Roux-en-Y gastric bypass (RYGB) has established itself as the standard for the surgical treatment of morbid obesity and its complications. The overwhelming success of RYGB in adult and pediatric patients has been accompanied by much interest in the mechanism(s) by which this and other bariatric procedures reverse the abnormal glucose metabolism seen in half of the patients. The early resolution of type 2 diabetes mellitus after RYGB has been shown to be independent of the loss of body fat, and likely involves alterations of one or more systems, which include incretin secretion [1], bile acid absorption [2], or gut microflora [3] to name just a few.

As gratifying as the resolution of type 2 diabetes mellitus after RYGB is, it remains to be seen whether this effect is permanent or merely temporary despite sustained weight loss, or whether the system(s) responsible for the reversal of abnormal glucose metabolism ever reverts to a normal or baseline condition. Evidence that it may not is deduced from the observation that an unknown number of both diabetic and nondiabetic patients who have undergone RYGB subsequently develop hypoglycemia and neuroglycopenia months to years after their surgery [4]. Some of these patients, the number of which is also unknown, develop such profound neuroglycopenia that they sustain life-threatening injuries or are disabled by their postbypass condition.

The syndrome of postbypass hyperinsulinemic hypoglycemia is now well recognized, but the details of its prevalence and even of its definition remain unclear [5]. The study in the current issue by Laurenius et al. [6] reveals that a cohort of post-RYGB patients with symptomatic and previously documented hypoglycemia had a glycemic response to a liquid test meal that was less abnormal than a cohort of post-RYGB patients with symptomatic and previously documented hypoglycemia...
patients who had no symptoms or documentation of hypoglycemia. Whereas 5 of 8 patients in the symptomatic cohort had a plasma glucose nadir of 3 mmol/L (54 mg/dL) or less, 7 of 8 patients in the asymptomatic cohort fell below this threshold, including 3 patients whose glucose levels fell to <2 mmol/L or 36 mg/dL. As the asymptomatic cohort was apparently selected merely because they resembled the demographic characteristics and postoperative period of the symptomatic group, the most striking conclusion of this study was that postprandial hypoglycemia after RYGB may be much more common than anyone has suspected. That such profound hypoglycemia was inconsistently accompanied by any symptom distress or discomfort is not entirely surprising, as the authors point out, because it is well known that the symptoms of neuroglycopenia are frequently subtle or absent entirely [7].

The hormonal responses to the test meal were provocative as well. The insulin responses to the ingested nutrients were similarly exaggerated in the 2 groups, compared to a nonoperated, nonobese control group, and GLP-1 levels were markedly elevated in both groups compared to controls as well. The GLP-1 response in the symptomatic cohort was greater than that in the asymptomatic cohort, although this difference failed to reach statistical significance, probably due to the small number of patients. GLP-1 hypersecretion has been suspected of being a cause of postprandial hypoglycemia after RYGB [8], and it is to be remembered that GLP-1 is not only an insulin secretagogue, but possesses insulinomimetic actions of its own [9]. These results are, therefore, consistent with the incretin hypothesis.

The syndrome of “late dumping” after gastrectomy was well recognized in the prehistamine receptor antagonist, preproton pump inhibitor, pre-Helicobacter pylori era. Postgastrectomy hypoglycemia was ultimately declared the cause of “late dumping” in about 5% of gastrectomy patients [10], and hyperinsulinemia was found to be the culprit [11]. The cause of the hyperinsulinemia was thought to be a “gastrointestinal factor” [12], but just as studies on the role of various gut hormones were being designed, the frequency of gastrectomy plummeted, and so did the attention to the syndrome. The current interest in post-RYGB hypoglycemia has resurrected some of the same studies, and it is likely that the prevalence of the problem will turn out to be at least that seen in the era of gastrectomy for peptic ulcer disease.

The authors of the Laurenius et al. [6] study fail to mention any strategy for treating the asymptomatic but clearly hypoglycemic cohort of their study, and herein lies the problem. We need good data to tell us the incidence and prevalence of post-RYGB hypoglycemia (with or without symptoms of neuroglycopenia), and these studies should include the other commonly used variations of bariatric procedures. This will require following and studying these patients for at least 5 years after their surgery, and the completeness of postoperative follow-up has been a challenge for observational studies of this patient population so far. Clinical trials of dietary alterations or drugs or surgical conversions will need to be conducted in patients with documented hypoglycemia, and these have been difficult to carry out with large enough cohorts to be meaningful. The National Institute of Diabetes and Digestive and Kidney Diseases is interested in supporting research in these areas, and clinical investigators are encouraged to contact Dr. Karen Teff (karen.teff@nih.gov) to learn more about funding opportunities.

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References