

# Adjustable Gastric Banding and Conventional Therapy for Type 2 Diabetes

## A Randomized Controlled Trial

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**S**IGNIFICANT SUSTAINED WEIGHT loss achieved using bariatric surgery has never been formally investigated as a treatment for type 2 diabetes in obese participants. Several observational studies suggest substantial benefit, but these have generally been restricted to severely obese participants; to our knowledge, there have been no published randomized controlled trials.

Obesity and type 2 diabetes are likely to be the 2 greatest public health problems of the coming decades.<sup>1</sup> The conditions are strongly linked, with the increased prevalence of diabetes correlating with the increased prevalence of obesity.<sup>2</sup> The adjusted relative risk of developing type 2 diabetes in participants with a body mass index (BMI) greater than 35 (calculated as weight in kilograms divided by height in meters squared) is 93 (95% confidence interval [CI], 81-107) for women<sup>3</sup> and 42 (95% CI, 22-81) for men,<sup>4</sup> compared

**Context** Observational studies suggest that surgically induced loss of weight may be effective therapy for type 2 diabetes.

**Objective** To determine if surgically induced weight loss results in better glycemic control and less need for diabetes medications than conventional approaches to weight loss and diabetes control.

**Design, Setting, and Participants** Unblinded randomized controlled trial conducted from December 2002 through December 2006 at the University Obesity Research Center in Australia, with general community recruitment to established treatment programs. Participants were 60 obese patients (BMI >30 and <40) with recently diagnosed (<2 years) type 2 diabetes.

**Interventions** Conventional diabetes therapy with a focus on weight loss by lifestyle change vs laparoscopic adjustable gastric banding with conventional diabetes care.

**Main Outcome Measures** Remission of type 2 diabetes (fasting glucose level <126 mg/dL [7.0 mmol/L] and glycated hemoglobin [HbA<sub>1c</sub>] value <6.2% while taking no glycemic therapy). Secondary measures included weight and components of the metabolic syndrome. Analysis was by intention-to-treat.

**Results** Of the 60 patients enrolled, 55 (92%) completed the 2-year follow-up. Remission of type 2 diabetes was achieved by 22 (73%) in the surgical group and 4 (13%) in the conventional-therapy group. Relative risk of remission for the surgical group was 5.5 (95% confidence interval, 2.2-14.0). Surgical and conventional-therapy groups lost a mean (SD) of 20.7% (8.6%) and 1.7% (5.2%) of weight, respectively, at 2 years ( $P < .001$ ). Remission of type 2 diabetes was related to weight loss ( $R^2 = 0.46$ ,  $P < .001$ ) and lower baseline HbA<sub>1c</sub> levels (combined  $R^2 = 0.52$ ,  $P < .001$ ). There were no serious complications in either group.

**Conclusions** Participants randomized to surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss. These results need to be confirmed in a larger, more diverse population and have long-term efficacy assessed.

**Trial Registration** [actr.org](http://actr.org) Identifier: ACTRN012605000159651

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with participants with a BMI less than 22 and less than 23, respectively. Approximately half of those diagnosed with type 2 diabetes are obese.<sup>5</sup>

Early and intensive treatment of type 2 diabetes is known to improve health outcomes and quality of life.<sup>6-9</sup> Weight control comprises perhaps the most im-

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portant aspect of type 2 diabetes management, with weight loss reducing morbidity and mortality.<sup>10</sup> Recent evidence indicates that improvement in blood glucose control is related to degree of weight loss.<sup>11</sup> Unfortunately, currently available lifestyle and pharmacological strategies provide only small to modest levels of weight loss, a problem compounded by patients with diabetes experiencing greater difficulty in losing weight than those without diabetes.<sup>12-14</sup> The costs associated with medical weight loss therapies for obese patients with type 2 diabetes are high and ongoing.<sup>15</sup>

Despite observational evidence suggesting that weight-loss surgery is associated with a 60% to 80% diabetes remission rate in severely obese persons and that earlier interventions are more likely to provide remission,<sup>16</sup> bariatric procedures fail to generate significant attention in diabetes guidelines.<sup>17</sup> Concerns exist regarding the lack of randomized controlled evidence, as well as the safety, invasiveness, and cost-effectiveness of surgical weight loss procedures. Providing appropriate evidence has previously proved problematic, because the invasive nature of the surgery makes participant recruitment difficult. However, with the advent of safer, less invasive surgical weight-loss procedures, randomized controlled trials are now feasible, and studies examining mild to moderate obesity, which is responsible for much of the diabetes burden, are possible.

Multiple case series have demonstrated that laparoscopic adjustable gastric banding (LAGB) results in significant weight loss,<sup>18-20</sup> with medium-term weight loss of approximately 20% of body weight<sup>21</sup>; perioperative mortality is approximately 0.05% for LAGB.<sup>21</sup>

Using the LAGB intervention, we conducted a 2-year randomized controlled trial involving 60 obese participants (BMI >30 and <40) to compare surgically induced weight loss with conventional therapy for the management of recently diagnosed type 2 diabetes (<2 years).

## STUDY DESIGN

### Patient Recruitment

Patients were recruited via newspaper advertisement and were not paid to participate, nor did they pay any medical costs. The study was reviewed and approved by the human ethics committees of The Alfred Hospital, The Avenue Hospital, and Monash University in accordance with the guidelines of the National Health and Medical Research Council and the Helsinki Declaration, as revised in 2000. Recruitment commenced in December 2002, the last participant was randomized in November 2004, and all data were available for analysis in December 2006. All participants provided written informed consent to participate in the study. Additional written informed consent was obtained prior to any surgical procedure.

### Inclusion Criteria

Patients were eligible if they were aged between 20 and 60 years, had a body mass index of 30 to 40, had been diagnosed with clearly documented type 2 diabetes within the previous 2 years, had no evidence of renal impairment or diabetic retinopathy, and were able to understand and comply with the study process.

### Exclusion Criteria

Candidates were excluded if they had a history of type 1 diabetes, diabetes secondary to a specific disease, or previous bariatric surgery; a history of medical problems such as mental impairment, drug or alcohol addiction, recent major vascular event, internal malignancy, or portal hypertension; or a contraindication for either study group. Participants were excluded if they did not attend 2 initial information visits.

### Assessment and Run-in Period

In addition to any assessments required for inclusion, each potential participant was assessed by a dietitian, a general physician, and a consultant endocrinologist specializing in diabetes (L.C.) to suggest any

changes required to maximize current management. A run-in period of at least 3 months was undertaken in which further alterations to eating, exercise, glucose self-monitoring, and medications were suggested. During this time, study compliance was assessed using attendance at appointments and completion of questionnaires. The endocrinologist independently determined when a patient was ready for randomization. Baseline weight, blood pressure, anthropometric measures, and biochemical data (levels of fasting plasma glucose, glycated hemoglobin [HbA<sub>1c</sub>], C-peptide, and serum insulin, and a lipid profile) were measured immediately prior to randomization.

### Randomization Process

Randomization was computer derived, with blocking into 3 groups to allow for orderly recruitment into both study groups and to reduce the risk of uneven recruitment late in the series. The study was not blinded.

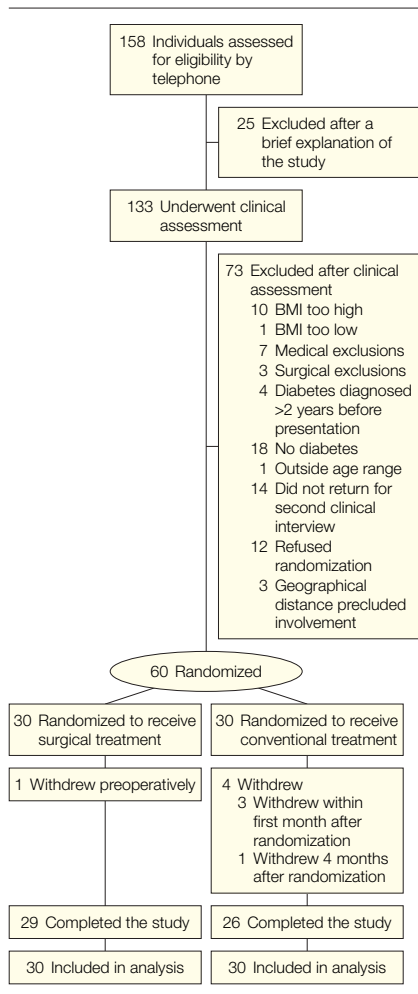
### Treatment Groups

#### Conventional-Therapy Program.

This program delivered best available medical practice for the treatment, education, and follow-up of patients with type 2 diabetes. Patients had open access to a general physician, dietitian, nurse, and diabetes educator and had visits with at least 1 team member every 6 weeks throughout the 2 years. Medical therapies, including pharmaceutical agents, were determined by an experienced diabetologist on an individual basis.

Lifestyle modification programs were individually structured to reduce energy intake, to reduce intake of fat (<30%) and saturated fats, and to encourage intake of low glycemic index and high-fiber foods. Physical activity advice encouraged 10 000 steps per day and 200 minutes per week of structured activity, including moderate-intensity aerobic activity and resistance exercise. Lifestyle was the primary approach to weight loss, but very low-

**Figure 1.** Participant Recruitment, Assessment, and Participation Throughout the Study



BMI indicates body mass index.

calorie diets and medications were discussed with all patients and used after consultation with the dietitian or general physician if the patient expressed a desire to use additional measures.

**Surgical Program.** In addition to all aspects of the conventional-therapy program, the surgical group underwent placement of a laparoscopic adjustable gastric band via the pars flaccida technique by 1 of 2 experienced surgeons within 1 month of randomization.<sup>22</sup> Progress was reviewed by the bariatric surgical team every 4 to 6 weeks throughout the study, and adjustments to band volume were made using standard clinical criteria.<sup>23</sup>

### Primary and Secondary Outcomes

The primary end points of the study related to glycemic control at 2 years after randomization. These were assessed as the proportion of participants achieving remission (exceptional glycemic control) of type 2 diabetes, defined as fasting plasma glucose levels less than 126 mg/dL (to convert to mmol/L, multiply by 0.0555) in addition to HbA<sub>1c</sub> values less than 6.2% without the use of oral hypoglycemics or insulin. The use of metformin posed a dilemma, because it may be recommended in the remitted diabetic state. Our protocol recommended cessation of metformin, if prescribed, when the fasting insulin concentration was normal (<17.0 uIU/mL [to convert to pmol/L, multiply by 6.945]) and the HbA<sub>1c</sub> value was less than 6.2% with a normal fasting plasma glucose level less than 108.0 mg/dL.

Secondary outcome measures included percentage change in HbA<sub>1c</sub> levels, weight, blood pressure, waist circumference, and levels of fasting lipids, including total cholesterol, triglycerides, and high-density lipoprotein cholesterol. Changes in medication use, changes in the proportion of participants with the metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria,<sup>24</sup> and changes in indirect measures of insulin resistance using the homeostatic model assessment method were assessed. Adverse events and effects were recorded.

### Statistical Analysis

**Sample Size.** Sample size was selected to provide a statistical power of 80% to detect a 1% difference in HbA<sub>1c</sub> values between the groups at 2 years (group mean, 6.5% vs 7.5% [SD, 1.3%]) ( $P < .05$ ).<sup>25</sup> The study was also powered for diabetes remission rates on the basis that we expected approximately 60% remission in the surgical group and 20% in the conventional-therapy group.<sup>25</sup> To allow for these scenarios, a minimum of 27 patients were required in each study group. Recruitment size was therefore set at 60.

**Data Analysis.** Univariate statistical analysis was performed using SPSS version 12.01 (SPSS Inc, Chicago, Illinois), with baseline comparisons made using  $\chi^2$  tests for equal proportion,  $t$  tests for normally distributed outcomes, or Mann-Whitney U tests otherwise. Multivariate longitudinal analysis was performed to assess weight and biochemical changes with time using the PROC Mixed procedure in SAS version 8.2 (SAS Institute Inc, Cary, North Carolina). All data were analyzed using a true intention-to-treat analysis for all 60 patients. Continuous variables were expressed as mean (standard deviation), with differences expressed as mean (95% CI). Binary logistic regression was used to examine the associates of diabetes remission. A 2-sided  $P$  value of .05 was considered statistically significant.

## RESULTS

### Study Participants

The flow of participants through the study is shown in FIGURE 1. One patient randomized to surgery withdrew from the study on the evening prior to scheduled operation and did not agree to be further followed up. The remaining 29 surgically treated patients (97%) completed the 2-year program. Of the conventionally treated patients, 26 (87%) completed the 2-year assessment. The baseline characteristics of the groups are shown in TABLE 1. There were no statistically significant differences in demographics or values contributing to study outcomes between the groups. There were only 13 participants with a baseline BMI less than 35—6 randomized to surgery and 7 to the conventional-therapy group. The mean BMI of those recruited to the study was 37.1.

All bands were placed laparoscopically, with a mean procedure time of 54 minutes (SD, 10.8; range, 40-74), and hospital admissions lengths were 1 day (23 [80%]), 2 days (5 [17%]), and 4 days (1 [3%]). The patient who stayed 4 days had the band removed on day 15 due to band intolerance. This patient underwent

follow-up for 2 years, in accordance with the intention-to-treat analysis. Sixteen of the 26 completers in the conventional-therapy group elected to use a very low-calorie diet (n=11) or sibutramine (n=7) at some stage during the 2 years. None elected to use orlistat.

### Diabetes Remission

Remission of type 2 diabetes was achieved by 26 study participants (43%) at 2 years (22/30 [73%] randomized to the surgical program and 4/30 [13%] to the conventional-therapy program) ( $P < .001$ ). This represented 76% and 15% remission rates among completers in the surgery and conventional-therapy groups, respectively. A most conservative analysis using the assumption that all 4 noncompleters in the conventional-therapy group achieved remission and that the only noncompleter in the surgical group did not indicate significantly greater remission in the surgically treated group (22/30 [73%] for surgery vs 8/30 [27%] for conventional therapy,  $P < .001$ ).

Greater percentage of weight loss at 2 years and lower baseline HbA<sub>1c</sub> values were independently associated with remission (Cox-Snell  $R^2 = 0.50$ ,  $P < .001$ ), but percentage of weight loss alone explained most of the variance (Cox-Snell  $R^2 = 0.46$ ,  $P < .001$ ). The patients' sex, age, baseline BMI, C-peptide level, time spent engaged in planned physical activity, and the group to which they were randomized were not predictive of remission after controlling for percentage of weight loss. FIGURE 2 shows individual percentage weight loss as well as baseline and 2-year measures of weight for patients randomized to each group.

Only 4 of 34 patients (12%) who lost less than 10% of body weight were in remission at 2 years (Figure 2). This group was characterized by significantly lower baseline HbA<sub>1c</sub> levels when compared with others who lost 10% or more. All were below 6.9%, with the median 6.45%, compared with me-

**Table 1.** Baseline Characteristics of Participants<sup>a</sup>

Characteristic	Surgery (n = 30)	Conventional Therapy (n = 30)
Age, mean (SD), y	46.6 (7.4)	47.1 (8.7)
Men, No. (%)	15 (50)	13 (43)
Hypertension, No. (%)	28 (93)	27 (90)
Metabolic syndrome, No. (%)	29 (97)	29 (97)
Coronary artery disease, No. (%)	0	1 (3)
BMI, mean (SD) <sup>b</sup>	37.0 (2.7)	37.2 (2.5)
Weight, mean (SD), kg	105.6 (13.8)	105.9 (14.2)
Waist circumference, mean (SD), cm	114.1 (10.2)	116.0 (10.0)
Waist to hip ratio, mean (SD)	0.96 (0.09)	0.96 (0.10)
Neck circumference, mean (SD), cm	41.8 (4.0)	42.4 (4.5)
Blood pressure, mean (SD), mm Hg		
Systolic	136.4 (15.6)	135.3 (14.4)
Diastolic	86.6 (9.4)	84.5 (9.8)
HbA <sub>1c</sub> , mean (SD), %	7.8 (1.2)	7.6 (1.4)
Plasma glucose, mean (SD), mg/dL	156.7 (38.5)	158.0 (48.7)
Plasma insulin, median (IQR), $\mu$ U/mL	19.7 (16.5-27.5)	18.7 (13.7-30.7)
Lipids, mean (SD), mg/dL		
Total cholesterol	201.8 (32.7)	198.2 (56.7)
Triglycerides	190.6 (106.6)	188.7 (111.8)
HDL-C	47.1 (10.1)	48.1 (11.1)
Total cholesterol to HDL-C ratio	4.41 (0.87)	4.23 (1.11)

Abbreviations: BMI, body mass index; HbA<sub>1c</sub>, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range.

SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; insulin to pmol/L, by 6.945; total cholesterol and HDL-C to mmol/L, by 0.0259; and triglycerides to mmol/L, by 0.0113.

<sup>a</sup>There were no statistically significant differences between the groups.

<sup>b</sup>Calculated as weight in kilograms divided by height in meters squared.

dian 7.6% for the remaining 30 ( $P = .02$  by Mann-Whitney U test). Only 4 of 26 (15%) losing more than 10% body weight did not achieve remission. There were no significant baseline predictors of this small group.

### Weight Loss

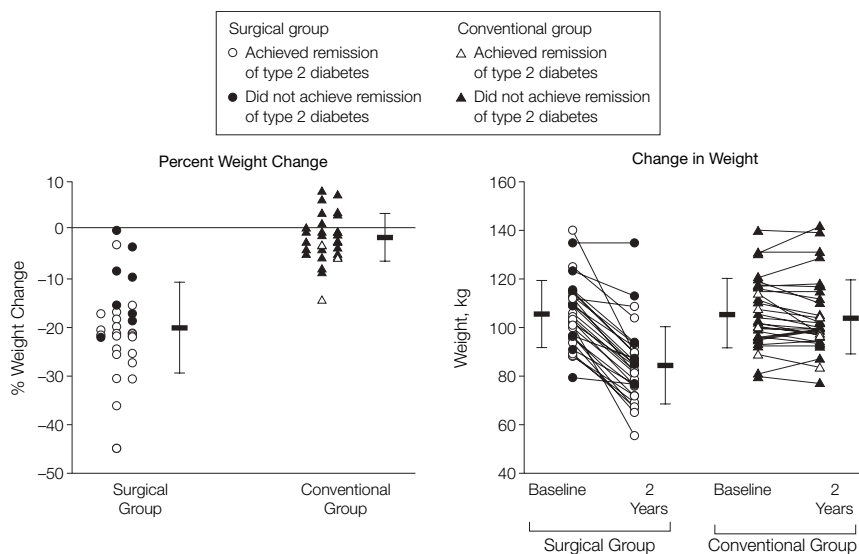
The surgical group achieved a mean 20.0% (SD, 9.4%) body weight loss at 2 years, compared with 1.4% (SD, 4.9%) among the conventional-therapy group ( $P < .001$ ) (Figure 2). This represents a loss of 62.5% of excess weight (using BMI of 25 as ideal weight) in the surgical group compared with 4.3% in the conventional-therapy group and a reduction of BMI from 36.9 to 29.5 compared with a reduction from 37.1 to 36.6. Individual and grouped mean (SD) weight changes for both groups are shown in Figure 2. The surgical group had a greater weight loss ( $P < .001$ ), and the difference between the groups increased with time ( $P < .001$ ).

### Physical Activity

There was a positive correlation between average times participants reported performing planned physical activity each week throughout the study and weight loss (Spearman  $r = 0.39$ ,  $P = .003$ ). Participants (n=29) who reported more than 3 periods of physical activity of greater than 30 minutes per week (median reported) had better mean weight loss (13.9 [SD, 10.9] kg compared with 7.8 [SD, 12.3] kg,  $P = .046$ ) and a higher likelihood of diabetes remission (odds ratio, 3.4; 95% CI, 1.2-10.1;  $P = .02$ ). However, reported physical activity was not an independent predictor of diabetes remission.

### Glycemic Control

Mean levels of HbA<sub>1c</sub> and fasting plasma glucose were significantly lower in the surgical group at 2 years ( $P < .001$  for both). At baseline there were 2 (7%) surgically treated and 4 (13%) conventionally treated participants with HbA<sub>1c</sub> levels less than

**Figure 2.** Percentage of Weight Loss Achieved Over the 2-Year Study Period (n=60) and Individual Weight Measures at Baseline and at 2 Years

Remission indicates those achieving remission of type 2 diabetes (see "Methods") at 2 years. Data markers with error bars indicate mean (SD).

6.2%; at 2 years, the numbers were 24 (80%) and 6 (20%), respectively. The proportion with HbA<sub>1c</sub> levels less than 6.2% improved significantly ( $P < .001$ ) in the surgical group but not in the conventional-therapy group.

### Use of Diabetes Medication

There was a significant reduction in the use of pharmacotherapy for glycemic control in the surgical group at 2 years. At baseline, 2 surgically treated and 4 conventionally treated patients were not using pharmacotherapy; at 2 years, the numbers were 26 and 8, respectively. In the surgical group at 2 years there were fewer using metformin (3 vs 28,  $P < .001$ ) and other hypoglycemic therapy (1 vs 9,  $P = .006$ ). The 1 surgical patient using insulin at baseline was in remission at 2 years. There were no significant changes in the use of therapy in the group randomized to receive conventional therapy. Metformin was used by 26 and 18, other oral hypoglycemic agents by 8 and 7, and insulin by 0 and 3, at baseline and 2 years, respectively.

### Other Health Outcomes

TABLE 2 shows changes in some clinical and laboratory measures of health at 24 months. The surgical group had a significantly greater improvement at 2 years in insulin resistance and in levels of triglycerides and high-density lipoprotein cholesterol. The metabolic syndrome was present in 29 patients (97%) in each group prior to commencement of treatment, and 21 (70%) of surgically treated and 4 (13%) conventionally treated participants did not fulfill the National Cholesterol Education Program Adult Treatment Panel III criteria at 2 years ( $P < .001$ ). The reduction in the metabolic syndrome was significant in the surgical group ( $P < .001$ ) but not in the conventional-therapy group ( $P = .23$ ). Caution is required in interpreting these results, as the study was not powered to assess multiple outcome measures.

### Use of Nondiabetes Medication

Although there was no significant blood pressure difference between completers in the surgical and conventional-therapy groups, there was a signifi-

cant ( $P = .005$ ) reduction in use of antihypertensive agents in the surgical group (20/29 at baseline and 6/29 at 2 years,  $P < .001$ ) compared with the conventional-therapy group (15/26 at baseline and at 2 years). There also was a reduction in the use of lipid-lowering medications in the surgical group (12/29 at baseline and 4/29 at 2 years,  $P = .02$ ) but no significant change in the conventional-therapy group (8/26 at baseline and 7/26 at 2 years).

### Adverse Events

**Surgical Group.** One patient developed a superficial wound infection over the access port site 2 weeks postplacement, which resolved with intravenous antibiotics. Two patients developed gastric pouch enlargement, both at 10 months after placement, and were treated with nonurgent laparoscopic revisional surgery to remove and replace the band. One patient experienced eating difficulties and persistent regurgitation with no saline in the band and no impedance of flow on contrast study. The band was removed 15 days after placement. Hospital stay for each revisional procedure was less than 1 day, and there were no complications. Other adverse events reported were postoperative febrile episodes in 1 patient. No cause was found, and the fever resolved. A minor hypoglycemic episode occurred in 1 patient and gastrointestinal tract intolerance to metformin in another.

**Conventional-Therapy Group.** Two patients had minor gastrointestinal tract adverse effects, and 1 had persistent diarrhea with metformin. One patient developed vasculitic rash, possibly related to rosiglitazone. All problems resolved when the medications were discontinued. One patient had multiple hypoglycemic episodes, and another was admitted to hospital with angina and a transient cerebral ischemic episode. Two patients were intolerant of very low-calorie meal replacement.

### COMMENT

This study, to our knowledge the first randomized trial comparing surgically induced loss of weight with con-

ventional therapy for management of type 2 diabetes in obese participants, demonstrates superior glycemic control and diabetes remission rates with adjustable gastric banding. After 2 years, the surgical group displayed a 5 times higher remission rate and 4 times greater reduction in HbA<sub>1c</sub> values than the conventional-therapy group. This study confirms the findings of several observational studies,<sup>25,27-30</sup> including the case-controlled Swedish Obese Subjects Study,<sup>31</sup> that found heightened diabetes remission rates among 2000 patients undergoing gastric stapling with follow-up for 10 years.

In addition to superior glycemic control, this study also demonstrates higher rates of resolution of the metabolic syndrome, confirming the finding of an earlier randomized controlled trial,<sup>32</sup> as well as improvements in insulin sensitivity and concentrations of triglycerides and high-density lipoprotein cholesterol in the surgical group. These changes in secondary outcome measures need to be examined with caution and are hypothesis-generating only, as the study was not powered for an examination of multiple secondary outcome measures. There also appeared to be significant reductions in the use of oral hypoglycemic, antihypertensive, and lipid-lowering medications in patients randomized to surgery. Although the physician responsible for altering medications was not blinded to treatment group, blood pressure and biochemical data indicate that decision-making was determined by clinical need.

An important finding of this study is that degree of weight loss, not the method, appears to be the major driver of glycemic improvement and diabetes remission in obese participants. This has important implications, as it suggests that intensive weight-loss therapy may be a more effective first step in the management of diabetes than simple lifestyle change. This study shows that few participants achieved remission with a body weight loss of less than 10%, a level expected to produce important health benefits.<sup>33</sup>

The aim of this current trial was to compare 2 established treatment programs that involve widely available and accepted therapies. The use of bariatric surgery is rapidly increasing, and more than 90% of procedures performed in Australia are LAGB. At the time this study was carried out, early intensive use of insulin was unusual practice in Australia, and access to thiozolidinedione medications was restricted for patients with poor glycemic control. The hypo-

glycemic agent exenatide was also unavailable. The results achieved by the surgical group in this study closely resemble those now being targeted by experimental intensive medical therapies using multiple hypoglycemic strategies, including exenatide and early insulin use.<sup>34</sup> It is worth noting that the results achieved by weight-loss surgery come without the risks of hypoglycemia and weight gain often associated with medical therapies.

**Table 2.** Primary and Secondary Outcomes at 2 Years<sup>a</sup>

Variable	Mean (SD)		Between-Group Difference, Mean (95% CI)	P Value
	Surgery (n = 30)	Conventional Therapy (n = 30)		
<b>Primary Outcome, No. (%)</b>				
Remission of diabetes, No. (%)	22 (73)	4 (13)	RR for surgical remission, 5.5 (2.2 to 14.0)	<.001
<b>Secondary Outcomes</b>				
Weight, kg	84.6 (15.8)	104.8 (15.3)		
Change, kg	-21.1 (10.5)	-1.5 (5.4)	-19.6 (-23.8 to -15.2)	<.001
Waist circumference, cm	95.8 (10.3)	112.7 (10.3)		
Change, cm	-17.9 (10.8)	-4.0 (9.1)	-13.9 (-19.0 to -8.7)	<.001
Waist to hip ratio	0.90 (0.06)	0.95 (0.08)		
Change	-0.06 (0.06)	-0.01 (0.06)	-0.05 (-0.07 to -0.007)	.02
Blood pressure, mm Hg				
Systolic	130.4 (19.0)	132.6 (17.7)		
Change	-6.0 (17.9)	-1.7 (14.2)	-4.3 (-13.6 to 5.1)	.37
Diastolic	85.4 (7.0)	83.1 (8.5)		
Change	-0.7 (11.1)	-0.9 (11.1)	0.2 (-5.4 to 6.0)	.92
HbA <sub>1c</sub> , %	6.00 (0.82)	7.21 (1.39)		
Change	-1.81 (1.24)	-0.38 (1.26)	-1.43 (-2.1 to -0.80)	<.001
Plasma glucose, mg/dL	105.6 (30.3)	139.6 (38.1)		
Change	-51.2 (37.6)	-18.4 (41.2)	-32.8 (-53.1 to -12.3)	.002
Plasma insulin, µIU/mL	9.8 (4.7)	24.1 (13.6)		
Change	-12.4 (8.4)	1.0 (14.8)	-13.4 (-19.6 to -7.3)	<.001
HOMA IR <sup>b</sup>	1.90 (0.73)	3.50 (0.97)		
Change, %	-45.5 (19.0)	-3.3 (35.4)	-42.2 (-57 to -26.8) <sup>c</sup>	<.001
Total cholesterol, mg/dL	205.4 (46.6)	197.8 (59.3)		
Change	3.6 (51.6)	-0.4 (31.4)	4.0 (-18.8 to 26.0)	.72
Triglycerides, mg/dL	118.9 (79.7)	186.7 (127.2)		
Change	-71.7 (92.9)	-2.1 (120.6)	-69.6 (-125.3 to -13.6)	.02
HDL-C, mg/dL	59.7 (13.6)	50.7 (12.1)		
Change	12.6 (9.8)	2.6 (6.1)	10.0 (5.8 to 14.2)	<.001
Total cholesterol to HDL-C ratio	3.58 (1.00)	4.1 (1.4)		
Change	-0.82 (1.9)	-0.14 (1.04)	-0.68 (-1.24 to -0.14)	.02

Abbreviations: CI, confidence interval; HbA<sub>1c</sub>, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA IR, insulin resistance by homeostatic model assessment; LDL-C, low-density lipoprotein cholesterol; RR, relative risk. SI conversion factors: see Table 1 footnote.

<sup>a</sup>Mean (SD) percentage change for participants with baseline values carried forward for those who dropped out of the study. A comparison of the actual change from baseline is also presented. Data include all 60 participants with baseline data carried forward for missing data.

<sup>b</sup>An indirect measure of insulin resistance calculated from levels of fasting plasma glucose and fasting C-peptide.<sup>26</sup>

<sup>c</sup>P < .05 calculated using independent t test.

Importantly, this study is the first, to our knowledge, to formally document change in glycemic control in patients with diabetes and BMI of 30 to 35 following surgically induced weight loss. Bariatric surgical guidelines include only BMI greater than 35 with comorbid type 2 diabetes as an indication for weight loss surgery.<sup>35,36</sup> In this study we found the benefits of weight loss as efficacious for participants with BMI in the 30 to 35 range as for those with BMI in the 35 to 40 range; however, analysis and conclusions are limited, as there were only 13 participants (22%) in this BMI category.

Our study did not include participants with a BMI greater than 40. We believed it inappropriate to recruit those with a BMI greater than 40 into the study, because a number of observational studies have shown effectiveness of bariatric surgery in these patients.

The adverse events observed in this trial were in line with expectations. Among patients undergoing LAGB surgery, rates of postoperative wound infection around the port were approximately 1% to 2%, and reoperation rates for gastric pouch enlargement were approximately 5%.

Several limitations of our study need to be recognized. First, we restricted the study to participants with a recent diagnosis (<2 years) of type 2 diabetes, and therefore results may not apply to those with a longer history of disease due to deterioration of  $\beta$ -cell function with time. Second, the experience of our bariatric surgical team with the LAGB procedure is extensive. Systematic review shows inverse correlation between the experience of the LAGB surgical team and incidence of early and late complications.<sup>21</sup> Third, our study was not powered for safety or to detect differences in hard end points, such as mortality or cardiovascular events. Such studies would require many more participants followed up over a much longer period. Our study only followed up participants for 2 years, and results cannot be readily extrapolated for longer periods. Clearly, weight re-

gain or simply the passage of time puts those achieving remission of type 2 diabetes at risk of relapsing back into diabetic status.

One patient from the surgical group and 4 from the conventional-therapy group did not complete the 2-year follow-up. To account for this missing information, the most conservative case scenario was considered, with the 4 noncompleters from the conventional-therapy group assumed to have achieved diabetic remission and the noncompleter from the surgical group assumed to have not achieved remission. Under this scenario, the difference between the surgical and the conventional-therapy groups for those achieving remission still remained highly significant (22/30 [73%] for surgery vs 8/30 [27%] for conventional therapy,  $P < .001$ ).

In conclusion, this randomized trial demonstrates that weight loss associated with adjustable gastric banding results in diabetes remission in the majority of obese participants recently diagnosed as having diabetes and was associated with greater improvements in features of the metabolic syndrome and use of related medications. While caution is required in interpreting the longer-term benefits of surgery and weight loss, this study presents strong evidence to support the early consideration of surgically induced loss of weight in the treatment of obese patients with type 2 diabetes.

**Author Contributions:** Drs Dixon and Bailey and Ms Anderson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Dixon, O'Brien, Schachter, Proietto.

**Acquisition of data:** Dixon, O'Brien, Playfair, Chapman, Schachter, Skinner, Anderson.

**Analysis and interpretation of data:** Dixon, O'Brien, Playfair, Bailey, Anderson.

**Drafting of the manuscript:** Dixon, O'Brien.

**Critical revision of the manuscript for important intellectual content:** Dixon, O'Brien, Playfair, Chapman, Schachter, Skinner, Proietto, Bailey, Anderson.

**Statistical analysis:** Dixon, Bailey, Anderson.

**Obtained funding:** Dixon, O'Brien.

**Administrative, technical, or material support:** Dixon, O'Brien, Playfair, Schachter, Skinner, Proietto, Anderson.

**Study supervision:** Dixon, O'Brien, Schachter, Anderson.

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## REFERENCES

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001; 414(6865):782-787.
2. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care*. 2000; 23(9):1278-1283.
3. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995;122(7):481-486.
4. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;17(9):961-969.
5. Leibson CL, Williamson DF, Melton LJ III, et al. Temporal trends in BMI among adults with diabetes. *Diabetes Care*. 2001;24(9):1584-1589.
6. UK Prospective Diabetes Study Group. UK prospective diabetes study 16: overview of 6 years' therapy of type II diabetes: a progressive disease [published correction appears in *Diabetes*. 1996;45(11):1655]. *Diabetes*. 1995;44(11):1249-1258.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853.
8. UK Prospective Diabetes Study Group. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). *Diabetes Care*. 1999;22(7):1125-1136.
9. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38 [published correction appears in *BMJ*. 1999;318(7175):29]. *BMJ*. 1998;317(7160):703-713.
10. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care*. 2000;23(10):1499-1504.
11. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. *Am J Med*. 2004;117(10):762-774.
12. Khan MA, St Peter JV, Breen GA, Hartley GG, Ves-

- sey JT. Diabetes disease stage predicts weight loss outcomes with long-term appetite suppressants. *Obes Res.* 2000;8(1):43-48.
13. Zimmet P, Shaw J, Alberti KG. Preventing type 2 diabetes and the dysmetabolic syndrome in the real world: a realistic view. *Diabet Med.* 2003;20(9):693-702.
14. Wing RR, Marcus MD, Epstein LH, Salata R. Type II diabetic subjects lose less weight than their overweight nondiabetic spouses. *Diabetes Care.* 1987;10(5):563-566.
15. Brandle M, Zhou H, Smith BR, et al. The direct medical cost of type 2 diabetes. *Diabetes Care.* 2003;26(8):2300-2304.
16. Dixon JB, Pories WJ, O'Brien PE, Schauer PR, Zimmet P. Surgery as an effective early intervention for diabetes: why the reluctance? *Diabetes Care.* 2005;28(2):472-474.
17. American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care.* 2007;30(suppl 1):S4-S41.
18. Favretti F, Segato G, Ashton D, et al. Laparoscopic adjustable gastric banding in 1,791 consecutive obese patients: 12-year results. *Obes Surg.* 2007;17(2):168-175.
19. Weiner R, Blanco-Engert R, Weiner S, Matkowitz R, Schaefer L, Pomhoff I. Outcome after laparoscopic adjustable gastric banding—8 years experience. *Obes Surg.* 2003;13(3):427-434.
20. Dargent J. Surgical treatment of morbid obesity by adjustable gastric band: the case for a conservative strategy in the case of failure—a 9-year series. *Obes Surg.* 2004;14(7):986-990.
21. Chapman AE, Kiroff G, Game P, et al. Laparoscopic adjustable gastric banding in the treatment of obesity: a systematic review. *Surgery.* 2004;135(3):326-351.
22. O'Brien PE, Dixon JB, Laurie C, Anderson M. A prospective randomized trial of placement of the laparoscopic adjustable gastric band: comparison of the perigastric and pars flaccida pathways. *Obes Surg.* 2005;15(6):820-826.
23. Favretti F, O'Brien PE, Dixon JB. Patient management after LAP-BAND placement. *Am J Surg.* 2002;184(6B):385-415.
24. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287(3):356-359.
25. Dixon JB, O'Brien PE. Health outcomes of severely obese type 2 diabetic subjects 1 year after laparoscopic adjustable gastric banding. *Diabetes Care.* 2002;25(2):358-363.
26. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27(6):1487-1495.
27. Ponce J, Haynes B, Paynter S, et al. Effect of Lap-Band-induced weight loss on type 2 diabetes mellitus and hypertension. *Obes Surg.* 2004;14(10):1335-1342.
28. Pories WJ, MacDonald KG Jr, Morgan EJ, et al. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. *Am J Clin Nutr.* 1992;55(2)(suppl):582S-585S.
29. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus. *Ann Surg.* 2003;238(4):467-485.
30. Sugeran HJ, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. *Ann Surg.* 2003;237(6):751-758.
31. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* 2004;351(26):2683-2693.
32. O'Brien PE, Dixon JB, Laurie C, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: a randomized trial. *Ann Intern Med.* 2006;144(9):625-633.
33. Oster G, Thompson D, Edelsberg J, Bird AP, Colditz GA. Lifetime health and economic benefits of weight loss among obese persons. *Am J Public Health.* 1999;89(10):1536-1542.
34. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widell MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med.* 2005;143(8):559-569.
35. National Institutes of Health. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am J Clin Nutr.* 1992;55(2)(suppl):615S-619S.
36. Snow V, Barry P, Fitterman N, Qaseem A, Weiss K. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2005;142(7):525-531.

[The medical career] is one in which it is possible for people—men or women—to pursue the dying ideal that an occupation for adults should allow of intellectual freedom, should give character as much chance as cleverness, and should be subject to the tonic and difficulty and the spice of danger.

—Wilfred Trotter (1872-1939)