Cure of Type 2 Diabetes by Metabolic Surgery? A Critical Analysis of the Evidence in 2010

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The prevalence of type 2 diabetes has markedly increased in the last decade worldwide, but in particular in Asian countries such as China and India (1–3), in strong correlation with a comparably steep increase in the prevalence of obesity (4). The primary risk factor for type 2 diabetes is obesity, and 90% of all patients with type 2 diabetes are overweight or obese. The relative risk of diabetes increases about 42-fold in men as the BMI increases from <23 kg/m^2 to >35 kg/m^2 (5) and approximately 93-fold in women as BMI increases from <22 kg/m^2 to >35 kg/m^2 (6).

Type 2 diabetes is a complex major endocrine disorder in which insulin resistance in the muscle and liver as well as β-cell failure represent the core pathophysiological defects. In addition to the muscle, liver, and β-cell, the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance) all play important roles in the development of type 2 diabetes (7). The development of type 2 diabetes is strongly associated with obesity and the accumulation of abdominal and ectopic fat, which are linked to peripheral and hepatic insulin resistance, inflammation, and subsequent "lipotoxicity" of β-cells (8,9). The adipose tissue of obese subjects is characterized by increased production and secretion of a wide panel of inflammatory molecules (10) such as tumor necrosis factor-α, interleukin-6, transforming growth factor-β, monocyte chemotactic protein-1, and plasminogen activator inhibitor-1. Evidence is increasing that chronic subclinical inflammation seems to be involved in the development of type 2 diabetes. Several prospective studies demonstrated that subjects who developed type 2 diabetes during the follow-up period had elevated levels of markers of inflammatory molecules at baseline compared with those who did not develop the disease. In one study (11), C-reactive protein showed a considerably stronger association with risk of type 2 diabetes in women (hazard ratio [HR] 7.60) than in men (HR 1.84), which may explain why morbidly obese women are at a much higher risk for developing diabetes than are men (5,6). Weight loss improves inflammatory status in obesity and subsequent comorbidities by decreasing numbers of circulating inflammatory molecules such as C-reactive protein, interleukin-6, monocyte chemotactic protein-1, and YKL-40 (12–16). Hypocaloric diet, exercise, and weight loss improve the pathophysiology of type 2 diabetes, preserve β-cell function, and represent the first-line treatment for newly diagnosed patients. Lifestyle intervention (diet and exercise), behavioral management, and drug therapy for patients with morbid obesity deliver a degree of weight loss, but because the benefit is modest, not long lasting (6 months to 1 year at best), and carries considerable side effects, this method is unattractive to patients. An ongoing trial investigates the utility of currently practiced and available bariatric surgical procedures as compared with multidisciplinary intensive medical and weight management for the treatment of type 2 diabetes with class 1 and class 2 obesity (http://clinicaltrials.gov/ct2/show/NCT01073020?term=joslin&rank=8).

WEIGHT LOSS IS RELATED TO THE METHODS OF GASTROINTESTINAL SURGERY

—Currently, bariatric surgery is the most effective treatment for obesity and is indicated for patients with a BMI >40 kg/m^2, or for individuals with a BMI >35 kg/m^2 and significant obesity-related comorbidities. A range of different bariatric procedures are available, some of which have been shown to reduce appetite and improve glucose homeostasis independently of weight loss (17–19). In view of its favorable metabolic effects (17), bariatric surgery is also referred to as "metabolic surgery" and is advocated for the treatment of type 2 diabetes even in overweight individuals who do not meet the current BMI criteria (20). In the recent Diabetes Surgery Summit consensus conference (19), clinical trials to investigate the exact role of surgery in patients with less severe obesity and diabetes were considered a priority.

Since its inception in the 1950s, bariatric surgery has become increasingly refined. Bariatric procedures were initially classified as restrictive, malabsorptive, or combined, reflecting the purported mechanism of weight loss. Restrictive procedures, such as laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG), greatly reduce the volume of the stomach to decrease food intake and induce early satiety. Malabsorptive procedures, such as biliopancreatic diversion (BPD), shorten the small intestine to decrease nutrient absorption. Combined procedures such as the Roux-en-Y gastric bypass (RYGB) incorporate both restrictive

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and malabsorptive elements. RYGB surgery is the current gold standard treatment for severe obesity. Both BPD and RYGB alter the secretion of orexigenic and anorexigenic gut peptides, which interact with appetitive centers in the arcuate nucleus of the hypothalamus to decrease appetite (21).

In the prospective nonrandomized Swedish Obese Subjects (SOS) study, weight change was maximal after 1 year in all three surgical subgroups (RYGB 38 ± 7%; VBG 26 ± 9%; and LAGB 21 ± 10%) (22). When the data were analyzed after 10 years of follow-up, patients in all three groups had regained weight, but the best long-lasting weight lowering effect was seen for RYGB. After 10 years, the maintained weight change was 25 ± 11% for RYGB, 16.5 ± 11 for VBG, and 13.2 ± 13% for LAGB. However, only 1,703 of the 4,047 subjects were available for the analysis after 10 years. Incidence of diabetes was only 1 and 7% after 2 years and 10 years in the surgery group in contrast to 8 and 24% in the control group (22).

META-ANALYSIS: RESOLUTION OF DIABETES BY BARIATRIC SURGERY—In 2009 a systematic review and meta-analysis about weight and type 2 diabetes after bariatric surgery was published by Buchwald et al. (23) including 621 studies with 888 treatment arms and 135,246 patients. At baseline, the mean age was 40.2 years, BMI was 47.9 kg/m^2, 80% were female, and 10.5% had previous bariatric procedures. Meta-analysis of weight loss overall was 38.5 kg or 55.9% excess body weight loss. Overall, 78.1% of diabetic patients had complete resolution and diabetes was improved or resolved in 86.6% of patients. Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by RYGB, and finally LAGB (Fig. 1). Meta-regression revealed evidence of an impact of mean change in BMI on diabetes resolution ($P < 0.01$). Insulin levels declined significantly postoperatively, as did HbA_{1c} (−2.1%) and fasting glucose values. Chipkin and Goldberg (24) criticized in an accompanied editorial that the study population of the meta-analysis consisted primarily (80%) of extremely obese and relatively young women (mean age 40 years) with an average BMI of 47.9 kg/m^2. The studies were largely retrospective (58%) and single armed (73%), and only 10 studies (1.6%) qualify as providing Class I evidence. Chipkin and Goldberg (24) concluded that the applicability of the findings of this meta-analysis to broader populations with type 2 diabetes remains unknown. Previous studies have noted that older patients or those with diabetes of longer duration are less likely to improve their diabetes (17). In type 2 diabetes patients with duration of diabetes <5 years, a resolution of the disease was obtained in 95%, whereas the rate of resolution was only 75 and 54% in those who had type 2 diabetes for 6–10 or >10 years. Patients with the shortest duration of diabetes, and those whose diabetes was controlled by diet preoperatively, are the most likely to improve their glucose tolerance (18).

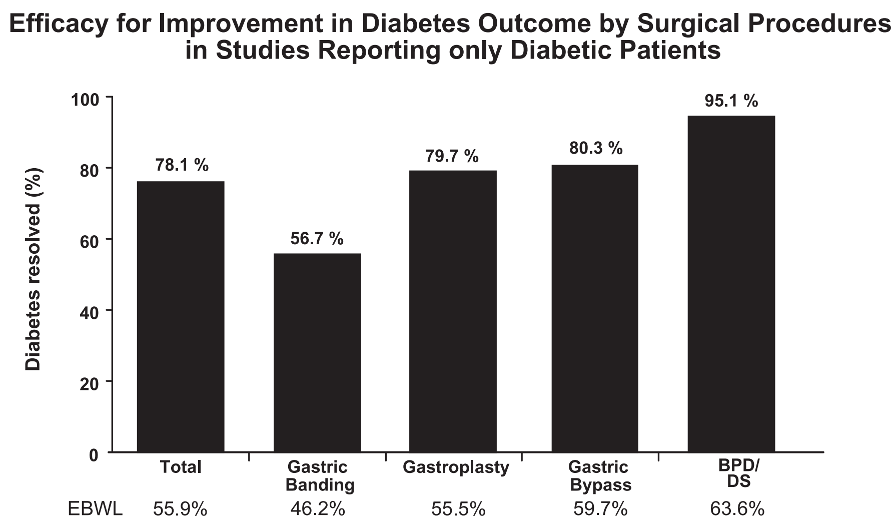


Figure 1—*Diabetes resolution according to the surgical procedures in studies reporting only diabetic patients (figure was made using the reported data by Buchwald et al. [23]).*

GASTROINTESTINAL SURGERY IN DIABETIC PATIENTS WITH A BMI OF 27–37 KG/M^2—Because most of the patients included in the meta-analysis (23) had an extremely high BMI (average ~48 kg/m^2), future studies in less extremely obese patients are needed to identify the optimal candidates for metabolic surgical interventions. Dixon et al. (25) have performed a randomized controlled trial in 60 patients with type 2 diabetes (mean age 47 years, 47% males) with a mean BMI of 37 kg/m^2 and a mean HbA_{1c} of 7.8%. Surgical and conventional therapy groups lost a mean of 20.7 and 1.7% of weight, respectively, at 2 years ($P = 0.001$). Remission of type 2 diabetes was achieved by 22 (73%) in the surgical group (gastric banding) and 4 (13%) in the conventional therapy group. Mean HbA_{1c} was 6.0% in the surgery and 7.2% in the conventional group. Remission of type 2 diabetes was related to weight lost ($P = 0.001$) and lower baseline HbA_{1c} levels ($P = 0.001$). In summary, patients randomized to surgery were more likely to achieve remission of type 2 diabetes through greater weight loss. However, in the conventional group the lifestyle program was not state of the art, and weight loss after 2 years was only 1.5 kg, whereas diabetic patients (n = 2.570) in the Look AHEAD (Action for Health in Diabetes) study (26) with a similar BMI at baseline (mean 36 kg/m^2) showed a weight loss of 8.6 kg after 1 year.

Lee et al. (27) have studied the mechanisms accounting for the beneficial effects of laparoscopic sleeve gastrectomy (LSG) on glucose homeostasis in 20 obese patients with type 2 diabetes (mean BMI 31.0 ± 2.9 kg/m^2, mean HbA_{1c} 10.1%). Resolution of type 2 diabetes was achieved in 2 (20%) patients at 4 weeks, 6 (30%) at 12 weeks, 8 (40%) at 26 weeks, and 10 (50%) at 52 weeks after LSG. The diabetes resolution rates for those with preoperative C-peptide <3, 3–6, and >6 ng/mL were 1/7 (14.3%), 7/11 (63.6%), and 2/2 (100%), respectively ($P < 0.05$). The authors reported very relevant findings: after only 1 week fasting plasma glucose (FPG) levels decreased from 240 ± 81 to 158 ± 52 mg/dL, whereas fasting and post-oral glucose tolerance test (OGTT) insulin levels did not increase but decreased significantly. Therefore, the authors concluded that LGS resulted in remission of poorly controlled nonmorbidly obese type 2 diabetic patients up to 50% at 1 year after the operation. However, the effect is related more to the decreasing of insulin resistance due to calorie restriction and weight loss rather than to the increase of insulin secretion. In addition, a C-peptide level >3 ng/mL is the most important predictor for a successful treatment. A recent 12-month prospective small study (28) that included patients with an even lower mean BMI of only 27.5 kg/m^2 (range 21.7–33.0 kg/m^2) could not demonstrate resolution of type 2 diabetes in any of the seven cases after duodenaljejunal bypass, although the patients demonstrated an overall improvement in their glycemic control with decreases of HbA_{1c} (8.5 vs. 9.4%) and FPG (154 vs. 209 mg/dL). The lack of resolution from type 2 diabetes might be explained by the long duration (10.7 years) and severity of their diabetes. The majority were on insulin and/or hypoglycemic agents, and the C-peptide values were lower than 3.0 ng/mL (0.5–2.5 ng/mL). These findings are at variance with a recent small study performed in 15 Asian Indian patients with type 2 diabetes (20) who had a similar mean BMI (28.9 kg/m^2), similar mean duration of diabetes (8.7 years), and were also—in 80%—treated with insulin. Three months after RYGB, HbA_{1c} decreased from 10.1 to 6.1%, and diabetes medications were no longer required. Because Asian patients with type 2 diabetes have more visceral fat and insulin resistance at relatively low BMI versus Caucasian patients, a direct comparison is not possible.

WHICH PREOPERATIVE FACTORS PREDICT REMISSION OF DIABETES AFTER METABOLIC SURGERY?—Evidence is increasing that the remission of type 2 diabetes after surgical intervention is related to a number of factors. Patients with a very high BMI presenting with a high insulin resistance state and high basal and postprandial insulin levels have the best prognosis for resolution of diabetes, in particular when their C-peptide levels are above 3 ng/mL and antidiabetic drugs were not needed presurgery. Table 1 shows the data for HbA_{1c}, glucose, and insulin levels after a 75-g OGTT as well as for homeostasis model assessment of insulin resistance in 1,005 Austrian patients with excessive obesity and presence of type 2 diabetes, impaired glucose tolerance, or normal glucose tolerance. Patients with type 2 diabetes were older than patients with normal or impaired glucose tolerance, but had significantly higher insulin levels in the basal state and during the OGTT and were the most insulin-resistant patients.

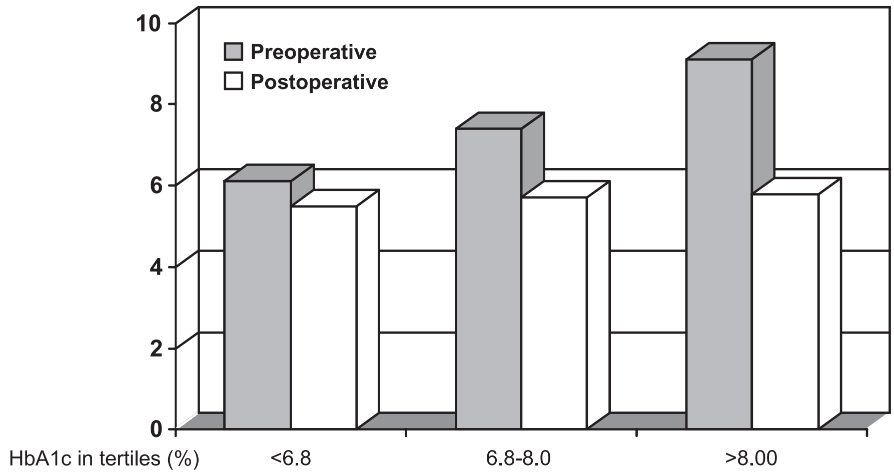
Recently, the prediction of preoperative factors for diabetes resolution was analyzed in 110 patients with type 2 diabetes undergoing RYGB (29). The patients had the classical criteria as reported in other studies: mean age was 45 years, 70% were female, and the mean BMI was 47 kg/m^2. The excess weight loss at 6, 12, and 24 months was 58, 63, and 84%. Diabetic medication was discontinued in 68% patients and reduced in a further 14%. Mean HbA_{1c} was 7.1 ± 2.0% preoperative and 5.48 ± 0.2% postoperative. Patients with a baseline HbA_{1c} >10 had a 50% rate of remission compared with 77.3% with an HbA_{1c} of 6.5–7.9. The mean duration of type 2 diabetes preoperatively was 5.5 ± 7 years. A preoperative duration of type 2 diabetes greater than 10 years was shown to significantly reduce the chances of remission (P = 0.005). The findings support the concept that a shorter duration and better control of diabetes prior to surgery corresponds to a higher rate of remission. Consequently, early surgical intervention in the morbidly obese diabetic patient should be preferred. According to our experience, a high HbA_{1c} is not a negative predicting factor for diabetes resolution, anticipated that the duration of diabetes is relatively short and severe insulin resistance, but not β-cell failure is the predominant mechanism of diabetes. Figure 2 shows the decline of HbA_{1c} values to normal in 60 patients with type 2 diabetes of the Vienna bariatric surgery center irrespective whether the preoperative HbA_{1c} levels were high, moderate, or low. Remarkably, all patients had a very high BMI and very high basal as well as poststimulation insulin levels (data not shown) presurgery, both of which declined significantly 2 years after RYGB.

Table 1—*Characteristics of three groups of patients (n = 1,005) with morbid obesity presenting with normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes*

	NGT	IGT	Type 2 diabetes
n	547	248	210
Age (years)	37 ± 11	41 ± 11	47 ± 11
BMI (kg/m^2)	44.2 ± 7.4	35.7 ± 13.0	45.8 ± 10.3
Glucose (mg/dL)			
Fasting	85 ± 8*	101 ± 12†	156 ± 55
1-h	139 ± 35*	185 ± 40†	246 ± 72
2-h	98 ± 22*	148 ± 32†	238 ± 61
Insulin (μU/mL)			
Fasting	23.1 ± 15.7*	30.5 ± 22.2	34.2 ± 27.8
1-h	141.5 ± 92.9	158.9 ± 97.2	134.7 ± 75.3
2-h	141.5 ± 92.9*	144.7 ± 126.4	161.2 ± 110.4
HOMA-IR	4.8 ± 3.5*	7.6 ± 5.5†	11.8 ± 10.9
HbA_{1c} (%)	5.5 ± 0.5*	5.8 ± 0.5†	7.8 ± 1.7

Data are means ± SD. In between group differences were analyzed by Student unpaired t test. An α-level <0.05 was considered statistically significant. HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance. *P < 0.001 normal glucose tolerance vs. type 2 diabetes. †P < 0.001 impaired glucose tolerance vs. type 2 diabetes.

OUTCOME STUDIES AFTER METABOLIC SURGERY—Coronary heart disease mortality is about threefold higher in extremely obese women (BMI >40 kg/m^2) compared with normal weight (BMI 25–29.9 kg/m^2) or overweight (BMI 30–34.9 kg/m^2) women (30). Unfortunately, very little information is available about outcome studies after bariatric surgery in general and no specific study has been performed in patients with type 2 diabetes. SOS is the only prospective but not randomized study (31) evaluating the effect of bariatric surgery on mortality, however only 10% in SOS had diabetes. After a mean follow-up of 10 years, 101 patients (5.0%) in the surgery group (n = 2,010) and 129 (6.3%) in the control group (n = 2,037) have died. Death from cardiovascular disease, myocardial infarction, and cancer was lower in the surgery versus control group, whereas sudden death and death from infection was lower in the control group. Because the annual death rates were only 0.5% and



	<6.8		6.8-8.0		>8.00	
HbA1c (%)	6.2	5.5	7.4	5.7	9.7	5.8
p-Value	0.004		<0.001		<0.001	
BMI (kg/m^2)	48.4	32.4	44.5	29.8	48.0	30.3
p-Value	<0.001		<0.001		<0.001	
Insulin fasting	33.7	11.1	37.7	8.5	29.3	7.4
p-Value	<0.001		<0.001		<0.001	

Figure 2—*Significant and similar decline of HbA_{1c}, BMI, and basal insulin levels in three groups of diabetic patients* (n = 20 *in each group) 2 years after RYGB, irrespective whether HbA_{1c} levels were relatively low, moderate, or highly elevated in the preoperative stage.*

0.6%, the statistical power did not allow determining whether the higher survival rate in the surgery group was explained only by weight loss or by other beneficial effects of the surgical procedures. Unfortunately, specific data in the diabetes subgroup were not yet published.

In a retrospective cohort study (32), the long-term mortality of 7,925 surgical patients (mean BMI 45.3 ± 7.4; mean age 39 years) was analyzed in comparison with 7,925 severely obese controls who applied for a driver's license. During a mean follow-up of 7.1 years, 213 (2.7%) patients in the surgery group and 321 (4.1%) patients in the control group died. Despite reductions in disease-related deaths after gastric bypass surgery, the risk of non–disease-related death, such as accidents and suicides, increased by a factor of 1.6, as compared with that in the control group. In addition, the survival benefit was mainly seen in patients with a mean BMI >45 kg/m^2. Because no information about the number of diabetic patients or treatment was available, validation of the findings is difficult. Surgical patients entering the medical care system could have been more aggressively treated for health issues after gastric bypass surgery, perhaps favorably influencing mortality.

DECREASE IN CANCER INCIDENCE AND MORTALITY AFTER BARIATRIC SURGERY—There is substantial evidence indicating that patients with type 2 diabetes or extreme obesity have an increased risk of cancer and cancer mortality (33,34). The relationship between type 2 diabetes and various forms of cancer is biologically plausible, with insulin resistance, hyperinsulinemia, and elevated levels of IGF-1 in patients with type 2 diabetes involved in promotion of tumor cell growth. In the SOS study (35), bariatric surgery resulted in a sustained mean weight reduction of 19.9 kg over 10 years, in contrast to a weight gain of 1.3 kg in the control group. The number of first-time cancers after inclusion was significantly lower in the surgery group (n = 117) than in the control group (n = 169; HR 0.67; P = 0.0009), but the beneficial effect was restricted to women (79 in the surgery and 30 in control group; HR 0.58; P = 0.001), whereas there was no effect of surgery in men. In the retrospective cohort study of Adams et al. (36), cancer incidence and mortality data were compared between 6,596 Utah patients who had gastric bypass and 9,442 severely obese persons who had applied for a Utah driver's license. After a mean follow-up of 12.5 years, both the total cancer incidence (HR 0.76; P = 0.0006) and the cancer mortality (HR 0.54; P = 0.001) were significantly lower in the surgery group compared with controls. Unfortunately, specific studies about a reduced risk in cancer incidence and mortality after weight loss induced by bariatric surgery are not available in morbidly obese patients with type 2 diabetes, but it seems likely that it will be similar in the diabetic patients.

CONTROVERSY ABOUT THE MECHANISM OF DIABETES RESOLUTION—Several studies including the meta-analysis (23) showed that the resolution in patients with type 2 diabetes after surgery is related to the weight loss achieved by morbidly obese diabetic patients. In addition to the weight reduction, starvation and changes in the gut hormone secretion could contribute to the high resolution of type 2 diabetes in particular after RYGB. Since type 2 diabetes can totally clear within days after RYGB—before there is any significant weight loss—it was debated that the surgical intervention per se and not the weight loss is responsible for the favorable outcome (19). However, the mechanisms for the early improvements remain uncertain. In recent years, numerous reports have evaluated the gastrointestinal endocrine changes associated with RYGB (37). The surgical bypass of the foregut and/or rapid nutrient exposure of the distal gut alters enterokine release, which has been proposed to result in improvements of glucose homeostasis. The incretins, namely glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide, are gut hormones that contribute to postprandial insulin secretion. GLP-1 shares several other glucoregulatory actions besides enhancement of glucose-dependent insulin secretion, namely suppression of inappropriately elevated postprandial glucagon secretion, reduction of food intake, and slowing of gastric emptying. In some studies, RYGB augmented GLP-1 secretion, however its impact on gastric inhibitory peptide is less consistent. By contrast, bariatric procedures that induce weight loss by caloric restriction in the absence of intestinal bypass, such as adjustable gastric banding, do not alter postprandial incretin levels. Ghrelin is another enterokine that is primarily ascribed a role in appetite stimulation, but also has glucose and insulin modulatory effects. Ghrelin levels are abnormally low in the obese and remain suppressed after RYGB (38), whereas weight loss by diet enhances ghrelin levels.

Because mixed results were recently reported for GLP-1, it remains unclear how important those changes are for the resolution of type 2 diabetes. Morinigo et al. (39) have studied the changes of active GLP-1 in response to a standard test meal in morbidly obese patients with or without diabetes. At 6 weeks after RYGB, despite the fact that subjects were still markedly obese, fasting plasma glucose and HbA_{1c} decreased and insulin sensitivity improved. Remarkably, GLP-1 increased only in nondiabetic patients but not in those with type 2 diabetes, indicating that GLP-1 is not a critical factor for the early changes in glucose tolerance. In a prospective 2-year study, Pournaras et al. (40) have evaluated satiety as well as secretion of GLP-1 and peptide YY after a mixed meal presurgery and after 6, 12, and 24 months. Satiety was significantly reduced postsurgery and peptide YY response increased, whereas no significant increase of GLP-1 was noted. Very recently, Isbell et al. (41) published elegant data suggesting that caloric restriction without substantial weight loss is of primary importance in the rapid improvement of insulin sensitivity within the first week following RYGB. The enhanced incretin response to surgery did not show any additional benefit beyond caloric restriction on glucose homeostasis and insulin sensitivity. Thus, caloric restriction and weight loss remain the dominant mechanisms of improved glucose metabolism. The former appears to account for the early postsurgical recovery of insulin sensitivity and secretory dynamics; the latter is the final determinant of the outcome once weight and caloric balance have stabilized.

CONCLUSIONS—There is no doubt that metabolic surgery is a very effective therapeutic option in patients with type 2 diabetes and excessive weight (BMI ≥45 kg/m^2), in particular when duration of diabetes is short and hyperinsulinemia and insulin are present. In most of the published studies, including the meta-analysis mentioned above, a significant decrease in insulin resistance and decreased but not increased insulin levels were observed, raising the question of whether using the term "cure" of diabetes by metabolic surgery is really appropriate. A recently published, very critical review (42) states that bariatric surgery does not "cure" diabetes. In addition, whether this acute "cure" will continue to be a long-term benefit in reducing cardiovascular disease morbidity and mortality as well as cancer mortality for patients with type 2 diabetes has to be documented in future studies. However, broadening the approach will require evaluation of well-defined cohorts of patients with type 2 diabetes with stringent follow-up for prolonged periods. Studies will need to address duration, sex, ethnicity, and severity of diabetes; they also will need to conduct comprehensive studies before and after surgery, record adverse events (immediate and long-term), and compare surgery with alternative medical and behavioral therapies.

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