Published in final edited form as:

Nat Rev Endocrinol. 2013 October ; 9(10): 572–574. doi:10.1038/nrendo.2013.159.

The search for the mechanisms underlying bariatric surgery

Rohit Kohli and

Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA

Randy J. Seeley

Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati, 2170 East Galbraith Road, Cincinnati, OH 45237, USA

Abstract

Bariatric surgery is an effective weight-loss strategy and often results in remission of type 2 diabetes mellitus (T2DM); however, it is not known how this surgery affects T2DM. A new study suggests that fibroblast growth factor 19 and bile acids are involved in remission of T2DM after bariatric surgery.

Bariatric surgery procedures, such as sleeve gastrectomy or Roux-en-Y gastric bypass (RYGB), have a high success rate in terms of both weight loss and metabolic improvements.¹ Although these procedures have a mechanical effect on the gastrointestinal tract, it has become clear that a small gastric pouch and/or reduced calorie absorption from the intestine cannot fully explain either weight loss or remission of type 2 diabetes mellitus (T2DM) following bariatric surgery. This finding has led to a growing research effort to identify the underlying physiological mechanisms that account for the metabolic improvement in patients who undergo bariatric surgery. Gerhard *et al.*² provide insights into one potential mechanism behind the metabolic benefits following RYGB that are unrelated to weight loss. This study shows that among patients who underwent RYGB, those with sustained remission of T2DM had the greatest increase in serum levels of bile acids and an ileal derived hormone, fibroblast growth factor 19 (FGF-19).

Increased serum levels of bile acids after RYGB have been reported by multiple research groups over the past 5 years.^{3–4} In 2009, one research group found that the levels of specific types of bile acids were increased after RYGB (such as cholic acid, deoxycholic acid and chenodeoxycholic acid).⁵ Other studies also showed that serum levels of cholic acid are raised in individuals who have undergone RYGB surgery but not with via other means such as the adjustable gastric band.⁶ Gerhard *et al.* found that the same types of bile acids show the greatest increase in patients with sustained remission of T2DM after RYGB surgery.

An important aspect of bile acid physiology is that endocrine fibroblast growth factors (FGFs) act as hormones rather than growth factors; FGF-19 is produced in the ileum and

Correspondence to: R. J. Seeley, randy.seeley@uc.edu.

Competing interests (print version)

R. Kohli declares an association with the following company: Ethicon Endo-Surgery. R. J. Seeley declares associations with the following companies: Angiochem, Boehringer-Ingelheim, Eli Lilly, Ethicon Endo-Surgery, Merck, Novartis, Novo Nordisk, Takeda, Zafgen. See the article online for full details of the relationships.

Competing interests (online version)

R. Kohli receives a research grant from Ethicon Endo-Surgery. R. J. Seeley has shares and stock options with Zafgen, and consults for and/or receives grant support from Angiochem, Boehringer-Ingelheim, Eli Lilly, Ethicon Endo-Surgery, Merck, Novartis, Novo Nordisk, Takeda, Zafgen.

acts on both the liver and the gallbladder to regulate production and secretion of bile acids show that patients with the most successful results in terms of sustained remission of T2DM, were also the ones with the greatest increase in serum levels of FGF-19 and bile acids. Although RYGB results in raised levels of FGF-19 and bile acids, these increases are not seen in BMI-matched control individuals not having had bariatric surgery⁵ or after every type of bariatric surgery. For example, adjustable gastric banding does not lead to altered levels of gut hormones or increased serum levels of bile acids even though patients generally lose weight.^{7,6} Gerhard *et al.* provide important evidence in humans for a link between alterations in the bile acid–FGF19 axis after bariatric surgery and improvement of T2DM.

The study by Gerhard *et al.* provides a framework for further experiments that can directly test the mechanisms behind these observations. A large body of literature has described the endocrine changes that occur in humans as a result of RYGB; however, this surgery is difficult to replicate in animal models. The lack of experimental systems to test molecular targets has greatly slowed the pace of our understanding of the metabolic changes that occur following bariatric surgery. However, data from rats published in 2013 support the contention that direct manipulation of the flow of bile acids can produce considerable metabolic improvements.^{8,9} Diverting the flow of bile acids to the mid-jejunum in rats leads to increased plasma levels of bile acids, improved glucose tolerance and increased secretion of glucagon-like peptide 1.^{8,9}

However, important questions remain, such as how RYGB results in changes in plasma levels of bile acids. Increased levels of FGF-19 results in a negative feedback loop, which leads to suppression of hepatic synthesis of bile acids¹⁰. To explain how individuals can have raised serum levels of both bile acids and FGF-19, we hypothesize that patients with T2DM, who have increased hepatic insulin resistance, have decreased uptake of bile acids by the liver cells. If true, this discrepancy could also explain why Gerhard *et al.* did not see a change in the levels of the enzymes involved in synthesizing bile acids in patients without T2DM undergoing RYGB.

Another key issue is the association between the bile acid–FGF-19 axis and fatty liver disease. In the study by Gerhard and co-workers, experienced pathologists used biopsy samples taken during the surgery to determine whether each patient had fatty liver disease and the disease stage where relevant. Unfortunately without postoperative liver biopsy samples, one cannot contrast changes in liver histology with the observed changes in body weight or correlate them with the changes identified in bile acid-FGF19 physiology in this report. Therefore, this approach is inherently limited and makes the results difficult to interpret. Further studies are needed to relate the changes in the levels of bile acids and FGF-19 to direct measurements of liver histology and function. Gerhard and colleagues have identified an important association between bile acids and the metabolic improvements that occur after RYGB surgery. This work will pave the way to the identification of the specific molecular targets that mediate the effects of RYGB and other effective bariatric procedures. A detailed understanding of the molecular mechanisms that are affected by bariatric surgery is key to improving the use of these procedures. Patients who are most likely to respond to a particular therapy could then be identified and less invasive therapies than RYGB could be designed on the basis of these mechanisms to treat patients with T2DM.

Biographies

Kohli Biography:

Dr. Rohit Kohli, MBBS, MS, is Associate Professor of Pediatrics at the University of Cincinnati, College of Medicine and the Co-Director of the Cincinnati Children's

Steatohepatitis Center. His research work has focused on the pathogenesis of obesity related fatty liver disease and impact of bariatric surgical procedures on co-morbidities of obesity.

Seeley Biography:

Dr. Randy Seeley Ph.D. is Professor of Medicine and holds the Donald C. Harrison Endowed Chair at the University of Cincinnati College of Medicine. Dr. Seeley is the Director of the Cincinnati Diabetes and Obesity Center (CDOC) and winner of the 2009 Outstanding Scientific Achievement Award winner from the ADA.

References

1. Schauer PR, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med*. 2012; 366:1567–76. [PubMed: 22449319]
2. Gerhard GS, et al. A Role for Fibroblast Growth Factor 19 and Bile Acids in Diabetes Remission After Roux-en-Y Gastric Bypass. *Diabetes Care*. 2013; 36:1859–64. [PubMed: 23801799]
3. Nakatani H, et al. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. *Metabolism*. 2009; 58:1400–7. [PubMed: 19570554]
4. Ahmad NN, Pfalzer A, Kaplan LM. Roux-en-Y gastric bypass normalizes the blunted postprandial bile acid excursion associated with obesity. *Int J Obes (Lond)*. 2013
5. Patti ME, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity (Silver Spring)*. 2009; 17:1671–7. [PubMed: 19360006]
6. Pournaras DJ, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. *Endocrinology*. 2012; 153:3613–9. [PubMed: 22673227]
7. Kohli R, et al. Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. *J Clin Endocrinol Metab*. 2013; 98:E708–12. [PubMed: 23457410]
8. Kohli R, et al. A surgical model in male obese rats uncovers protective effects of bile acids post-bariatric surgery. *Endocrinology*. 2013; 154:2341–51. [PubMed: 23592746]
9. Mencarelli A, et al. Dissociation of intestinal and hepatic activities of FXR and LXRalpha supports metabolic effects of terminal ileum interposition in rodents. *Diabetes*. 2013
10. Shin DJ, Osborne TF. FGF15/FGFR4 integrates growth factor signaling with hepatic bile acid metabolism and insulin action. *J Biol Chem*. 2009; 284:11110–20. [PubMed: 19237543]

Key points

Roux-en-Y gastric bypass (RYGB) leads to weight loss and remission of type 2 diabetes mellitus (T2DM)

Levels of bile acids and their intestinal signal fibroblast growth factor 19 (FGF-19) are increased after RYGB

Patients with sustained remission of T2DM after RYGB surgery have the highest increase in serum levels of both FGF-19 and bile acids

The bile acid–FGF-19 axis might be an important mechanism by which RYGB improves T2DM