Postprandial Insulin Secretion After Gastric Bypass Surgery

The Role of Glucagon-Like Peptide 1

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Given the availability of human studies of the relatively specific and potent glucagon-like peptide (GLP)-1 receptor antagonist exendin (Ex) 9–39, it was just a question of time for the first study of GLP-1 receptor blockade after gastric bypass surgery to appear. In this issue of *Diabetes*, Salehi et al. (1) report such studies in two groups of individuals previously operated on for obesity with Roux-en-Y gastric bypass (RYGB) surgery: one asymptomatic group and one control group with recurrent hypoglycemia after the operation.

The background is that these operations not only bring about a massive weight loss (reductions in BMI from 52 to 33/32 kg/m^2 in the current study), but also bring about resolution of type 2 diabetes, if present, in a high percentage (80–90%) of patients. In the current study, three of twelve individuals in both operated groups had type 2 diabetes before the operation, which was resolved completely in all cases. RYGB was originally conceived as a restrictive and malabsorptive procedure, but actually it is neither. The normal function of the stomach is to retain and process food stuff until allowing a controlled emptying precisely adjusted to the digestive capacity of the proximal intestine. The reservoir is lost after the operation and, in effect, a straight tube is constructed that allows unimpeded passage of ingested nutrients directly to the alimentary limb of the Y-anastomosis and directly onwards to the "common limb," where nutrients are admixed with digestive secretions and digestion starts. This is nicely illustrated in studies of acetaminophen absorption, which proceeds at a maximal rate immediately upon meal ingestion without the slightest retardation (2). Furthermore, balance studies have documented that there is no malabsorption of macronutrients after RYGB (3).

So what is the mechanism of both the weight loss and the diabetes resolution? The abnormal passage of nutrients to a site some 1.5–2 m more distal to the duodenum clearly poses a dramatic exposure of nutrients to the mucosa there, and this is clearly reflected in a grossly exaggerated secretion of gut hormones (4,5). These include peptide YY $(PYY)_{3–36}$, a powerful anorexic hormone (6), and GLP-1, a peptide that powerfully inhibits appetite and food intake and, in addition, stimulates insulin secretion (7). While PYY has no effect on insulin secretion, the effects of GLP-1 are sufficiently powerful to allow development of GLP-1 receptor agonists for the treatment of diabetes (8). Clinical studies have clearly supported an association between the exaggerated secretion of these two hormones and the weight loss (3). Regarding diabetes resolution, it was recently reported that a patient with type 2 diabetes who was newly operated on received a test meal either orally (following the bypass) or via a gastrostomy catheter (following the preoperative nutritional pathway) on 2 consecutive days. When fed via the bypass, the patient had normal glucose tolerance, but when fed through the stomach he had diabetes. Bypass feeding was associated with a large insulin response and a grossly exaggerated GLP-1 response; in fact, the two were highly correlated (r = 0.93) (9). In the current study by Salehi et al. (1), meal-infused responses were studied under the conditions of a hyperglycemic clamp (of approximately 14 mmol/L) with or without a high rate, primed infusion of Ex 9–39 (in other studies was demonstrated to block the actions of exogenous GLP-1). After plateau glucose levels were established, a 375-kcal test meal (Ensure) was given, and insulin secretion and gut hormone profiles were followed. Compared with control subjects, the surgical group had greatly elevated insulin responses, approximately half of which were eliminated by the GLP-1 receptor antagonist. As expected, GLP-1 responses to the test meal were also greatly increased (and, in agreement with previous studies [10,11], the antagonists actually increased GLP-1 responses).

These observations seem to strongly support the hypothesis that an important part of the antidiabetic effect of RYGB is due to exaggerated secretion of GLP-1, which in turn stimulates insulin secretion (Fig. 1). One can discuss whether the infusion rate of Ex 9–39 and the design of the study allow for a full appreciation of the effects of GLP-1, but at any rate, the difference in insulin responses must reflect the effects of GLP-1 receptor activation. So far, so good. But the picture seems to be more complicated. The study included two groups of operated individuals—one that developed recurrent hypoglycemia, which was also demonstrated during a separate meal tolerance test. Surprisingly, the two groups had almost identical insulin and GLP-1 responses (as well as secretion of GIP, the other incretin hormone from the proximal gut, which is variably influenced by bypass surgery). This, however, is at variance with earlier studies of patients with postbypass hypoglycemia (which typically develops 1–3 years after surgery), where both exaggerated GLP-1 and insulin responses were typically found (12,13). This raises the question of whether the mechanism of the postoperative hypoglycemia can be studied appropriately using the clamp

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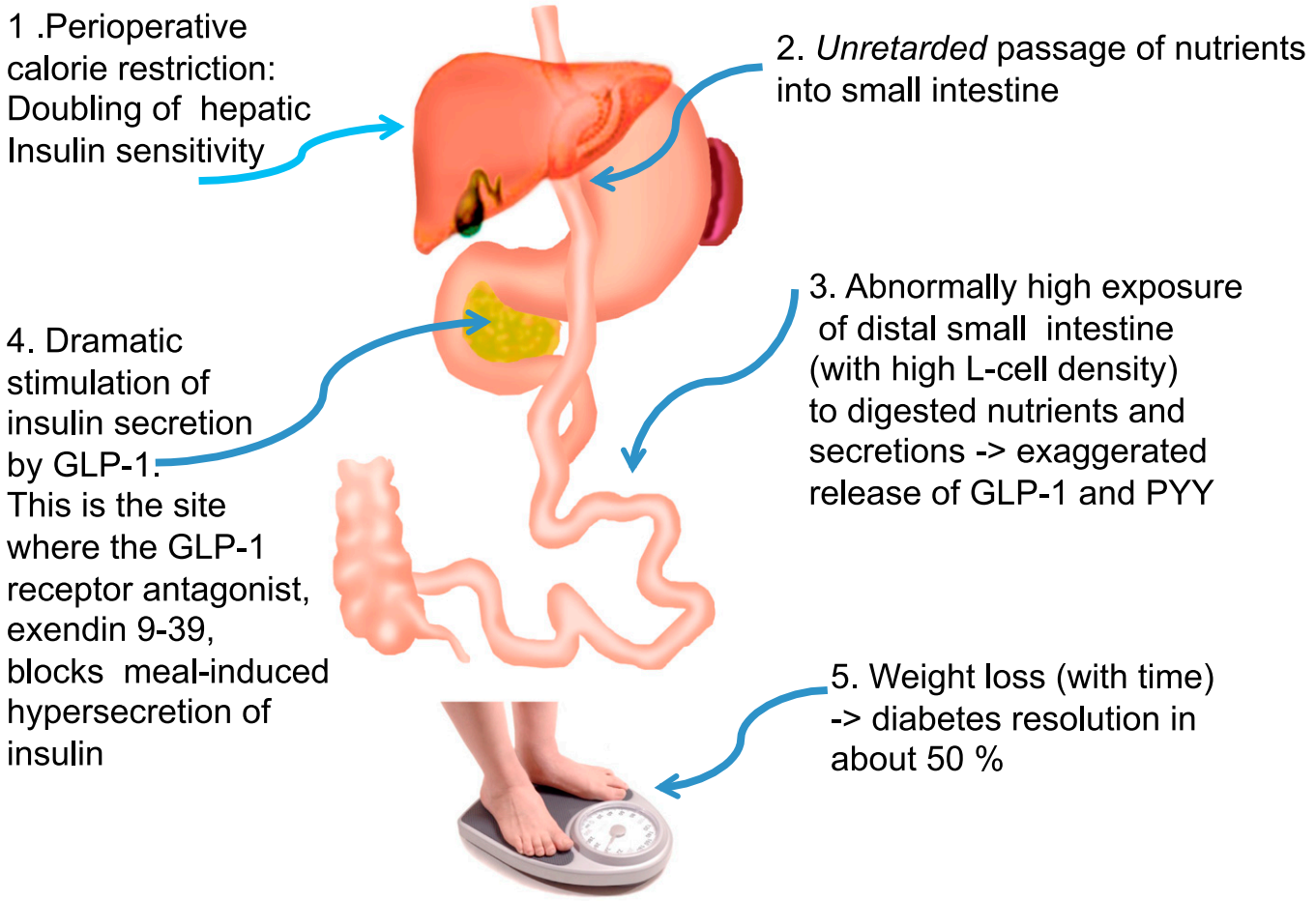

FIG. 1. Proposed mechanism of diabetes resolution after RYGB surgery.

approach used here. Obviously, because of the clamp, hypoglycemia was not present. In the separate meal test, 10 out of 12 members of the hypoglycemia group did develop hypoglycemia, leading to termination of the experiment. Only two individuals remained toward the end of the meal experiment (while all 12 completed the test in the asymptomatic group), which means that comparisons between glucose, insulin, and gut hormone responses (not reported) are impossible. Thus, the mechanism of postoperative hypoglycemia probably deserves further investigation, for instance in experiments with smaller meals where hypoglycemia is less dramatic, and where insulin and gut hormones responses can be adequately compared. In fact, in a recent study of a patient with postoperative hypoglycemia, feeding via a gastrostomy catheter eliminated both the exaggerated GLP-1 response—the hyperinsulinemia—and the hypoglycemia (14).

Another result that is not easily interpreted in terms of diabetes resolution after RYGB is the glucagon responses to the test meal. Whereas in control subjects, glucagon concentrations fell in response to the hyperglycemic clamp and did not change much during the test meal, the surgical groups showed dramatic and similar elevated meal responses that were (in agreement with earlier studies [10,15]) increased by Ex 9–39. Similar postprandial glucagon increases have been observed in other studies (2,12) and are seemingly incompatible with the antidiabetic effects of RYGB and with the inhibitory effects of GLP-1 on glucagon secretion (7). One possibility might be that the elevated levels are gut-derived and represent *N*-terminally elongated, biologically inactive forms, e.g., proglucagon 1–61 (16). The processing of proglucagon in the L cells may include formation of this molecular form (17), which could be pronounced given the dramatic overstimulation of the L cells after bypass surgery. Currently available glucagon assays would not be able to differentiate between the two molecular forms.

Finally, it is worth noting that Ex 9–39 had effects on both insulin secretion and GLP-1, also before meal ingestion. This raises the question of whether Ex 9–39 acts exclusively as a competitive antagonist or whether it may also act as an inverse agonist, inhibiting GLP-1 receptor signaling in the absence of GLP-1 (18). This problem needs to be addressed when using Ex 9–39 for delineation of physiological effects of GLP-1.

A recently published study by Hansen et al. (19) measured insulin and gut hormone responses to test meals delivered either orally or via a gastrostomy catheter early after RYGB surgery, but in that study there were no clear differences between responses to orally and tube-delivered meals, and there was no conspicuous insulin release postoperatively. This led the authors to question the mechanisms for diabetes resolution outlined above. However, the samples in that study were not obtained in the period 20–80 min after the meal. Upon inspection of the responses in the article by Salehi et al. (1) in this issue of *Diabetes* and

in the earlier studies cited (2,5,12), it is clear that the hyperinsulinemia and exaggerated GLP-1 responses occur exactly in that interval, which therefore was missed by Hansen et al. (19). Currently, therefore, hypotheses regarding the diabetes resolution after RYGB surgery based on GLP-1 have gained further support from the studies of Salehi et al.

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