Refractory Hyperglycemia After Gastric Bypass Surgery: A Novel Subtype of Type 2 Diabetes?

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Patients failing to respond to radically effective therapies can provide clues to identify distinct disease subtypes. For example, the recognition of insulin-sensitive and insulin-insensitive patients helped reveal diabetes variants now classified as type 1 and 2.

After Roux-en-Y gastric bypass (RYGB), 40–80% of patients with type 2 diabetes (T2DM) experience diabetes remission, and nearly all enjoy improved glycemic control (1–3). Studying absolute nonresponders to RYGB may reveal disease subtypes with distinct pathophysiology. Published series of bariatric surgery, however, usually describe general rates of remitters and nonremitters but do not distinguish between partial responders versus absolute nonresponders.

Long diabetes duration (>10 years), preoperative insulin use, and lesser postoperative weight loss are associated with lower diabetes remission rates after RYGB (4), suggesting that insufficient insulin reserve at late-stage T2DM and/or inadequate weight loss may reduce diabetes responsiveness to surgery. Precise clinical and laboratory characterization of nonremitters in traditional bariatric surgery series, however, is problematic because diabetes-specific measures are not typically assessed (5).

We have routinely used diabetes-specific parameters for preoperative workup and as a measure of outcome in a metabolic surgery program specifically designed to treat T2DM (5). In this setting, we sought to characterize patients with refractory post-RYGB hyperglycemia.

A prospective database including 60 patients with T2DM (BMI >35 kg/m^2) who underwent RYGB with ≥1-year postoperative follow-up was analyzed. The patients were operated on by one of us (F.R.) at the Gastrointestinal Metabolic Surgery Section of Weill Cornell Medical College/NewYork-Presbyterian Hospital (New York, NY). Absolute nonresponders were identified as patients who at no time experienced decreased glycemia below diabetic thresholds, and who 1 year after surgery had unchanged or worsened HbA_{1c} and fasting glucose with unchanged or increased diabetes medications.

Four patients meeting our definition of absolute nonresponders were identified. Preoperatively, there was no evidence of insulin deficiency in these individuals, as shown by normal fasting C-peptide levels in all. Only one patient was anti-GAD65 antibody–positive (though her C-peptide levels were normal), excluding autoimmune diabetes in the others. Two patients had diabetes for <10 years (3 and 7 years), and two had never been on insulin preoperatively (Table 1).

Two patients experienced excess weight loss >50%, as expected after RYGB, and all had at least 8% body weight loss (range 7.5–28%), a level usually associated with improved glycemic control. Hypertension and dyslipidemia also were not improved postoperatively in these patients (Table 1).

Although the vast majority of patients with T2DM enjoy remission or improved glycemic control after RYGB, we show that hyperglycemia may be completely refractory to RYGB in some individuals.

Given the relatively small size of this study, we cannot determine the exact prevalence or cause of this phenomenon. Our observation, however, has several implications.

First, refractory hyperglycemia in patients with >50% excess weight loss further supports the idea that the antidiabetes mechanisms (and failure) of RYGB are partially weight-independent.

Furthermore, the observation of refractory hyperglycemia in subjects with normal preoperative C-peptide levels and/or short disease duration or no prior insulin therapy does not explain the lack of response to RYGB as merely a consequence of pancreatic insufficiency and/or late-stage disease.

As RYGB has been shown to improve all known aspects of T2DM pathophysiology (6,7), the observation that some patients with typical T2DM fail to show any improvement of hyperglycemia after

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Table 1—Preoperative characteristics and postoperative clinical outcomes of nonresponders

Preoperative characteristics

Case	Age (years)	Sex	Duration of diabetes (years)	Insulin therapy	C-peptide (ng/mL)	GAD65 antibody	BMI (kg/m^2)	HbA_{1c} (%)	Hypertension	Dyslipidemia	Diabetes medication
1	44	Male	3	No	3	Negative	43.6	8.1	Yes	No	Pioglitazone, exenatide
2	64	Male	20	No	3.6	Negative	37.9	9.0	No	Yes	Metformin, exenatide
3	51	Female	25	Yes	2.7	250	36.1	9.6	Yes	Yes	Metformin, insulin
4	56	Male	7	Yes	3.1	–	35.7	8.3	No	Yes	Metformin, pioglitazone, insulin

Postoperative clinical outcomes at 12 months

Case	Weight loss (%)	BMI (kg/m^2)	Excess weight loss (%)	HbA_{1c} (%)	Hypertension*	Dyslipidemia**	Diabetes medication
1	19.2	32.5	42	8.4	Not improved	NA	Metformin, exenatide
2	7.5	34	18	9.7	NA	Not improved	Metformin, pramlintide
3	23	28	62	9.4	Not improved	Not improved	Metformin, sitagliptin
4	28.2	25	76	8.3	NA	Not improved	Metformin, insulin

*Improvement of hypertension = blood pressure <130/80 with less medication than preoperative. **Improved lipids = LDL <100, triglyceride <150; with less medication than preoperative.

RYGB raises the intriguing hypothesis that subtypes of T2DM exist, characterized by distinct pathophysiologic defects that are not addressed by this operation.

Determining the exact prevalence of refractory hyperglycemia in larger multicenter studies of metabolic surgery may inform clinicians about preoperative counseling of patients who seek surgery specifically to treat T2DM. Future investigations designed to elucidate the genetic and metabolic profiles of patients with T2DM and refractory post-RYGB hyperglycemia also may provide opportunities to identify new diabetes subtypes.

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