Bariatric/Metabolic Surgery to Treat Type 2 Diabetes in Patients With a BMI <35 kg/m²

Diabetes Care 2016;39:924–933 | DOI: 10.2337/dc16-0350

OBJECTIVE
Global usage of bariatric surgery has been dictated for the past quarter century by National Institutes of Health recommendations restricting these operations to individuals with a BMI ≥35 kg/m². Strong evidence now demonstrates that bariatric procedures markedly improve or cause remission of type 2 diabetes mellitus (T2DM), in part through weight-independent mechanisms, and that baseline BMI does not predict surgical benefits on glycemic or cardiovascular outcomes. This impels consideration of such operations as “metabolic surgery,” which is used expressly to treat T2DM, including among patients with a BMI <35 kg/m² who constitute the majority of people with diabetes worldwide. Here, we review available evidence to inform that consideration.

RESULTS
A meta-analysis of the 11 published randomized clinical trials (RCTs) directly comparing bariatric/metabolic surgery versus a variety of medical/lifestyle interventions for T2DM provides level 1A evidence that surgery is superior for T2DM remission, glycemic control, and HbA₁c lowering. Importantly, this is equally true for patients whose baseline BMI is below or above 35 kg/m². Similar conclusions derive from meta-analyses of high-quality nonrandomized prospective comparisons. Meta-analysis of all pertinent published studies indicates that T2DM remission rates following bariatric/metabolic surgery are comparable above and below the 35 kg/m² BMI threshold. The safety, antidiabetes durability, and benefits on other cardiovascular risk factors from bariatric/metabolic surgery appear roughly comparable among patients with a BMI below or above 35 kg/m². Further studies are needed to extend long-term findings and measure “hard” macrovascular/microvascular outcomes and mortality in RCTs.

CONCLUSIONS
Extant data, including level 1A evidence from numerous RCTs, support new guidelines from the 2nd Diabetes Surgery Summit that advocate for the consideration of bariatric/metabolic surgery as one option, along with lifestyle and medical therapy, to treat T2DM among patients with a BMI <35 kg/m².

For the past quarter century, worldwide usage of bariatric surgery has largely been governed by a 1991 set of recommendations from the National Institutes of Health (NIH) that limit these operations to severely obese individuals (BMI ≥40 kg/m²) or to patients with a BMI ≥35 kg/m² and serious obesity-related comorbidities, such as type 2 diabetes mellitus (T2DM) (1).

In the time since those NIH recommendations were written, a large new evidence base has been generated demonstrating powerful effects of most bariatric
operations on T2DM (2,3). It has also become very clear within the past decade that the antidiabetes impact of some bariatric procedures results from not only secondary consequences of reduced food intake and body weight but also additional weight-independent mechanisms (4–6).

These findings have led to a paradigm shift of thought in the field, propelling an increasingly popular view that some operations should be viewed not just as “bariatric surgery” but also “metabolic surgery” (7,8). A natural consequence of this change in mind-set is to consider the use of bariatric/metabolic surgery to treat T2DM in less obese or even merely overweight patients, with BMI levels below existing NIH cutoffs.

Here, we discuss the conceptual logic for contemplating the use of bariatric/metabolic surgery to treat T2DM in patients with a BMI <35 kg/m², along with available evidence pertinent to that consideration. Elsewhere in this issue of the Diabetes Care, new guidelines from the 2nd Diabetes Surgery Summit (DSS-II) are published to inform the proper place for bariatric/metabolic surgery in the overall T2DM treatment algorithm (9). These guidelines, which are intended to replace the conspicuously outdated 1991 NIH recommendations (1), advocate for the consideration of surgery as one option, along with lifestyle and medical approaches, to treat T2DM in patients with a BMI as low as 30 kg/m², or as low as 27.5 kg/m² for Asian populations. This article evaluates the evidence supporting these new clinical practice guidelines.

RATIONAL FOR CONSIDERING METABOLIC SURGERY FOR T2DM IN LOWER-BMI PATIENTS

Several lines of evidence and logic justify contemplating the use of bariatric/metabolic operations in lower-BMI patients who have T2DM that is not adequately controlled with behavioral/pharmaceutical interventions.

First, the impact of bariatric/metabolic surgery on T2DM, especially from operations involving intestinal bypasses, is very impressive. Although diabetes is traditionally considered a progressive, relentless disease in which mitigation of end-organ complications is the primary therapeutic goal, a large majority of patients with T2DM who undergo bariatric/metabolic surgery experience remission of this disease and thereafter manifest non-diabetic glycemia off all diabetes medications (2,3,10). For example, the T2DM remission rate after Roux-en-Y gastric bypass (RYGB) is typically 70–80%, and it is even higher for biliopancreatic diversion (BPD). Such percentages vary depending on the HbA1c threshold used to define “remission,” but by any definition, these operations yield T2DM remission in most cases. Across many studies, the best preoperative predictors of failure to remit diabetes are long duration of disease, use of insulin, high glycemia, and very low C-peptide levels. As these probably all reflect advanced diabetes with irreversible β-cell destruction, the implication is that surgery should not merely be considered as a salvage option to be used after failing many years of other therapies. Although many people with T2DM who initially experience postoperative diabetes remission ultimately develop recurrence, the median disease-free period among such individuals after RYGB is 8.3 years, for example (11). Most of this evidence derives from studies of people with a BMI ≥35 kg/m², but there is no a priori reason to predict that the antidiabetes effects of surgery would disappear among patients below that BMI level, which was defined relatively arbitrarily in 1991 as a cutoff for bariatric surgery (1).

Second, although high BMI has traditionally been used as the primary criterion to select patients for bariatric surgery, no data demonstrate that baseline BMI predicts the success of such operations on metabolic, cardiovascular, or other “hard” clinical outcomes (even though higher baseline BMI does predict greater weight loss). Instead, strong evidence indicates that preoperative BMI, at least within the obese range, does not predict the benefits of surgery on diabetes prevention (12,13), remission (11,14–19), and recurrence after initial remission (15) or the magnitude of its effects on heart attacks, strokes (20,21), cancer (22), or death (11,12,17,18,20,22,23). In contrast, high levels of baseline fasting insulin and/or glucose (presumably reflecting insulin resistance) do predict the benefits of surgery on most of these end points. This strongly suggests that the advantages of bariatric/metabolic surgery on key clinical outcomes result more from improved glucose homeostasis than from weight loss per se (12,14,20,22–26). These data also indicate that high fasting insulin and glucose levels, or some other measure of insulin resistance, would be better evidence-based criteria for surgical selection than BMI is.

Third, use of metabolic surgery to treat T2DM in lower-BMI patients makes conceptual sense if it improves diabetes at least in part through weight-independent effects, and considerable evidence now demonstrates such mechanisms (3,5). Regarding RYGB, for example, the following five bodies of evidence attest to weight-independent antidiabetes mechanisms engaged by this operation, in addition to the well-known glycemic benefits of weight loss (4).

1. Diabetes remission frequently occurs very fast, long before substantial weight loss has occurred. At least some of this might result from perioperative acute caloric restriction, which is well known to improve insulin sensitivity and glycemia, although it is not clear why it is observed more after bariatric/metabolic surgery than other gastrointestinal operations.
2. Glucose homeostasis improves more after a given amount of RYGB-induced weight loss than with equivalent weight reduction achieved by diet/exercise or laparoscopic adjustable gastric banding (LAGB).
3. There is an inconsistent correlation between the amount of weight lost after RYGB and the degree of diabetes improvement.
4. Novel experimental operations that replicate some of the intestinal anatomy and physiology of RYGB without compromising the stomach can exert powerful antidiabetes effects with little or no weight loss.
5. Rare cases of extreme hyperinsulinemic/hypoglycemia that occasionally develop many years after RYGB (typically during partial weight regain) suggest the possible existence after surgery of chronic β-cell-stimulatory effects unrelated to weight change.

Potential mechanisms mediating direct antidiabetes effects of metabolic surgery include enhanced secretion of lower intestinal hormones such as glucagon-like peptide 1, altered physiology due to...
excluding ingested nutrients from the upper intestine, upregulation of one or more putative "anti-incretins" or "decretins," compromised ghrelin secretion, modulations of intestinal nutrient-sensing pathways that regulate insulin sensitivity, changes in bile acid signaling, perturbations of gut microbiota, alterations of intestinal glucose transport and metabolism, attenuation of intestinal sodium–glucose cotransport, and other changes not yet fully characterized (5). Many of the observations that identify these candidate mechanisms derive primarily from animal experiments and need to be verified in humans, but it is an active area of research.

Last, the 1991 NIH recommendations that restrict bariatric surgery to people with a BMI $\geq 35$ kg/m$^2$ were based almost exclusively on data from Caucasian patients, but all other large racial groups tend to develop T2DM at lower BMI levels than those in this population (27). Hence, the NIH standards deny access to metabolic surgery for the large majority of patients with diabetes worldwide who might benefit from this option to treat their disease. For example, in Taiwan, the median BMI of patients with T2DM is approximately 24 kg/m$^2$, and $<2$% have a BMI $\geq 35$ kg/m$^2$ (28). Thus, NIH recommendations exclude >98% of these East Asian patients from considering metabolic surgery to treat T2DM. Similar comments pertain to South Asians. Even in the U.S., the peak of the BMI distribution curve for patients with T2DM lies between 30 and 35 kg/m$^2$ (29), so a very substantial proportion of American patients with diabetes have a BMI too low to qualify for surgery by existing standards. In short, the 1991 NIH recommendations exclude hundreds of millions of patients with diabetes from access to a highly effective T2DM treatment option.

EVIDENCE REGARDING THE USE OF BARIATRIC/METABOLIC SURGERY TO TREAT T2DM IN PATIENTS WITH A BASELINE BMI $<35$ KG/M$^2$

Effects of Bariatric/Metabolic Surgery on Diabetes in Patients With a BMI $<35$ kg/m$^2$

Several excellent, recent systematic reviews and meta-analyses help summarize and interpret findings from the large, growing number of publications reporting data on bariatric/metabolic surgery for people with a preoperative BMI $<35$ kg/m$^2$.

Before discussing these, it is important to note that evidence in this field is muddied by the fact that there is no universally agreed-upon standard for measuring the success of bariatric/metabolic surgery to treat T2DM, even though standard definitions for diabetes "remission" have been published by prominent authorities (30). Various investigators define remission differently, typically as an HbA$_1c$ level below some threshold, off diabetes medications. However, remission rates differ greatly even within the same study depending on whether the required HbA$_1c$ threshold is 6.0%, 6.5%, or 7.0%. In addition, many physicians commonly leave patients on metformin even after normoglycemia is achieved, using it for prevention of relapse, hoped-for cardiovascular benefits independent of glycemia, polycystic ovarian syndrome treatment, and so forth. This practice confounds any definition of diabetes remission that requires patients to be off all diabetes medications, and there is no widely accepted standard in bariatric/metabolic research for how to deal with this issue.

Müller-Stich et al. (31) recently published a high-quality systematic review and pooled meta-analysis of only level 1 and level 2 evidence from studies directly comparing surgical versus medical/lifestyle interventions for T2DM among patients, at least some of whom in each study had a baseline BMI $<35$ kg/m$^2$. This included seven randomized clinical trials (RCTs) and six high-quality prospective observational comparisons, encompassing 818 participants with diabetes, with follow-up of 1–3 years. No deaths were reported.

Every one of these studies found that various surgical interventions were statistically significantly superior to a variety of nonsurgical interventions in causing either diabetes remission (i.e., nondiabetic HbA$_1c$ levels off all diabetes medications) (Fig. 1) and/or glycemic control (i.e., nondiabetic HbA$_1c$ with or without diabetes medications) (31). The overall odds ratio (OR) for surgical superiority in diabetes remission was 14.1 among all studies and 22 among those that exclusively examined patients with a preoperative BMI $<35$ kg/m$^2$.

These results persisted with fixed- versus random-effects models, in subgroup analyses of only RCTs or only prospective observational comparisons, and with or without adjustment for potential publication biases. The overall average percent HbA$_1c$ dropped by 1.5 points more after surgical compared with nonsurgical interventions, even though patients in the former group used far fewer diabetes medications compared with the latter at the end of these studies. The ORs for surgical superiority over medical/lifestyle interventions regarding diabetes remission were similar for each individual operation in this meta-analysis compared with a prior meta-analysis of RCTs examining surgical versus nonsurgical T2DM approaches among patients with a baseline BMI $\geq 35$ kg/m$^2$ (32). For example, the OR for surgical superiority in diabetes remission after LAGB was 12 versus 5 in the former versus latter analysis, respectively, and approximately 30–50 in both analyses for RYGB, vertical sleeve gastrectomy (VSG), and BPD.

Not surprisingly, Müller-Stich et al. (31) found that BMI fell much more with surgery than medical/lifestyle interventions in every case except one. The exception was an investigation of an experimental operation that replicates the proximal intestinal bypass of RYGB without affecting the stomach, i.e., duodenal-jejunal bypass surgery. It caused substantially greater glycemic control than did nonsurgical care, despite equal weight change in both groups, further demonstrating weight-independent antidiabetes effects of proximal intestinal bypass (33). As is commonly observed, the effects of surgery on blood pressure and plasma lipids were less impressive than those on glycemia. Nevertheless, the surgical groups overall were four times less likely to have hypertension and five times less likely to have dyslipidemia compared with medical groups at the end of these studies (31).

A smaller systematic review and meta-analysis recently published by Rao et al. (34) examined the effects of RYGB on T2DM among studies whose participants exclusively had a baseline BMI $<35$ kg/m$^2$. This encompassed nine publications, describing a total of 343 participants (baseline BMI range 19–35 kg/m$^2$, follow-up 1–7 years.)
Again, there were no deaths, and surgical complication rates were 6–20%, which is similar to published rates for patients with a baseline BMI $\geq 35$ kg/m$^2$ (9). All nine articles reported significant HbA1c reductions after surgery, with an average percent HbA1c lowering of 2.8 points (34). Overall, surgery reduced fasting blood glucose by 60 mg/dL more than did the various nonsurgical comparator interventions. Rates of diabetes remission (defined here as HbA1c, $6.5\%$ off all diabetes medications) ranged from 65 to 93%, which is at least as high as is reported historically among patients with a baseline BMI $\geq 35$ kg/m$^2$ (2,3,10).

Comparing the Effects of Surgery in Patients With a Preoperative BMI Below Versus Above 35 kg/m$^2$

In considering whether to lower the BMI threshold for contemplating the use of bariatric/metabolic surgery to treat inadequately controlled T2DM in less obese patients—as recommended by the new DSS-II guidelines published this issue of the Diabetes Care (9)—a crucial question is whether the antidiabetes effects of surgery are attenuated in lower-BMI patients compared with severely obese individuals, who have been more extensively studied to date. Intuitively, one might speculate that rates of diabetes remission and/or glycemic control would be lower among leaner patients because such individuals lose less body weight after surgery (both in percent and absolute terms) than do people with higher BMI values. Indeed, we have heard this view expressed by prominent figures at scientific meetings for some time. However, recent evidence from large meta-analyses and RCTs does not support that assertion.

Panunzi et al. (18) performed an extensive systematic review searching for predictors of diabetes remission after bariatric/metabolic surgery. They examined all publications up through 2015 reporting postsurgical diabetes remission rates: a total of 94 articles describing 94,579 surgical patients with T2DM (Fig. 2). Notably, they found that the overall rate of diabetes remission was equivalent among the 60 studies in which mean preoperative BMI was $\geq 35$ kg/m$^2$ compared with the 34 studies with mean preoperative BMI $<35$ kg/m$^2$ (71% vs. 72%, respectively). Rates of diabetes remission were also similar within each individual operation among patients with a baseline BMI above versus below 35 kg/m$^2$ (overall remission 89% for BPD, 77% for RYGB, 62% for LAGB, and 60% for VSG). Surprisingly, among many baseline patient characteristics examined, the only significant predictor of the magnitude of postoperative fall in HbA1c was lower preoperative waist circumference. A major strength of this systematic review is that it included all extant publications on the topic and was thus very large. However, the authors did not limit their analyses to only high-quality studies.

Accordingly, a meta-analysis was performed for the DSS-II conference examining only level 1 evidence from the 11 published RCTs directly comparing surgical versus nonsurgical approaches to diabetes care, including among many patients with a baseline BMI $<35$ kg/m$^2$ (9). These trials analyzed 1,090 randomized participants. Together they examined all four clinically practiced bariatric/metabolic operations (RYGB, VSG, LAGB, and BPD), as well as a variety of behavioral/medical approaches, including very
intensive lifestyle interventions (35) modeled after Look AHEAD (Action for Health in Diabetes) and Diabetes Prevention Program (DPP). As shown in Fig. 3A, all 11 RCTs reported superior results from surgery compared with medical/lifestyle interventions for diabetes remission and/or glycemic control, with an overall OR for surgical superiority of about 10. This constitutes unanimous level 1A evidence (i.e., meta-analysis of only RCTs) demonstrating that surgery improves diabetes more than medical/lifestyle interventions do. The only study in which the Peto OR confidence intervals crossed 1 was for LAGB, which is generally found to be the least effective of these four operations for T2DM treatment.

Importantly, the magnitude of surgical superiority over medical/lifestyle interventions for diabetes remission and/or glycemic control was similar among the trials in which the average baseline BMI of the study cohort was below versus above 35 kg/m² (Fig. 3A). There was no trend toward reduction in the relative benefit of surgical compared with nonsurgical interventions on these glycemic parameters based on decreasing preoperative BMI. Moreover, among the RCTs that have now reported both early and later follow-up data, the magnitude of surgical superiority over medical/lifestyle interventions for glycemic outcomes is similar at 1–2 years and at 2–5 years (Fig. 3B). As with the end points of diabetes remission and glycemic control, the degree of superiority for lowering HbA1c levels with surgical compared with nonsurgical interventions is similar among RCTs wherein the study cohorts started with a mean baseline BMI below or above 35 kg/m² (Fig. 4). This finding is clearly displayed in the data from Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, arguably the best RCT in this arena to date. At all time points over the course of 3 years, surgical patients consistently displayed greater HbA1c lowering compared to patients treated with medical/lifestyle interventions, but this finding was equivalent among participants whose average baseline BMI was below versus above 35 kg/m² (Fig. 5).

A very important point to emphasize in interpreting all of the above studies comparing surgical versus nonsurgical approaches to diabetes is that in most
of them, the intensity of the lifestyle intervention and/or rigor of pharmaceutical care (including use, or more typically lack of standardized use, of medication-assisted weight loss) was not as aggressive as is possible. Although some of these RCTs have involved quite intensive lifestyle/medical interventions (35,37,38), more work is needed in this domain.

Safety of Bariatric/Metabolic Surgery in Patients With a Baseline BMI <35 kg/m²

The safety of bariatric/metabolic surgery compared with medical/lifestyle treatments for diabetes is thoroughly examined in a systematic review by the Agency for Healthcare Research and Quality (39). It examined the safety of surgical versus non-surgical approaches to metabolic conditions such as diabetes among patients with a preoperative BMI of 30–35 kg/m². The comprehensive report confirmed that surgery caused greater reductions of BMI, HbA₁c, hypertension, LDL, and triglycerides than did medical/lifestyle interventions. Importantly, the final summary statement reported that “rates of adverse events of surgery were relatively low,” surgical mortality was 0.0–0.3% (which is similar to historical data for patients with a BMI ≥35 kg/m²) (2), and “most surgical complications were minor and tended not to require major interventions” (39). They also concluded that excessive (i.e., too much) weight loss is not a problem for standard proximal RYGB, VSG, or LAGB.

Figure 3—A: Forest plot of Peto ORs of main glycemic end points (Glyc. Endp.), as defined in each trial, from published RCTs of bariatric/metabolic surgery compared with medical/lifestyle treatments for diabetes. B: Forest plot of the trials depicted in panel A that have published both their initial shorter-term data and subsequent longer-term results from the same study. In both panels, data are arranged in order of ascending mean baseline BMI; the dotted line separates trials performed with cohorts exhibiting an average baseline BMI above or below 35 kg/m². Study duration and HbA₁c end point thresholds are shown in column 1, where “off meds” indicates a threshold achieved off all diabetes medications; otherwise, end points represent HbA₁c thresholds achieved with or without such medications. ORs >1 indicate a positive effect of surgery compared with medical/lifestyle treatment. For each study, the OR is shown with its 95% CI. The pooled Peto OR (95% CI) for all data were calculated under the assumption of a fixed-effects model. SG, sleeve gastrectomy.

Long-term Effects of Surgery in Patients With a Baseline BMI <35 kg/m²

Although long-term data regarding bariatric/metabolic surgery in lower-BMI patients is relatively limited, some pertinent evidence has begun to emerge in this arena.
We prospectively studied the efficacy and safety of RYGB among 66 patients with T2DM and a baseline BMI of 30–35 kg/m², who were followed with 100% retention for 6 years (25). The study cohort had severe, long-standing diabetes (at baseline: average duration of diabetes 13 years, mean HbA1c 9.7%, with 40% on insulin and the rest on oral medications). Nevertheless, we observed a rapid decrease of average HbA1c within the first few months, from nearly 10% down to nondiabetic levels, with subsequent maintenance of that degree of improved glycemia for 6 years (Fig. 6 A). At the end of the study, 88% of participants still enjoyed diabetes remission (defined here as HbA1c ≤ 6.5% off all diabetes medications), another 11% clearly had improved diabetes status, and only 1 patient out of 66 was unchanged. We found no relationship at any time point from 1 month to 6 years between the magnitude of weight loss and the degree of improvement in any glycemic variable (e.g., HbA1c, fasting plasma glucose, insulinogenic index during a standardized meal test, and HOMA-insulin resistance). Systolic and diastolic blood pressure decreased progressively throughout the study, as did total cholesterol, LDL cholesterol, and triglycerides, and HDL cholesterol increased progressively for 6 years. These changes yielded substantial, highly significant improvements in estimated 10-year risks of fatal and nonfatal heart attacks and strokes.

A large, recent study by Hsu et al. (41) reported similar findings among East Asian patients with T2DM and a baseline BMI < 35 kg/m². Over 5 years, the authors examined the effects of either RYGB or VSG compared with medical/lifestyle diabetes care among 351 patients with initial diabetes who were matched between the surgical and nonsurgical groups for age, BMI, and diabetes duration. Despite this matching attempt, the surgical group had a higher baseline average HbA1c (9.1% vs. 8.1%) and longer duration of diabetes (5.0 vs. 2.7 years), both of which introduce conservative biases against finding surgical

| Study (Operation) [Follow-up; HbA1c endpoint] | Surgery | Medical/Lifestyle | Mean Differences in HbA1c |
|------------------------------------------------|---------|-----------------|--------------------------|
| Wentworth 2014 (LAGB) [24 mo; ≤ 7.0%] | 6.1 (0.8) 23 | 7.3 (1.4) 25 | 6.5% [-1.02, -1.0] |
| Liang 2013 (RYGB) [12 mo; ≤ 7.0% off meds] | 6.0 (0.3) 31 | 7.6 (1.4) 70 | 7.3% [-1.6, -1.5] |
| Parkh 2013 (RYGB/LAGB/SG) [9 mo; ≤ 6.5% off meds] | 6.2 (0.9) 20 | 7.8 (1.7) 24 | 6.1% [-1.6, -2.3] |
| Ikramuddin 2013 (RYGB) [12 mo; ≤ 7.0%] | 6.3 (0.9) 57 | 7.8 (1.5) 57 | 7.0% [-1.5, -1.05] |
| Ikramuddin 2015 (RYGB) [24 mo; ≤ 7.0%] | 6.5 (1.6) 56 | 8.4 (2.9) 54 | 5.8% [-1.9, -2.8] |
| Courcoulas 2015 (RYGB/LAGB/SG) [12 mo; ≤ 6.5% off meds] | 6.6 (0.8) 41 | 7.9 (0.9) 17 | 6.9% [-0.4, 0.09] |
| Courcoulas 2015 (RYGB/LAGB) [12 mo; ≤ 6.5% off meds] | 7.1 (0.4) 38 | 7.2 (0.4) 14 | 7.5% [-0.1, 0.35] |
| Halpern 2014 (RYGB) [12 mo; ≤ 6.5% off meds] | 6.2 (1.4) 19 | 8.8 (1.1) 19 | 6.1% [-2.6, -1.3] |
| Ding 2015 (LAGB) [12 mo; ≤ 6.5%] | 7.1 (0.3) 18 | 7.1 (0.5) 28 | 22 | 7.5% [0.16, 0.20] |
| Dixon 2004 (LAGB) [24 mo; ≤ 6.2% off meds] | 6 (0.8) 30 | 7.2 (1.4) 30 | 6.7% [-1.2, -1.7] |
| Schauer 2012 (RYGB/SG) [12 mo; ≤ 6.0%] | 6.5 (0.95) 99 | 7.5 (1.8) 41 | 6.7% [-1.0, -1.5] |
| Schauer 2014 (RYGB/SG) [16 mo; ≤ 6.0%] | 6.8 (1.3) 97 | 8.4 (2.2) 40 | 6.3% [-1.5, -2.2] |
| Cummings 2015 (RYGB/LAGB) [12 mo; ≤ 6.5% off meds] | 6.4 (1.6) 15 | 6.9 (1.3) 17 | 5.3% [-0.5, 0.5] |
| Mingrone 2012 (RYGB/BPD) [24 mo; ≤ 6.5% off meds] | 6.65 (0.95) 20 | 7.69 (0.57) 20 | 7.0% [-2.0, -2.3] |
| Mingrone 2015 (RYGB/BPD) [60 mo; ≤ 6.5% off meds] | 6.55 (0.5) 38 | 6.9 (0.6) 15 | 7.3% [-0.3, 0.09] |

Random Effect Model

| Study (Operation) | Follow-up | HbA1c endpoint |
|-------------------|-----------|----------------|
| Wentworth 2014    | 24 mo     | ≤ 7.0%         |
| Liang 2013        | 12 mo     | ≤ 7.0% off meds |
| Parkh 2013        | 9 mo      | ≤ 6.5% off meds |
| Ikramuddin 2013   | 12 mo     | ≤ 7.0%         |
| Ikramuddin 2015   | 24 mo     | ≤ 7.0%         |
| Courcoulas 2015   | 12 mo     | ≤ 6.5% off meds |
| Courcoulas 2015   | 12 mo     | ≤ 6.5% off meds |
| Halpern 2014      | 12 mo     | ≤ 6.5% off meds |
| Ding 2015         | 12 mo     | ≤ 6.5%         |
| Dixon 2004        | 24 mo     | ≤ 6.2% off meds |
| Schauer 2012      | 12 mo     | ≤ 6.0%         |
| Schauer 2014      | 16 mo     | ≤ 6.0%         |
| Cummings 2015     | 12 mo     | ≤ 6.5% off meds |
| Mingrone 2012     | 24 mo     | ≤ 6.5% off meds |
| Mingrone 2015     | 60 mo     | ≤ 6.5% off meds |

Figure 4—Forest plot of mean differences (MDs) of HbA1c serum levels after bariatric/metabolic surgery compared with medical/lifestyle treatments in published RCTs related to diabetes. Data are arranged in order of ascending mean baseline BMI; the dotted line separates trials performed with cohorts exhibiting an average baseline BMI above or below 35 kg/m². Study duration and HbA1c end point thresholds are shown in brackets in column 1, where “off meds” indicates a threshold achieved off all diabetes medications; otherwise, end points represent HbA1c thresholds achieved with or without such medications. Negative MDs denote lower HbA1c levels following surgery than medical/lifestyle treatment. Data for each study are shown as the MD with its 95% CI. A random-effects model was used to calculate the pooled standardized MD.

Figure 5—Change in mean ± SE HbA1c levels over 3 years in a large RCT comparing surgical (either RYGB or VSG) vs. intensive medical therapy for T2DM. Each treatment group is divided into two subgroups defined by an average baseline BMI < 35 kg/m² vs. ≥ 35 kg/m², as indicated in the figure. Mean values in each group are provided below the graph, with median values in parentheses. P = 0.008 for comparison between the surgical and medical groups within the subgroup of patients with a baseline BMI < 35 kg/m²; P < 0.001 for that comparison within the subgroup with a baseline BMI ≥ 35 kg/m². Reprinted with permission from Schauer et al. (36).
superiority regarding glycemia. Nevertheless, HbA1c and BMI were both reduced to a far greater degree in the surgical group, and these changes were largely stable from 6 months to 5 years (Fig. 6B), even though surgery patients ended up on fewer diabetes medications, including insulin. Follow-up at 5 years was 96% in the surgical group and 84% in the medical/lifestyle group. Maintenance of an HbA1c <6.5% off all diabetes medications at the end of the study was achieved in 64% of surgery patients compared with 3% of patients treated with medical/lifestyle interventions. At 5 years, the surgical group also displayed greater reductions in waist circumference, central adiposity, LDL cholesterol, triglycerides, blood pressure, and the percent of participants with hypertension. Death rates were statistically equivalent (1.9% with surgery, 3.0% with medical/lifestyle interventions).

A long-term study of South Asian patients reported somewhat less durable effects on diabetes than were observed in the two articles highlighted in Fig. 6. Lakdawala et al. (42) performed a prospective observational analysis of 52 Asian Indian patients with a BMI of 30–35 kg/m² and poorly controlled T2DM at baseline who underwent RYGB and were followed for 5 years. Although the rate of complete diabetes remission at 1 year was high at 73% (similar to that typically seen at this time point after RYGB in patients with BMI $\geq 35$ kg/m² [2,3,10]), full remission had dropped to 58% by 5 years. However, this type of erosion of diabetes remission rates over time is compatible with what is observed among patients with a preoperative BMI $\geq 35$ kg/m², in whom 35–50% of individuals who initially achieve diabetes remission also eventually experience relapse (11,15,16,36). With or without diabetes recurrence, the large majority of patients with a baseline BMI either above or below 35 kg/m² who undergo bariatric/metabolic surgery maintain substantial improvement of glycemic control for many years, and Lakdawala et al. (42) reported that 96% of their study participants had improved metabolic status at 5 postoperative years.

Overall, these findings among lower-BMI patients compare favorably with long-term studies of bariatric/metabolic surgery for individuals with T2DM and a baseline BMI $\geq 35$ kg/m² (11–13,43). However, apart

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**Figure 6**—Long-term studies of bariatric/metabolic surgery to treat T2DM in patients with a preoperative BMI $<35$ kg/m². A: Change in mean ± SE HbA1c levels following RYGB among 66 patients with a baseline BMI of 30–35 kg/m², studied with 100% follow-up for 6 years. HbA1c decreased from values representing poorly controlled diabetes, despite all patients being on diabetes medications at baseline, to nondiabetic or normal-range levels from 6 months to 6 years after RYGB, with 88% of participants off all diabetes medications at the end of the study. Reprinted with permission from Cohen et al. (25). B: Changes over 5 years in mean HbA1c and BMI among 351 Asian patients with T2DM and a BMI $<35$ kg/m² at baseline who underwent surgical (RYGB or VSG) vs. medical/lifestyle care for T2DM. *P < 0.001 for comparison between the surgical group and medical group, calculated from a repeated-measures model that considers data over time. Reprinted with permission from Hsu et al. (41).
from the above-mentioned 3-year data from STAMPEDE (36), long-term results from RCTs of lower-BMI patients are still pending. Another understudied area is the relative cost-effectiveness of bariatric/metabolic surgery compared with conventional care among less obese patients with T2DM, and RCTs powered to observe “hard” outcomes such as cardiovascular events, cancer, and death are needed among patients of any BMI level.

CONCLUSIONS
Numerous RCTs and high-quality non-randomized comparisons now demonstrate that bariatric/metabolic surgery is more effective than a variety of medical/lifestyle interventions for weight loss, glycemic control, T2DM remission, and improvements in other cardiovascular disease risk factors, with acceptable complications for at least 1–5 years (2). Even though individuals with lower baseline BMI levels lose less weight after surgery than do more obese people, the safety and efficacy of surgery for improving T2DM and other metabolic disorders appear to be similar among patients with a baseline BMI below versus above 35 kg/m², the threshold used to determine surgical candidacy for the past 25 years. Available evidence indicates that this rather arbitrary cut point should be lowered for patients with T2DM, in accordance with new DSS-II guidelines published in this issue of Diabetes Care (9).

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