A Randomized Controlled Trial of Multidisciplinary Diabetes Care with and without Bariatric Surgery in Overweight People (BMI 25-30kg/m^2).

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Abstract

Background

Bariatric surgery dramatically improves glycemia in obese people with type 2 diabetes (T2D), but its effects in overweight people with T2D is uncertain.

Methods

We tested the hypothesis that laparoscopic adjustable gastric band surgery (LAGB) also improved glycemia in overweight people with T2D by performing an unblinded randomized trial at a single Melbourne center. Fifty one participants with T2D whose body mass index (BMI) ranged from 25 to 30kg/m^2 were randomized by a third party to receive multidisciplinary diabetes care (MDC) or MDC combined with LAGB. The primary outcome was remission of diabetes two years after randomization, defined as glucose levels below 7.0 and 11.1mmol/L before and 2h after 75g oral glucose.

Findings

Twenty-six and 25 people were assigned to the MDC and LAGB groups respectively. Twenty-five MDC and 23 LAGB participants completed 2-year follow-up. Of these, 12 participants (52%) in the LAGB group and 2 participants (8%) in the MDC group were in diabetes remission (difference in proportions 0.44, 95% CI 0.17-0.71; p=0.0012). One LAGB participant required revisional surgery and four others experienced a total of five episodes of food intolerance due to excessive adjustment of the band.

Interpretation

When added to multidisciplinary care, LAGB for overweight people with T2D improves glycemic control with an acceptable adverse event profile. LAGB is a reasonable treatment option for this population.

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Introduction

Excess body weight is known to be a dominant driver of type 2 diabetes (T2D), a disease that places a huge burden on individuals and society through reduced wellbeing and productivity, and increased health costs [1]. Management of T2D is generally framed in a chronic disease model, with expectation of progressive deterioration in glucose control over time [2]. This approach has recently been challenged by randomized trials of lifestyle change [3] or bariatric surgery [4-7], which show weight loss in obese people with T2D reduces medication burden and frequently achieves diabetes remission within two years.

The impact of substantial weight loss on T2D outcomes in overweight but not obese people (body mass index (BMI) between 25 and 30kg/m^2) is less well established. The Look AHEAD investigators showed that, after one year, modest weight loss of 8.6% body weight following lifestyle intervention was associated with a diabetes remission rate of around 10% in people whose starting BMI was less than 32.5kg/m^2 [3]. Reports of the effect of bariatric surgery in overweight people with T2D are limited to observational studies of bypass, intestinal exclusion or interposition surgery [8-12], which describe improved glycaemic control following surgery and serious perioperative complications in up to 7% of patients. To date, no randomized trials of bariatric surgery in overweight but not obese people have been reported and its true benefit, if any, remains uncertain.

Laparoscopic adjustable gastric banding (LAGB) is a common outpatient operation for obese people that has a favorable safety profile compared to other bariatric operations [13, 14] and provides a durable effect with substantial weight loss sustained for at least 15 years [15]. Our previous randomized trial in moderately obese people with T2D (BMI between 30 and 40kg/m^2) showed LAGB induced diabetes remission more commonly than medical therapy after two years of follow-up. We performed this trial to determine if LAGB had a similar impact on glucose control in people with T2D who were overweight but not obese (BMI 25-30kg/m^2). Our hypothesis was that LAGB in addition to multidisciplinary diabetes care (MDC) would improve glycemic control with acceptable comparative costs and safety when compared to MDC alone.

Methods

Study Design

This was a single center, non-blinded randomized controlled trial with two parallel arms in which 51 eligible patients were assigned to a two year program of MDC plus LAGB (LAGB group) or MDC alone (MDC group). The study was approved by the Human Ethics committees of Monash University and The Avenue Hospital and was registered with the Australasian Clinical Trials Registry (ACTRN12609000286246).

Participants

Participants were recruited between November 2009 and June 2011. Inclusion criteria were age between 18 and 65 years, BMI between 25 and 30kg/m^2, diabetes duration less than five years, willing to be randomized to either arm of the trial and able to comply with the treatment protocol. Exclusion criteria were positive glutamic acid decarboxylase autoantibody titre, pancreatic disease, prior bariatric surgery or contra-indication to LAGB surgery (including prior upper GI surgery, hypothalamic disease, pregnancy, history of psychosis and myocardial infarct in preceding six months). If HbA1c was less than 6.5% (48mmol/mol), diabetes was confirmed by oral glucose tolerance test (OGTT). One participant with abnormal OGTT had a baseline HbA1c of 4.3% (23mmol/mol) in the setting of moderate splenomegaly and raised mean corpuscular volume of uncertain cause. Randomization was by computer-derived random allocation (without blocking or stratification) until both groups had at least 25 participants. A third party assigned treatment groups using numbered envelopes, which were opened by the participant immediately after consenting to join the study.

Multidisciplinary Diabetes Care (MDC)

MDC was based on ADA guidelines [16] and delivered in Melbourne by one endocrinologist (JMW). Biochemistry and physician review occurred every three months in year one and six-monthly in year two. Consultations with dietician and diabetes educator were arranged within three (MDC group) or six months (LAGB group) of enrolment. Additional consultations with members of the care team were arranged if deemed necessary by either JMW or participant. If HbA1c was greater than 7% in the second year of the trial, endocrinology review was scheduled every three months.

Participants were advised to perform at least 150 minutes of moderate-intensity physical activity each week. HbA1c was targeted to less than 7.0% (54mmol/mol) using, where necessary, medications available through the Australian Pharmaceutical Benefit Scheme. Metformin was recommended to all participants unless it was not tolerated or an OGTT was normal at one year. Sitagliptin or exenatide were commenced if HbA1c was greater than 7.0% despite metformin and/or sulfonylurea therapy. Blood pressure was targeted to <120/80mmHg in participants with albuminuria or a history of cardiovascular disease, and to <130/80mmHg for others. Antihypertensive drug therapy was intensified if these targets were not achieved following a 3-month period of lifestyle change. Anti-platelet therapy and statins were prescribed to all participants with a history of cardiovascular disease and to those over the age of 40 who had an additional cardiovascular risk factor. Annual ophthalmology review was arranged through the family physician. Medications were weaned if JMW judged that the participant would continue to meet treatment targets, which were reassessed within three months of such medication change.

The dietician recommended a tailored calorie-restricted diet to all participants. Multivitamin supplements were recommended to all LAGB participants. The diabetes educator session(s) focused on diabetes self-management, including blood glucose monitoring and sick day management.

LAGB surgery

Within three months of randomization, the LAP-BAND APS (Allergan Inc, Irvine, CA) was placed via the pars flaccida pathway and sited over the gastric cardia within 1 cm of the esophago-gastric junction by one of three surgeons (PEO, WAB, PB). The basal fluid within the system at the completion of the procedure was usually 4 ml. Incidental hiatal hernia was repaired as a part of the procedure. Patient discharge was planned for approximately 3hr after completion of the procedure, which occurred for all but one person. Aftercare to adjust the band and optimize eating and exercise behaviors was provided at The Centre for Bariatric Surgery, Melbourne, according to the management algorithms established by the center [17].

Outcomes

The primary outcome was used to test the hypothesis that LAGB increases the likelihood of diabetes remission two years after randomization. Remission was defined as fasting glucose and 2h glucose levels less than 7.0 mmol/L and 11.1 mmol/L at least two days after stopping glucose-lowering medication. Participants could be classified as in remission even if they had been taking diabetes medications continuously up until two days before this test. Exploratory secondary outcomes, assessed during the trial and after two years, were weight change, glycemic control (fasting glucose, HbA1c), blood pressure, lipid profile, medication burden, quality of life and costs.

Data collection

Clinical biochemistry was performed by Melbourne Pathology (Collingwood, Australia). The oral glucose tolerance test to assess diabetes status was only performed at two-year follow-up if HbA1c was less than 6.5% (48mmol/mol) and fasting blood glucose less than 7.0 mmol/L irrespective of whether the participant was taking diabetes therapy. Anthropometric data and blood pressure, measured by automated sphygmomanometer (Philips SureSign VS2; Andover Massachussetts), were collected by a study nurse. Quality of life was assessed at baseline and two years using the SF-36 questionnaire [18], standardized to Australian norms (Australian Bureau of Statistics Catalogue 4399.0). Adverse events were collated prospectively by the research nurses (JP and CL), verified by contacting the relevant health practitioner or hospital, and adjudicated by the authors. There was no data safety monitoring board.

Identification and measurement of costs

Trial intervention costs comprised costs of LAGB surgery, treatment of surgical adverse events and outpatient consultations (physician, dietician, diabetes educator and surgeon). Surgery costs were sourced from The Avenue Hospital and the relevant medical specialists. The cost of the LAGB prosthesis is based on commercial prices. Drug costs and units costs for medical and allied health consultations were obtained from pricing schedules of the Australian Government Pharmaceutical Benefits Scheme (PBS) and the Medicare Benefits Schedule (MBS). Other relevant health costs (eg other hospital admissions, time off work) were not included in the economic analysis. Costs are reported in Australian dollars (AUD) at 2013 values.

Statistical analyses

The power calculation was based on our prior RCT [4] and assumed 60% of the LAGB and 15% of the MDC group would achieve diabetes remission. Allowing for 5 drop-outs in each arm, enrolment of 25 participants into each arm afforded 93% power to detect the assumed difference of 45% in the rate of diabetes remission between the groups ($p<0.05$). Baseline and two-year data were present for all participants who completed the study. Two missing HbA1c values at 18 months (one in each group) were filled by carrying forward prior values. Analyses were performed using Prism 6.0b software (Graphpad, CA) and R (www.**r**-project.org). Data were analysed using intention-to-treat for all patients. Categorical data were compared using Fisher's exact test, and confidence intervals for the difference in proportions between the LAGB and MDC groups calculated using the approach of Wilson with continuity correction. Continuous data were compared using the Student's t test, with mean differences and 95% CIs reported. However, some outcomes were non-normally distributed according to the Shapiro-Wilks test, so we have provided supplementary tables showing data as median [Q1, Q3] with p-values from a non-parametric Mann-Whitney U test. For changes in HbA1c and weight loss over time (Figure 2b), the area enclosed by the abscissa and the curve was calculated for each patient using the trapezoid rule. Logistic regression was performed using the glm function from the stats package in R, with the significance of each variable determined via analysis of deviance using a Chi-square test. Diabetes status was the outcome and the input variables were a combination of factors that were either known (baseline BMI, percent weight loss at two years, diabetes duration, insulin use, HbA1c, and fasting glucose, insulin and C-peptide [19-21]) or hypothesized (baseline age, sex, number of diabetes medications, waist circumference, blood pressure, lipid levels and presence of albuminuria) to associate with diabetes remission following bariatric surgery. In all analyses, p-values reported are unadjusted and a p-value of less than 0.05 (based on a two-sided test where appropriate) was considered statistically significant.

Role of funding source

This study was funded by a research grant from Allergan Inc and Applied Medical to the Monash University Centre for Obesity Research and Education, which sponsored this trial. The funding source did not participate in study design, data collation and analysis or preparation of this manuscript. JMW and PEO had full access to all of the data and were ultimately responsible for the decision to submit for publication.

Results

Participants

Patient flow is depicted in Figure 1. Fifty-one people were randomized to receive either best practice diabetes care (MDC group; n=26) or best practice care combined with LAGB (LAGB group; n=25). Their baseline characteristics are given in table 1. One MDC group member and two LAGB group members did not complete 2-year follow-up and one of the 23 retained LAGB participants declined surgery. Consultation compliance with the physician and the dietician was similar between the LAGB and MDC groups. One participant from each group failed to attend scheduled physician reviews, and 9 LAGB and 2 MDC participants did not consult with the dietician. LAGB participants were less likely to consult with the diabetes educator, with eighteen compared to one MDC participant failing to attend at least one appointment.

Glucose control

The primary outcome of diabetes remission was assessed at least two days after stopping diabetes medication. Twelve (52%) LAGB and two (8%) MDC participants achieved remission (difference in proportions 0.44, 95%CI 0.17-0.71; p=0.0012; Table 2). This difference remained significant if we assumed the two LAGB participants lost to follow-up did not remit whereas the one MDC participant lost to follow-up achieved diabetes remission at two years (difference in proportions 0.36, 95%CI 0.09-0.64; p=0.0059). In both groups, remission of diabetes was associated with weight loss of greater than 8% body weight (Figure 2a). The time-course of the effects of each intervention on weight and glucose control in people who completed 2-year follow-up is depicted in Figure 2b.

The degree of weight loss was significantly greater in the LAGB compared to the MDC group, with mean two-year weight loss of 11.5kg (-11.5kg change, 95% CI -14.1 to -8.9kg; p<0.0001) and 1.6kg respectively (-1.6kg change, 95% CI -4.3 to +1.0kg; p=0.2079). HbA1c progressively declined (Figure 2b), reaching an average reduction of 0.8 percentage points (95% CI -1.1 to -0.5; p<0.0001) at two years in LAGB participants despite four of them stopping insulin (Figure 2c) and another five ceasing oral glucose-lowering drugs. In contrast, although glucose-lowering medication was used more frequently in the MDC group (Figure 2c), HbA1c decreased to a lesser extent, and this reduction was not sustained at two years (0.1 percentage point change, 95% CI -1.2 to +1.4; p=0.9188; Figure 2b and Table 3).

Other outcomes

Other outcomes for participants who completed 2-year follow-up are summarized in Table 3. LAGB had a less dramatic impact on other vascular disease risk factors in the context of relatively constant use of blood pressure- and lipid-lowering medications (Figure 2c). LAGB was associated with meaningful changes in diastolic blood pressure, and levels of HDL cholesterol and triglycerides, whereas MDC participants had reduced levels of total cholesterol, LDL cholesterol and triglycerides at two years (Table 3). Neither treatment strategy had a significant impact on the number of participants meeting blood pressure, smoking and albuminuria treatment targets. Composite measures of physical (PWB) and mental (MWB) wellbeing were assessed using the SF-36 tool [18]. Baseline scores were slightly below the Australian population mean±SD of 50±10, being 48±8 and 48±8 for PWB (no difference, 95% CI -5 to 4; p=0.9139), and 49±11 and

48±12 for MWB (1 point difference, 95% CI -8 to 6; p=0.7960) in the LAGB and MDC groups respectively. The improved physical wellbeing observed in LAGB participants (Table 3) was due to improved scores in the domains of physical function, body pain and general health.

Factors associated with diabetes remission

We performed regression analysis to determine factors associated with diabetes remission at two years irrespective of the mode of therapy. This identified weight loss as the factor most strongly associated with diabetes remission, with an odds ratio (95% CI) per 1% weight loss of 1.6 (1.2 to 2.9; p<0.0001). Baseline measures of glycemia were the only other factors significantly associated with diabetes remission (odds ratio per 1mmol/L glucose: 1.2×10^{-14} 95% CI 5.6×10^{-36} to 1.1×10^{-3}; p=0.0028 and odds ratio per 1 HbA1c percentage unit: 0.04; 95% CI 0.0004 to 0.4; p=0.0004). Of the 23 people who attained more than 8% weight loss at two years, 14 entered diabetes remission and 9 did not. In these people, no baseline characteristic was significantly associated with diabetes remission.

Adverse events

One patient developed a symmetrical enlargement of the stomach above the band that required revision surgery as an outpatient at the 99^{th} week of the study. Four LAGB patients had a total of five episodes of food intolerance that required a reduction of the fluid volume in the band as outpatients. There were five unplanned surgical procedures (knee arthroscopy, uterine curettage, inguinal hernia repair, cholecystectomy and transurethral resection of prostate) affecting four participants in the LAGB group compared to one (knee arthroscopy) in the MDC group. Two MDC patients required retinal photocoagulation and one was admitted to hospital for two months to manage eosinophilic fasciitis, possibly precipitated by atorvastatin.

Health costs

The total cost (95% CI) of treatment per patient was AUD$13,024 ($11664 to $14385) in the LAGB group compared to AUD $3,918 ($3093 to $4743) in the MDC group (difference $9106, 95% CI $7588 to $10625; p<0.0001). Table 4 shows the mean costs per patient by resource category for the two groups. The LAGB group had a median [Q1, Q3] of 26 [18, 29] outpatient visits during the two year follow up and had 9 [5, 14] adjustments made to the volume of saline in the band. The MDC patients had a median of 10 [9, 13] visits to the endocrinologist or other healthcare providers. The incremental cost effectiveness ratio (ICER) for the LAGB group compared with the MDC group based on intention to treat was AUD$20,695 for each remission of diabetes.

Discussion

This is the first randomized trial of bariatric surgery in people with T2D who are overweight but not obese. The control group received best practice diabetes care, enabling us to draw firm conclusions as to the role of LAGB in this population. LAGB was well-tolerated and achieved superior weight and glycemic outcomes after two years, with the majority of LAGB participants achieving diabetes remission. These weight and glycemic outcomes are comparable to those observed in our RCT of LAGB in obese people [4] and in trials of other bariatric operations in obese people with poorly controlled (mean HbA1c>8.5%) T2D [5-7], which used less rigorous definitions of diabetes remission based on HbA1c levels and, in two of the studies [6, 7], ongoing diabetes therapy. These data highlight the utility of weight loss for glycemic control across the BMI spectrum, consistent with diabetes outcomes from the Look AHEAD trial of lifestyle intervention in T2D [3] and from a recent RCT of gastric bypass surgery[7]. In light of unsatisfactory weight and diabetes outcomes for lifestyle intervention [22], these findings challenge current guidelines for the use of bariatric surgery in T2D, which recommend a BMI threshold of 35kg/m^2 [16, 23].

Regression analysis indicated a strong relationship between the amount of weight lost and the probability of diabetes remission regardless of the mode of therapy. Two MDC patients who lost more than 15% body weight were in remission as were 12 LAGB patients, 11 of whom lost more than 10% body weight. These findings highlight the importance of weight loss in managing glucose levels in overweight people with T2D. However, three LAGB patients who lost more than 20% body weight did not achieve diabetes remission, indicating that excess fat mass is not the only factor driving the disease. The regression analysis also identified lower baseline fasting glucose and HbA1c were associated with diabetes remission. Poor glucose control has been associated with reduced likelihood of diabetes remission following bariatric surgery[20], and baseline levels of these variables were marginally higher in MDC compared to LAGB participants (Table 1). Whilst these differences were not statistically significant, it is possible that they may have biased our primary outcome in favor of LAGB.

The cardiovascular risk profile of the LAGB group was superior to that of the MDC group at completion despite similar baseline characteristics and comparable changes in blood pressure- and lipid-lowering drugs. After two years, diastolic blood pressure, triglycerides, HDL cholesterol and insulin resistance (HOMA-R) improved following LAGB, although only levels of triglycerides and HOMA-R were different between the groups after two years (Table 3). These findings highlight the effectiveness of medical therapy to reduce cardiovascular risk in T2D [24] and question the impact of substantial weight loss on cardiovascular disease and other 'hard' diabetes outcomes in this population. This is especially relevant given the recent findings of the Look AHEAD study, which showed that moderate weight loss leads to similar changes in surrogate markers of cardiovascular disease but does not reduce the incidence of cardiovascular events in T2D [22]. Together, these findings argue that future trials of bariatric surgery in T2D should be designed to determine whether substantial weight loss protects against cardiovascular events and other key diabetes outcomes such as retinopathy and kidney disease.

LAGB appears to be a cost-effective option for managing T2D in the overweight person with a cost of remission of approximately AU$ 21,000. The annual cost of diabetes care in 2002 was reported to be AU$10,900 [25], which was equivalent to AU$14,715 in 2013. If we assume diabetes remission halves this cost and that LAGB-induced remission is sustained over the medium term, cost-recovery could be expected within five years. These findings are similar to our previous RCT-based economic analyses of LAGB as a therapy for moderately obese people (BMI 30-40kg/m^2) with T2D [26, 27].

This study was limited by its small sample size, open label design, conduct in a single center and relatively short duration, factors which may bias our results. Although the LAGB weight outcomes were similar to those seen in obese people treated by our clinic and by other groups [15], poor LAGB weight outcomes have been reported, particularly if inadequate post-operative care is provided [28]. We did not provide intensive lifestyle counseling (ILC) to achieve better weight loss in the MDC group, so we cannot conclude ILC or other non-surgical therapies wouldn't deliver results comparable to LAGB combined with MDC. In addition, it remains uncertain whether similar glycaemic benefits of LAGB would be seen in people with longer-standing or poorly controlled (HbA1c>8%) T2D, or if these benefits protect against diabetes complications. Furthermore, the study population, which consisted of people with recently diagnosed T2D who were willing to be randomized to LAGB, may not faithfully represent the overall population of overweight people with T2D. Finally, our economic evaluation may not reflect the true cost (or benefit) from LAGB because it was limited to direct costs of delivering MDC with or without LAGB. A comprehensive economic analysis of two-year data is planned.

We conclude that LAGB combined with MDC for overweight people with T2D is more effective at controlling blood glucose levels than MDC alone. The favorable safety profile and widespread acceptance of LAGB [13, 29] argue for a more prominent place for this surgery in managing T2D in overweight people.

Putting research into context

Systematic Review

To identify evidence supporting bariatric surgery in overweight people with type 2 diabetes, we searched Pubmed for articles published up to December 2013 using search terms 'diabetes', 'obesity', 'BMI', 'HbA1c', 'bariatric' and 'surgery'. There were several case series, which in general described glycemic benefits from bariatric surgery at the expense of surgical morbidity. There were also four RCTs of bariatric surgery compared to medical management of diabetes[4-7], which confirmed these findings. The prior studies of the effect of bariatric surgery on overweight but not obese people with diabetes[8-12] were limited to case series in the context of ill-defined diabetes care, so the true benefit of bariatric surgery in overweight people with diabetes was uncertain.

Interpretation

Our findings show that, in the setting of multidisciplinary diabetes care, LAGB in overweight people improves glucose control and reduces the medication burden over a two-year time frame, with an acceptable adverse event and cost profile. Whether these benefits are sustained and ultimately reduce the burden of diabetes complications in this population is an important question that requires further study.

Author contributions

PEO and JMW designed the study, PEO, WAB and PB performed LAGB surgery, CL and JP provided nursing care and collated data, JMW, PEO and MER analyzed the data, JMW and PEO wrote the manuscript and all authors reviewed and edited the manuscript. JMW and PEO 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. All authors state they have no conflict of interest to declare.

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Table 1. Participant characteristics at baseline

	LAGB Group (n=25)	MDC Group (n=26)
Age (years)	53±6 (36-64)	53±7 (34-62)
M/F (n)	6/19	9/17
Weight (kg)	81±10 (64-103)	83±12 (62-108)
Height (m)	1.67±0.10 (1.50-1.87)	1.69±0.12 (1.48-1.90)
BMI (kg/m^2)	29±1 (26-30)	29±1 (26-30)
Systolic blood pressure (mmHg)	130±18 (90-160)	131±11 (112-152)
Diastolic blood pressure (mmHg)	83±10 (65-114)	84±9 (67-105)
Diabetes duration (months)	26±20 (5-60)	33±22 (5-60)
Using insulin (n)	4	0
Prior smoker (n)	7	11
Current smoker (n)	4	5
Fasting glucose (mmol/L)	7.4±2.1 (4.4-13.7)	8.2±2.3 (4.9-13.1)
HbA1c (%)	6.9±1.2 (4.3-10.5)	7.2±1.1 (5.6-9.4)
HbA1c (mmol/mol)	52±13 (24-91)	56±12 (38-79)

Continuous data are mean±SD (range). There were no significant differences between the LAGB and MDC groups.

Table 2. Primary outcome

	LAGB (n=23)	MDC (n=25)
Diabetes	11 (48%)	23 (92%)
No diabetes	12 (52%)	2 (8%)

Difference in proportions for diabetes remission 0.44, 95%CI 0.17-0.71; p=0.0012.

Table 3. Secondary outcomes at two years

	LAGB Group (n=23)		MDC Group (n=25)			
	Two-year value	Change from baseline (95%CI)	Two-year value	Change from baseline (95%CI)	Difference between groups (95% CI)	p-valu
Weight (kg)	70±11	-11.5 (-14.1, -8.9)	81±12	-1.6 (-4.3, 1.0)	11.2 (4.5, 17.9)	0.0015
BMI (kg/m^2)	25±2	-4.1 (-5.1, -3.2)	28±2	-0.5 (-1.3, 0.3)	3 (2, 5)	<0.000
Waist circumference (cm)	89±8	-9.7 (-13.1, -6.2)	98±8	-1.9 (-4.5, 0.6)	9 (5, 14)	0.0002
Systolic BP (mmHg)	124±13	-6.0 (-13.3, 1.3)	129±9	-2.0 (-7.8, 3.8)	5 (-1, 11)	0.1273
Diastolic BP (mmHg)	77±10	-5.7 (-10.0, -1.4)	82±7	-2.8 (-7.1, 1.5)	4.6 (-0.2, 9.4)	0.0591
Fasting Biochemistry [1]						
Glucose (mmol/L)	6.5±1.5	-1.0 (-1.7, -0.3)	8.4±2.6	0.1 (-1.2, 1.4)	1.9 (0.6, 3.1)	0.0038
HbA1c (%)	6.1±1.0	-0.8 (-1.1, -0.5)	7.3±1.4	0.0 (-0.5, 0.5)	1.2 (0.5, 1.9)	0.0013
HbA1c (mmol/mol)	43±10	-9 (-12, -6)	56±15	0.3 (-5.8, 6.4)	13 (5, 21)	0.0013
C-peptide (nmol/L)	0.97±0.38	-0.10 (-0.33, 0.12)	1.21±0.68	0.17 (-0.11, 0.47)	0.25 (-0.08, 0.57)	0.1308
Insulin (mIU/L) [2,3]	11.2±6.4	-7.1 (-16.7, 2.5)	14.0±7.1	-1.5 (-4.4, 1.5)	2.8 (0.2, 3.8)	0.1895
HOMA-R (mmol.mIU/L/22.5)[2,3]	3.1±1.9	-3.1 (-6.5, 0.2)	5.2±3.5	-0.6 (-2.2, 0.9)	2.0 (0.2, 3.8)	0.0269
Cholesterol (mmol/L)	4.7±1.0	-0.3 (-0.9, 0.3)	4.6±0.9	-0.5 (-1.0, -0.1)	-0.1 (-0.6, 0.4)	0.7181
Triglyceride (mmol/L)	1.1±0.6	-0.5 (-1.0, -0.1)	1.7±0.9	-0.5 (-0.9, -0.1)	0.6 (0.2, 1.1)	0.0081
HDL cholesterol (mmol/L)	1.50±0.46	0.30 (0.19, 0.41)	1.25±0.47	0.05 (-0.10, 0.20)	-0.26 (-0.53, 0.01)	0.0629
LDL cholesterol (mmol/L) [4]	2.7±1.0	-0.3 (-0.9, 0.3)	2.6±0.7	-0.6 (-1.1, -0.04)	-0.1 (-0.6, 0.4)	0.7018
No. meeting treatment targets						
HbA1c<7% (54mmol/mol)	21	+9	15	+1	0.31 (0.05, 0.58)	0.0188
Blood pressure [5]	17	+5	16	-2	0.1 (-0.20, 0.40)	0.5419
Not smoking	20	+1	23	+2	-0.05 (-0.27, 0.17)	0.6602
No albuminuria	20	-1	23	+2	-0.05 (-0.27, 0.17)	0.6602
Quality of life score						
Physical wellbeing (PWB)	56±6	7.7 (5.0, 10.4)	46±9	-1.7 (-5.3, 1.9)	-10 (-14, -5)	0.0001
Mental wellbeing (MWB)	48±14	-0.13 (-6.8, 6.5)	47±11	-0.82 (-5.2, 3.6)	-2 (-9, 6)	0.6598

Continuous data are mean±SD. For continuous and categorical variables, changes from baseline and differences between groups are expressed as mean and proportional differences respectively. p values were not adjusted for multiple comparisons. Significant changes and differences between groups indicated by grey shading.

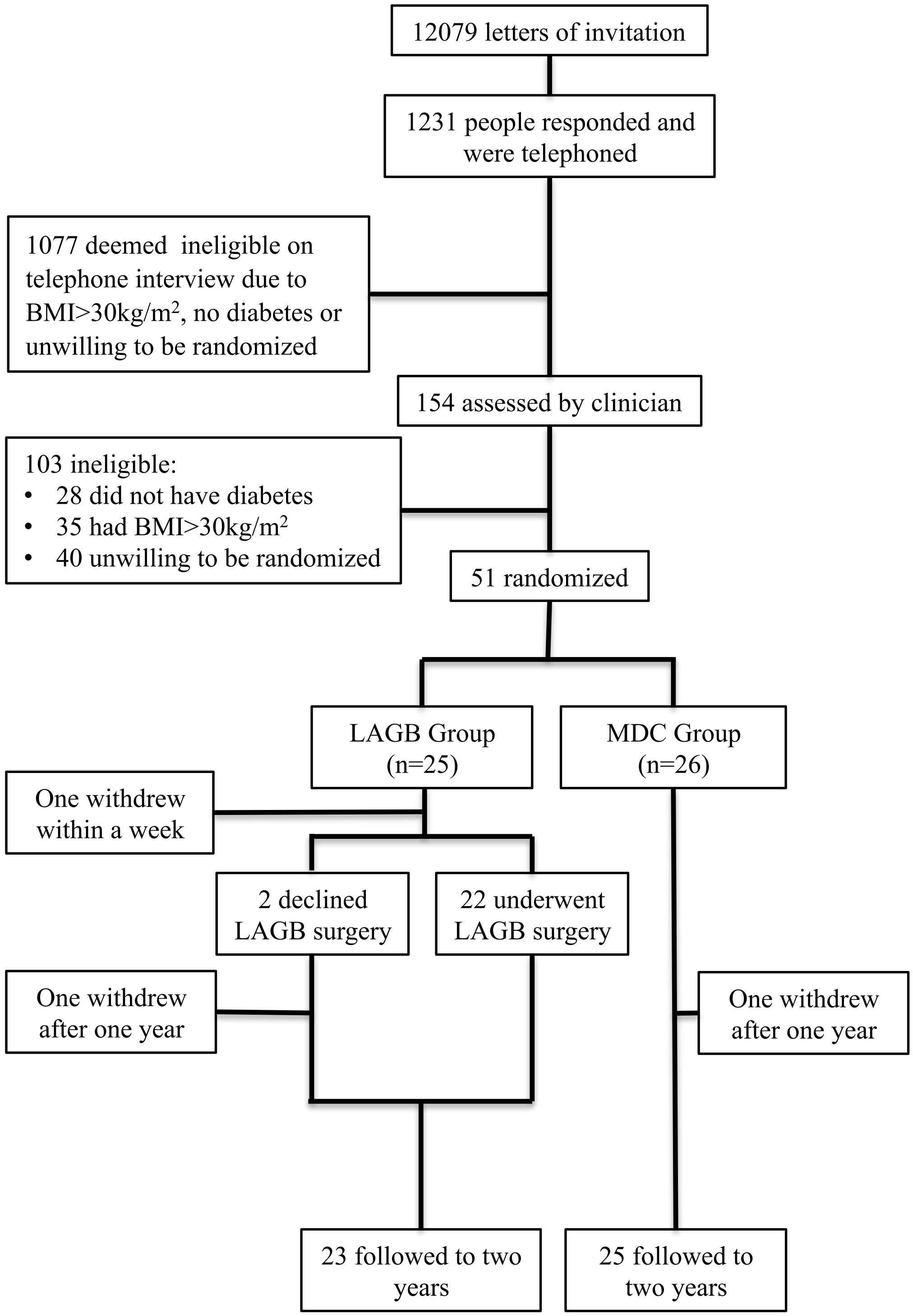
1: Participants withheld all medication on the morning of the test; 2: Excluding participants treated with insulin at any stage during the trial; 3: Outlying data from one MDC participant (insulin 62.4mU/L and HOMA-R 41.0mU/L.mmol/L/22.5) excluded; 4: LDL cholesterol calculation not possible for one LAGB participant at baseline; 5:Target described in methods.

Table 4. Health costs in Australian dollars

		LAGB Group (n=23)		MDC Group (n=25)	
	Cost/unit	Units	Cost/participant	Units	Cost/participant
LAGB Surgery					
Theatre fee	$2,679.50	22	$2,563.00	-	-
Lap-Band	$3,753.60	22	$3,590.40	-	-
Anaesthetist and surgeon fee	$3,450.00	22	$3,300.00	-	-
LAGB Aftercare				-	-
Surgeon review	$43.00	106	$198.17	-	-
Surgeon review with adjustment	$97.95	132	$562.15	-	-
Physician review	$36.30	42	$66.29	-	-
Physician review with adjustment	$97.95	80	$340.70	-	-
Barium swallow	$89.95	35	$136.88	-	-
Revision surgery	$6,129.50	1	$266.50	-	-
Diabetes Care					
Endocrinologist	$75.50	167	$548.20	182	$549.64
Dietician	$62.65	40	$108.96	64	$160.38
Diabetes educator	$63.80	10	$27.74	33	$84.22
Pathology	$82.60	148	$531.51	166	$548.46
Drug Costs [1]					
Glucose-lowering drugs	n/a	n/a	$198.96	n/a	$1279.57
Blood pressure-lowering drugs	n/a	n/a	$160.23	n/a	$311.64
Lipid-lowering drugs	n/a	n/a	$413.78	n/a	$920.31
Anti-platelet drugs	n/a	n/a	$11.02	n/a	$64.07
Total cost/participant (95% CI)		**$13,024 ($11664 to $14385)**		**$3,918 ($3093 to $4743)**	

Costs in Australian dollars have been derived from 2013 price schedules from the Australian Medical and Pharmaceutical Benefits Schemes, and from The Avenue Hospital. 1: Mean baseline drug costs/person/month (95% CI) were $120.33 ($33.58 to $207.10) and $74.75 ($40.01 to $109.50) in the LAGB and MDC groups respectively. n/a: not applicable.

Figure 1. Participant recruitment



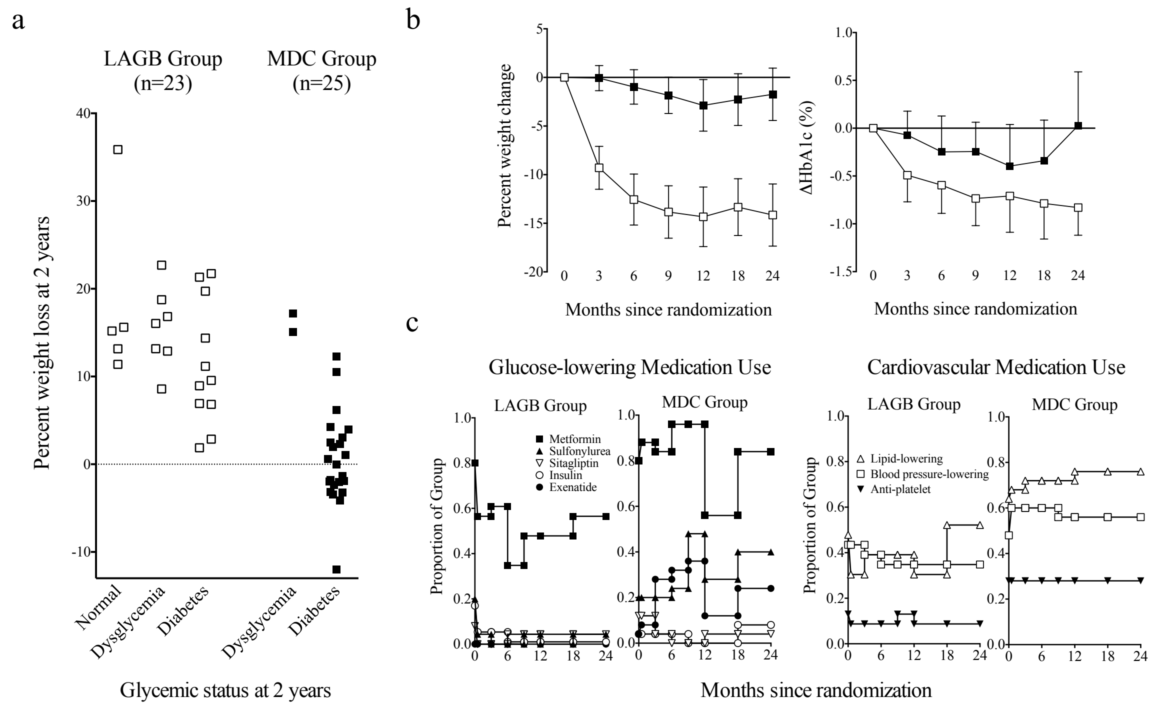


Figure 2. Primary and secondary outcomes in participants who completed two-year follow-up.

a. Weight loss according to diabetes status at two years in LAGB (open squares) and MDC (filled squares) participants. Normal: normal glucose tolerance; Dysglycemia: impaired fasting glucose and/or impaired glucose tolerance. Of the 14 'normal' and 'dysglycemia' participants, 6 in the LAGB group were taking no diabetes medication and the other 8 were taking metformin monotherapy. **b.** Change in percent weight and in HbA1c over time in LAGB (open squares) and MDC (filled squares) participants. Data are mean with 95% CI.

The mean±SD area under the abscissa for LAGB and MDC participants were, respectively, 294±138 and 41±108 percent.month for weight loss (difference 254, 95% CI 182 to 325; p<0.0001), and 16±16 and 5±20 percent.month for HbA1c (difference 10, 95% CI -0.1 to 21; p=0.0520).

c. Time courses showing the proportion of participants in each group who were taking the glucose-lowering and cardiovascular medications indicated in the figure legends.

Supplementary Table 1. Participant characteristics at baseline with continuous data presented as median [Q1, Q3]

	LAGB Group (n=25)	**MDC Group (n=26)**	p-value
Age (years)	53.5 [50.3, 56.5]	54.5 [48.8, 58.5]	0.5904
M/F (n)	6/19	9/17	0.5414
Weight (kg)	80 [75, 87]	83 [73, 93]	0.6436
Height (m)	1.65 [1.63, 1.73]	1.69 [1.57, 1.79]	0.5276
BMI (kg/m^2)	29.4 [28.2, 29.7]	29.4 [27.8, 29.9]	0.8408
Systolic blood pressure (mmHg)	130 [118, 142]	130 [123, 139]	0.8624
Diastolic blood pressure (mmHg)	80 [78, 90]	84 [80, 89]	0.6815
Diabetes duration (months)	18 [8, 48]	30 [12, 60]	0.1948
Using insulin (n)	4	0	0.0506
Prior smoker (n)	7	11	0.3823
Current smoker (n)	4	5	1.0000
Fasting glucose (mmol/l)	7.4 [6.0, 8.2]	7.6 [6.7, 10.4]	0.3465
HbA1c (%)	6.7 [6.2, 7.3]	6.8 [6.6, 8.0]	0.3414
HbA1c (mmol/mol)	50 [44, 56]	51 [48, 64]	0.3414

For continuous and categorical variables, p values were determined by Mann-Whitney U test and Fisher's exact test respectively.

Table 1 Baseline characteristics of the LAGB and AusDiab cohorts and their subgroups

Characteristic/variable	LAGB				AusDiab		
	All (19±13% WL)	Tertile 1 (6±9% WL)	Tertile 2 (19±3% WL)	Tertile 3 (32±8% WL)	All	Non-obese	Obese
n	281	94	94	93	1043	721	322
Percentage female	75	80	69	75	35**	45	30††
Age (years)	46±9	45±9	47±10	45±10	46±7	46±7	46±7
Weight (kg)	127±27	120±22	126±27	134±31††	84±16**	77±11	100±15†††
Height (cm)	167±9	166±8	168±9	167±9	172±9**	173±9	171±10
BMI (kg/m^2)	46±9	44±7	45±8	48±10††	28±5**	26±3	34±4†††
Fasting blood indices							
Glucose (mmol/l)	5.9±0.3	5.9±0.3	5.9±0.3	6.0±0.3	5.9±0.3	5.9±0.3	6.0±0.3
HbA_{1c} (%)	5.7±0.4	5.7±0.4	5.7±0.4	5.7±0.5	5.2±0.3**	5.2±0.3	5.3±0.3
HbA_{1c} (mmol/mol)	39±4	39±4	39±4	39±5	33±3**	33±3	34±3
Total cholesterol (mmol/l)	5.5±1.0	5.5±1.0	5.6±1.1	5.6±1.0	5.7±1.0	5.7±1.0	5.8±1.0
Triacylglycerol (mmol/l)	2.0±1.2	2.0±1.0	2.0±1.5	2.0±0.9	1.7±1.2	1.6±1.0	2.0±1.5††
HDL-cholesterol (mmol/l)	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.3	1.3±0.3	1.2±0.3†

Continuous data are mean ± SD

* and † denote significant between- and within-group differences, respectively, with one, two and three symbols representing $p<0.05$, $p<0.01$ and $p<0.001$, respectively. Within-group differences of LAGB patients were determined by χ^2 test for trend or ANOVA followed by post test for linear trend

WL, weight loss

Table 2 Five-year incidence of diabetes among women and men undergoing LAGB, according to weight loss

	Women				Men				Entire LAGB group			
	n	%WL	Cases	Incidence	*n*	%WL	Cases	Incidence	*n*	%WL	Cases	Incidence
Entire group	210	18±13	12	9.2	71	20±11	2	4.9	281	19±13	14	8.2
Tertile 1	70	5±10	9	20.6	24	10±5	2	14.4	94	6±9	11	19.1
Tertile 2	70	18±3	2	4.5	24	20±3	0	0	94	19±3	2	3.4
Tertile 3	70	32±7	1	2.4	23	32±9	0	0	93	32±8	1	1.8

%WL, percentage weight loss as mean ± SD

Incidence is cases/1000 person-years

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