

Removal of Duodenum Elicits GLP-1 Secretion

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OBJECTIVE—To evaluate the effect of removal of the duodenum on the complex interplay between incretins, insulin, and glucagon in nondiabetic subjects.

RESEARCH DESIGN AND METHODS—For evaluation of hormonal secretion and insulin sensitivity, 10 overweight patients without type 2 diabetes (age 61 ± 19.3 years and BMI 27.9 ± 5.3 kg/m²) underwent a mixed-meal test and a hyperinsulinemic-euglycemic clamp before and after pylorus-preserving pancreatoduodenectomy for ampulloma.

RESULTS—All patients experienced a reduction in insulin ($P = 0.002$), C-peptide ($P = 0.0002$), and gastric inhibitory peptide (GIP) secretion ($P = 0.0004$), while both fasting and postprandial glucose levels increased ($P = 0.0001$); GLP-1 and glucagon responses to the mixed meal increased significantly after surgery ($P = 0.02$ and 0.031). While changes in GIP levels did not correlate with insulin, glucagon, and glucose levels, the increase in GLP-1 secretion was inversely related to the postsurgery decrease in insulin secretion ($R^2 = 0.56$; $P = 0.012$) but not to the increased glucagon secretion, which correlated inversely with the reduction of insulin ($R^2 = 0.46$; $P = 0.03$) and C-peptide ($R^2 = 0.37$; $P = 0.04$). Given that the remaining pancreas presumably has preserved intraislet anatomy, insulin secretory capacity, and α - and β -cell interplay, our data suggest that the increased glucagon secretion is related to decreased systemic insulin.

CONCLUSIONS—Pylorus-preserving pancreatoduodenectomy was associated with a decrease in GIP and a remarkable increase in GLP-1 levels, which was not translated into increased insulin secretion. Rather, the hypoinsulinemia may have caused an increase in glucagon secretion.

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Bariatric surgery has recently been suggested as a new treatment for type 2 diabetes. After gastric bypass, glycemic improvements in type 2 diabetes occur after few days—long before weight loss. This suggests that mechanisms related to the reconstruction of the gastrointestinal tract and the secretion of gastrointestinal hormones may be responsible for the antidiabetes effect (1). According to Rubino and Marescaux (2), exclusion of the duodenum provides the key explanation: because of the exclusion, an “anti-incretin factor” is no longer secreted (“the upper gut hypothesis”).

Other studies have supported the concept that early exposure of the distal ileum to undigested nutrients (“lower gut hypothesis”) with a subsequent release of antidiabetes hormones gives rise to this phenomenon (1,3–7). Nevertheless, these studies do not rule out that exclusion of the duodenum may contribute to the antidiabetes effects of gastric bypass surgery. In the current study, we examined the effect of duodenum removal in patients undergoing the duodenum pancreatotomy for reasons different from obesity and diabetes. This surgical procedure is associated with a reduction in

β -cell mass, which leads to decreasing systemic insulin levels. Since hemipancreatectomy, while lowering insulin levels, is not expected to modify the intraislet relationship between α - and β -cells, we also looked at the relationship between postsurgical insulin and glucagon levels.

RESEARCH DESIGN AND METHODS

A total of 10 patients (6 male and 4 female) undergoing pylorus-preserving pancreatoduodenectomy with curative intent at the Hepato-biliary Surgery Unit, Department of Surgery, Agostino Gemelli University Hospital, Rome, Italy, were consecutively enrolled. Indication for surgery was tumor of ampulla of Vater. Pancreatoduodenectomy was carried out according to the pylorus-preserving technique (8). Briefly, the pancreatic head, duodenum, common bile duct, and gallbladder were removed en bloc, leaving a functioning pylorus at the gastric outlet intact. All adjacent lymph nodes were carefully removed. The continuity of the gastrointestinal tract was restored by an end-to-side invaginated pancreaticojejunostomy. Further downstream, an end-to-side hepaticojejunostomy and side-to-side gastroenterostomy or an end-to-side pylorus jejunostomy was made. The pancreas volume removed during the surgery is ~50%, as previously reported by Schrader et al. (9). Figure 1 gives a schematic presentation of the surgical procedure. Only patients with normal cardiopulmonary and kidney functions, as determined by medical history, physical examination, electrocardiography, and urinalysis; without known diabetes; and free of any antidiabetes medication were enrolled for the studies. Patients were studied 1 week before and after a variable period of recovery from the surgical procedure (a sufficient recovery period was judged on normalization of inflammatory parameters such as C-reactive protein and erythrocyte sedimentation rate, stability of weight, and normal diet without any clear symptoms of abnormal intestinal motility or exocrine pancreatic deficiency). The study protocol was approved by the local ethics committee.

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