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Bariatric surgery-mediated weight loss and its metabolic consequences for type-2 diabetes

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Abstract

The worldwide epidemic of obesity and its medical complications are being dealt with a combination of life style changes (*e.g.*, healthier diet and exercise), medications and a variety of surgical interventions. The Roux-en Y gastric bypass (RYGB) and laparoscopic adjustable gastric banding (LAGB) are two of the most common weight loss surgeries for morbid obesity-associated metabolic syndrome and insulin resistance. A vast majority of patients that undergo RYGB and LAGB are known to experience marked weight loss and attenuation of diabetes. A number of recent studies have indicated that the rates of remission in glycemic control and insulin sensitivity are significantly greater in patients that have undergone RYGB. A plausible hypothesis to explain this observation is that the gastric bypass surgery as opposed to the gastric banding procedure impinges on glucose homeostasis by a weight loss-independent mechanism. In a recent paper, Bradley *et al* have experimentally explored this hypothesis. The authors compared several clinical and laboratory parameters of insulin sensitivity and β-cell function in cohorts of RYGB and LAGB patients before and after they lost approximately 20% of their body mass. After weight loss, both groups of patients underwent similar changes in their intra-abdominal and total adipose tissue volume, hepatic triglyceride and circulating leptin levels. The RYGB patients who lost 20% body mass, manifested higher postprandial output of glucose, insulin and glucagon-like peptide-1; these laboratory parameters remained unchanged in LABG patients. Irrespective of the observed differences in transient responses of RYGB and LAGB patients to mixed meal, the overall glycemic control as judged by glucose tolerance, multi-organ insulin sensitivity and β-cell function were nearly identical in the two groups. Both RYGB and LAGB patient cohorts also experienced similar changes in the expression of a number of pro- and anti-inflammatory markers. Based on these analyses, Bradley *et al* concluded that similar restoration of insulin sensitivity and b-cell function in non-diabetic obese patients that have undergone RYGB and LAGB were directly due to marked weight loss. These data have important implications for the risk/benefit analysis of weight loss therapy by bariatric procedures.

Key words: Bariatric surgery; Roux-en Y gastric bypass; Laparoscopic adjustable gastric banding; Weight loss; Type-2 diabetes

Core tip: This report demonstrates that the positive effects of Roux-en Y gastric bypass and laparoscopic adjustable gastric banding are mainly caused by weight loss. Quantitatively similar losses of intra-abdominal and total adipose were seen in both groups of patients who also experienced improved glucose tolerance, multi-organ insulin sensitivity and cell function. Weight loss was associated with positive changes in a number of pro- and anti-inflammatory markers, regardless of the type of gastric surgery. In light of these findings the risk/benefit ratio of weight loss therapy by bariatric procedures with varying degrees of invasiveness, post-surgical complications and cost need to be re-evaluated.

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COMMENTARY ON HOT TOPICS

Obesity-associated type-2 diabetes mellitus (T2DM) and metabolic syndrome, and the cardiovascular consequences of chronic obesity are steadily emerging as key global healthcare challenges of the 21st century (World Health Organization Global Infobase: data on overweight and obesity mean body mass index, healthy diets and physical inactivity; www.who.int/mediacenter/). Surgical procedures such as gastric banding, gastric bypass and biliopancreatic diversion/duodenal switch have proven to be highly effective therapies for weight loss in morbidly obese individuals[1-4]. Regardless of whether weight loss is achieved by a combination of diet and/or exercise, or by surgery, such interventions, invariably, lead to improved metabolic profiles and amelioration of diabetes.

A comprehensive review and meta-analysis of 621 studies involving different types of bariatric surgeries revealed that a vast majority of patients that underwent weight loss following these procedures also experienced improvement in the clinical and laboratory manifestations of their diabetes[5]. Furthermore, it was noted that the improved glucose homeostasis and weight loss were progressively more significant with laparoscopic adjustable gastric banding (LAGB), gastroplasty, Roux-en-Y gastric bypass (RYGB) and bilio-pancreatic diversion/duodenal switch procedures[5]. Whether variable metabolic outcome of different types of bariatric procedures is caused by weight loss alone or involves other factors remains controversial. Two common bariatric surgeries used for weight loss therapy are RYGB that diverts the ingested food from passage through the upper gastrointestinal (GI) tract[6] and the laparoscopic adjustable gastric banding (LAPG) technique that reduces the size of the stomach[7]. The meta-analytical observations of Buchwald *et al*[5] and a number of other experimental findings have led some investigators to question the exclusive cause and effect relationship between weight loss and diabetes in patients undergoing bariatric surgeries[8,9]. In light of these data, it has been posited that bariatric interventions impinge on the mechanisms of glucose homeostasis that may be independent of weight loss[8,10]. However, unequivocal experimental data that support this tantalizing hypothesis are currently missing. In the December 2012 issue of the *Journal of Clinical Investigation*, Bradley *et al*[11] have described a set of experiments that were specifically aimed at testing this hypothesis. Based on these data authors concluded that upper GI tract diversion by RYGB improved insulin sensitivity and β-cell function by a weight loss-dependent mechanism.

Bradley *et al*[11] recruited two groups of obese subjects, ten in each cohort, that were insulin-resistant, as judged by homeostasis model assessment of insulin resistance (HOMA-IR) values of > 2.5. The choice of insulin-resistant obese patients that were not diabetic was made specifically with a goal to minimize the confounding variables of baseline glycemic control, glucose toxicity and interference with medications used to treat diabetes. The patient cohorts underwent RYGB or LAGB surgeries and were allowed to reach the target weight loss of 20% at 22 ± 7 and 16 ± 2 wk, respectively. The clinical and laboratory measurements that included body composition, insulin sensitivity and metabolic response to mixed meal were carried out in both groups of patients, before and after weight loss. These analyses revealed that total fat mass, intra-abdominal adipose tissue volume, intrahepatic triglyceride content and plasma leptin concentration were altered similarly in RYGB and LAGB subjects after weigh loss. Both cohorts of patients also elicited similar beneficial changes in the steady state levels of their plasma glucose, C-peptide, adiponectin and C-reactive protein.

Bradley *et al*[11] noted that following approximately 20% weight loss, the HOMA-IR scores decreased by more than 2-fold in both LAGB and RYGB patients who also displayed similar reductions in total insulin secretion rates (ISR) and total β-cell sensitivity. However, the kinetics of plasma glucose concentration after a mixed-meal was significantly different in RYGB and LAGB cohorts after target weight loss. Thus, postprandial rate of appearance (Ra) of glucose in RYGB patients increased from 70% ± 19% to 92% ± 2%, before and after weight loss, respectively; the RYGB patients also showed a higher peak in the rise of plasma insulin, C-peptide, and a marked increase in glucagon-like peptide-1 (GLP-1) after a mixed meal. The higher values of glucose in RYGB patients after weight loss likely reflected a more rapid emptying of their meal into small intestine; a higher dynamic ISR in these patients reflected a rapid rise in circulating glucose combined with increased plasma GLP-1. This explanation of greater dynamic ISR in RYGB patients is reasonable since postprandial rates of endogenous glucose production (EGP) were similar before and after weight loss in LAGB patients. In contrast, following a mixed meal, RYGB subjects elicited a faster and almost complete suppression of EGP that also rapidly returned to baseline. These differences in kinetics of EGP underscore a critical role of hepatic gluconeogenesis in preventing postprandial hypoglycemia in RYGB patients. The observed differences Ra to mixed meal notwithstanding, the area under the curve measurements of plasma insulin and C-peptide values, decreased to a similar extent in LAGB and RYGB patients after undergoing weight loss; both groups of patients also exhibited a near doubling of their disposition index (DI). It should be noted that the plasma concentration of glucagon did not change in either group of patients.

The authors observed that the whole body rise in insulin sensitivity, as judged by a 25% decline in insulin secretion in response to oral glucose challenge, occurred in

both LAGB and RYGB patients. However, as assessed by DI, there was a 2-fold enhancement of insulin sensitivity. Thus, β-cell function, assessed as total meal-induced insulin secretion in relationship to DI increased by about 75% in both LAGB and RYGB patients. Based on these data strongly suggested that weight loss, regardless of whether it occurred as a result of upper GI tract diversion or gastric banding could restore β-cell function, insulin sensitivity and oral glucose tolerance in non-diabetic patients.

Since a 5%-10% weight loss was shown to be insufficient to alter insulin sensitivity of skeletal muscle in previous studies[8,12-14], Bradley *et al*[11] speculated that for skeletal muscle to become more insulin sensitive a more marked weight loss is needed. The data in the current study support this notion as judged by nearly 2-fold improvement in skeletal muscle insulin sensitivity after 20% weight loss in both LAGB and RYGB patients. It should be pointed out however, that weight loss in either group of patients did not change the intramyocellular content of diacylglycerol or ceramide; these two lipids have been associated with skeletal muscle insulin resistance in rodents[15,16].

Finally, Bradley *et al*[11] reported that weight loss following either RYGB or LAGB led to amelioration of pro-inflammatory factors putatively involved in aberrant regulation of metabolism in morbidly obese animals and man. They measured the steady state levels of mRNA encoding EMR1 and CD11B, cell surface markers of pro-inflammatory macrophages as well as the expression of pro-inflammatory cytokines [*e.g.*, colony-stimulating factor, interleukin-6 (IL-6), tumor necrosis factor-α, and leptin]. Weight loss led to reduced expression of markers of inflammation and a concomitant enhancement of expression of IL-10, an anti-inflammatory cytokine. It is noteworthy that concomitant up-regulation of pro-inflammatory and down-regulation of anti-inflammatory signals occurred to a similar extent in both RYGB and LAGB patients. These observations demonstrate that in addition to restoring insulin sensitivity and β-cell function, weight loss impinges on the pathways of inflammation known to exacerbate insulin resistance and T2DM.

In conclusion, the data of Bradley *et al*[11] indicate that marked weight loss in obese subjects is accompanied by changes in key parameters of postprandial glucose homeostasis, multi-organ insulin sensitivity, β-cell function and adipose tissue inflammation. The authors' assertion that manifestly different response of RYGB patients to a mixed meal, as judged by increased transient levels of plasma glucose, insulin and GLP-1 are unlikely to play a therapeutic role in alleviating insulin resistance is reasonable. Based on these data authors concluded that restoration of β-cell function and insulin sensitivity occurred primarily as a result of weight loss. Although this study employed non-diabetic obese patients who underwent RYGB- or LAGB-dependent weight loss, the insights of this excellent study are highly relevant to the causes and consequences of morbid obesity-associated T2DM and its attenuation by weight loss. The data of this study also have serious implications for the choices of bariatric procedures that differ in their pre- and post-surgical preparations and complications and cost.

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