Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: a case report

Running title: Improved Glucose Tolerance After Gastric Bypass

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**Objective:** To examine after gastric bypass the effect of peroral vs. gastroduodenal feeding on glucose metabolism.

**Research Design and Methods:** A type 2 diabetic patient was examined on two consecutive days 5 weeks after gastric bypass. A standard liquid meal was given, on the first day into the bypassed gastric remnant and on the second day perorally. Plasma glucose, insulin, C peptide, glucagon, incretin hormones, peptide YY and free fatty acids were measured.

**Results:** Peroral feeding reduced 2-h-postprandial plasma glucose (7.8 vs. 11.1 mM) and incremental-area-under-the-glucose-curve (0.33 vs. 0.49 mM×min) compared with gastroduodenal feeding. β-cell function (IAUC_{peptide/Glu}) was more than 2-fold improved during peroral feeding and the GLP-1 response increased nearly 5-fold.

**Conclusions:** Improvement in postprandial glucose metabolism after gastric bypass is an immediate and direct consequence of the gastrointestinal rearrangement, associated with exaggerated GLP-1 release and independent of changes in insulin sensitivity, weight-loss and caloric restriction.
Resolution of type 2 diabetes after Roux-en-Y gastric bypass (RYGB) has been observed in several studies and involves mechanisms associated with the surgical rearrangement of the gastrointestinal tract in addition to the effect of weight loss (1). The mechanisms have not been established, but changed gut hormone levels after surgery may play a role (2).

Recently, we had the unique opportunity to examine the effects of feeding either perorally, and thereby bypassing the stomach, duodenum and proximal jejunum, or through a gastric tube inserted into the bypassed gastric remnant on the glucose metabolism in a single patient.

**RESEARCH DESIGN AND METHODS**

**Subject:** A 51-year-old male patient with type 2 diabetes (BMI 50.2 kg/m², HbA1c 8.0%) treated with metformin, sulfonylurea and insulin underwent a laparoscopic RYGB for morbid obesity.

On the 2nd post-operative day a leakage from the gastro-jejunostomy was suspected because of fever and abdominal pain. Acute re-operation showed no firm signs of leakage, but nevertheless a percutaneous gastric tube was inserted into the bypassed gastric remnant. The tube served as the only route of nutrition during the following 3 weeks, after which the patient again was allowed peroral feeding according to a standard nutrition protocol (1200 kcal/day). Treatment with insulin and metformin was temporarily required after the re-operation, but could be discontinued 3 weeks post-operatively.

We examined the patient 5 weeks postoperatively, at which time the patient was fed perorally, but still had the gastric tube. The patient had lost 14 kg (BMI 45.2 kg/m²). Informed consent was obtained prior to examination.

**Design And Method:** On two consecutive days at 8.30 AM after an overnight fast (8 h) a standard 200-mL liquid meal (Nutridrink, Nutricia), containing 300 kcal with 16% protein, 49% carbohydrate and 36% fat, was given over a period of 10 minutes; on the first day through the gastric tube and on the second day perorally. Blood samples were drawn from an antecubital vein at 15-30 minutes intervals (see figure 1).

**Laboratory Analyses:** Plasma glucose was measured by a glucose-oxidase method (ABL800Flex, Radiometer, Denmark), peptide YY3-36 with a RIA-kit (LINCO Research, USA) and free fatty acids by an enzymatic colorimetric method (Wako, Germany). Plasma insulin, C peptide, glucagon and incretin hormone were quantified as earlier described (3).

**Calculations:** Incremental-area-under-the-curve (iAUC) was calculated using the trapezoidal model. β-cell function was evaluated by iAUC_insulin, iAUC_Cpeptide, insulinogenic index (IGI), calculated as (insulin₃₀ − insulin_fasting)/(Glu₃₀ − Glu_fasting), and iAUC_Cpeptide/Glu-ratio. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as (insulin_fasting × Glu_fasting)/22.5.

**RESULTS**

Plasma concentrations and iAUC for glucose, insulin, C peptide, glucagon, total glucagon-like peptide-1 (GLP-1), intact glucagon-dependent insulinotropic polypeptide (GIP), peptide YY3-36 (PYY) and free fatty acids (FFA) after peroral and gastroduodenal feeding are shown in figure 1.

Plasma glucose concentration peaked earlier and returned more rapidly to fasting values after peroral than gastroduodenal feeding, as illustrated by a markedly reduced 2-h plasma glucose concentration (7.8 vs. 11.1 mM). Incremental-area-under-the-glucose-curve (iAUC_Glu) was noticeably lower after peroral feeding. The peak values...
of plasma insulin and C peptide were higher after peroral than gastroduodenal feeding (4-fold and 2-fold, respectively) and iAUC\text{insulin} and iAUC\text{Cpeptide} were also clearly elevated. IGI was improved after peroral feeding (115 vs. 72 pmol/mmol) and the iAUC\text{Cpeptide/Glu}\text{-ratio}, was more than 2-fold increased (0.90 vs. 0.40 nmol×mmol\(^{-1}\)). HOMA-IR remained unchanged on the two examination days (3.3 vs. 3.5).

GLP-1 plasma concentration peaked simultaneously after peroral and gastroduodenal feeding, but the peak value was more than 3-fold increased (87 vs. 28 pM) and iAUC\text{GLP-1} was nearly 5-fold increased after peroral feeding. Insulin and GLP-1 correlated strongly after peroral (r=0.92, p<0.001), but not gastroduodenal feeding (r=0.55, p=0.08). Plasma concentrations of glucagon and intact GIP were similar on both days. Responses of PYY and FFA are depicted in the figure.

**CONCLUSIONS**

Rapid improvement in glucose tolerance after RYGB surgery is a clinical reality (2). We here report important differences in \(\beta\)-cell function and glucose metabolism after peroral compared with gastroduodenal feeding in a patient with RYGB and a gastrostomy, where differences in insulin sensitivity, weight-loss and caloric restriction can be ruled out as explanations for the improved glucose tolerance.

Our results show marked improvement in glucose tolerance with near normalization of 2-h-postprandial plasma glucose value and a 33% reduction in iAUC\text{Glu} after peroral feeding compared with gastroduodenal feeding. In contrast, during gastroduodenal feeding glucose tolerance was diabetic with a 2-h-postprandial plasma glucose value around 11 mM. The improvement was accompanied by a 2-fold increase in \(\beta\)-cell secretory response (AUC\text{Cpeptide/Glu}), which was associated with a 5-fold increase in iAUC\text{GLP-1}. Insulin and GLP-1 concentrations during peroral feeding were strongly correlated suggestive of a causal relationship. Interestingly the insulin and C peptide response-curves found after gastroduodenal feeding resemble the responses found in type 2 diabetic patients, whereas the response-curves after peroral feeding are similar to those found in healthy control subjects (4). The emptying time is likely to be slower after feeding into the bypassed gastric remnant, which could explain the slower peak in plasma glucose observed after gastroduodenal feeding, but would also per se be expected to result in decreased postprandial glucose excursions.

The observed improvements in glucose tolerance and GLP-1 secretion are in concordance with earlier findings from patients examined before and after RYGB-surgery (5-13). Regarding GIP, some studies have demonstrated increased (7,10) and others decreased responses (9,13) after RYGB. In our patient, GIP responses were similar on the two days, suggesting that changes in GIP were not responsible for the differences in insulin secretion and glucose tolerance. Also glucagon responses were similar.

In conclusion, our results suggest that RYGB has a direct beneficial effect on postprandial glucose metabolism most likely due to an increased insulin secretion caused by the massive increase in GLP-1 that is probably due to the rapid exposure of L-cells in the distal small intestine to nutrients (14). It has been suggested that duodenal exclusion inherent in the RYGB somehow might be responsible for the improvement in glucose tolerance (15). In this respect it is of interest that the secretion of the upper jejunal hormone, GIP, was similar during peroral or gastroduodenal feeding.
REFERENCES

Figure 1: Plasma concentrations of glucose (A), insulin (B), C peptide (C), glucagon (D), GLP-1 (E), intact GIP (F), PYY (G) and FFA (H) after peroral or gastroduodenal feeding in a RYGB-operated patient. Figure includes incremental-area-under-the-curve estimations. Triangles and dotted lines = peroral feeding; circles and solid lines = gastroduodenal feeding.
Figure 1

A. Glucose (mM)

- iAUC 0.33 mM min
- iAUC 0.49 mM min

B. Insulin (pM)

- iAUC 48 nM min
- iAUC 24 nM min

C. C-peptide (pM)

- iAUC 268 nM min
- iAUC 196 nM min

D. Glucagon (pM)

- iAUC 0.37 nM min
- iAUC 0.04 nM min

E. GLP-1 (pM)

- iAUC 3.84 nM min
- iAUC 0.79 nM min

F. Incretin GLP (pM)

- iAUC 6.71 nM min
- iAUC 7.34 nM min

G. PYY (pg/mL)

- iAUC 8.42 ng/mL min
- iAUC 2.53 ng/mL min

H. FFAs (mM)

- iAUC 41.3 mM min
- iAUC 42.3 ng/mL min

Time (min)