Elucidating the Mechanisms Behind the Restoration of Euglycemia After Gastric Bypass Surgery

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According to the U.S. Centers for Disease Control and Prevention (CDC), in the United States in 2010, 78 million adults were obese, 79 million had prediabetes, and 26 million had diabetes. Bariatric surgery in obese persons has been shown to be an effective method for resolving and preventing type 2 diabetes (1,2). However, not all bariatric surgery is the same. After gastric banding, where the amount of food consumed is limited by an inflatable band around the cardia of the stomach, the improvement seen in diabetes is associated to the amount of weight lost (3). In contrast, after Roux-en-Y gastric bypass (RYGB) surgery—where most of the stomach, duodenum, and the first 40 cm of the jejunum are bypassed and nutrients enter directly into the jejunum—an improvement in diabetes occurs a few days after surgery, before any weight has been lost (4). It was recently demonstrated in a randomized trial that gastric bypass is more effective than medical treatment in resolving diabetes in patients with a BMI starting at 27 kg/m^2 (5). This raises the possibility that more patients with diabetes will undergo bariatric surgery in the future.

Several mechanisms have been proposed for this early improvement in glycemic control seen after gastric bypass (Fig. 1). These include, but are not limited to, improvements in hepatic insulin sensitivity due to energy restriction (6) and alterations in the secretion of incretin hormones due to the altered passage of nutrients. Increases in plasma concentrations of glucagon-like peptide-1 (GLP-1) are seen as soon as on day 2 after gastric bypass surgery (7). The study by Jiao et al. (8) in this issue of *Diabetes* has further elucidated the mechanisms behind the resolution of diabetes after gastric bypass by utilizing a surgical model in obese diabetic rats. In this model (duodenal-jejunal bypass [DJB]), the duodenum and 10 cm of the jejunum is bypassed and resembles the bypassed duodenum and jejunum of an RYGB however without the restrictive component of the small pouch that is created in RYGB operations in humans. The authors then performed an extensive number of studies using this surgical model in obese insulin-resistant Zucker (*fa/fa*) rats to assess the effect of the duodenal bypass on glucose homeostasis compared with pair-fed, sham-operated, and lean animals.

The article by Jiao et al. presents several interesting findings. The duodenal bypass restored both hepatic and peripheral insulin sensitivity independent of body weight. The rapid improvement in hepatic glucose production required intact vagal innervation while the restoration of peripheral insulin sensitivity was not dependent on vagal innervation. Furthermore, the DJB induced downregulation of regulatory genes involved in both glucose and lipid metabolism and an increase in the total content of the insulin receptor substrate-2 in the liver. The investigators also demonstrated different patterns of change in plasma and tissue concentrations of incretin hormones following the DJB. Plasma concentrations of peptide YY and glucose-dependent insulinotropic polypeptide were unchanged, whereas the concentrations of these peptides in the duodenum and ileum were increased. In contrast, plasma concentrations of GLP-1 were increased postprandially but unchanged in the intestine.

The advantage of rodent models is that one can subject the animals to more advanced and complete studies than humans. Herein lies the strength of the current study. However, there are several limits as to what conclusions that can be drawn with regards to the effects seen after RYGB surgery in humans. Firstly, there is no restrictive component of the DJB, and the emptying of nutrients into the jejunum is likely to be at least partially retarded in the stomach. Studies in humans have demonstrated a very rapid entry of nutrients from the small pouch to the jejunum after RYGB surgery (7). Also, standard rat chow differs significantly from the standard food consumed by humans. One strength of this study was the use of pair-fed, sham-operated controls, which allowed for the study of the DJB effects independent of weight loss. Interestingly, in a study in humans with type 2 diabetes who underwent either RYGB surgery or were treated with low-calorie diets and studied after the same amount of weight loss, similar results were found. Insulin sensitivity was only improved in patients who underwent RYGB surgery (9).

Although the present article by Jiao et al. (8) has added important information regarding the effects of intestinal bypass on glucose homeostasis, there are still areas that need further clarification. It is still not fully clear how much the changes in gastrointestinal anatomy (bypass of the stomach and upper intestine) cause additional improvement in insulin sensitivity independent of energy restriction. Here the article by Jiao et al. would have benefited from the use of antagonists to the peptides studied. Furthermore, the field would benefit from a standardization of the models used. Some utilize the DJB while others perform an RYGB in rats. It is important to report the pouch size created and the length of the different intestinal limbs in order to be able to judge to what extent the rodent model differs from an RYGB in humans. From a clinical perspective, there is a need to understand why some patients relapse in their diabetes after a few years of remission while others do not (10). Also, there is a need to elucidate why bariatric surgery seems particularly good at

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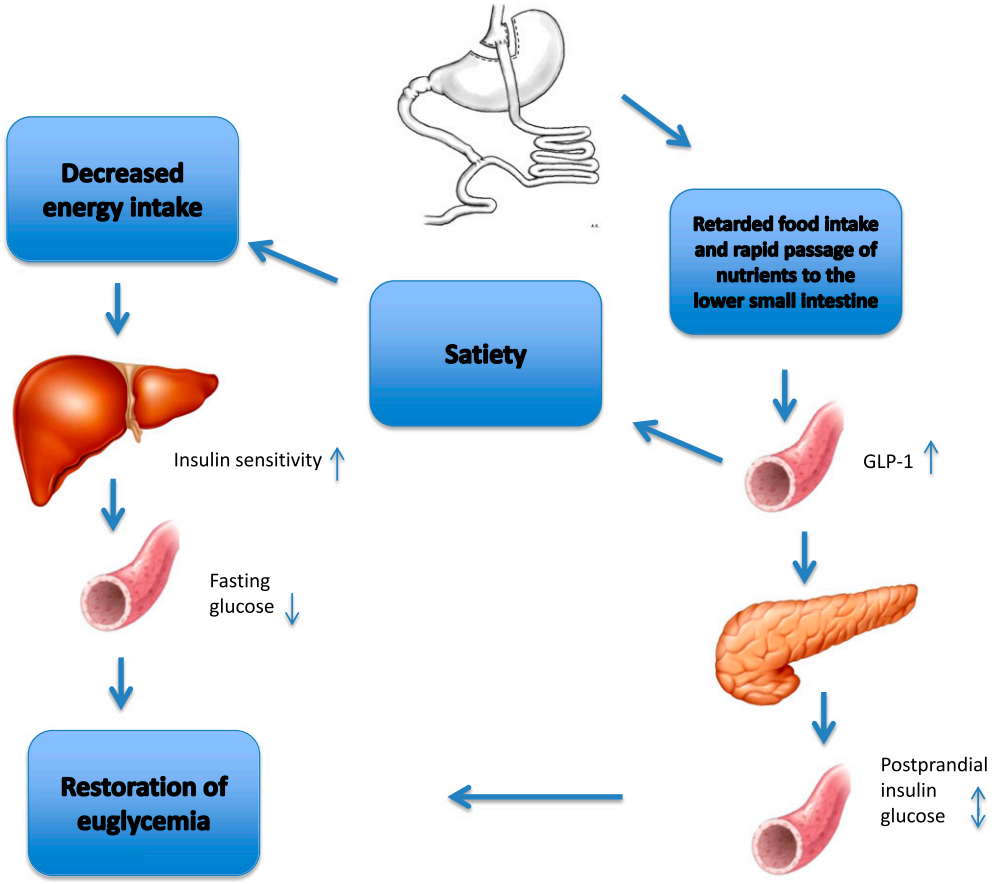

FIG. 1. Schematic representation of some early mechanisms responsible for euglycemia seen after gastric bypass. Modified from Dirksen et al. (11).

preventing the progression to diabetes after surgery (2). Further studies, using surgical models, such as those undertaken by Jiao et al. (8) can yield important results.

A further understanding of the mechanisms and endocrine signaling behind the improvements in glucose homeostasis and hepatic function after RYGB surgery is of major importance (11). The basic idea is to find the pivotal biomarkers that stand for the crucial improvements in metabolism. Of those, GLP-1 stands out as the hitherto most promising candidate where not only surgery but also direct administration of the peptide or similar analogs have shown that new treatment principles of type 2 diabetes (and obesity) are within reach. With more work such as that by Jiao et al. in this issue of *Diabetes*, perhaps one can "bypass bariatric surgery" as they so aptly end their article. However, until then, bariatric surgery remains the best prevention and treatment of diabetes in obese patients.

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