OVERVIEW

Targeting the gut to treat obesity and its metabolic comorbidities: focus on bariatric surgery - view from the chair

AC Carpentier

Over the past decade, bariatric surgery emerged as the most effective treatment modality for obesity and its complications, especially type 2 diabetes. Initially introduced on the basis of their capacity to restrict food intake and/or induce dietary fat malabsorption, the current bariatric surgery procedures result in many more physiological changes that may also partly explain their potent and sustained anti-obesity and anti-diabetic effects. In the session 2 of the 17th International Symposium of the Université Laval Research Chair in Obesity, outstanding speakers have provided insight into novel clinical and pathophysiological aspects in bariatric surgery. Dr Blandine Laferrère discussed the growing body of evidence implicating incretin hormones in the anti-diabetic effects of bariatric surgery and Dr Hans-Rudolf Berthoud explored emerging evidence suggesting that bariatric surgery may reset the defended body mass set point. As data are rapidly accruing about the beneficial effects of bariatric surgery, these procedures not only take a greater place in clinical practice, but they also offer outstanding occasions to peek into the intricate and complex links between diet and gastrointestinal track, and obesity and its complications.

International Journal of Obesity Supplements (2016) 6, S6–S7; doi:10.1038/ijosup.2016.7

According to the World Health Organisation, 39 and 13% of the world's adult population were overweight and obese, respectively, in 2014, worldwide prevalence that more than doubled since 1980 (<http://www.who.int/mediacentre/factsheets/fs311/en/>). In turn, this worldwide epidemic of obesity has driven a massive increase in the incidence of type 2 diabetes and mitigated the gains made over the past half-century against cardiovascular diseases. In Canada, half of the diabetic population is between 25 and 64 years old with the highest incidence occurring between 35 and 45 years old (<http://www.phac-aspc.gc.ca/cd-mc/diabetes-diabete>). The incidence of comorbidities of obesity is likely to increase further in the young adult population in the near future with the recent rapid increase of obesity in children and adolescents.

As medical therapy of obesity faced repeated drawbacks including unexpected side effects and relative inefficiency over the long term,¹ bariatric surgery emerged as the most effective and relatively safe therapy to meet the challenge posed by obesity and its complications. In Canada and most developed countries, bariatric surgery is indicated in people with a body mass index (BMI) $\geq 40 \text{ kg m}^{-2}$ without an excessive surgical risk or in people with a BMI $\geq 35 \text{ kg m}^{-2}$ with significant comorbidity.² Although 30-day morbidity and mortality is increased in patients with poor functional status, history of deep vein thrombosis or sleep apnea, the overall complication and mortality rates remain very low with the current selection criteria.³ One of four surgical procedures have been widely used:

1. Gastric banding;
2. Vertical sleeve gastrectomy (VSG);
3. Roux-in-Y gastric bypass (RYGB); and
4. Biliopancreatic diversion with duodenal switch (BPD-DS).

The first two procedures have been introduced on the basis of restriction of food intake, whereas the other two procedures reduce dietary fat absorption together with food restriction. In most centers, vertical sleeve gastrectomy has now replaced gastric banding as the most frequently performed procedure.

The body resists weight loss by reducing energy expenditure (adaptive thermogenesis) and increasing appetite, as if body mass is set. This adaptive thermogenesis intensifies and is sustained over time as weight loss occurs.^{4,5} During the Symposium, Dr Hans-Rudolf Berthoud reviewed the intriguing possibility that bariatric surgery may reprogram the body mass set point through modification of the brain's response to peripheral signals and/or modification of gastrointestinal hormones-mediated satiety signals (Hao *et al.*, this issue).

Many studies have established the efficacy of bariatric surgery for the treatment of obesity and its major complications, especially type 2 diabetes. The Swedish Obesity Study (SOS), a prospective, non-randomized controlled study including 2010 obese patients who underwent RYGB, VSG or gastric banding, and 2037 obese patients who underwent conventional medical care showed a significant reduction in mortality, including a reduction of close to 90% of clinical events linked to diabetes.⁶ Remission of diabetes, defined as fasting blood glucose of $< 6.1 \text{ mmol l}^{-1}$ without anti-diabetic medication, was 13 and 6 times that of the medically managed patients after 2 and 15 years of follow-up, respectively, in the surgical groups.⁷ Micro- and macrovascular complications of diabetes were reduced by 56 and 32%, respectively, with better outcome when bariatric surgery was performed shortly after diagnosis of type 2 diabetes.⁷ Several controlled, randomized trial have now confirmed the marked superiority of RYGB, VSG and BPD-DS compared with the medical treatment for obese patients with type 2 diabetes at least over the first years after these procedures.^{8,9}

The beneficial metabolic effects of bariatric surgery start to appear as early as a few days after the procedures, before significant weight loss has occurred.¹⁰ For example, improvement of hepatic insulin sensitivity with normalization of *in vivo* postprandial beta cell function occurs as soon as 5 days after BPD-DS.¹¹ This normalization of postprandial beta cell function is also observed after RYGB and is maintained up to 3 years after surgery.¹² RYGB, BPD-DS and VSG all rapidly increase circulatory levels of glucagon-like peptide-1 (GLP-1), a gastrointestinal hormone that stimulates beta cell function and markedly improves glucose homeostasis in patients with type 2 diabetes. During the Symposium, Dr Blandine Laferrère made an exhaustive review of the evidence for and against the role of GLP-1 and other incretin hormones in the anti-diabetic effects of bariatric surgery (Laferrère, this issue).

Many groups have investigated other potential mechanisms of the rapid and profound anti-diabetic effects of bariatric surgery procedures. One hypothesis is that early and profound restriction of food intake may be important in the very early improvement in glucose homeostasis. This has recently been supported by experimental evidence.^{11,13} Restriction of food intake by itself is, however, unlikely to explain the long-term efficacy of bariatric surgery for the treatment of type 2 diabetes. As the long-term anti-diabetic effects appear more important in procedures associated with dietary fat malabsorption,⁹ and because dietary fat may have a role in the development of type 2 diabetes and its end-organ complications,^{14,15} it is tempting to speculate that the anti-diabetic effects of bariatric surgery may be related to its capacity to reduce access of dietary fat to several organs susceptible to lipotoxicity. Recent data also emerge to suggest some role for changes in the gut microbiota¹⁶ and bile acid metabolism¹⁷ for bariatric surgery-induced anti-obesity and anti-diabetic effects.

CONFLICT OF INTEREST

ACC is the recipient of the CIHR-GSK Chair in Diabetes, and owns equity in Bibraine GGCACC has received grant support from Caprion, UniQure, GlaxoSmithKline, Canadian Institutes of Health Research, Canadian Diabetes Association, Heart and Stroke Foundation of Canada Faculty of Medicine and Health Sciences (funded by Merck Canada grant) and Fonds de recherche du Québec—Santé. The author declared no competing interest.

ACKNOWLEDGEMENTS

Publication of this article was sponsored by the Université Laval's Research Chair in Obesity in an effort to inform the public on the causes, consequences, treatments and prevention of obesity.

REFERENCES

- 1 Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U *et al.* Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015; **100**: 342–362.
- 2 Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M *et al.* Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update. *Surg Obes Relat Dis* 2013; **9**: 159–191.
- 3 Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, King WC, Wahed AS, Berk P *et al.* Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009; **361**: 445–454.
- 4 Camps SG, Verhoef SP, Westerterp KR. Weight loss, weight maintenance, and adaptive thermogenesis. *Am J Clin Nutr* 2013; **97**: 990–994.
- 5 van Gemert WG, Westerterp KR, Greve JW, Soeters PB. Reduction of sleeping metabolic rate after vertical banded gastroplasty. *Int J Obes Relat Metab Disord* 1998; **22**: 343–348.
- 6 Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H *et al.* Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 2007; **357**: 741–752.
- 7 Sjostrom L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden A *et al.* Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014; **311**: 2297–2304.
- 8 Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE *et al.* Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012; **366**: 1567–1576.
- 9 Mingrone G, Panunzi S, De GA, Guidone C, Iaconelli A, Leccesi L *et al.* Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012; **366**: 1577–1585.
- 10 Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes. *Gastroenterology* 2012; **143**: 897–912.
- 11 Plourde CE, Grenier-Larouche T, Caron-Dorval D, Biron S, Marceau S, Lebel S *et al.* Biliopancreatic diversion with duodenal switch improves insulin sensitivity and secretion through caloric restriction. *Obesity* 2014; **22**: 1838–1846.
- 12 Dutia R, Brakoniecki K, Bunker P, Paultre F, Homel P, Carpentier AC *et al.* Limited recovery of beta-cell function after gastric bypass despite clinical diabetes remission. *Diabetes* 2014; **63**: 1214–1223.
- 13 Isbell JM, Tamboli RA, Hansen EN, Saliba J, Dunn JP, Phillips SE *et al.* The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. *Diabetes care* 2010; **33**: 1438–1442.
- 14 Kunach M, Noll C, Phoenix S, Guerin B, Baillargeon JP, Turcotte EE *et al.* Effect of sex and impaired glucose tolerance on organ-specific dietary fatty acid metabolism in humans. *Diabetes* 2015; **64**: 2432–2441.
- 15 Carpentier AC. The 2012 CDA-CIHR INMD Young Investigator Award Lecture: dysfunction of adipose tissues and the mechanisms of ectopic fat deposition in type 2 diabetes. *Can J Diabetes* 2013; **37**: 109–114.
- 16 Tremaroli V, Karlsson F, Werling M, Stahlman M, Kovatcheva-Datchary P, Olbers T *et al.* Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab* 2015; **22**: 228–238.
- 17 Penney NC, Kinross J, Newton RC, Purkayastha S. The role of bile acids in reducing the metabolic complications of obesity after bariatric surgery: a systematic review. *Int J Obes* 2015; **39**: 1565–1574.