The Great Debate: Medicine or Surgery

What is best for the patient with type 2 diabetes?

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Received 29 September 2010 and accepted 19 December 2010.

DOI: 10.2337/dc10-1859

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DIABETES CARE, VOLUME 34, MARCH 2011

763
transposition experiments, in which a segment of the ileum is moved proximally to the duodenal-jejunal junction, leading to reduced food intake and weight loss without fat malabsorption and associated with increased glucagon-like peptide-1 (GLP-1), peptide YY, and preproglucagon (23). Alternatively, an “upper intestinal hypothesis” theorizes that diverting nutrient flow from the proximal small bowel removes the stimulus for the production of a “diabetogenic signal” (14,24), as best demonstrated by Rubino and colleagues (25) in a series of elegant surgical experiments demonstrating glyemic improvement with duodenal-jejunal bypass (DJB) compared with sham-operated or diet-treated GK nonobese diabetic rats. Glycemic improvements were not sustained when gastrojejunal nutrient transit was restored. Glycemic improvement without weight loss has also been seen in humans with DJB procedures. Perhaps the RYGB is so effective in reducing weight and hyperglycemia because it incorporates the multiple mechanisms discussed above.

The study of enterohormonal changes after different bariatric surgeries and how these relate to metabolic change and sustained weight loss is an emerging field. Among the best studied enterohormones is ghrelin, which is synthesized in the stomach. Concentrations increase before meals and stimulate appetite, participating in the initiation of feeding. Specific dietary lipids may serve as substrates for acylation of ghrelin, which modify its activity, thereby providing a mechanism for communication between nutrient availability and metabolic status (26). With diet-induced weight loss ghrelin concentrations increase, driving appetite and promoting weight regain. In contrast, after RYGB ghrelin levels decrease, contributing to reduced food-seeking activity and promoting sustained weight loss (27). At the same time, peptides produced postprandially from the β-cells of the ileum, including GLP-1, peptide YY, and oxyntomodulin, all increase, likely because of early nutrient delivery to the ileum and neuronal mechanisms (21,22). All of these peptides have been associated with satiation, likely further contributing to sustained weight loss. These changes are not seen with LABG or diet-induced weight loss. Some of these enterohormonal changes, including increased GLP-1, may promote pancreatic islet regeneration or maintenance of mass or function. Expression of pancreatic duodenal homeobox-1, an early and essential transcription factor in the β-cell lineage, and bromodeoxyuridine (a synthetic thymidine analog that gets incorporated into a cell’s DNA when the cell is dividing) uptake into β-cells are both increased after RYGB, supporting positive islet effects (28). However, whether there is increased islet mass or function after gastric bypass remains highly controversial (29). Very recent feeding tube case reports suggest that the route of nutrient delivery seems to be a primary and potentially reversible event in eliciting this enteroendocrine and β-cell response (19,20).

**Type 2 diabetes: a surgical disease?**

The ongoing diabetes epidemic, the impressive effectiveness of bariatric surgical procedures in treating type 2 diabetic patients, and the lines of evidence suggesting weight-independent effects of these procedures on glycemia, considered together, have resulted in substantial enthusiasm in the surgical community for lowering the minimal BMI criteria for bariatric surgical candidates with type 2 diabetes. This would in effect be the first step in making type 2 diabetes a surgically treated disease, and this proposal has been the subject of two recent international consensus conferences (30).

However, treating type 2 diabetes with bariatric surgery remains highly controversial in the endocrinology community (12). First, it must be emphasized that the evidence suggesting that bariatric surgical procedures may have direct effects on glycemia independent of weight loss include very few randomized controlled trials, and most surgical outcomes are from uncontrolled case series with considerable missing data (9). In one meta-analysis, a large number of studies did not report enrolling consecutive patients, and less than half reported the number of patients available for follow-up (7). To date, the only prospective randomized controlled trial on the subject evaluated the effects of the LAGB, a procedure generally thought to not have weight-independent effects on glycemia (6). Thus, the substantial lack of level 1 evidence precludes achieving a consensus across specialties.

Second, concurrent to the advances in the surgical treatment of type 2 diabetes, there have been significant advances in the medical management of the disease. Since 1995 there have been multiple new drugs approved by the Food and Drug Administration for the treatment of hyperglycemia in patients with type 2 diabetes, including the biguanide metformin, α-glucosidase inhibitors, thiazolidinediones, glinides, GLP-1 analogs, amylin analogs, dipeptidyl peptidase-IV inhibitors (31), a bile acid sequestrant (32), and most recently a dopamine receptor agonist (33). In addition, multiple insulin analogs are now available (34) with improved kinetics and safer dosing profiles permitting more individualized and safer regimens compared with prior preparations. Novel pharmacologic agents to promote weight loss are also under development (35,36). Together these agents hold great promise for generating improved health outcomes for type 2 diabetic patients, and with them more patients are achieving metabolic targets. However, long-term safety remains incompletely understood, and some agents may impart undesirable risks for adverse outcomes, such as the potential for cardiovascular risk with rosiglitazone (37) or pancreatitis with exenatide (38). Optimal treatment strategies and glycemic goals for patients with type 2 diabetes remain incompletely understood, and very tight glycemic control may not reduce cardiovascular event rates, and may even lead to increased mortality (39). Thus, just as with surgical therapy of the disease, further study is needed on the effects of current combination and long-term medical therapeutic regimens on type 2 diabetes. Understanding the long-term safety and efficacy of pharmacologic weight loss agents will likewise be important to consider (36,40).

A growing number of investigators have initiated efforts to provide level 1 data relevant to determining optimal treatment regimens for type 2 diabetes given the current equipoise for the clinician to recommend surgical or medical interventions. There are currently 11 studies registered on Clinicaltrials.gov comparing various bariatric and medical interventions (Table 1) (clinicaltrials.gov, accessed 20 September 2010). The National Institute of Diabetes and Digestive and Kidney Diseases has funded four prospective pilot and feasibility trials in the past year, possibly in consideration of a larger nationally based outcome trial to follow. With the societal imperative to provide optimal care for the growing population of patients with diabetes, the intense scientific focus on medical and surgical option effectiveness, and such a rapid expansion of clinical trials on the matter, a number of relevant issues are brought to bear by those designing,
Table 1—Ongoing randomized controlled trials comparing various surgical and medical treatment strategies for type 2 diabetes (as listed on Clinicaltrials.gov)

<table>
<thead>
<tr>
<th>Study name [trial identifier]</th>
<th>Institution</th>
<th>Interventions</th>
<th>Primary outcomes</th>
<th>BMI range (kg/m²)</th>
<th>Duration of follow-up</th>
<th>Estimated enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery or Lifestyle Intervention for Type 2 Diabetes (SOLID) [NCT01040468]</td>
<td>University of Pennsylvania</td>
<td>Surgical: RYGB; LAGB&lt;br&gt;Medical: intensive lifestyle modification</td>
<td>Rates of diabetes remission over 1 year (definition not specified)</td>
<td>30–40</td>
<td>1 year</td>
<td>32</td>
</tr>
<tr>
<td>Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes (TRIABETES) [NCT01047735]</td>
<td>University of Pittsburgh</td>
<td>Surgical: RYGB; LAGB&lt;br&gt;Medical: lifestyle weight loss intervention</td>
<td>Feasibility study</td>
<td>30–40</td>
<td>1 year</td>
<td>60</td>
</tr>
<tr>
<td>Diet and Medical Therapy Versus Bariatric Surgery in Type 2 Diabetes (DIBASY) [NCT00888836]</td>
<td>Catholic University of the Sacred Heart</td>
<td>Surgical: RYGB; BPD&lt;br&gt;Medical: antidiabetic drugs and behavioral suggestions</td>
<td>Inductions of partial or total remission of diabetes (definition not specified)</td>
<td>&gt;35</td>
<td>2 years</td>
<td>100</td>
</tr>
<tr>
<td>Laparoscopic Bariatric Surgery to Treat Type 2 Diabetes in Obese Patients [NCT00428571]</td>
<td>McMaster University (Canada)</td>
<td>Surgical: RYGB; LAGB&lt;br&gt;Medical: intensive medical management (medication, diet, lifestyle)</td>
<td>Diabetes control as assessed by HbA₁c</td>
<td>30–40</td>
<td>1 year</td>
<td>72</td>
</tr>
<tr>
<td>Surgery or Lifestyle With Intensive Medical Management in the Treatment of Type 2 Diabetes (SLIMM-T2D) [NCT01073020]</td>
<td>Joslin Diabetes Center and Brigham and Women’s Hospital</td>
<td>Surgical: RYGB; LAGB&lt;br&gt;Medical: intensive medical diabetes and weight management</td>
<td>Diabetes control at 1 year, defined by FPG &lt;126 mg/dL and HbA₁c &lt;6.5%</td>
<td>30–42</td>
<td>3 years</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes Surgery Study: Intensive Medical Management of Type 2 Diabetes With and Without Gastric Bypass Surgery (DSS) [NCT010428571]</td>
<td>Multinational (University of Minnesota, Columbia University; Taiwan)</td>
<td>Surgical: RYBG&lt;br&gt;Medical: intensive medical management</td>
<td>HbA₁c &lt;7%&lt;br&gt;SBP &lt;130 mmHg&lt;br&gt;LDL &lt;100 mg/dL</td>
<td>30–40</td>
<td>1 year</td>
<td>120</td>
</tr>
<tr>
<td>A Surgical Approach to the Management of Type 2 Diabetes Mellitus in Patients With a BMI Between 25 and 35 kg/m² [NCT01197963]</td>
<td>University of Texas Health Science Center, Houston</td>
<td>Surgical: sleeve gastrectomy and ileal transposition&lt;br&gt;Medical: dietary and medical management</td>
<td>Resolution of diabetes defined by FPG &lt;100 mg/dL and HbA₁c &lt;6%</td>
<td>25–35</td>
<td>Not provided</td>
<td>20&lt;sup&gt;(Not yet enrolling)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) [NCT00432809]</td>
<td>The Cleveland Clinic</td>
<td>Surgical: RYGB&lt;br&gt;Medical: advanced medical therapy for diabetes</td>
<td>Resolution of diabetes at 1 year, defined by HbA₁c &lt;6%</td>
<td>27–43</td>
<td>1 year</td>
<td>150</td>
</tr>
</tbody>
</table>
conducting, reviewing, and ultimately interpreting such trials.

**Bariatric surgical procedures**

When either recommending surgery to a patient or designing a trial, it is important to consider which surgical procedure to select. There are several options.

The LAGB is a commonly chosen bariatric surgical procedure in the U.S. and has a highly acceptable safety risk profile, making it attractive for less obese patients as an alternative to medical therapy. Thirty-day mortality was zero in 1,198 patients who underwent LAGB placement (41). Most surgical studies report results as mean percent excess body weight loss calculated as the percent of body weight above Metropolitan Life table “ideal” (42), or alternatively BMI of 25 kg/m². The mean percent excess body weight loss after LAGB in published series is 46%, and the mean resolution in diabetics is 56% (2), both substantially lower than after RYGB (2). Studies that directly compare the RYGB and LAGB also suggest substantially greater weight loss and resolution of comorbidities after RYGB (43).

There are no studies to date suggesting that the LAGB has a specific effect on type 2 diabetes beyond that of inducing caloric restriction and subsequent weight loss. However, as noted above, the only level 1 data comparing medical with surgical interventions specifically for the treatment of type 2 diabetes evaluates LAGB as the surgical procedure. Dixon et al. (6) randomized patients recently diagnosed with type 2 diabetes (diagnosis ≤2 years) with BMI 30–40 kg/m² (inclusive of some patients whose weight was below current bariatric surgical criteria) to LAGB or an intensive lifestyle modification with medical management, and demonstrated surgically treated patients were more likely to achieve diabetes “remission” (defined as fasting glucose level <126 mg/dL and glycated hemoglobin <6.2% without glycemic therapy) (73 vs. 13%, P < 0.001), with a 5.5 relative risk for remission in the surgically treated group. Notably, the magnitude of weight loss achieved in this study substantially exceeds that typically realized in U.S. clinical practice (2). Whether with similar techniques and management algorithms the same level of results can be attained in a less obese population with type 2 diabetes in the U.S. remains unknown. The LAGB seems to have the lowest complication and adverse outcome rate among commonly performed bariatric surgical procedures.
procedures (41,43). More frequent complications of LAGB include gastric erosion or perforation, band slippage or migration, esophageal dilation, port problems, incisional hernias, and acute respiratory distress and pulmonary embolism (44). Therefore, despite the lack of evidence for a specific effect, with a low-risk profile and impressive results from Dixon and colleagues’ prospective randomized series, the LAGB certainly is an attractive therapeutic option. Although, it is important to note that the band will require adjustments, potentially over the patient’s lifetime.

The RYGB is also a commonly performed procedure, and despite the lack of randomized clinical trials comparing RYGB with medical intervention, much of the enthusiasm for expansion of BMI criteria for bariatric surgical procedures in type 2 diabetic patients has been fueled by RYGB outcomes demonstrated in multiple large observational studies that show improvement or resolution of diabetes in 80% of patients who undergo this procedure (2). Despite early concerns over safety profiles, the laparoscopic RYGB has been judged to be an extremely safe procedure. Estimates of early operative mortality, defined as mortality at 30 days or less, vary, but in general are at 0.1–0.33% (4,45), and this has been supported by a recent large prospective multi-institutional trial involving 2,975 laparoscopic RYGB procedures, showing a 0.2% 30-day postoperative mortality rate (41). Higher rates exist for open RYGB, with elderly patients and with less experienced surgeons (46). Complications of RYGB can occur in up to 10% of patients. Other risks include reoperation during the same admission in 6–9%; technical complications, including obstruction, anastomotic, hemorrhagic, wound, and splenic injury in 1–2%; and systemic complications in 3–7%, which most commonly involve the pulmonary system (4). In addition, the rate of overall hospital admissions in the year after RYGB surgery may be increased twofold, with most admissions for gastrointestinal or surgical-related complications (45). Many of these risks are continuing to diminish over time with the increasing prevalence of laparoscopic techniques and growing clinical experience and prevalence of bariatric surgical centers of excellence (47). As discussed above, there is mounting evidence that improvement or resolution of diabetes after RYGB includes mechanisms beyond weight loss alone. Although there are no randomized controlled trials of RYGB compared with nonsurgical interventions, the proven effectiveness and safety profile cautiously support the preferential use of this procedure specifically for type 2 diabetes treatment.

It is important to note there are variations in the specific surgical techniques of the RYGB procedure. These include concomitant vagotomy or vagal-sparing maneuvers (48) at the time of RYGB, as well as variable limb length. With regard to limb lengths, a “standard limb length” RYGB procedure includes a 30–50 cm pancreaticobiliary limb and a 75–100 cm Roux limb (49). Lengthening the pancreaticobiliary and Roux limbs to 150 cm significantly increases malabsorption and potential complications (49). Thus, outcomes after RYGB need to be interpreted with differences in surgical technique taken into account.

Several other bariatric surgical procedures options exist. The bilipancreatic diversion and duodenal switch are extremely effective at reducing weight and hyperglycemia but have documented higher perioperative mortality rates and induce substantial malabsorption (50), which are less appropriate for a population with lower BMI. The laparoscopic sleeve gastrectomy (LSG) is a newer procedure that is rapidly gaining favor nationally. To date, most studies using this procedure on less obese type 2 diabetic patients have been in conjunction with ileal interposition, which significantly increases the complexity of the operation but may contribute positively to effects on the incretin axis (51). Rapid adoption of the LSG technique in many centers throughout the U.S. is likely to provide relevant data in the near future, and as such, going forward, the LSG may be an important option to be considered in clinical trials.

Novel procedures that have been designed specifically to address type 2 diabetes include the ileal interposition and the DJB, mentioned above (25). However, there are insufficient human clinical data to justify using them broadly at this time. The DJB involves division and Anastomosis of the duodenum and thus also likely carries a higher risk for perioperative morbidity and mortality (52).

Finally, minimally invasive devices, such as the intraluminal duodenal sleeve, have been demonstrated in preclinical models to effectively reduce weight without malabsorption and improve oral and intraperitoneal glucose tolerance (53). Early clinical trials suggest similar devices may promote weight loss and glycemic improvements in patients with type 2 diabetes (54).

Differences in surgical approaches must be considered when weighing the most appropriate intervention at this time either for individual therapy or for study in a prospective trial evaluating surgical approaches directed at type 2 diabetes. To change practice guidelines to use bariatric procedures in lesser degrees of obesity and earlier in the course of diabetes, specifically for diabetes treatment, studies must be conducted to compare surgical with medical management. From a trial perspective, consideration as to the type of surgical procedure(s) to include must also hinge on currently accepted insurance practices. It is unlikely larger trials would have sufficient funding to bear the entire clinical cost of the surgical procedures, and thus would have to rely on some of the clinical costs being covered by multiple funding agencies, including insurers, to successfully complete a large adequately powered outcome study.

**Advanced nonsurgical management of weight and type 2 diabetes**

Patients with type 2 diabetes have difficulty losing weight and maintaining weight loss. Pharmacologic management of diabetes remains controversial, both from the perspective of the best medications to prescribe and the optimal glycemic targets. Many new classes of drugs have been Food and Drug Administration approved for the management of type 2 diabetes on the basis of glucose-lowering properties. Although many diabetes medications are associated with weight gain, including insulin, sulfonylureas, and thiazolidinediones, more recently approved medications are weight neutral (dipeptidyl peptidase-4 inhibitors or bile acid sequestrants) or promote weight loss (GLP-1 analogs and amylin analogs). However, the long-term risks of newer agents remain less certain, and these agents are considered tier 2 in consensus algorithms (55).

Nonsurgical behavioral approaches to weight loss have been studied for decades. Most evidence supports the effectiveness of combining moderate dietary changes and increased physical activity—an approach referred to as a “lifestyle intervention”—for achieving modest weight loss and maintaining weight improvements over time. Long-term evidence is now available supporting the power of lifestyle interventions to prevent the onset of type 2 diabetes in high-risk populations (56); however, patients already diagnosed with...
The great debate: medicine or surgery

diabetes may have a harder time achieving and maintaining weight loss than patients without diabetes (57). The LookAHEAD trial (Action for Health in Diabetes) is a large-scale, multicenter clinical trial investigating the impact of lifestyle intervention on cardiac outcomes in more than 5,000 patients with type 2 diabetes. Four-year follow-up data from LookAHEAD support the successful impact of lifestyle interventions in achieving weight loss and improved glycemic control in type 2 diabetic patients (58). Participants in the lifestyle arm initially lost an average of 8.6% of their initial weight and experienced a mean decrease in glycohemoglobin from 7.3 to 6.6% during their first year of LookAHEAD. After 4 years, 6.2% weight reduction was sustained in the lifestyle group compared with only 0.9% reduction in the control group; glycohemoglobin was reduced 0.4% in the lifestyle group compared with 0.09% in the control group. Lifestyle participants showed sustained improvements in blood pressure, cholesterol, and physical fitness. Current results of LookAHEAD (58) and other studies already support the use of lifestyle interventions to improve overall health and wellness of patients with diabetes.

The best weight loss outcomes result from interventions that include multidisciplinary teams with behavioral modification components, frequent contact individually or in group programs, and administration of long-term support. Substantial funding is needed to carry out these interventions in research or clinical care settings. Private insurance reimbursement for such programs may become more widely available now that Medicare recognizes obesity as a chronic disease. Thus, insurance-billable, cost-effective multidisciplinary approaches are emerging in clinical practice that target both diabetes and weight management. One such example is the Why WAIT (Weight Achievement and Intensive Treatment) program, which consists of 12 weekly group sessions led by nutrition, exercise physiology, mental health, and diabetes care providers, followed by monthly support aimed at long-term maintenance of weight loss and diabetes control (59). Unfortunately, on a national level, few patients participate in these types of intensive medical management programs.

Bariatric surgery or medical management? The informed decision

Prospective randomized studies to evaluate the important question of whether medical or surgical management is optimal for treatment of type 2 diabetes in moderately obese patients are now warranted. Trials should aim to identify characteristics of patients who do well and have improved outcomes compared with those who do not so that therapeutic recommendations can be individualized when possible. Trials must be designed to optimize the quality and applicability of the information generated, and there are multiple important methodological issues. Foremost, is the type of surgical procedures to be considered and whether one or more procedures would be compared with standard care or an intensive diabetes and weight management program? If multiple procedures were to be considered, patients may be unwilling to relegate the choice of procedure to a randomized process, and this could represent a significant impediment to subject accrual and study feasibility or generalization of findings. Patient preference toward a specific procedure is strong; in a survey of 2,046 patients in our surgical clinic, 46% preferred RYGB, 42% preferred LAGB, and only 12% had no preference (D.L., unpublished data). Patient and provider biases may differ for patients selected from surgical clinics compared with primary care or endocrine practices. To inform the decision on the relative benefit of surgery to medical care, it is essential to optimize the medical diabetes and weight management for appropriate comparison, rather than compare with standard of care, where many patients may not meet combined glycemic, blood pressure, and lipid goals.

Many deem it most important to study patients with type 2 diabetes who are not currently approved for bariatric procedures, that is, those with a BMI <35 kg/m². In further consideration of patient selection, excluding patients with very poor glycemic control may be prudent to avoid excess perioperative risks. Conversely, including only patients with poor glycemic control or requiring patients to have inadequately achieved weight loss or glycemic improvement after a period of medical management (typically a 6-month period is currently necessary for many health insurance providers) could bias study results against the medical intervention, because the study would then specifically be selecting those who have been unable to achieve optimal control with nonsurgical treatments. In addition, requiring patients to have higher glycohemoglobin concentrations may select against those with more recent onset of disease who may benefit most by long-standing disease resolution (10). In consideration of current medical treatment for diabetes, some data suggest patients using insulin may not achieve the same degree of resolution of diabetes after surgical procedures (60), possibly because insulin use is more prevalent in patients with more long-standing or advanced disease. However, insulin is now frequently used as a second or early pharmacologic intervention because of the clear success in improving glycemia (55), making it difficult to justify exclusion of insulin-treated patients. Stratification for some of these important covariates may be necessary to apply future study findings to specific patient populations.

Finally, the outcome measures relevant to clinical trials designed to compare the efficacy of surgical and medical management of type 2 diabetes will undoubtedly include achievement of glycemic targets, such as fasting and postprandial blood glucose levels, glycohemoglobin concentrations, continued use of diabetes medications, weight loss, or a combination of these variables. Although defining improvement in glycemic control may be straightforward, defining “cure” of the disease has proven controversial; “remission” is likely a more accurate term. In 2009, a consensus group defined remission of diabetes as achievement of glycemia below the diabetic range (HbA1c <6.5%, fasting glucose 100–125 mg/dL [5.6–6.9 mmol/L]) for at least 1 year; complete remission was defined as a return to normoglycemia (normal HbA1c and fasting glucose <100 mg/dL [5.6 mmol/L]) for at least 1 year; and prolonged remission was defined as complete remission for at least 5 years (61).

Although improved glycemia is recognized to be an important outcome in patients with diabetes, diabetes is characterized by high rates of microvascular and macrovascular complications; thus, well-designed long-term studies will be needed to determine the effect of each management strategy on the risk of such complications. Following surrogate endpoints, such as albuminuria, lipid profiles, hypertension, markers of inflammation, and other cardiovascular risk factors, in studies of shorter duration
may be useful until longer-term data become available. Longer-term studies should also help clarify the postoperative health risks that may arise over time, such as changes in micronutrients, bone mineral density and fracture risk, the risk of postoperative hypoglycemia, and others.

Conclusions
Emerging data suggest that bariatric surgery results in substantial improvements in glycemia, blood pressure, and cholesterol; weight loss is durable; survival may be improved; and surgical risks are low. Novel surgical approaches are under development. At the same time, there have been substantial medical advances, and multiple pharmacologic agents are now available to treat diabetes and manage cardiovascular risk; pharmacologic weight loss agents and multipronged lifestyle strategies with multidisciplinary care are showing promise. Understanding the relative risks and benefits of different treatment approaches for individuals with type 2 diabetes, as well as the health care and other costs of such treatments, on a societal level will be of utmost importance in the coming years. Lessons from the study of the neurohormonal changes after bariatric surgery may inform not only the best surgical procedure but also lead to development of novel medical therapies, gastrointestinal interventions, or combination approaches to offer optimal management for the prevention or treatment of type 2 diabetes.

Acknowledgments—This research was supported by National Institutes of Health Grants R1C1-DK-086918 and KL2-RR-025757 (to F.H.), and DERC P30-DK-36836.

Additional funds and supplies to support the trial are provided by Coviden; Nestle; LifeScan, a Division of Johnson & Johnson; and Mercodia. D.L. has worked occasionally as a consultant for Coviden, largely reviewing their instrumentation; this has always been less than $2000/year and has always been vetted by the Brigham and Women’s Hospital Corporate Sponsored Research office. Neither D.L. nor A.B.G. has personal financial interest in Coviden. No other potential conflicts of interest relevant to this article were reported. The authors note they are conducting an investigator-initiated clinical trial sponsored by the National Institutes of Health/ National Institute of Diabetes and Digestive and Kidney Diseases (clinical trials identifier NCT01073020).

D.L., F.H., A.G.-F., and A.B.G. researched data and wrote and edited the article. The authors thank Dr. Mary Elizabeth Patti, Joslin Diabetes Center, and Dr. Donald Simonson, Brigham and Women’s Hospital, for thoughtful discussions.

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The great debate: medicine or surgery

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