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 (AUC0–180) started decreasing in magnitude (P < 0.05) 1 month after surgery. GLP-1 AUC0–180 increased in magnitude 1 month after GBP (P < 0.05), with increased variance only after 1 year (Pα² ≤ 0.001). GLP-1 AUC0–180 was positively associated with insulin AUC0–180 (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.

RESULTS—All 15 patients completed the study. Because of difficult intravenous access, one patient had no isoGVT. 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 AUC0–180, 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 AUC0–180 became significant at 2 years. HOMA-B levels showed an increasing trend that was not statistically significant at any post-GBP interval. Insulin AUC0–30, GLP-1 AUC0–180, and incretin effect on insulin secretion increased significantly 1 month after GBP with no further changes at 1 and 2 years.

Variance of glucose AUC0–180 decreased starting 1 year after GBP. Variance decreased starting at 1 month after GBP for HOMA-IR and at 2 years for HOMA-B (Fig. 1A). Variances of weight and incretin effect on insulin showed a decreasing trend (Fig. 1B). The variance of insulin AUC0–30 and GLP-1 AUC0–180 increased after GBP starting at 1 month and...
1 year, respectively (Fig. 1C). The variances of insulin AUC$_{0-180}$ and ISI composite did not change (Fig. 1D).

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
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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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**Figure 1**—Continued.

![Figure 1](https://example.com/figure1.png)

**D** Mean

| Insulin AUC_{gl} (pmol/L·min) | Pre-GBP | 1 Month | 1 Year | 2 Years |
|-------------------------------|--------|--------|--------|--------|
| 0                             | 60000  | 80000  | 100000 | 120000 |
|                               |        |        |        |        |

**Variance**

| Pre-GBP | 1 Month | 1 Year | 2 Years |
|---------|---------|--------|---------|
| 0       | 2.00E+09| 2.50E+09| 3.00E+09|

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![Figure 1](https://example.com/figure1.png)

**D** Mean

| ISI Composite | Pre-GBP | 1 Month | 1 Year | 2 Years |
|---------------|--------|--------|--------|--------|
| 0             | 2      | 3      | 4      | 5      |
|               |        |        |        |        |

**Variance**

| Pre-GBP | 1 Month | 1 Year | 2 Years |
|---------|---------|--------|---------|
| 0       | 10      | 20     | 30      |
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