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Bile acids and bariatric surgery

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ABSTRACT

Bariatric surgery, specifically Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), are the most effective and durable treatments for morbid obesity and potentially a viable treatment for type 2 diabetes (T2D). The resolution rate of T2D following these procedures is between 40 and 80% and far surpasses that achieved by medical management alone. The molecular basis for this improvement is not entirely understood, but has been attributed in part to the altered enterohepatic circulation of bile acids. In this review we highlight how bile acids potentially contribute to improved lipid and glucose homeostasis, insulin sensitivity and energy expenditure after these procedures. The impact of altered bile acid levels in enterohepatic circulation is also associated with changes in gut microflora, which may further contribute to some of these beneficial effects. We highlight the beneficial effects of experimental surgical procedures in rodents that alter bile secretory flow without gastric restriction or altering nutrient flow. This information suggests a role for bile acids beyond dietary fat emulsification in altering whole body glucose and lipid metabolism strongly, and also suggests emerging roles for the activation of the bile acid receptors farnesoid x receptor (FXR) and G-protein coupled bile acid receptor (TGR5) in these improvements. The limitations of rodent studies and the current state of our understanding is reviewed and the potential effects of bile acids mediating the short- and long-term metabolic improvements after bariatric surgery is critically examined.

1. Introduction – the obesity epidemic

The prevalence of obesity has continued to increase over the past 30 years and is associated with increased risk of numerous comorbid medical conditions, including insulin resistance, type 2 diabetes (T2D), and cardiovascular disease. Obesity and these associated conditions contribute to increased all-cause mortality (Flegal et al., 2013). In 2008, an estimated 1.46 billion adults globally were overweight (BMI > 25 kg/m^2) and 502 million adults were obese (BMI >30 kg/m^2). The economic costs associated with obesity are staggering, with healthcare costs alone in the United States at that time being an estimated at $147 billion (Finkelstein et al., 2009). Given current trends, approximately 50% of American adults will be obese by 2030 (Swinburn et al., 2011) and the economic burden will be unsustainable (Trogdon et al., 2008).

2. Bariatric surgery is the most effective and durable treatment for obesity

Numerous studies have demonstrated that intensive lifestyle intervention consisting of rigorous exercise and dietary restriction can be effective, but result in only modest weight loss (~5–6% of baseline body weight) (Ikramuddin and Livingston, 2013). Importantly, this weight loss is not sustained long-term (The Look AHEAD Research Group, 2014) despite a few individuals losing significant excess body weight (Blackburn, 1995). Even this small degree of weight loss has been shown to be associated with decreased cardiovascular risk, but over time these improvements are lost with weight regain (Wing et al., 2011).

Unlike intensive lifestyle intervention, metabolic and bariatric surgery is the most effective and durable treatment for class III obesity (BMI ≥40 kg/m^2) with and without diabetes (Pories et al., 1995). In fact, revised guidelines for the management of T2D from the 2nd Diabetes Surgery Summit (2015), endorsed by numerous professional organizations, including the International Diabetes Federation and American Diabetes Association, recommends metabolic and bariatric surgery for the treatment of T2D in

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individuals with a BMI >35 kg/m^2. Moreover, these new guidelines stress that individuals with difficult to control diabetes who are obese but with a BMI <35 kg/m^2 should also be evaluated for metabolic surgery (Cefalu et al., 2016; Rubino et al., 2016).

The long-term efficacy of bariatric surgery is demonstrated by more significant weight loss compared to intensive medical therapy (Dixon et al., 2008; Mingrone et al., 2012; O'Brien et al., 2006; Schauer et al., 2012) in patients with T2D, resulting in decreased overall mortality (Sjöström et al., 2004, 2007). In particular, RYGB is associated with durable remission of T2D, achieving target HbA1C (glycated hemoglobin levels of ≤6.5%) in ~70% of subjects beyond 3 years (Arterburn et al., 2012; Schauer et al., 2014).

The benefits of metabolic and bariatric surgery are not limited to improved insulin and glucose handling. Cardiovascular disease (Lavie et al., 2009; Sjöström et al., 2004, 2012), cancer risk (Adams and Hunt, 2009; Ashrafian et al., 2011; Sjöström et al., 2009), nonalcoholic fatty liver disease (de Almeida et al., 2006; Lassailly et al., 2013; Vernon et al., 2011) and even pulmonary hypertension (Mathier et al., 2008; Pugh et al., 2013; Sheu et al., 2015) are all markedly improved after these procedures. While many of these improvements are undoubtedly attributable to long-term weight loss, additional data support a weight-independent role for other hormonal or metabolic mediators of the early effects of these operations.

Currently, the two most popular bariatric procedures in the United States are Roux-en-Y gastric bypass (RYGB; Fig. 1) and vertical sleeve gastrectomy (VSG; Fig. 2). Both operations are effective in promoting weight loss, and data suggest that RYGB may be slightly superior in the long-term. Longitudinal cohorts have demonstrated an average weight loss with RYGB of 10% at 1 month (Dunn et al., 2012), 27% at 6 months, 34% at 1 year (Fabbrini et al., 2010), 33% at 2 years (Tamboli et al., 2014) and 27% at 5 years. The weight loss in these studies was characterized by improved insulin sensitivity and glycemic control, findings consistent with previous reports (Buchwald et al., 2004, 2009). Interestingly, the metabolic improvements occur as early as one week postoperatively, at a time when weight loss is minimal to none; we attribute at least some of these improvements to caloric restriction (E. N. Hansen et al., 2011; Isbell et al., 2010), suggesting the involvement of other additional factors involved in driving the metabolic improvements after bariatric procedures.

Fig. 1. Roux-en-Y Gastric Bypass. The proximal stomach is divided creating a stomach pouch (~30 ml) that continues to have nutrient flow and the remaining stomach, referred to as the gastric remnant, is removed from enteral nutrient contact. A portion of jejunum is transected and connected to the stomach pouch forming the Roux limb, the length of which can vary depending on patient and/or surgeon factors. Intestinal continuity is restored by attaching the biliopancreatic limb to the Roux limb downstream via a connection referred to as a jejunojejunostomy. The remaining bowel distal to this connection is referred to as the common channel.

Fig. 2. Vertical Sleeve Gastrectomy. In this operation, approximately 70% of the stomach is removed (shaded) and a tube-like gastric 'sleeve' remains. There is no anatomical rearrangement of the small bowel in this operation, but the stomach volume is significantly decreased.

3. What are the mechanisms behind the effectiveness of bariatric surgery?

3.1. Malabsorptive and restrictive

While the terms "malabsorptive" and "restrictive" have continued to fall out of favor as the field of metabolic and bariatric surgery has matured over the last two decades, it is important to understand the historical context in which these terms originally developed. As surgical and medical management of abdominal trauma improved after the Second World War, survival increased following traumatic bowel resection, despite associated significant weight loss. Specific macronutrient and micronutrient malabsorption were well-documented sequelae of extensive bowel resections (Kremen et al., 1954). From these case series it became obvious that the small bowel was not merely a "uniform tube" and that different regions (e.g. duodenum, jejunum, ileum) had different absorptive capacities and selectivity for nutrients and other molecules (Weckesser et al., 1949). These findings led to the development of deliberate intestinal bypasses (e.g. jejuno-ileal bypass) and resections to promote weight loss in obese subjects. Interestingly, it was documented that bypassing a particular length of small bowel could reliably lead to weight loss; however, operative reversal led to weight regain almost to the exact body weight preoperatively (Payne et al., 1963) – an early example of body weight set-point theory (Harris, 1990). Thus, originally the term 'malabsorptive'