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GLP-1 as a Mediator in the Remission of Type 2 Diabetes After Gastric Bypass and Sleeve Gastrectomy Surgery

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COMMENTARY

Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) have been shown to cause remarkable improvement in type 2 diabetes, often with complete remission within days after surgery and before any significant weight loss (1). The mechanisms explaining the benefit on glycemic control independent of weight loss are still not entirely clear, but enhanced postprandial insulin secretion induced by exaggerated secretion of glucagon-like peptide 1 (GLP-1) has been suggested to be an important contributor (1). Indeed, several studies have highlighted the crucial role of GLP-1 in the improvement of β-cell function after RYGB (2–7). GLP-1 is an incretin hormone that is released into the bloodstream postprandially from the intestine (8). Among its multiple actions, GLP-1 stimulates insulin secretion and decreases appetite (8). Type 2 diabetic patients have severely impaired incretin effect, which improves after surgery (5).

In the current issue of *Diabetes*, this view is challenged. In the article by Jiménez et al. (9), the GLP-1 receptor was pharmacologically blocked with exendin (9–39) in patients who had undergone SG and presented with long-term type 2 diabetes remission. The blockade of the GLP-1 system resulted in impaired insulin secretion but limited deterioration of glucose tolerance. In another protocol, subjects with type 2 diabetes antedating SG but with different long-term (>2 years) outcomes (remission, relapse, or lack of remission) had a comparable GLP-1 response to a mixed-meal, which was observed regardless of outcome (9). Not surprisingly, the β-cell function was most impaired in the nonremitting patients. In a previous study of long-term remission after RYGB, the same group of researchers concluded that the enhanced GLP-1 secretion after surgery is neither sufficient nor critical to maintain normal glucose tolerance in subjects with type 2 diabetes (10). RYGB and SG both have an effect on diabetes remission (although RYGB seems to be superior), and the GLP-1 responses to meal ingestion do not seem to differ a lot between the two operations (11,12).

Previous studies, however, have reached the opposite conclusion; namely, that one of the major factors for the marked improvement of glucose tolerance after RYGB and SG is the 5- to 10-fold increase in postprandial GLP-1 secretion reported after RYGB and SG (2–7,13–15).

Several studies have shown that blockade of the GLP-1 receptor increases fasting glucose levels and increases glucagon levels during a meal test; in all studies, impairment of the glucose tolerance was induced with exendin (9–39) infusion compared with saline infusion (4,6,7). In Jiménez et al. (9), the increase in mean glucose level during the meal test was from 139 to 156 mg/dL, while insulin secretion was blunted. Salehi et al. (6) found about 30% decrease in insulin secretion, and Jørgensen et al. (4) reported that β-cell function 1 week and 3 months after surgery was reduced to preoperative levels by blocking the GLP-1 receptor after RYGB, while incremental glucose areas increased by about 60% and 40%, respectively. Thus, all the studies—including the current one—demonstrated reduced insulin secretion and impairment in glucose tolerance after a mixed meal on the day when the GLP-1 receptor was blocked compared with a control day. All the studies also underlined the importance of the exaggerated GLP-1 response for the improved β-cell function after RYGB and SG. Notably, the insulin response in the individual patient is dependent of the functional secretory capacity of the β-cell mass, even in the context of enhanced GLP-1 response after RYGB and SG (9,10). The patients showing lack of remission are the ones

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that have the most impaired insulin secretion during a mixed meal before and after surgery (9,10).

How can we reconcile these contrasting views regarding the importance of the enhanced GLP-1 response for remission of type 2 diabetes after RYGB and SG? Type 2 diabetes develops in subjects with a combination of two core defects—insulin resistance along with defects in insulin secretion. The weight loss induced by bariatric surgery is associated with increased insulin sensitivity, and not surprisingly, preoperative β-cell function in combination with the degree of weight loss are predictors of postoperative remission of diabetes (15,16). The relative importance of these factors may shift with time after surgery. From the first days after surgery an improvement in β-cell function is observed using oral glucose or a mixed-meal test (3). This improvement is closely associated with the exaggerated GLP-1 response, which can be demonstrated from a few days to years after surgery (2,3). Within the first days after surgery a significant improvement in hepatic insulin sensitivity is also evident, probably induced by the hypocaloric postoperative diet (13). In contrast, the improvement in muscle insulin sensitivity is first observed months after surgery, associated with the progressive weight loss (13). The peripheral disposal of glucose is an important factor for glucose clearance during a meal and therefore for glucose tolerance.

Taken together, these observations suggest that an exaggerated GLP-1 response inducing an improved β-cell function is the key factor for improvement in glucose tolerance from day 1 after surgery. After a few days, the improved hepatic insulin sensitivity also plays a role, especially for the normalization of fasting glucose concentrations (13,17). Several months after surgery and after a major weight loss, insulin-mediated glucose disposal turns out to be the major determinant of glucose tolerance, with the insulin response being of relatively lesser importance (Fig. 1).

Therefore, the relative importance of the GLP-1 and insulin response versus improvement in insulin action in the liver and skeletal muscles for the glucose tolerance after RYGB and SG depends on when the patients are studied after surgery (Fig. 1). The clinical consequence of this stepwise improvement in glucose metabolism is that the chances of remission of type 2 diabetes increase from the first days after surgery until the maximal weight loss and improvement in insulin action have been reached. However, even after the weight loss, the major determinant for remission remains the insulin secretory capacity of the β-cell mass in the individual patient. Patients with severe diabetes and minimal endogenous insulin secretion do experience improvements in glucose tolerance after the operation but may not reach a full remission of diabetes despite a GLP-1 response that is similar to that observed in patients with full remission of diabetes (9,10). The similar GLP-1 responses in the different patient groups are not surprising as the response is caused by

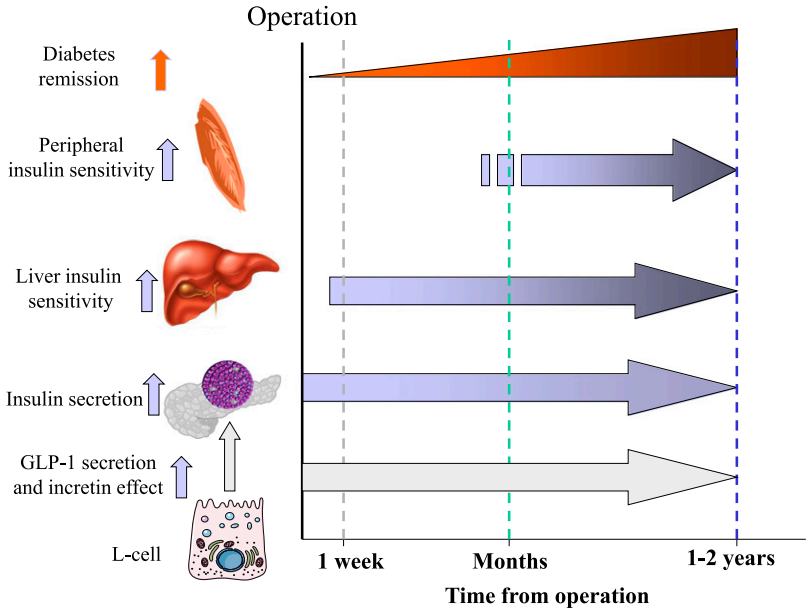

Figure 1—From the first day after RYGB or SG the GLP-1 responses to a meal are exaggerated, resulting in an improved β-cell function. The hypocaloric diet per se and the improvement in liver insulin sensitivity within the first week after surgery have a marked effect on fasting plasma glucose concentration. After months and a major weight loss, peripheral skeletal muscle insulin sensitivity also is enhanced. Therefore, the importance of the different physiological mechanisms for remission of type 2 diabetes may differ in relation to time from surgery. The importance of noninsulin-mediated glucose disposal (glucose effectiveness) for glucose tolerance has not been described in detail after RYGB and SG. The red bar illustrates that glucose tolerance improved from time of operation until maximal weight loss is obtained.

accelerated nutrient entry and absorption in the small intestine after both SG and RYGB, factors that are relatively uninfluenced by the β-cell function and metabolic regulation of the patients (18,19).

When comparing SG and RYGB, it should be recalled that the secretion of the other incretin hormone, gastric inhibitory polypeptide (GIP), is relatively unaffected after RYGB but may be greatly elevated after SG (12). An elevated secretion of GIP may, particularly under conditions of improved metabolic control, play a significant role in glucose metabolism (20). The effect of GIP is not antagonized by exendin (9–39). The increased glucagon levels after bariatric surgery are another factor that may influence the results. The increase is likely to have a diabetogenic effect, and this may be differentially affected by bariatric surgery and exendin (9–39).

The analysis of glucose metabolism after bariatric surgery is like a puzzle where some of the pieces may still be missing.

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

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