Published in final edited form as:

Surg Obes Relat Dis. 2012 ; 8(5): e66–e68. doi:10.1016/j.soard.2011.07.007.

Diabetes Remission Without Weight Loss Following Duodenal Bypass Surgery

Ricardo V. Cohen, MD^a, Francesco Rubino, MD^b, Carlos Schiavon, MD^a, and David E. Cummings, MD^c

^aThe Center of Excellence in Bariatric and Metabolic Surgery, Oswaldo Cruz Hospital, São Paulo, Brazil

^bSection of Metabolic Surgery, Diabetes Surgery Center, Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY, USA

^cDiabetes & Obesity Center of Excellence and Veterans Affairs Puget Sound Health Care System, University of Washington School of Medicine, Seattle, WA, USA

Keywords

bariatric surgery; type 2 diabetes; ghrelin; gastrointestinal hormones; gastrectomy

Roux-en-Y gastric bypass surgery (RYGB) causes complete remission of type 2 diabetes mellitus (T2DM) in 80–85% of cases, often before substantial weight loss occurs [1]. Mounting evidence indicates that this remarkable effect results from mechanisms beyond just reductions in food intake and body weight; among the implicated weight-independent anti-diabetes mechanisms, a role has been hypothesized for physiologic changes caused by excluding the proximal intestine from contact with ingested nutrients [2]. Here we report evidence supporting that assertion.

Reasoning that the effects of proximal intestinal bypass on diabetes, without confounding from bariatric surgery-induced weight loss, might have been observed among patients undergoing gastrectomies with varied intestinal reconstructions, we searched existing literature for relevant information. With difficulty, we located scattered, mostly old reports of gastrectomies performed for cancer or ulcer disease in non-obese patients, after which T2DM resolved following Billroth II or Roux-en-Y intestinal reconstructions, which bypass the duodenum, but not after Billroth I reconstructions, which preserve duodenal passage (Fig. 1) [3–9]. In contradistinction to these findings is the observation that when the

© 2011 American Society for Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Corresponding Author: David E. Cummings, M.D. Professor of Medicine, University of Washington, Box 358280 (mail stop 111), Seattle, WA 98195, Tel: 206-764-2335, FAX: 206-764-2689, davidec@u.washington.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

duodenum is excluded in gastrectomized patients without diabetes, there can be a mild worsening of glucose tolerance [5,10]. In this setting, duodenal bypass causes postprandial hyperglycemia, whereas duodenal passage preserves normal glucose homeostasis, as predicted from the effects of food to stimulate secretion of the incretin hormone glucose-dependent insulinotropic polypeptide from nutrient-sensing cells K cells in the proximal intestine [11].

Our literature research therefore suggested that isolating the duodenum from contact with ingested food exerts opposite effects on glucose homeostasis among patients with vs. without T2DM. If valid, this paradox could implicate the duodenum in diabetes pathogenesis. However, reports of diabetes remission following duodenal exclusion with non-bariatric operations are primarily from old, retrospective clinical observations, where diabetes endpoints were not expressly followed in advance, and none describe the effects of converting a gastrectomy from duodenal-inclusive to duodenal-bypassing anatomy. Thus, we examined this issue prospectively when a unique clinical opportunity arose.

Case Report

A 52-year-old woman with T2DM and a body mass index (BMI) of 31.1 kg/m² underwent a modest partial gastrectomy with Billroth I intestinal reconstruction (Fig. 1), to treat refractory peptic ulcer disease. Despite treatment with metformin 2 g/day and glimepiride 2 mg/day, her diabetes was inadequately controlled, with hemoglobin A1c (HbA1c) 7.5% and fasting plasma glucose (FPG) 154 mg/dL. Ten years later, she presented with refractory alkaline reflux gastritis (a known complication of Billroth I reconstructions), which had been unresponsive to medical therapy for >1 year. Her diabetes had progressively worsened during the interim: in addition to the aforementioned medications, now both increased to maximum doses, she was also taking maximum-dose pioglitazone. Despite these three medicines, she remained in even worse glycemic control (HbA1c 8.7%, FPG 165 mg/dL, post-oral-glucose-tolerance-test plasma glucose 269 mg/dL). Her BMI had remained essentially stable, at 30.1 kg/m².

Her alkaline reflux gastritis was treated by converting the Billroth I intestinal configuration, in which bile reflux is commonplace, into a Roux-en-Y configuration, which reduces reflux and also bypasses the duodenum. This generated intestinal anatomy identical to that after a standard RYGB (Fig. 1). Because promoting weight loss was not an objective, however, the gastric reservoir was made 15 times larger than a typical functional RYGB gastric pouch, and the gastrojejunal anastomosis was designed not to restrict food passage, having a 3-cm diameter instead of the usual <1 cm RYGB diameter.

After mild, transient weight loss immediately following surgery, the patient described normal eating and maintained a stable body weight (64.9 kg before surgery and 64.6, 64.0, and 64.8 kg at 1, 3, and 6 months after surgery, respectively). Nevertheless, her diabetes quickly and durably resolved. From 3 days through 3 months following surgery, her mean ($\pm$ SD) fasting and 2-hour postprandial blood glucose values (measured daily via glucometer) were 98 $\pm$ 11 and 141 $\pm$ 7 mg/dL, respectively. At 3 months, her HbA1c had decreased to 6.9% (from 8.7% preoperatively), so glimepiride and pioglitazone were discontinued. At 6

months, her HbA1c had decreased further to 5.6%, FPG was 102 mg/dL, and maximum plasma glucose after an oral glucose tolerance test was only 115 mg/dL. Because these values were no longer in the diabetic range, metformin was withdrawn. She has subsequently remained euglycemic off all diabetes medications and without weight loss for >2 years.

Discussion

We documented complete, durable remission of severe, longstanding T2DM, without weight loss or other interventions, following conversion from a duodenum-preserving to a duodenum-excluding partial gastrectomy. Our prospective findings corroborate evidence from prior retrospective observations primarily published several decades ago, largely in non-English-language journals^{3–5,7–9}. These obscure reports warrant newfound attention, given our new findings and the burgeoning worldwide interest in the glycemic effects of RYGB^[1,2]. In patients with T2DM, gastrectomies involving intestinal reconstructions that bypass the duodenum (Billroth II or Roux-en-Y) lead to marked improvement or remission of diabetes, independent of weight loss^[3–5,7–9]. In contrast, equivalent manipulations of the proximal intestine among patients without diabetes yield the opposite effects on glucose tolerance. In this setting, gastrectomies that exclude duodenal passage of food cause early postprandial hyperglycemia with the potential for glucosuria, and possibly late postprandial hypoglycemia^[5,10]. Gastrectomies with intestinal reconstructions that leave the duodenum in digestive continuity (Billroth I or operations involving an interposed intestinal pouch) exert little or no effect on glucose homeostasis in patients with or without diabetes^[5,6,9], as also shown as part of this report.

In summary, our investigations indicate that bypassing the proximal intestine, as is accomplished during RYGB, engages weight-independent anti-diabetes actions, specifically in patients with T2DM. Conversely, duodenal bypass impairs glucose tolerance in patients without diabetes^[5,10]. This paradox suggests a possible role for the duodenum in T2DM pathogenesis, impelling research into proximal intestinal glucoregulatory mechanisms. Our findings may help guide the individualized choice of post-gastrectomy intestinal reconstructions, the design of new operations intended specifically to treat diabetes, and research into novel gastrointestinal mechanisms governing glucose homeostasis.

Acknowledgments

The patient described in this paper provided written, informed consent to have her clinical course summarized and published. We thank Antonello Forgione, MD (Azienda Ospedaliera Niguarda Ca' Granda; Milano, Italy) for his help searching for very old, difficult-to-locate publications, and for coordinating their translation into English, with assistance from medical students at the Universities of Strasbourg (France) and Heidelberg (Germany). We also thank Yuko Tonohira (Weill Cornell Medical College/New York Presbyterian Hospital; New York, NY) for her expert artistry in producing the figure. DEC is supported by NIH grants RO1 DK517498, RO1 DK61516, RO1 DK089528, UO1 DK66568, and P30 DK17047.

References

1. Rubino F, Schauer PR, Kaplan LM, Cummings DE. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. *Annual Rev Med*. 2010; 61:393–411. [PubMed: 20059345]

2. Thaler JP, Cummings DE. Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology*. 2009; 150:2518–2525. [PubMed: 19372197]
3. Friedman NM, Sancetta AJ, Magovern GJ. The amelioration of diabetes mellitus following subtotal gastrectomy. *Surg Gynecol Obstetr*. 1955; 100:201–204.
4. Forgacs S, Halmos T. Improvement of glucose tolerance in diabetics following gastrectomy (author's translation of title). *Z Gastroenterol*. 1973; 11:293–296. [PubMed: 4803427]
5. Bittner R, Bittner B, Beger HG. Homeostasis of glucose and gastric resection. The influence of the food passage through the duodenum (author's translation of title). *Z Gastroenterol*. 1981; 19:698–707. [PubMed: 7032098]
6. Dousei T, Miyata M, Tanaka Y, Izukura M, Kawashima Y, Matsuda H. Gastric inhibitory polypeptide secretion after gastrectomy in patients with diabetes mellitus. *Surg Today*. 1993; 23:954–959. [PubMed: 8292862]
7. Angervall L, Dotevall G, Tillander H. Amelioration of diabetes mellitus following gastric resection. *Acta Med Scand*. 1961; 169:743–748. [PubMed: 13683582]
8. Wustenberg PW. Stomach resection and the carbohydrate metabolism picture in diabetics (author's translation of title). *Dtsch Z Verdau Stoffwechselkr*. 1965; 25:232–233. [PubMed: 5888905]
9. Zervos EE, Agle SC, Warren AJ, et al. Amerloration of insulin requirement in patients undergoing duodenal bypass for reasons other than obesity implicates foregut factors in the pathophysiology of type II diabetes. *J Am Coll Surg*. 2010; 210:564–572. [PubMed: 20421005]
10. Schwartz A, Büchler M, Usinger K, et al. Importance of the duodenal passage and pouch volume after total gastrectomy and reconstruction with the Ulm pouch: prospective randomized clinical study. *World J Surg*. 1996; 20:60–67. [PubMed: 8588415]
11. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007; 132:2131–2157. [PubMed: 17498508]

Figure 1.

Operations Discussed in This Report. Ingested food is depicted with brown spheres; biliopancreatic secretions are depicted with green arrows. Lightly shaded areas represent gastrointestinal regions that are excluded from the passage of food. (A) Partial gastrectomy with Billroth I intestinal reconstruction. A small portion of the distal stomach is excised, and the larger remaining stomach is connected to the beginning of the duodenum. The entire intestine remains in digestive continuity. (B) Partial gastrectomy with Billroth II intestinal reconstruction. Similar to (A), but the duodenum is bypassed and no longer comes in contact with ingested nutrients. Food empties from the stomach into the proximal jejunum. (C) Partial gastrectomy with Roux-en-Y intestinal reconstruction, as performed in the patient highlighted herein. The upper intestinal anatomy includes a 100-cm biliopancreatic limb (primarily duodenum, with passage of digestive secretions but no food) and a 150-cm alimentary limb (proximal jejunum, with passage of food but no biliopancreatic digestive secretions). Although neither of these intestinal limbs contributes to nutrient absorption, the intact common channel downstream of them is many meters long, constituting a large majority of the total small intestinal length. Thus, clinical indicators of macronutrient malabsorption are not observed. This intestinal configuration is identical to that performed in a standard RYGB (D). Unlike a typical RYGB designed to promote weight loss, however, in our patient's operation (C), neither gastric volume nor the passage of food was clinically significantly restricted. A very wide gastrojejunal anastomosis was used, and the remaining stomach volume was ~500 cc, which is 15 times larger than the residual functional gastric pouch in a normal RYGB performed to treat obesity (D).