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FIELD OF VISION

Ménage-à-trois of bariatric surgery, bile acids and the gut microbiome

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Abstract

Bariatric surgeries have emerged as highly effective treatments for obesity associated type-2 diabetes mellitus. Evidently, the desired therapeutic endpoints such as rates of weight loss, lower levels of glycated hemoglobin and remission of diabetes are achieved more rapidly and last longer following bariatric surgery, as opposed to drug therapies alone. In light of these findings, it has been suspected that in addition to causing weight loss dependent glucose intolerance, bariatric surgery induces other physiological changes that contribute to the alleviation of diabetes. However, the putative post-surgical neuro-hormonal pathways that underpin the therapeutic benefits of bariatric surgery remain undefined. In a recent report, Ryan and colleagues shed new light on the potential mechanisms that determine the salutary effects of bariatric surgery in mice. The authors demonstrated that the improved glucose tolerance and weight loss in mice after vertical sleeve gastrectomy (VSG) surgery were likely to be caused by post-surgical changes in circulating bile acids and farnesoid-X receptor (FXR) signaling, both of which were also mechanistically linked to changes in the microbial ecology of the gut. The authors arrived at this conclusion from a comparison of genome-wide, metabolic consequences of VSG surgery in obese wild type (WT) and FXR knockout mice. Gene expression in the distal small intestines of WT and FXR knockout mice revealed that the pathways regulating bile acid composition, nutrient metabolism and anti-oxidant defense were differentially altered by VSG surgery in WT and $FXR^{-/-}$ mice. Based on these data Ryan *et al*, hypothesized that bile acid homeostasis and FXR signaling were mechanistically linked to the gut microbiota that played a role in modulating post-surgical changes in total body mass and glucose tolerance. The authors' data provide a plausible explanation for putative weight loss-independent benefits of bariatric surgery and its relationship with metabolism of bile acids.

Key words: Vertical sleeve gastrectomy; Bile acids; Farnesoid-X-receptor; Type-2 diabetes mellitus; Gut microbiome; Bariatric surgery

Core tip: The report of Ryan *et al*, raises a number of questions with regard to the prevailing notion that

mechanical restriction of the stomach and weight loss are the sole mechanisms that mediate the therapeutic effects of bariatric surgery. The authors showed that both lowering of body mass index and improved glucose tolerance after vertical sleeve gastrectomy (VSG) surgery were mechanistically linked to an altered composition of circulating bile acids and their ability to modulate farnesoid-X receptor (FXR) mediated signaling mechanisms. Additionally, it was observed that the wild type and FXR knockout mice, after receiving VSG surgery, were significantly different with respect to the make up of their gut microbiomes. Finally, the experiments revealed that the composition of gut microbiota in wild type VSG and $FXR^{-/-}$ VSG mice were highly correlated with their differential abilities to lose weight and acquire glucose tolerance.

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COMMENTARY ON HOT TOPICS

The provocative mechanism proposed by Ryan *et al*[1], that mechanistically links bile acids, farnesoid-X receptor (FXR) nuclear receptor signaling and microbial ecology of the gut to therapeutic superiority of bariatric surgery over intensive drug therapies, opens up new avenues of clinical research that deserves serious consideration.

According to the World Health Organization (WHO), obesity associated type-2 diabetes mellitus (T2DM) and cardiovascular diseases represent a looming health-care crisis of the 21st century [WHO Global Infobase: data on overweight and obesity mean body mass index (BMI), healthy diets and physical inactivity; www.who.int/mediacenter/]. Traditionally, obesity, T2DM and their co-morbidities have been treated with anti-diabetic drugs combined with behavioral modification therapies (*e.g.*, better nutrition and regular exercise). However, in recent years, a number of surgical interventions, that include Roux-en Y gastric bypass, vertical sleeve gastrectomy (VSG), laparoscopic adjustable gastric banding and bilio-pancreatic diversion, have emerged as highly effective treatments for obesity-associated diabetes[2].

There is a growing body of evidence to indicate that patients undergoing bariatric surgery, achieve desirable clinical endpoints more rapidly and for a longer duration compared with therapeutic benefits obtained with anti-diabetic drug therapy alone[2]. A recently completed, randomized clinical trial revealed that the superior post-surgical therapeutic benefits (*e.g.*, improved glucose tolerance and lower BMI) of bariatric surgery over intensive drug treatment persisted for at least three years, when the study ended. Additionally, patients receiving bariatric surgery not only achieved their main therapeutic goal of weight loss and alleviation of diabetes but also enjoyed a better quality of life, with fewer obesity-associated complications[3]. Similar beneficial effects of bariatric surgery have also been observed in rodent models of obesity[4,5]. The strikingly more effective therapeutic outcomes of surgical procedures over pharmacological and behavioral interventions in the treatment of obesity-associated diabetes represent an unsolved medical puzzle[6,7].

The hormonal and metabolic underpinnings of surgical interventions and how they differ from conventional drug therapy in shaping the anabolic and catabolic pathways are being actively pursued[6-8]. Obviously, much of this research is prompted by a desire to define the basic mechanisms involved in the clinical outcome of bariatric surgery. An additional motivation for such studies is the fact that bariatric surgery poses definite risks, and thus there is an urgent need for safer, less invasive therapies to assuage obesity associated diabetes and its complications. Investigations into the putative mechanisms that differentially regulate the therapeutic outcomes of bariatric surgery *vs* conventional drug therapies have led to somewhat conflicting findings[6,9,10]. According to the prevailing view, a reduced intake and absorption of macronutrients by surgically downsized stomach is responsible for the post-surgical insulin sensitivity and weight loss after bariatric surgery[2]. Although this scenario is generally supported by the data gathered from rodent models of obesity and in humans, this mechanism fails to explain the paradoxical finding that a substantial fraction of patients experienced remission of their diabetes long before they exhibited a significant weight loss[6,7]. This has led some investigators to posit that in addition to causing weight loss bariatric surgery also leads to other physiological changes in the gastrointestinal (GI) tract. One of the key pieces of evidence in support of this view includes post-surgical changes in circulating bile acids seen in both rodents and humans after bariatric surgery[11,12]. It has been suggested that simultaneous changes in the composition of bile acids and gut microbiota may be causally related to obesity and a loss of BMI[13,14]. A highly revealing study, carried out with human twins discordant for obesity, showed that obese and lean individuals had unique gut microbial ecology; transplantation of the fecal microbiota from the obese or lean patients conferred analogous BMI and adiposity to the germ-free mice[15]. Differences in body composition were correlated with differences in the metabolism of short chain fatty acids, branched chain amino acids, and altered bile acids and FXR signaling[15]. These tantalizing correlations notwithstanding, the underlying mechanism by which gut microbiota regulates total body weight and glucose tolerance remain to be fully elucidated.

The experiments of Ryan *et al*[1], reported in a recent issue of *Nature*, bring us a step closer to defining the molecular interactions that mediate the metabolic effects of VSG surgery in mice. Since bariatric surgery is known

to enhance enterohepatic circulation of bile acids[16] that signal *via* nuclear FXR, Ryan *et al*[1] hypothesized that altered bile acid homeostasis and FXR signaling were mechanistically involved in the weight loss and glucose tolerance. To test this hypothesis, the authors compared the gene expression profiles in the distal small intestines of wild type (WT) and FXR knockout mice after VSG surgery. These analyses led to the discovery of "glutathione-mediated detoxification", "nuclear receptors in lipid metabolism and toxicity", "meta-pathway biotransformation" and "type Ⅱ interferon signaling" pathways that were highly suggestive of a role of the gut microbiome in the metabolic changes elicited by VSG surgery.

The authors undertook an empirical investigation of this hypothesis. The WT and $FXR^{-/-}$ mice, kept on high fat diet to induce obesity, showed similar rates of body weight loss in the first week after surgery. However, the $FXR^{-/-}$ mice were compromised with respect to sustained (at 5 wk and after) losses of BMI and body fat. Interestingly, while the WT and $FXR^{-/-}$ mice consumed lower calories in the first week after surgery only the former continued to maintain their hypophagic behavior. The cumulative caloric intake by sham-operated and VSG $FXR^{-/-}$ mice were similar; both cohorts of animals consumed 15% higher than VSG WT mice. Thus, the authors concluded that the inability of $FXR^{-/-}$ animals for sustained loss of body weight and total body fat were a result of their feeding behavior. Since $FXR^{-/-}$ mice were also refractory to the metabolic benefits of VSG surgery, it became apparent that the metabolic outcomes of surgery were also influenced by the genotype of the mice. Nevertheless, VSG surgery had a more pronounced effect on the bacterial ecology of the gut than the absence of a functional *FXR* gene. Un-weighted UniFrac-based comparison of bacterial 16S rRNA data in sham-operated and VSG mice revealed that the population of *Bacterioides* was significantly reduced after VSG surgery in WT mice whose guts also showed greater abundance of *Porphyromonadaceae* and *Roseburia*. Genotype independent post-surgical changes in the populations of *Lactobacilli* and *Lactococci* in the guts were also observed. The abundance of *Roseburia* in the WT VSG correlated negatively with glucose intolerance. The abundance of *Roseburia* in the guts of sham operated and VSG $FXR^{-/-}$ was similar and was significantly lower than in WT VSG guts. Thus, the authors posited that a functional FXR signaling was involved in the mechanisms of VSG-induced weight loss, feeding behavior and insulin sensitivity.

The current study did not directly address the molecular basis of how FXR contributes to the metabolic consequences of VSG surgery. The authors acknowledged however[1], that in light of the inherent signaling complexity of bile acids that activate FXR as well as a G-protein coupled receptor, takeda G-protein-coupled receptor-5[16], the explanation of these data is unlikely to be straightforward. This sentiment is supported by the contradictory phenotype of $FXR^{-/-}$ mice elicited in this study; thus, FXR knockout mice were resistant to some of the deleterious effects of high fat diet while remaining less responsive to the therapeutic benefits of VSG surgery. The apparently paradoxical phenotype of $FXR^{-/-}$ mice is likely to be caused by (1) unique tissue-specific mechanisms involved in the activation of FXR; and (2) a possible induction of compensatory mechanisms that result from a global knockout of FXR. The data contained in this paper also did not directly address the key question of how post-surgical changes in bile acids modulate the gut microbial ecology, and vice versa. Finally, a role of the gut microbiota in differentially regulating the metabolism and energetics of WT and $FXR^{-/-}$ mice could only be speculated upon in light of the limited information contained in this paper. It worth remembering however, that a number of earlier studies were driven by the hypothesis that obesity-associated microbiome was more efficient at extracting energy from lipids and carbohydrates[13,14]. The observed differences in the abundance of common fatty acids and related metabolites among the WT and $FXR^{-/-}$ mice following VSG surgery were not sufficiently clear to warrant an unequivocal explanation. Nevertheless, the mechanism involving more efficient extraction of energy from macronutrients by the microbiota appears to be too simplistic in light of some recent data showing that changes in gut microbial ecology impinged on the signaling mechanisms underlying satiety and motility of the GI tract[17,18]. Despite these caveats, the experiments of Ryan *et al*[1], have broken a new ground in elucidating a functional connection of FXR signaling and microbial ecology with the metabolic consequences of bariatric surgery. These exciting findings deserve to be systematically validated and extended in humans with an aim to discover less invasive therapies to treat obesity and its complications.

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