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Commentary

Could micro changes in β-cells enable major changes in metabolism?

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The rates of obesity and type 2 diabetes (T2D) continue to rise, placing enormous demand on global health care systems to deal with the fallout of the co-morbidities derived from these diseases. It is clear that the metabolic dysfunction of T2D strongly associates with heart disease, cancer, respiratory and vascular complications, increasing the need to develop better therapies to treat this condition. While significant advancements have been made in the development of diabetic therapies that target hyperglycemia, current efforts in the advancement of new diabetes medications look beyond glucose management, including an emphasis on weight loss, hepatic steatosis, improved lipid metabolism, and enhancing β-cell function. One intervention that consistently and efficaciously targets these end-points is bariatric surgery. However, it is impractical to perform surgery on the millions of people that require radical improvements in their metabolic portfolio: this has provided the inspiration to develop novel therapies that can replicate the efficacy of bariatric surgery. Yet, in order to achieve this ideal elixir, the field must first delineate the underpinning mechanisms by which bariatric surgery facilitate rapid and sustained improvements in metabolism, which to date remain largely unresolved.

In this article of *EBioMedicine*, Fabrizio Andreelli and colleagues [1] show that bariatric surgery in obese, hyperglycemic mice induces robust weight-independent changes in β-cell pathways that are intimately linked with insulin secretion. They conducted enterogastro-anastomosis with pyloric ligature (EGA) in ob/ob mice, utilizing a pair-fed, sham-treated group to control for differences in food intake. EGA is a surrogate for Roux-en-Y gastric bypass (RYGB), a common bariatric surgery performed in obese humans, that connects the distal jejunum directly to the stomach and prevents food from entering the duodenum. The result is nutrient exclusion from the duodenum and proximal jejunum, with direct delivery of nutrients from the stomach to the distal jejunum. Unlike RYGB, which involves excision of the majority of the stomach volume, EGA does not involve modification to the stomach. Thus, where RYGB contains elements of both restriction (smaller stomach) and malabsorptive (bypass the proximal intestine), EGA is primarily malabsorptive. These studies were conducted in ob/ob mice, which is a commonly used mouse model of metabolic dysfunction, where deficiency in leptin production results in extreme obesity and hyperglycemia. Interestingly, ob/ob mice do not have similar decrease in food intake, energy expenditure or changes in body composition following bariatric surgery, making them a unique model for establishing weight-independent effects of surgical interventions. The EGA procedure in the current study produced decreases in food intake and body weight, along with rapid improvement in glucose tolerance, that is in line with previous results from this group [2], and other reports using RYGB [3] or vertical sleeve gastrectomy [4] in preclinical models. Indeed, it is remarkable that multiple different interventions that are varied in their alterations of the gut anatomy ubiquitously produce similar improvements in metabolic outcomes in preclinical models and clinical populations. In addition, all forms of bariatric surgery universally enhance the endocrine function of the gut [5], which are essential for metabolic control [6]. While the exact connection between altered gut activity and improvements in the metabolic outcomes following surgery have yet to be established, these concepts reinforce the notion that the gut possesses tremendous control over systemic metabolism. Mimicking the increased gut hormone activity induced by bariatric surgery is a cornerstone driving the development of multi-receptor peptide drugs for the treatment of diabetes [7].

A striking feature of bariatric surgery is the resolution of hyperglycemia in a rapid and weight-independent manner [5]. Moreover, pair-feeding studies in preclinical models have demonstrated the robust glucose lowering and improved glycemic control following bariatric surgery involves mechanisms independent from reductions in food intake. Indeed, the current work by Andreelli and colleagues elegantly demonstrates EGA improves ambient glycemia, glucose tolerance, and in vivo insulin secretion compared to pair-fed ob/ob sham controls that have similar food intake, body weight, and peripheral insulin resistance. The weight-independent mechanisms invoked by bariatric surgery that enhance glycemic control has focused much of the recent work in this field on the pancreatic islets. β-cell function is the primary determinant of glucose regulation, as insufficient insulin secretion to meet peripheral metabolic demand is the hallmark of diabetic hyperglycemia. Thus, a central hypothesis driving much of this field, including the current work by Andreelli and colleagues, is that bariatric surgery induces intrinsic changes in β-cells to enhance insulin

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secretion. This hypothesis is reinforced by the consistent observation of markedly elevated insulinotropic gut factors following bariatric surgery, including GLP-1, GIP, PYY, and bile acids [5]. Yet, single gene knockout models have largely failed to identify individual factors as essential for the improvements in β-cell function and glucose homeostasis. Consequently, it remains unclear why or how altering the gut anatomy induces positive changes in pancreatic islets to drive the rapid and significant improvements in glycemia.

To address this gap in knowledge, Andreelli and colleagues initiated a series of unbiased approaches to understand how bariatric surgery alters β-cell function. Using microarray to assess the transcriptome of pancreatic islets, they identified 458 genes that were differentially expressed between ob/ob sham controls and EGA treated mice, many of which were involved in essential β-cell functions. These data support the hypothesis that bariatric surgery induces intrinsic changes in islets, a conclusion that strongly aligns with previous work in high-fat fed mice following vertical sleeve gastrectomy [4]. In an effort to take the transcriptomic data one step further, the investigators conducted a series of assays to test β-cell function ex vivo and correlated the results with some of the identified differentially expressed genes. Glucose-stimulated insulin secretion correlated with the most robustly altered genes such as *Trpm2* and *Trpm5*, while in vivo insulin secretion correlated with key β-cell genes *Slc2a2* (GLUT2), *Ucp2*, and *Gck*. However, an important novel finding in this work is the investigation of micro RNA (miRNA) expression in the islets from control and EGA-treated mice. A detailed profiling of the miRNA expression identified 22 miRNAs that were upregulated and 5 that were downregulated. Remarkably, EGA treatment induced changes in miRNAs away from the levels measured in obese, hyperglycemic ob/ob mice and towards levels measured in lean, healthy wild-type mice, suggesting a positive trend in the miRNA transcriptome. To further emphasize this, the circulating plasma levels of a subset of miRNAs that functionally intervene on altered hormone secretion mRNA pathways were measured in the sham versus EGA treated mice and compared to the levels measured in humans with diabetes resolution following gastric bypass. The levels of miR106b-5p and miR210-3p were significantly elevated in both the EGA treated mice and human subjects that demonstrated diabetes resolution. This exciting finding warrants further studies to extend this data set beyond a correlative observation to directly test the contribution of these miRNAs to the improvements in β-cell function that are responsible for the resolution of hyperglycemia following bariatric surgery.

The studies by Andreelli and colleagues further emphasizes the need to understand how alterations in the gut induce profound changes in islet function that facilitate diabetes resolution. While there are a number of outstanding questions, there is no doubt that significant advancements can be made by understanding the mechanisms that drive this phenomenon. It is interesting to note that much of the analysis in the current report were done in whole islets, yet the findings are described as specific to β-cells. How much of these findings are due to alterations in the α-cells remains unknown and an important avenue of future investigations. Indeed, the investigators report a significant increase in α-cell mass in the islets from EGA treated mice, hinting that this cell population is also impacted by bariatric surgery. Although glucagon levels were not measured, circulating GLP-1 levels were elevated in ob/ob EGA treated mice, potentially reflecting increased α-cell GLP-1 production [8]. Recently work has revealed the importance of α-cell control of β-cell function [9], with some evidence that this may be essential for the positive effects following vertical sleeve gastrectomy [10]. Much of the reported literature, including the current manuscript, have focused on the communication between the altered gut and the β-cell following bariatric surgery. There is a consensus based on this work that bariatric surgery induces important and efficacious changes to pancreatic islets that enhance insulin secretion and lower glycemia. Expanding this body of work beyond the β-cell to include the α-cell could be a productive step towards understanding the mechanisms by which bariatric surgery enhances islet function. Understanding these mechanisms can provide a foundation to develop novel therapies that replicate the remarkable effects of bariatric surgery on diabetes resolution.

Declaration of Interests

Dr. Capozzi has nothing to disclose. Dr. Campbell has nothing to disclose.

CRediT authorship contribution statement

Megan E. Capozzi: Writing - original draft, Writing - review & editing. **Jonathan E. Campbell:** Writing - original draft, Writing - review & editing.

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