

Obesity Surgery and Diabetes: Does a Chance to Cut Mean a Chance to Cure?

When insulin was initially discovered by Banting and Best in 1922, it was hailed as a cure for type 1 diabetes. Given the ability of insulin to reverse ketoacidosis and severe hyperglycemia, who could doubt that the ravages of type 1 diabetes would be relegated to the archives of medical history? However, within a few short decades of insulin's discovery, it became apparent that the short-term mortality associated with type 1 diabetes was being replaced by longer term morbidities related to renal failure, blindness, nerve damage and vascular disease. The "cure" had treated the short-term sequelae related to the metabolic derangements of insulin deficiency but unfortunately had not (in its initial use) affected the longer-term consequences of hyperglycemia.

It was only after careful follow-up from prospective epidemiologic studies that we realized that type 1 diabetes had been transformed but not cured. The acquisition of knowledge and insights into the natural history of diabetes did not, however, minimize the significance of the discovery of insulin (for which the investigators received the Nobel Prize) but highlighted the importance of judiciously evaluating how a new therapy impacts a disease. After 70 years, the role of insulin, not as a way to resolve type 1 diabetes, but, as a means to reduce the risk of serious complications through rigorous control of serum glucose levels, was established by the results of the multi-center DCCT.¹

In this issue of the *The American Journal of Medicine*, Buchwald et al report on a meta-analysis of the impact of bariatric surgery in severely obese patients with type 2 diabetes of varying duration.² Using data compiled from 621 studies involving more than 4000 patients with diabetes, the authors conclude that bariatric surgery "resolved or improved" diabetes in the "greater majority" of patients with type 2 diabetes. The authors define "resolved" as being off medications, having a fasting glucose at follow-up of < 100 mg/dL and/or having an HgA1c < 6%; "improved" was defined as the use of fewer medications and/or fasting glucose levels between 100-125 mg/dL. The results of this summary overview, which also has some methodologic

limitations noted by the authors, raise the question of whether we have indeed found a "cure" for type 2 diabetes.

The first issue is to decide whether these trials in morbidly obese patients have adequately studied the problem of surgical approaches to patients with obesity and type 2 diabetes. Although this meta-analysis included a large sample of patients with diabetes of varying duration, the study population consisted primarily of markedly obese women and subjects who were relatively young (mean age = 40 years); the average BMI was 47.9 kg/m². The studies were largely retrospective (58%) and single armed (73%); only 10 studies (1.6%) qualify as providing Class I evidence. Previous studies have noted that older patients or those with diabetes of longer duration are less likely to improve their glucose tolerance³; conversely, 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.⁴ The applicability of the findings of this meta-analysis to broader populations with type 2 diabetes is unknown. Prospective surgical studies need to enroll more varied patient populations, both in terms of diabetes duration, and severity, as well as according to age, sex, and ethnicity. Based on the results of these prospective investigations, new insights would be obtained into the contemporary natural history of diabetes in morbidly obese patients and the risks and benefits associated with surgical intervention.

Assessing benefits of any therapy on type 2 diabetes must demonstrate (at a minimum) an acceptable impact on HgA1c and fasting glucose levels. The present meta-analysis reports a change in HgA1c of 2.1% which is obtainable with many currently available pharmacologic regimens. In addition, many of the macrovascular complications of type 2 diabetes have been linked to insulin resistance⁵ yet this meta-analysis cites only a single study on changes in fasting insulin concentrations (a suboptimal indicator). To assess changes in insulin sensitivity following bariatric procedures, better studies using more sophisticated techniques are needed.

Determining the long-term impact of any therapy is highly dependent on the completeness of follow-up as well as whether the treatment modality was assessed using an observational or randomized trial design approach. The au-

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thors note that the “accepted” follow-up rate in studies reporting outcomes of surgery for obesity is 50%. Follow-up rates at this level are clearly insufficient to allow for the systematic evaluation of the effectiveness of surgery as a therapeutic modality for type 2 diabetes because patients lost to follow up might have a different disease experience and incidence rate of important disease-related outcomes than those remaining under prolonged surveillance. The increasing emphasis on clinical outcomes over reductions in surrogates such as HgA1c for pharmaceutical therapies⁶ raises interesting questions for the evaluation of bariatric surgery. If bariatric surgery were a drug, it seems unlikely that the FDA would accept studies providing only 50% follow-up on surrogate measures such as HgA1c values and medication use.

Complications and negative outcomes associated with bariatric surgery should figure strongly into deciding whether surgery is a preferred option for the treatment of type 2 diabetes in patients with obesity. Unfortunately, there appears to be a limited amount of data available on adverse events related to obesity surgery. Observational studies involving investigators without conflicts of interest related to surgical procedures would provide crucial data regarding the relative safety of these procedures. Meta-analyses should present both the positive and negative consequences of the therapy being evaluated.

Bariatric surgery for those with morbid obesity who cannot lose weight by other means represents an important treatment option for a select group of patients. The weight loss, more consistently apparent with more aggressive procedures, is an important benefit for patients suffering with severe obesity. However, whether this acute “cure” will continue to be a long-term remedy for patients with type 2 diabetes will depend on several factors. Just as insulin was so beneficial for the acute health needs of those with type 1 diabetes, surgery might play an important role for short-term changes in glucose control in (some) patients with type

2 diabetes. However, broadening the approach will require evaluation of diverse cohorts of patients with type 2 diabetes with ardent follow-up for prolonged periods. Studies will need to address duration, gender, 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 therapies (medical and behavioral). Only then will we know whether surgery is a “cure” or another effective treatment option to be used in patients with a more narrowly defined clinical and/or demographic profile.

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