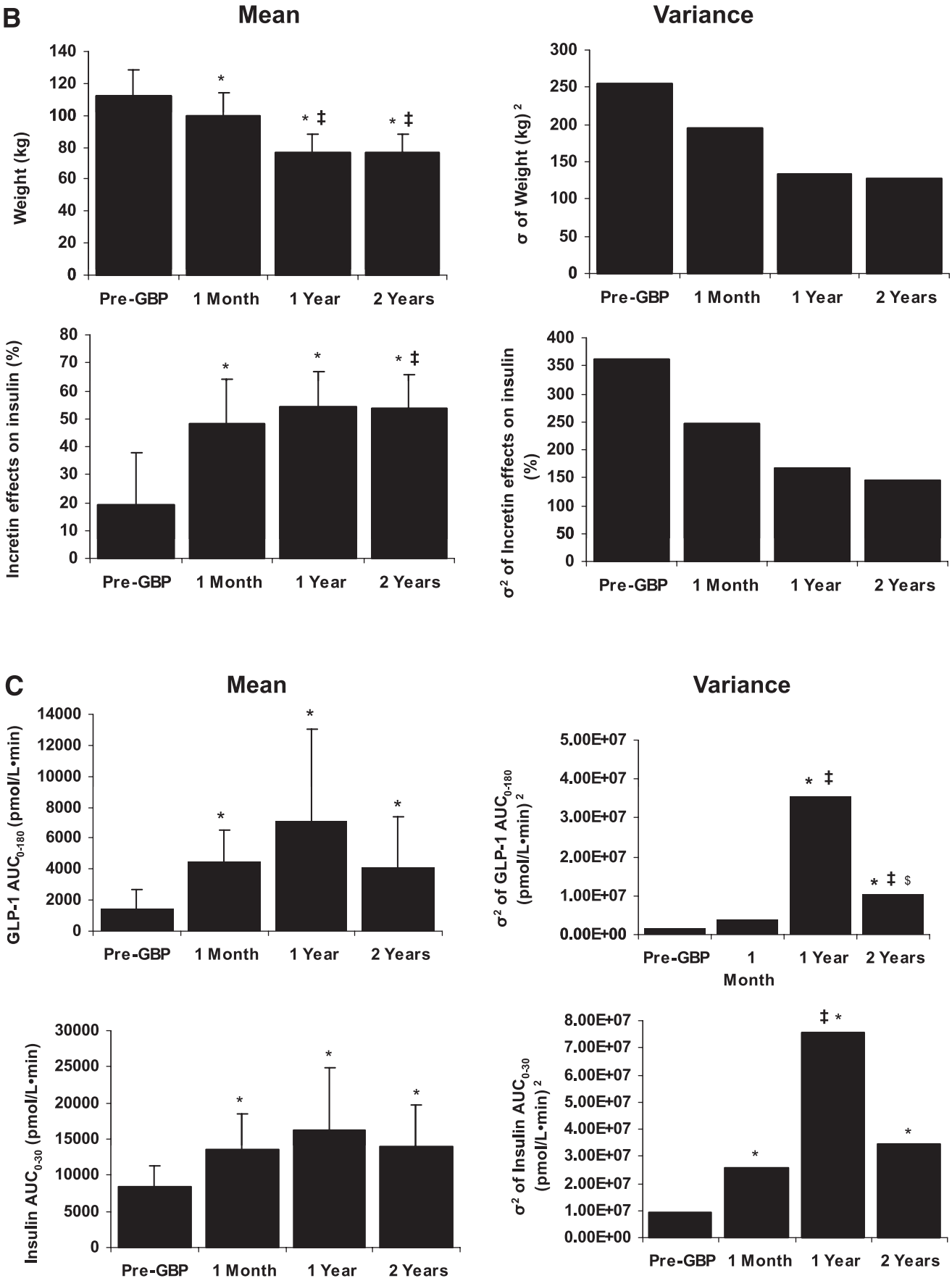

Figure 1—*Continued.*

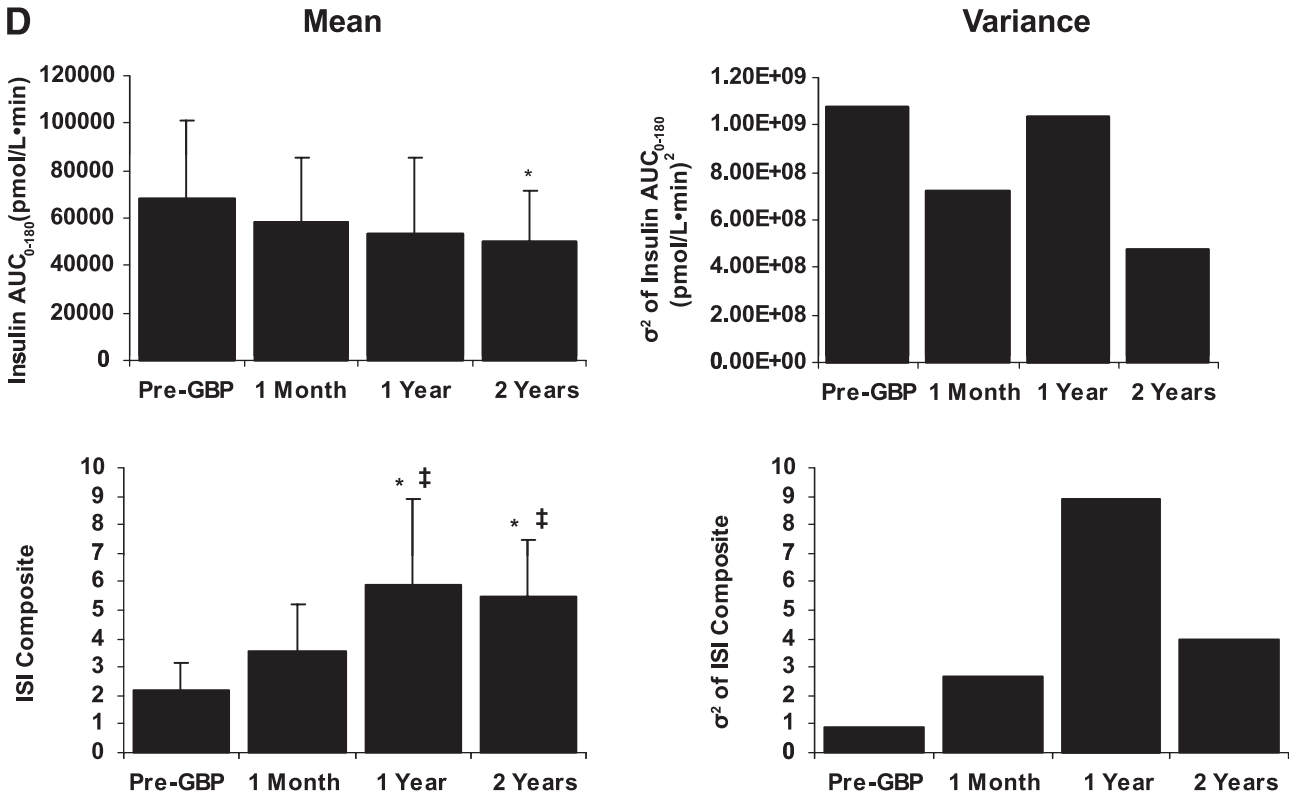

Figure 1—*Continued.*

the bypass of the foregut and the accelerated intestinal transit time, which occur immediately after GBP, enhances the GLP-1 response (9,10). Adaptation of the intestinal mucosa (11) and gut microbiota (12), which have been suggested to play a role in the enhanced GLP-1 response after GBP, could be responsible for the progressive increase in the variance of GLP-1 response over time. Furthermore, as the variance of GLP-1 increases, the variance of incretin effect on insulin secretion decreases after GBP. This discrepancy illustrates that the improvement of incretin effect on insulin after GBP is far more complex than an increase of GLP-1 levels alone. Changes in β-cell sensitivity to GLP-1 after GBP may be involved, a hypothesis that needs further testing.

The present data confirm previous reports of the role of weight loss in the improvement of diabetes after GBP (13,14). The strong association between GLP-1 and insulin concentrations supports the involvement of GLP-1 in glucose control after GBP, as shown previously (3,10,15). The β-cell reserve, estimated by HOMA-B and ISI, is another key determinant of improved glucose homeostasis after GBP. This suggests that interventions for type 2 diabetes, including GBP, should be considered early on when functional β-cell mass is preserved. This is in line with clinical findings that long-standing diabetes and the use of insulin, indicative of failing β-cell function, are predictors of diabetes relapse after surgery (4,5). However, surgical intervention is not without risks, and introduction of bariatric surgery early on in the treatment of type 2 diabetes remains controversial.

Although our study has limitations in size and duration, it suggests that careful longitudinal phenotyping of large groups of patients in regard to changes in weight and postprandial glucose and GLP-1 concentrations might hold clues on the underlying mechanisms of long-term glucose control after GBP. A better understanding of mechanisms might lead to new, less invasive treatment paradigms.

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B.J.V.d.S. performed the statistical analysis of the data and wrote the manuscript. P.H. helped with statistical analysis of the data and reviewed and edited the manuscript. M.A. helped with data collection and statistical analysis. K.A., G.W., and D.R. collected the data. B.L. designed the study, collected and reviewed the data, wrote the manuscript, and as corresponding author and guarantor, takes full responsibility for the work as a whole.

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References

1. Bose M, Teixeira J, Oliván B, et al. Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. J Diabetes 2010;2:47–55
2. Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab 2008; 93:2479–2485
3. Falkén Y, Hellström PM, Holst JJ, Näslund E. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: role of gut peptides. J Clin Endocrinol Metab 2011;96:2227–2235
4. DiGiorgi M, Rosen DJ, Choi JJ, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. Surg Obes Relat Dis 2010;6:249–253
5. Chikunguwo SM, Wolfe LG, Dodson P, et al. Analysis of factors associated with durable remission of diabetes after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2010; 6:254–259
6. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 1986;29:46–52
7. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
9. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg 2006;244:741–749
10. Morínigo R, Moizé V, Musri M, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab 2006;91:1735–1740
11. Speck M, Cho YM, Asadi A, Rubino F, Kieffer TJ. Duodenal-jejunal bypass protects GK rats from beta-cell loss and aggravation of hyperglycemia and increases enteroendocrine cells coexpressing GIP and GLP-1. Am J Physiol Endocrinol Metab 2011;300:E923–E932
12. Li JV, Ashrafian H, Bueter M, et al. Metabolic surgery profoundly influences gut microbial–host metabolic cross-talk. Gut 2011;60:1214–1223.
13. Hamza N, Abbas MH, Darwish A, Shafeek Z, New J, Ammori BJ. Predictors of remission of type 2 diabetes mellitus after laparoscopic gastric banding and bypass. Surg Obes Relat Dis 7 Apr 2010 [Epub ahead of print] DOI:10.1016/j.soard.2010.03.292
14. Kadera BE, Lum K, Grant J, Pryor AD, Portenier DD, DeMaria EJ. Remission of type 2 diabetes after Roux-en-Y gastric bypass is associated with greater weight loss. Surg Obes Relat Dis 2009;5:305–309
15. Laferrère B, Heshka S, Wang K, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care 2007;30:1709–1716