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A closer look at diabetes remission after gastric bypass surgery: a case study

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Roux-en-Y gastric bypass (RYGB) results in 30–40% weight loss, often sustained over time, and remission of type 2 diabetes (T2DM) in 50–80% of cases.^{1–3} In addition to weight loss, the enhanced post-prandial incretin release may play an important role in diabetes improvement after RYGB.^{3,4}

Herein we report on a 54 year old woman with 3 years of known T2DM, well-controlled by metformin and glipizide. As part of a research study, the patient underwent an oral glucose tolerance test (OGTT) and an isoglycemic intravenous glucose test (IVGT) before and at 1, 6 months, 2, 3, 4, 5 and 6 years after laparoscopic RYGB (100 cm Roux limb, 50 cm bilio-pancreatic diversion limb, 15 ml gastric pouch), for measurement of circulating glucose, insulin and incretins concentrations, and of the incretin effect on insulin secretion, as previously described.^{3,4} Initial body mass index (BMI) was 42 kg/m². The weight loss was -37 kg at 6 years, a 31% weight loss. The homeostatic model assessment of insulin resistance (HOMA-IR) decreased by half, from 11.81 pre-surgery to 5.34 6 years post-surgery. The insulin secretory rate (ISR), β -cell glucose sensitivity, and insulinogenic indices all followed similar pattern of change, increasing at 1 month, decreasing from 3–5 years, and increasing at year 6. Fasting glucose improved, but remained impaired at 6 years (164 before surgery vs. 112 mg/dL); the 120' and peak glucose remained higher than 140 mg/dl and 200mg/dL respectively, at almost all study periods (Figure 1). The patient never experienced post-prandial hypoglycemia. The diabetes was well controlled pre-surgery and therefore the glycated hemoglobin (HbA1c) decreased only minimally from 6.6% before surgery to 6.4% at 6 year, likely due to a 'ceiling effect'.

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In agreement with previously published data,^{3, 5, 6} the glucagon-like peptide-1 (GLP-1) response to oral glucose increased by a factor of 4 at 1 month (Figure 1). However, surprisingly, and contrary to the general trend seen in patients after GBP,⁹ GLP-1 response decreased to pre-surgery levels between 6 months and 2 years. It was not until 3 years post RYGB that glucose-stimulated GLP-1 concentrations began to increase gradually every year, to reach the 1 month post-operative concentrations at 6 years. Glucose-dependent insulintropic polypeptide (GIP) response followed the same pattern as that of GLP-1 (Figure 1). In spite of the blunted GLP-1 and GIP release from 6 months through 2 years, the incretin effect on insulin, which increased at 1 month (from -15.6 to 52.9%), remained elevated between 30-52% throughout the 6 years of study.

This case raises several questions. In spite of 31% weight loss, the diabetes, already well controlled at baseline, did not fully remit, albeit did not worsen, with lesser treatment (low dose of metformin only from year 4 to 6), demonstrating maintained insulin secretion. The sub-optimal improvement of insulin sensitivity, assessed by HOMA-IR, could be related to the persistent overweight with a BMI >29 kg/m² at all time points after the surgery. However, most patients who remain obese after surgery, experience greater improvements in insulin resistance.⁷ The suboptimal HOMA-IR could be explained by a low level of self-reported physical activity, a centrally distributed fat mass, or high level of stress, although these were not measured. This highlights the importance of studying predictors of T2DM remission in patients after RYGB. The second lesson from this case derives from the 6-year perspective and the changes in incretin release. Most patients^{4, 6, 8} demonstrate rapid enhanced incretin release as early as 1 week, sustained over years^{8, 9}. This case illustrates a different pattern of incretin response after surgery. The GLP-1 and GIP response, initially elevated at 1 month, was blunted and comparable to pre-surgery levels between 6 months to 2 years after RYGB, to increase again after year 3. The proposed mechanism of enhanced incretin release after RYGB is accelerated nutrient transit.¹⁰ It is therefore difficult to explain why the GLP-1 and GIP response did not remain elevated between 1 and 6 months post-surgery. Neither the lifestyle nor the diet, assessed by questionnaires, nor the low intra-assay variability in our laboratory, could explain this pattern. One can speculate that the steady increase in the postprandial GLP-1 and GIP concentrations from year 3 to 6 after surgery could be due to a different mechanism than the accelerated transit time, which is unlikely to change over time after the surgery. Gut nutrient sensing and its effect on hepatic gluconeogenesis¹¹, microbiota¹² or bile acids¹³ could be explanations, and these may be a major mechanisms in long term diabetes improvement after surgical weight loss.

Another interesting feature of this patient is the association between weight regain and blunted GLP-1 levels after RYGB, and the weight loss response to a short trial of exenatide. This suggests that GLP-1 could be involved in weight maintenance after the surgery. This case challenges the notion of diabetes remission after RYGB and the role of enhanced incretin concentrations in diabetes improvement and/ or weight loss maintenance. The careful study of one patient's changes in glucose handling over 6 years post-RYGB provides an example of the significant variation of the incretins, insulin secretion, insulin resistance and glycemic control after surgery, while also raising questions about the mechanisms which regulate glucose homeostasis. This case illustrates a rare occurrence of a fluctuating incretin response over years after GBP, and the absence of complete diabetes remission in the presence of significant weight loss and elevated incretins. All other subjects have shown sustained elevated incretin levels through six years, and full diabetes remission. This study highlights the importance of longitudinal studies and careful phenotyping of patients after RYGB to understand the wonders of this surgery and identify markers of diabetes remission or relapse.

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Figure 1.

Fasting glucose and 120min glucose (Panel A), total glucagon-like peptide-1 (GLP-1) and total glucose-dependent insulintropic polypeptide (GIP) (Panel B) during oral glucose tolerance test, and weight loss (Panel C), before and up to 6 years after gastric bypass surgery. Reference lines indicate fasting glucose values for the diagnosis of impaired glucose tolerance (IGT) with 120 min glucose at 140mg/dL, type 2 diabetes (T2DM) with fasting glucose at 126mg/dL, and impaired fasting glucose (IFG), with fasting glucose at 110mg/dL.

AUC GIP Total: Area under the curve of the GIP response over 180min.

AUC GLP-1 Total: Area under the curve of the GLP-1 response over 180min.

Time points: Pre-surgery (Pre-RYGB), 1 Month (1M), 6 Months (6M), 2 Years (2Y), 3 Years (3Y), 4 Years (4Y), 5 Years (5Y), 6 Years (6Y).