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GLP-1—A Candidate Humoral Mediator for Glucose Control After Roux-en-Y Gastric Bypass

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The worldwide increase in obesity is associated with a higher prevalence of type 2 diabetes (T2D), and severe obesity occurs with the greatest risk (1). Bariatric surgery is currently the most effective treatment not only for weight loss but also for prevention or treatment of T2D in such patients (2). It leads to remission or improvement of T2D in the majority of morbidly obese (3,4). Roux-en-Y gastric bypass (RYGB) is one of the most frequently performed procedures. With RYGB, the stomach is reduced to a small proximal pouch (30–50 mL) and anastomosed to the jejunum, thereby bypassing the majority of the stomach and duodenum. After RYGB, T2D improves rapidly often before significant weight loss occurs. The mechanisms behind this phenomenon are not clearly resolved. Caloric restriction contributes. Extreme caloric restriction to the limit just tolerated in patients after surgery improved insulin resistance in obese subjects similarly as found in after the first week after RYGB (5). Of interest, the malabsorptive component of the RYGB procedure approximately accounts only for up to 11% of the total reduction in combustible energy absorption (6). Changes of adipokine-induced inflammation and insulin resistance (7) and reduction of branched-chain amino acids correlating with insulin resistance (8) have been proposed as further mechanisms operating after bariatric surgery complementing the sole weight loss.

A popular hypothesis points to an antidiabetic effect after RYGB of postprandially exaggeratedly released gut peptides, such as glucagon-like peptide 1 (GLP-1), already starting early after surgery. The release of GLP-1 depends on gastric emptying (GE) velocity (9). It lowers postprandial glycemia by stimulation of insulin, inhibition of glucagon secretion, and delay of GE. For example, Laferrère et al. (10) reported a sixfold increase in GLP-1 plasma levels and a fivefold increase of the incretin effect in obese patients with T2D 1 month after RYGB. In this

issue, Shah et al. (11) addressed the contribution of endogenous GLP-1 to the meal-induced glucose metabolism, islet secretion, and GE after RYGB in 12 nondiabetic obese patients 5 ± 0.9 years after RYGB and 8 weight-matched control subjects twice using the GLP-1 receptor (GLP-1R) antagonist exendin(9–39). After ingestion of a 220 kcal mixed-meal, glucose metabolism was measured using the isotope dilution method. Indices of insulin action and β -cell glucose responsiveness and the resulting glucose disposition indices were calculated using the oral minimal model. GE was measured by scintigraphy. As expected, GE (gastric pouch in the post-RYGB subjects) was greatly accelerated, leading to a several-fold increase in postprandial GLP-1, insulin, and C-peptide responses after RYGB. The GLP-1R antagonist increased the postprandial glucose excursions in both groups. Exendin(9–39) decreased insulin and C-peptide concentrations in subjects post-RYGB by about 30% with no effect in control subjects. The calculated β -cell response to glucose was significantly reduced in both groups. In neither group, exendin(9–39) changed the insulin action. It, however, decreased the glucose disposition index in control subjects but not after RYGB. This study clearly demonstrates that GLP-1 supports the improvement of glucose metabolism after RYGB. The authors, however, question the role of GLP-1 for an improvement in β -cell function post-RYGB. This is because the glucose disposition index as a measure of net β -cell function was not changed by exendin(9–39).

Since its introduction for human studies in 1998 (12), exendin(9–39) has increasingly been used for physiological studies addressing the role of endogenous GLP-1. Using exendin(9–39), it has been shown that endogenous GLP-1 inhibits glucagon, stimulates insulin, and contributes to the incretin effect in both healthy subjects and patients with T2D (13–15). So far, studies employing

the GLP-1R antagonist after RYGB revealed that GLP-1 contributed to an exaggerated insulin response after RYGB (16–18). β -Cell glucose sensitivity was doubled within 3 months after surgery, reversed by exendin(9–39) (17). The current study adds important findings demonstrating that exendin(9–39) has no effects on insulin action or on the glucose disposition index. This observation supports earlier studies in healthy subjects using euglycemic clamps showing no effect of synthetic GLP-1 on insulin sensitivity (19,20). However, the lacking effect on the disposition index is not easy to understand since it is a function of both β -cell glucose responsiveness and insulin action. Thus, the reduction of the β -cell glucose responsiveness by exendin(9–39) may be not great enough to overcome the effects on insulin action. Possibly, the employed load of exendin(9–39) was insufficiently blocking the very high GLP-1 levels occurring after RYGB. Recently, we extended previous dose-finding studies (12) aiming to completely block the insulinotropic effects of synthetic GLP-1 by the antagonist in healthy subjects. Exendin(9–39) inhibited dose-dependently the GLP-1 induced insulin secretion exerting an exponential pattern of the dose-response curve (21) (Fig. 1). Exendin(9–39) at 300 pmol/kg/min, as used in the study of Shah et al., blocked the insulinotropic action of GLP-1 by approximately 90%. Thus, on a qualitative basis this dosage should have been great enough. On the other hand, the study was done in subjects without diabetes. Because of the glucose-dependence of its insulinotropic action it cannot be excluded that GLP-1

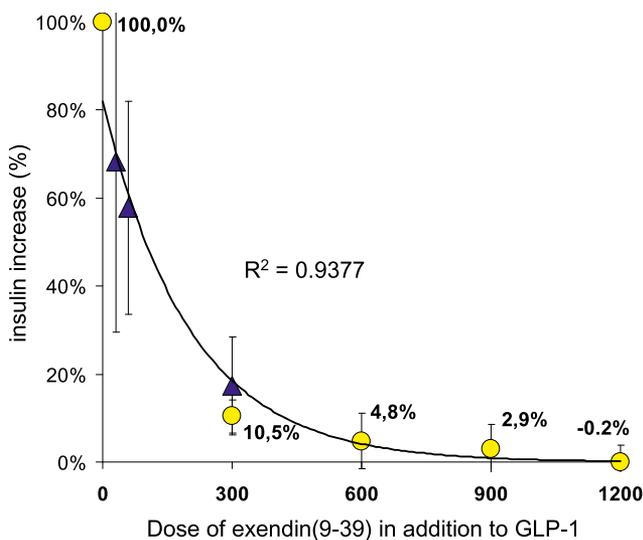
has an effect on the disposition index in T2D early after surgery.

What are the metabolic effects occurring in patients with T2D after RYGB? Two years after surgery, insulin sensitivity was significantly increased by 2.7-fold from baseline and β -cell function (disposition index) was increased 5.8-fold (22). The reduction in abdominal (truncal) fat was inversely correlated with the β -cell function. The marked improvements in insulin sensitivity may depend on factors specifically released from visceral fat.

Almost all studies after RYGB demonstrated an increase in postprandial glucagon levels. This paradoxical glucagon increase is incompatible with the inhibitory effects of GLP-1 on glucagon secretion, the more so as exendin(9–39) further raised the levels. As discussed earlier by Holst (23), it may represent elongated untruncated biologically inactive forms of proglucagon as a result from overstimulation of the L cells post-RYGB. The finding of Shah et al. (11) that endogenous glucose production does not differ in subjects after RYGB and control subjects at higher glucagon levels post-RYGB is compatible with this assumption.

As proposed 20 years ago by Horowitz et al. (24), GE is a strong determinant of both peak plasma glucose and early postprandial plasma glucose excursions. This is impressively shown in the current study. Here, GLP-1 acts as an inhibitory regulator of gastroduodenal motility (13,25). The detection of a measurable acceleration of GE may be dependent on the extent of the postprandial

A GLP-1 at 0.3 pmol/kg/min



B GLP-1 at 0.9 pmol/kg/min

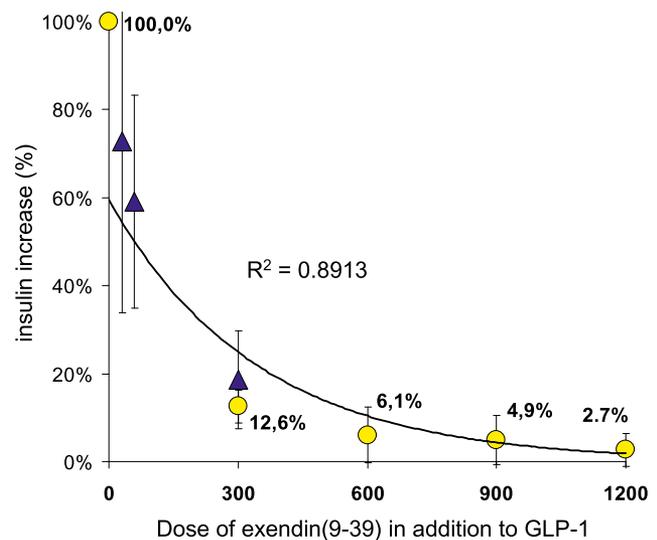


Figure 1—Effect of intravenous GLP-1 at a low (A) and high dose (B) during a hyperglycemic clamp of 8 mmol/L with and without intravenous exendin(9–39). The percentage increase of plasma insulin is shown in six healthy volunteers. GLP-1 plasma concentrations during the low dose of GLP-1 were within the high physiological range. They clearly exceed the physiological range under the high dose of GLP-1. Each point represents the mean \pm SEM of six experiments. Blue triangles represent data from a previous study using the identical study design (ref. 12).

GLP-1 increase. Consistent with this opinion, Shah et al. (11) found an acceleration of GE of the gastric pouch under exendin(9–39) post-RYGB but not in control subjects. The glucose rate of appearance, however, remains unaffected. More than 60% of the meal emptied in a dumping-like manner within the first 15 min. The volume remaining within the short gastric pouch and under regulation by exendin(9–39) may have been too small to exert an effect on the glucose rate of appearance. Moreover, the egg was labeled for scintigraphy but not the Jell-O, which contained the glucose. Jell-O behaves as a liquid, so it cannot be excluded that the Jell-O was almost emptied before the regulation by exendin(9–39) occurred.

The study of Shah et al. (11) convincingly shows that endogenous GLP-1 has an effect on glucose metabolism after RYGB. Still, GLP-1 does not completely explain all the antidiabetic effects occurring after RYGB. The data further support a significant role for GLP-1 in resolution of T2D early after surgery.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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