Surgery as an Effective Early Intervention for Diabesity

Why the reluctance?

JOHN B. DIXON, MBBS, PHD[1]
WALTER J. PORIES, MD[2]
PAUL E. O'BRIEN, MD[1]
PHILLIP R. SCHAUER, MD[3]
PAUL ZIMMET, MD, PHD[4]

We are currently in the midst of two closely linked epidemics: type 2 diabetes and obesity (1,2). At the present time, it is estimated that 190 million people worldwide have diabetes and that this will increase to 324 million by 2025 (3). This epidemic is taking place in both developed and developing nations. In the U.S. alone, at least 16 million people have type 2 diabetes, with 1 million more diagnosed annually (4). Obesity is also increasing at alarming rates. In the U.S., the majority diagnosed with type 2 diabetes are overweight, with 50% obese (i.e., BMI >30 kg/m^2) and 9% morbidly obese (BMI >40 kg/m^2) (5).

There is a strong relationship between obesity and type 2 diabetes, and the term "diabesity" has been coined to suggest a single problem (6,7). A substantial portion of the health costs attributed to obesity is related to type 2 diabetes (8). The socioeconomic impact of type 2 diabetes and its complications are substantial to individuals and their families and to society (9). In particular, it is an inexorably progressive disease, leading to deterioration in multiple organs and systems, and is the most common cause of adult blindness, limb amputations, and renal failure in western communities, as well as the leading independent risk factor for coronary artery disease (10).

Prevention of this diabesity epidemic through effective public health lifestyle and environmental initiatives to change the population's dietary and movement behaviors should be of highest priority (2). For those already suffering from diabesity, effective treatment is important. A therapy that provides remission of both diabetes and obesity should attract enormous interest and activity.

Theoretically, weight loss is such a therapy (11,12). However, although intentional weight loss through diet and exercise is associated with better control, fewer complications, and reduced mortality (12–14), achieving and sustaining weight loss in those with type 2 diabetes has been an elusive goal (15). Poor weight loss outcomes for those with type 2 diabetes have been consistently demonstrated with the standard range of weight loss methods of less food consumption, increased exercise and activity, behavioral modifications, very-low-calorie diets, and pharmacotherapy (16–18). As a result, current type 2 diabetes treatment guidelines are more likely to include the goal of weight "control" rather than weight "loss."

Where can physicians look for effective therapy in severely obese (BMI >35 kg/m^2) type 2 diabetic patients who are unable to achieve and sustain significant improvement through intensive lifestyle change and weight loss?

We believe that bariatric surgery has an important role and should be recommended as an early intervention in the management of severely obese subjects with type 2 diabetes if intensive lifestyle interventions fail to achieve and maintain significant weight loss. Recent publications have confirmed earlier research that substantial and durable weight loss is achieved by current bariatric surgical procedures and that all these procedures provide a strongly beneficial effect in subjects with type 2 diabetes.

An early study to show this clinical improvement consisted of 608 patients followed for up to 14 years after a Greenville-type open gastric bypass (19). Weight loss was 55% of excess weight at 10 years and 49% at 14 years. There were 146 type 2 diabetic patients, and 121 (83%) achieved and maintained a nondiabetic clinical state with normal fasting plasma glucose, GHb, and serum insulin levels. Additionally, 150 of 152 patients with impaired glucose tolerance became normoglycemic. The weight loss was accompanied by major improvements or resolution of other obesity-related comorbidities, including hypertension, sleep apnea, and infertility. This study also showed a significant reduction in mortality in the patients treated surgically when compared with a similar morbidly obese group who did not proceed with operation, principally due to reduced cardiovascular deaths (14). However, remission of type 2 diabetes was less likely in older subjects and in those who had a longer history of type 2 diabetes (20). In addition, the authors of this study have hypothesized that the diversionary component of some bariatric procedures may provide benefit beyond that of weight loss (21).

Others have confirmed that major weight loss has been associated with durable remission of diabetes in 86% of subjects 5–7 years after the gastric bypass procedure (22). The Swedish Obese Subjects Study Group (23) reported similar major reductions in the prevalence of type 2 diabetes after gastroplasty. This study involved subjects electing to undergo a restrictive bariatric surgical procedure, who were then compared with well-matched control subjects. A major reduction in the prevalence of type 2 diabetes at

From the [1]Centre for Obesity Research and Education, Monash University, Alfred Hospital, Prahran, Victoria, Australia; the [2]Department of Surgery, East Carolina University, Greenville, North Carolina; the [3]Department of Surgery, Pittsburgh University, Pittsburgh, Pennsylvania; and the [4]International Diabetes Institute, Caulfield, Victoria, Australia.

Address correspondence and reprint requests to Dr. John Dixon, Centre for Obesity Research and Education, Monash University, Alfred Hospital, Melbourne 3181, Australia. E-mail: john.dixon@med.monash.edu.au.

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2, 8, and now 10 years after the surgical intervention was reported (23,24).

An Australian study of type 2 diabetic subjects after laparoscopic adjustable gastric banding found, using strict criteria, a 64% remission in type 2 diabetes 1 year after surgery, major improvements in blood glucose control in 26%, and little change in 10% (25). Remission was predicted by greater weight loss and a shorter history of diabetes (pseudo $r^2 = 0.44$, $P < 0.001$). Further analysis showed that improvement in insulin sensitivity following surgery was best predicted by the extent of weight loss. Improvement in β-cell function, however, was predicted by a shorter history of diabetes (26). Of those with preoperative impaired fasting glucose, 95% became normoglycemic and none have gone on to develop type 2 diabetes over a follow-up period of up to 4 years. This represents a zero progression to type 2 diabetes in 114 patient-years (25). Weight loss was also accompanied by major improvements in dyslipidemia, blood pressure, sleep apnea, depression, body image, and quality of life. This group has also reported the durability of both weight loss and improved glycemic control after laparoscopic adjustable gastric banding (27).

More recently, the effect of weight loss following laparoscopic Roux-en-Y gastric bypass (LRYGB) in 192 severely obese patients with type 2 diabetes or impaired fasting glucose has been reported. Clinical remission of those with type 2 diabetes occurred in 83% of patients, and the remaining 17% improved significantly. This study found that a shorter history of diabetes and milder disease was associated with an increased likelihood of remission (28).

A key finding of these studies is the significantly greater likelihood of complete remission if the patient has a shorter history of diabetes. This is to be expected, given the progressive deterioration of β-cell function (29,30) that characterizes this disease. The glucotoxicity associated with diabetes, especially if poorly controlled, accelerates β-cell failure. This produces a vicious cycle of deteriorating glycemic control and the need for more and more hypoglycemic therapy. There is a reversible component of β-cell deterioration, with weight loss improving β-cell responsiveness to glucose (31,32). If the bariatric surgical procedure is performed before irreversible β-cell failure has occurred, then durable weight loss will be accompanied by a high likelihood of long-term remission (19,22).

There have been major advances in bariatric surgery over the last 10 years with the application of the laparoscopic approach and the introduction of adjustable gastric banding. Despite these improvements of reduced invasiveness and increased safety and efficacy, as well as the overwhelming evidence of a beneficial effect, it is disappointing to note that bariatric surgery is not generally considered a core element in the management of type 2 diabetes, with major reviews of therapy failing to mention this option (33,34). The reasons may include perceptions of invasiveness, risk and cost associated with surgical therapy, traditional divisions between medical and surgical therapy with type 2 diabetes very much regarded as a medical disease, an acceptance that diabetes is a disease worthy of treatment but that obesity may not be, and perhaps a willingness to simply wait and hope for the development of a drug with a similar effect. It may also relate to inadequate evidence collection, communication, and guidance from bariatric surgical organizations that have tended to specify those in whom surgical therapy may be considered rather than to clearly define groups in whom referral for surgical therapy is recommended—an important difference.

Providing an appropriate level of evidence is problematic with surgical procedures. There are inherent ethical and legal difficulties with randomized controlled trials in providing true placebo groups, and many excellent surgical treatments become standard care without being subjected to the rigors of randomized controlled trials. The treatment effects of surgical therapy often rely on the weight of evidence from well-conducted observational or cohort studies. The considerable treatment effect demonstrated by many bariatric surgical observational studies is overwhelming, and the risk of overestimating treatment effect is low (35,36). On the other hand, unblinded randomized controlled trials are feasible, and comparisons of obese diabetic subjects treated surgically with those receiving conventional therapy are urgently needed.

Early and intensive treatment of type 2 diabetes reduces morbidity, mortality, poor quality of life, and the deterioration of pancreatic β-cell function (29,37–39). Despite enthusiastic attempts to improve metabolic factors, blood pressure, and weight control through intensive lifestyle change and multiple drug therapy, failure is common and costs considerable (40). Unfortunately, with the exception of metformin and acarbose, hypoglycemic medications, including insulin, often lead to weight gain. The currently available weight loss medications, such as orlistat or sibutramine, provide significant but small weight loss that may not be sustained, and the role of these medications in the management of type 2 diabetes has not been established (41).

Substantial and sustained weight loss should be considered a first-line therapy for the severely obese patient diagnosed with type 2 diabetes. While randomized controlled trials involving obesity surgery are needed, evidence of the effects of bariatric surgery on type 2 diabetes is strong and, importantly, the earlier the intervention, the greater the chance of remission through retrieval and retention of β-cell function. We recommend that bariatric surgery be discussed with all severely obese type 2 diabetic subjects (BMI >35 kg/m^2) who have not adequately responded to intensive lifestyle measures to control weight.

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