MOLECULAR METABOLISM

Mining the mechanistic underpinnings of bariatric surgery: A gateway to novel and non-invasive obesity therapies?

Ana B. Emiliano Assistant Professor of Medicine

The review "Regulation of body weight: lessons learned from bariatric surgery" by Albaugh et al. in the current issue of Molecular Metabolism critically examines the available rodent and human literature on vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). The authors' goal was to shed light on the mechanisms underlying bariatric surgery's beneficial metabolic effects. Bariatric surgery still is the most effective therapy for severe obesity.

Bariatric surgery dates back to the early 1950's, preceding the start of the obesity epidemic in the United States by at least four decades [1]. Jejunoileal bypass (JIB), the first bariatric surgery to be developed, had a clear mechanistic rationale [2]. By leading to severe malabsorption through the establishment of a short bowel syndrome, JIB promoted dramatic weight loss [3]. Due to an unacceptably high rate of complications and mortality, JIB was eventually abandoned in favor of the precursors of modern bariatric surgery procedures, such as VSG and RYGB. Although VSG and RYGB are the two most performed bariatric procedures worldwide [4], how they promote durable weight loss and type 2 diabetes clinical improvement is incompletely understood. As Albaugh and his co-authors point out, the classification as restrictive or malabsorptive is rather simplistic, not fully explaining the metabolic effects of either VSG or RYGB [5].

The authors carefully and extensively reviewed substantial evidence that indicates that bariatric surgery promotes weight loss and blood glucose lowering through multiple mechanisms (Figure 1). These mechanisms include changes in GLP-1 secretion, bile acid and gut-brain neural signaling, and gut intestinal reprogramming of glucose metabolism. Front and center in their critical analysis is the increased incretin response after VSG and RYGB, which acts as a driver of both weight loss and glucose homeostasis improvement. The authors highlight that the most effective pharmacological therapy for obesity, the GLP-1 receptor agonists, emulates the increase in incretin secretion observed after VSG and RYGB [6,7]. Although the review points out that therapies based on the manipulation of bile acid signaling have not come to fruition yet, there is compelling evidence that changes in bile acid signaling may be involved in the weight and glucose homeostasis effects of bariatric surgery. In preclinical studies, both the farnesoid x receptor and the G coupled bile acid receptor TGR5 signaling have been implicated as effectors of the changes in circulating bile acids that occur post bariatric surgery. Whether through increased or reduced FXR signaling, studies have suggested that manipulating signaling at this receptor can lead to weight loss and improvement of glucose homeostasis [8,9]. Although TGR5 signaling was not found to contribute to weight loss in preclinical models of bariatric surgery, increased TGR5 signaling was associated with improved glucose tolerance and hepatic insulin signaling [10]. More importantly, to some extent, human studies have supported these preclinical findings by revealing an association between RYGB and increased postprandial bile acid plasma levels and FGF19 plasma levels — FGF19 is a hormone that regulates bile acid synthesis [11,12]. Regarding changes in sensory nerve signaling, preclinical studies have suggested a role for changes in signaling in vagal afferents in the decreased energy intake observed after RYGB [13,14]. Lastly, although one preclinical study showed that RYGB led to increased glucose metabolism by intestinal epithelial cells through mechanisms that involve increased GLUT1 expression, it is not clear whether intestinal reprograming of glucose metabolism occurs in humans or whether it important for the metabolic benefits of RYGB in human patients [15].

An important omission by the present review is the lack of a discussion on metabolic adaptation and weight regain in the context of bariatric surgery. The decrease in energy expenditure that accompanies any type of weight loss is known as metabolic adaptation [16,17]. One striking feature of bariatric surgery is that is causes more limited metabolic adaptation than weight loss induced by diet and exercise, as elegantly shown in the landmark study by Kevin Hall's group [18]. Weight regain, which has replaced the use of the negative term 'obesity recidivism', is estimated to affect at least 30—40% of bariatric patients [19—22]. A recurrence or new onset of obesity co-morbidities often accompanies weight regain.

Despite an incomplete mechanistic understanding of modern bariatric surgery, more than 250,000 Americans undergo these procedures annually [23]. And this number is estimated to represent only approximately 1—2% of all individuals with obesity deemed eligible by NIH criteria [24]. Most patients lack access to bariatric surgery. Thus, this is a timely review that emphasizes the importance of identifying the molecular and signaling pathways that are the gateways to bariatric surgery's durable weight loss and blood glucose lowering. Once we understand how bariatric surgery works, effective, less-invasive or

Division of Endocrinology and Metabolism, Naomi Berrie Diabetes Center, Columbia University Irving Medical Center, New York, NY, USA

E-mail: abe2123@cumc.columbia.edu.

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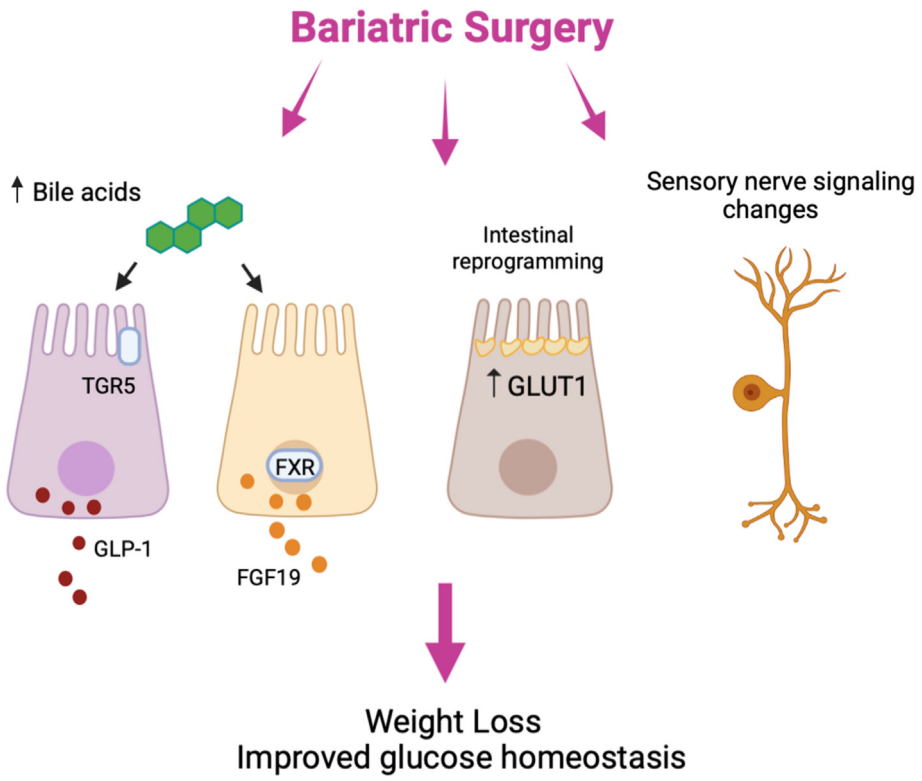

Figure 1: Possible mechanisms through which bariatric surgery leads to durable weight loss and glucose homeostasis improvement. GLP-1 — glucagon-like peptide 1; FGF19 — fibroblast growth factor 19; FXR — farnesoid receptor; TGR5 -Takeda G-protein receptor. Created with BioRender.com.

non-invasive therapies can be developed to replace the surgical procedures that are needed today.

CONFLICT OF INTEREST

The author has no conflict of interest.

DATA AVAILABILITY

No data was used for the research described in the article.

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