HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2016 May 18.

Published in final edited form as:

Obesity (Silver Spring). 2015 October ; 23(10): 1942–1943. doi:10.1002/oby.21259.

New Lessons From Gastric Bypass: Impact of Glucose-Independent Islet Function

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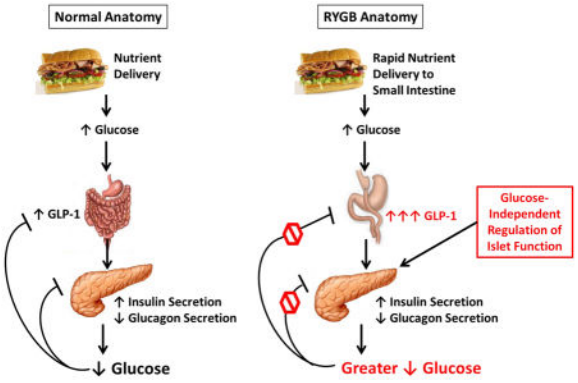
Graphical Abstract



The World Health Organization has proclaimed obesity and type 2 diabetes (T2D) to be amongst the most important threats to global public health. Roux-en-Y gastric bypass surgery leads to substantial and sustained weight loss and has become a widely-used approach to manage obesity related conditions, although physiologic mechanisms leading to metabolic improvements remain incompletely understood. Insulin sensitivity is improved post-RYGB, typically in parallel to the magnitude of weight lost ([1]). In contrast, insulin secretion and islet β-cell glucose sensitivity may be disproportionately increased post-RYGB ([2]).

One major contributor to improved glycemia and β-cell function post-RYGB may be enhanced secretion of the incretin peptide hormone glucagon-like peptide 1 (GLP-1) by intestinal L-cells in response to nutrients. In turn, GLP1 stimulates insulin and inhibits glucagon secretion in a glucose-dependent manner ([3]). GLP-1 concentrations are increased in post-RYGB patients as early as one week post-operatively and higher levels are sustained ([4]). The incretin effect accounts for a larger proportion of the insulin secretory response in patients who have had RYGB as compared with nonsurgical controls, and inhibition of GLP-1 signaling using the exendin$_{9–39}$ peptide, which binds to the GLP-1 receptor without activation, reduces insulin secretion in post-RYGB patients ([5]). Recent studies demonstrate persistent increased insulin secretion rates in post-RYGB patients in the later postprandial phase - even when blood glucose and GLP-1 concentrations have fallen to basal levels - suggesting glucose- and incretin-independent mechanisms ([6]).

Salehi *et al.* ([7]) now provide additional strong evidence for glucose and incretin-independent mechanisms underlying changes in β-cell function post-RYGB. Using a hyperinsulinemic clamp procedure, the investigators induced mild hypoglycemia to 54–63 mg/dl, a value which would generally suppress insulin secretion in response to GLP-1 ([3]). In this setting, post-RYGB patients had less suppression of fasting insulin secretion as compared to both lean and obese control groups. Moreover, meal-provoked insulin secretion persisted, despite mild hypoglycemia. Additionally, glucagon responses to both hypoglycemia and meal ingestion were lower in post-RYGB than control groups. Together, persistent insulin secretion and reduced glucagon at relative hypoglycemia - in both fasting and post-meal states -support the existence of factors beyond circulating glucose concentrations and GLP-1 to regulate islet function after RYGB.

Limitations of this work include indirect estimations of insulin secretion and clearance in the setting of insulin administration during the clamp procedures, differences in insulin concentrations achieved in post-RYGB versus the obese control group, and absence of direct measure of oral compared to hepatic glucose appearance following the mixed meal.

Glucose and GLP-1-independent mechanisms regulating islet biology remain incompletely understood. However, the very high levels of GLP-1 achieved in the postprandial state post-RYGB may have glucose-independent effects, as demonstrated by the development of hypoglycemia in some post-RYGB patients ([5]) and in a patient with a GLP-1-secreting tumor ([8]). Additional contributors may include neural mechanisms, other gastrointestinal (or peripheral) metabolites or hormones, non-carbohydrate nutrients in the mixed meal, and signals from intestinal microbiota. Careful studies will now be required to elucidate the factors beyond glucose that regulate pancreatic islet function following RYGB, in order to develop novel therapeutic approaches for metabolic disease.

Acknowledgments

NIH P30-DK03836

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