Original Contribution

Gastric band surgery leads to improved insulin secretion in overweight people with type 2 diabetes

Secondary outcomes of a randomized controlled trial

John M Wentworth PhD [1,2], Julie Playfair [1], Cheryl Laurie [1], Wendy A Brown PhD [1], Paul Burton PhD [1], Jonathan E Shaw PhD [3], Paul E O'Brien MD [1].

1. Centre for Obesity Research and Education (CORE), Monash University, Melbourne, Australia
2. Molecular Medicine Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Melbourne, Australia
3. Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Correspondence to:
Emeritus Professor Paul E. O'Brien
The Alfred Centre,
99 Commercial Road, Melbourne, 3004,
Victoria, Australia
Phone: (613) 9903 0725 ; Fax: (613) 9903 1017
Email: paul.obrien@monash.edu

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ABSTRACT

Introduction

We aimed to determine the effects of LAGB on beta-cell function in overweight people with type 2 diabetes and to assess the relationship between baseline beta-cell function and glycemic outcomes.

Methods

We studied 44 overweight but not obese people with type 2 diabetes who participated in a randomized trial whose primary outcome was the rate of diabetes remission after 2 years of multidisciplinary diabetes care (MDC group) or multidisciplinary care combined with LAGB. Dynamic beta-cell function was assessed by intravenous glucose challenge and basal beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) were determined using the homeostatic model.

Results

Twelve and 2 participants in the LAGB and MDC groups respectively were in diabetes remission at 2 years. The C-peptide response to intravenous glucose and HOMA-S increased significantly in LAGB but not in MDC participants. The insulin response to glucose did not change in LAGB participants whereas their fasting C-peptide/insulin ratio increased. Baseline measures of beta-cell function correlated with diabetes remission but not with reduction in HbA1c following LAGB.

Conclusions

In overweight people with diabetes, LAGB improves endogenous beta-cell function after 2 years. Baseline beta-cell function correlated with diabetes remission, but not with HbA1c change following LAGB.

INTRODUCTION

Randomized trials have shown that bariatric surgery for obese people with type 2 diabetes achieves diabetes remission more frequently than medical care [1-4]. We recently reported outcomes of a randomized trial of laparoscopic adjustable gastric band surgery (LAGB) in people with diabetes and body mass index (BMI) between 25 and 30kg/m^2 that showed similar surgical benefits [5]. In these studies it was not clear why a substantial proportion of surgical participants did not achieve diabetes remission, and factors associated with reductions in HbA1c after bariatric surgery were not reported.

Type 2 diabetes occurs when the chronically increased demands for insulin due to insulin resistance, which is aggravated by obesity, cannot be compensated by the genetically defective β-cell [6]. Improved glycemic control following weight loss is therefore dependent on increased insulin sensitivity, improved beta-cell function, or a combination of the two. Retrospective analyses of cohorts undergoing bariatric surgery have shown that weight loss is strongly associated with diabetes remission [7,8], arguing that improved insulin sensitivity is a key driver of remission. In addition, several studies of obese people with type 2 diabetes have shown the beta-cell response to *oral* glucose increases following gastric bypass or biliopancreatic diversion (reviewed in [9]). This improvement is primarily due to incretin effects rather than increased endogenous beta-cell function because the C-peptide response to parenteral glucose does not appear to change [10,11]. Whilst these findings suggest that dynamic beta-cell function in people with type 2 diabetes would not change after LAGB, this assumption has not been tested by prior studies.

Identifying baseline predictors of diabetes remission and of reduced HbA1c following bariatric surgery may help target this expensive and at times dangerous therapy to those most likely to benefit [12]. Current evidence, mostly derived from retrospective analyses, suggests diabetes duration [7,8,13-15], baseline levels of C-peptide [13,14] and beta-cell responsiveness to glucose [16] predict diabetes remission. This suggests baseline pancreatic beta-cell function is a key determinant of glycemic outcome following surgery. To date, no studies have tested this hypothesis in the LAGB context.

We incorporated a 15-minute intravenous glucose tolerance test into the protocol of our randomized trial of LAGB in overweight but not obese people. Its purpose was to determine if beta-cell function changed after LAGB, and to determine if baseline beta-cell function correlated with diabetes remission and reductions in HbA1c following LAGB-induced weight loss.

METHODS

Participants

Fifty-one participants who were overweight and had type 2 diabetes for less than five years were recruited between November 2009 and June 2011. They were randomized to receive multidisciplinary medical care (MDC group; n=26) or MDC combined with laparoscopic adjustable gastric band surgery (LAGB group; n=25). Twenty-five MDC and 23 LAGB participants completed 2 year follow-up, but 3 MDC and 1 LAGB participant did not undergo intravenous glucose tolerance testing, including the sole LAGB participant who declined LAGB surgery but remained in the study [5]. Their reasons for not having the test were poor venous access (n=3) and participant refusal (n=1). This study was approved by the Human Research Ethics Committees of The Avenue Hospital and Monash University, and was registered as ACTRN12609000286246. Informed consent was obtained from all individual participants included in the study.

Data collection

Clinical data were collected as previously described [5] by study nurses (JP and CL), who were not blinded to treatment group. HbA1c, lipid and OGTT glucose levels, and urine albumin/creatinine ratio were performed by Melbourne Pathology (Abbotsford, Australia).

Intravenous glucose tolerance test

Participants withheld glucose-lowering drugs for 24h prior to the test, which was performed between 9am and 11am in the fasting state. A cannula was inserted into a cubital vein and baseline venous samples collected at 5, 3 and 1 minute prior to injection of 50mL 50% w/v glucose over 1 minute followed by 10ml saline over 10 seconds. Then, 5mL of venous blood was withdrawn from the same cannula over the next 2 minutes and discarded, followed by sample collection at 4, 6, 8, 10, 12 and 15 minutes after the start of the glucose injection. Blood samples were collected into 4.7ml serum tubes (*Monovette*, Starstedt, Germany) and allowed to clot on ice for up to 30 minutes. The tubes were then centrifuged and serum stored at -70˚C. Levels of glucose, insulin and C-peptide were determined in one batch by Melbourne Health Pathology (Parkville,

Australia), using a 2700 Autoanalyser (Olympus, USA) for glucose assays (CV<2%) and the Immulite 2000 assay (Siemens, Germany) for insulin and C-peptide (CVs <9% and <8% respectively). Beta-cell function was defined as the trapezoidal area under the curve (AUC) of the incremental insulin (AUC_{INS}) or C-peptide (AUC_{CP}) responses to intravenous glucose. The HOMA2 calculator version 2.2.3 [17] was used to impute beta-cell function from the mean baseline levels of glucose and C-peptide (HOMA-B). Insulin sensitivity was calculated using the baseline levels of glucose and insulin (HOMA-S_{INS}) or glucose and C-peptide (HOMA-S_{CP}). Two methods were used because whilst HOMA-S_{INS} is generally a better measure of systemic insulin sensitivity [17], we anticipated that HOMA-S_{CP} would be a better measure of insulin sensitivity after LAGB because weight loss increases hepatic insulin clearance [18]. Insulin concentrations could not be assessed at baseline in one LAGB participant with allergy to exogenous insulin and serum levels of more than 1800pmol/l.

Definition of diabetes remission

Diabetes status was assessed 2 years after randomization in people whose HbA1c was less than 7.0% by 75g oral glucose tolerance test, which was performed a week prior to IVGTT and at least 2 days after stopping diabetes medication. Participants were categorized as having diabetes if the fasting value was 7.0mmol/l or greater and/or the 2-hour value was more than 11.0mmol/l. Dysglycemia was defined as a fasting level between 5.6 and 7.0mmol/l and/or a 2h level ranging from 7.8 to 11.0mmol/l. Six of the 12 LAGB participants who achieved diabetes remission were taking metformin monotherapy and the other six had not been taking diabetes medication for at least six months prior to the glucose tolerance test.

Statistical analyses

We did analyses with Prism software (version 6.0b) and included only patients who underwent IVGTT. We compared categorical data with the Fisher's exact test and Chi square test for trend. Because few variables were normally distributed according to the Shapiro-Wilk test, continuous data are presented as median [Q1, Q3], and we used the Wilcoxon matched-pairs signed rank test and the Mann-Whitney U test to compare paired

and unpaired datasets respectively. Median differences and confidence intervals of the median were determined using the Wilcoxin test, which generated exact confidence intervals that ranged from 95 to 98%. In all analyses, p values reported are unadjusted and based on a two-sided test.

RESULTS

Twenty-two participants in each of the LAGB and MDC groups underwent the intravenous glucose tolerance test (IVGTT) at baseline and at 2 years. The baseline characteristics of both groups were similar (Table 1). Two years after joining the study, participants in the LAGB group had better glucose control despite decreased diabetes treatment intensity (Table 2), with 12 (55%) of them achieving diabetes remission, compared to 2 participants (9%) in the MDC group (Table 2). Derived measures of insulin sensitivity (HOMA-S_{INS} and HOMA-S_{CP}) increased following LAGB. These measures, together with imputed beta-cell function (HOMA-B), were higher in LAGB compared to MDC participants at 2 years.

The IVGTT results are provided in Figure 1a and in Tables 1 and 2. The glucose excursions were similar in both groups and at both timepoints. At baseline, the insulin and C-peptide responses in LAGB and MDC groups were biphasic and their respective areas under the curve (AUC) were not significantly different. At 2 years, the biphasic pattern of insulin and C-peptide was attenuated in the LAGB group, with the AUC_{INS} not changing significantly in either patient group. However, the median [Q1, Q3] AUC_{CP} in the LAGB group increased significantly (p=0.0059) from 2.11 [0.89, 5.19] nmol.min.l^{-1} at baseline to 3.60 [1.33, 8.23] nmol.min.l^{-1} at 2 years, whereas AUC_{CP} did not change significantly in MDC participants. AUC_{INS} did not change significantly in either patient group whilst the fasting C-peptide to insulin ratio, a marker of hepatic insulin clearance, increased in LAGB participants at 2 years (Table 2). Weight loss correlated with improved AUC_{CP} at 2 years, which was observed in 4 of 11 participants (36%) who did not lose weight, 7 of 14 (50%) who lost between 0 and 10% body weight and 16 of 19 (84%) who lost more than 10% body weight (p=0.0064). The Supplementary Table describes weight, glycemic and IVGTT outcomes across the weight loss tertiles of the entire group of 44 participants. A significant improvement in AUC_{CP} was observed in participants in the top tertile of weight loss and C-peptide/insulin ratios were higher for participants in the middle and top tertiles. The Supplementary Figure shows the incremental glucose, insulin and C-peptide responses to IV glucose according to weight

loss tertile. An increased C-peptide response over the latter half of the IVGTT was seen in participants belonging to the middle and top tertiles.

To determine the association between of beta-cell function and diabetes remission, we compared the twelve LAGB participants who entered diabetes remission (five with normoglycemia and seven with dysglycemia at two years) to the ten who did not. Their baseline characteristics are presented in Table 3, which shows that, compared to non-remitters, the remitters had significantly higher levels of HOMA-B, lower levels of fasting glucose and higher serum creatinine concentrations. Two-year outcomes for these groups are presented in Table 4, which describes similar weight loss in both groups. The IVGTT analysis shows that both groups had a similar glucose excursion, with remitters characterized by higher insulin and C-peptide responses at both baseline and at 2 years. Furthermore, only remitters showed improved C-peptide responses, evident at 8, 12 and 15 minutes after the intravenous glucose challenge (Figure 1b), which was reflected by an increase in AUC_{CP} at 2 years (Table 4). Thus, compared to non-remitters, remitters had greater baseline beta-cell function that improved after 2 years.

Finally, among the LAGB participants, we examined the relationship between baseline beta cell function (as either HOMA-B or as AUC_{CP}) and absolute reduction in HbA1c at 2 years, and found no significant correlation. This finding accorded with the similar HbA1c reductions of 7mmol/mol in remitters and 9mmol/mol in non-remitters despite similar treatment intensities (Table 4).

DISCUSSION

These randomized trial outcomes show that, in overweight but not obese people who had diabetes for less than five years and received multidisciplinary diabetes care, LAGB improved insulin sensitivity and increased the amount of C-peptide released in response to intravenous glucose. In addition, beta-cell function correlated with diabetes remission but not with improved glucose control following LAGB.

In the LAGB group but not the MDC group, insulin sensitivity (HOMA-S) improved at 2 years, but did not reach 'normal' levels of 100% seen in healthy people [19]. We described similar LAGB outcomes in obese people with type 2 diabetes [1,20], which accord with those reported following other bariatric procedures (reviewed in [9]). Weight loss was the predominant predictor of diabetes remission in the entire group of LAGB and MDC participants [5], which together with the HOMA-S data argues that improved insulin sensitivity from weight loss contributed to improved glycaemia in the LAGB group.

The C-peptide response to intravenous glucose, a marker of dynamic beta-cell function [21], also improved following LAGB. This novel finding reflects intrinsic beta-cell recovery following LAGB-induced weight loss. However, it is at odds with two recent studies of obese people with type 2 diabetes that described no effect of gastric bypass surgery on C-peptide release following intravenous glucose. In one study, a combined glucose/glucagon challenge was performed a year after bypass surgery in 10 people whose diabetes duration varied between 1 and 11 years [11]. Possibly the stronger beta-cell stimulus provided by the glucose/glucagon combination together with the use of a smaller, more heterogeneous study population introduced type 2 error into this study. The other [10] reported outcomes of 14 people with type 2 diabetes who were given a varying infusion of intravenous glucose to match glucose excursions observed after oral glucose challenge. The authors modeled data from eight samples collected over 3 hours to calculate C-peptide secretion rate, which did not change despite substantial weight loss up to three years after surgery. Again, methodological differences and patient heterogeneity may have prevented detection of improved endogenous beta-cell function after bariatric surgery. Long-term outcomes of intravenous glucose testing have not previously been

reported in the context of LAGB or sleeve gastrectomy. However, a small study reported no change in the C-peptide response to a glucose increment of ~7mmol/l in 7 people (3 LAGB and 4 sleeve gastrectomy) who lost around 7% body weight four weeks after restrictive surgery [22]. Taken with our findings, these results suggest that beta-cell recovery following LAGB or sleeve gastrectomy may require more substantial and prolonged weight loss. We did not elucidate the mechanism underlying beta-cell recovery after LAGB, but its correlation with weight loss suggests weight loss as a potential mechanism, perhaps via sustained reductions in circulating glucose, lipid, leptin or other inflammatory factors that are associated with obesity and known to adversely affect beta-cell function and survival [23].

In contrast to the improved C-peptide response, LAGB had minimal effect on the insulin response to intravenous glucose, with only the eight-minute value different between the LAGB and MDC groups at 2 years and no significant change over time. This paradox is probably explained by increased hepatic insulin clearance after LAGB, reflected by a significant increase in the fasting C-peptide/insulin ratio. Weight loss is the likely reason for this because we found this to correlate with increased C-peptide/insulin ratio, and because similar changes were seen in obese people with diabetes who underwent weight loss through a very low calorie diet [18] or gastric bypass surgery [11]. Nonetheless, it is notable that the first phase of insulin release, occurring from baseline up to 8 minutes in our study, did not change significantly in LAGB participants. This finding is at odds with prior reports of dramatically improved first phase insulin release in severely obese people after gastric bypass or biliopancreatic diversion [24,25]. The reason for this discrepancy is not clear, but may relate to differences in study populations or to greater weight loss and its associated metabolic improvements observed in these two studies. Nonetheless, the unchanged acute insulin response coupled with improved insulin sensitivity observed in our study implies LAGB improved the disposition index to intravenous glucose [21], consistent with similar outcomes for people with diabetes who lose weight through diet [18] or gastric bypass surgery [10,11,24].

Our subgroup analysis of LAGB participants revealed an association between the 2-year values for HOMA-B, AUC_{INS} and AUC_{CP} and diabetes remission, consistent with the prevailing view that beta-cell function is a key determinant of type 2 diabetes [6]. More striking was the finding that baseline beta-cell function derived from fasting glucose and C-peptide levels (HOMA-B) was most strongly associated with diabetes remission 2 years after LAGB, with a HOMA-B threshold of 80% predicting diabetes remission with a sensitivity of 83% and specificity of 90%. Further study is needed to confirm this finding and to assess its generalizability to obese patients and those with longer-standing diabetes. It is also important to note that baseline beta-cell function was not associated with the absolute reduction in HbA1c among the LAGB participants. Thus, people with low levels of beta-cell function may still derive significant glycemic benefit from LAGB, even if diabetes remission is not achieved.

This study was limited by relatively small patient numbers and there was a high degree of inter-individual variability in glucose, insulin and C-peptide excursion following the intravenous glucose challenge. These features limited our ability to detect differences between the groups studied. The use of HOMA-S to assess insulin sensitivity may also have introduced error because, although HOMA-S has been shown to correlate well with euglycemic clamp-derived measures of insulin sensitivity [19], it has not been validated following substantial weight loss. Because we find evidence for increased hepatic insulin clearance after LAGB and marked discrepancy between HOMA-S_{CP} and HOMA-S_{INS} values after LAGB, it seems HOMA-S_{CP} is the better of the two measures of insulin sensitivity in this context. Finally, it is not known if our findings are relevant to obese populations with type 2 diabetes. However, the metabolic effects of weight loss observed in this study [5] were comparable to those observed in obese cohorts [1-4], consistent with a similar mechanism of disease remission across the BMI spectrum from 25kg/m^2 to over 40kg/m^2. It is also important to note that although the insulin and C-peptide responses to intravenous glucose improved after LAGB, their incremental responses remained much lower than those observed in people with normal glucose tolerance [26]. In addition, because these improvements occurred during the second and not the first phase of the IVGTT, they may not have contributed to diabetes remission.

In summary, we show clear evidence that overweight but not obese people with type 2 diabetes have enhanced beta-cell responsiveness to intravenous glucose 2 years after LAGB surgery, with baseline beta-cell function a major predictor of diabetes remission, but not of the absolute reduction in HbA1c. These findings recommend further study to determine the durability of beta-cell recovery and glycemic improvement after LAGB and whether HOMA-B and other makers of beta-cell function are robust predictors of diabetes remission in other populations undergoing bariatric surgery.

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STATEMENT OF ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONFLICT OF INTEREST

Paul Burton has received an honorarium, to speak at an education conference, from Covidien Australia, manufacturer of surgical stapling devices that are used in procedures designed to treat obesity. No other author reports a conflict of interest.

AUTHOR CONTRIBUTIONS

PEO and JMW designed the study, analysed the data and prepared the manuscript. PEO, WAB and PB did the LAGB surgery. JMW, CL and JP performed the IVGTTs. All authors contributed to, reviewed and approved 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.

FIGURE LEGEND

Figure 1. *IVGTT outcomes at baseline and 2 years.*
a Median glucose, insulin and C-peptide responses to intravenous glucose in MDC and LAGB participants.
b LAGB outcomes stratified according to diabetes remission at 2 years.
Statistical comparisons at each timepoint were performed by t-test as indicated with 1, 2 and 3 symbols representing $p<0.05$, $P<0.01$ and $P<0.001$ respectively. Median [Q1, Q3] AUC data for each curve are provided in Tables 1 to 4.

Supplementary Figure. *IVGTT outcomes according to weight loss at 2 years*
Median glucose, insulin and C-peptide responses to intravenous glucose for each weight loss tertile. Statistical comparisons at each timepoint were performed by t-test as indicated with 1 and 2 symbols representing $p<0.05$ and $p<0.01$ respectively. Median [Q1, Q3] AUC data are provided in the Supplementary Table.

Table 1. Participant characteristics at baseline

	LAGB Group (n=22)	MDC Group (n=22)
Age (years)	53 [49, 56]	55 [49, 60]
M/F (n)	11/11	11/11
Duration of diabetes (months)	27 [8, 48]	30 [12, 60]
Weight (kg)	80.7 [75.3, 87.5]	82.3 [73.0, 93.1]
Height (m)	1.65 [1.62, 1.75]	1.69 [1.57, 1.79]
BMI (kg/m^2)	29.4 [28.5, 29.7]	29.4 [27.8, 29.9]
Waist circumference (cm)	100 [95, 103]	102 [97, 104]
Systolic blood pressure (mmHg)	135 [119, 144]	130 [120, 137]
Diastolic blood pressure (mmHg)	80 [78, 90]	84 [80, 86]
Smoker (n)	4	5
Albuminuria (n)	2	4
Diabetes regimen		
no drugs	5	4
oral drug(s)[1]	13	17
injectables±oral drug(s) [2]	4	1
Fasting biochemistry		
glucose (mmol/l)	7.4 [6.7, 8.4]	7.7 [6.8, 10.1]
HbA1c (%)	7.1 [6.3, 7.3]	7.1 [6.6, 8.4]
HbA1c (mmol/mol)	54 [45, 57]	54 [49, 68]
insulin (pmol/l) [3]	80 [62, 136]	109 [73, 155]
C-peptide (nmol/l)	0.91 [0.77, 1.17]	1.06 [0.79, 1.49]
C-peptide/insulin ratio	11.3 [8.7, 13.8]	9.8 [8.3, 11.9]
creatinine (µmol/l)	72 [57, 82]	71 [60, 78.25]
cholesterol (mmol/l)	4.5 [4.2, 5.9]	4.9 [3.9, 5.9]
triglyceride (mmol/l)	1.4 [0.9, 2.3]	1.8 [1.5, 2.4]
HDL cholesterol (mmol/l)	1.18 [1.02, 1.49]	1.08 [0.93, 1.34]
HOMA-B (%)	81 [55, 103]	73 [56, 94]
HOMA-S_{INS} (%) [3]	47 [32, 72]	39 [25, 53]
HOMA-S_{CP} (%)	46 [33, 52]	35 [26, 51]
IVGTT findings		
AUC_{GLUC} ($mmol.min.l^{-1}$)	132 [122, 157]	127 [106, 150]
AUC_{INS} ($pmol.min.l^{-1}$)	543 [150, 1036]	538 [297, 1072]
AUC_{CP} ($nmol.min.l^{-1}$)	2.11 [0.89, 5.19]	2.21 [1.33, 4.28]

Continuous data are median [Q1, Q3]. AUC: area under the curve from 0 to 15 minutes.
1. Oral drugs were metformin, sulfonylurea or sitagliptin
2: Injectables were insulin and/or exenatide.
3. Excluding data from one LAGB participant with insulin allergy.

Table 2 Changes in clinical and biochemical variables at 2 years

	LAGB Group (n=22)		MDC Group (n=22)			
	2 year value	**Change from baseline (98% CI)**	**2 year value**	**Change from baseline (98% CI)**	**Difference between groups (95% CI)**	**p-value**
Weight (kg)	68.3 [62.0, 77.9]	-11.7 (-14.3 to -8.5)	80.3 [72.5, 89.6]	-0.2 (-3.0 to 2.0)	12.0 (3.7 to 19.5)	0.0028
BMI (kg/m^2)	25.0 [23.4, 26.5]	-3.9 (-5.3 to -2.9)	28.4 [27.3, 30.0]	-0.1 (-1.1 to 0.6)	3.5 (2.3 to 4.8)	< 0.0001
Waist circumference (cm)	91 [86, 93]	-11 (-16 to -5)	98 [94, 103]	-2 (-3 to 3)	7 (4 to 14)	< 0.0001
Diabetes treatment intensity						
no drugs	10	+5	2	-2	-8	
oral drug(s) [1]	12	-1	13	-4	1	0.0005
injectables±oral drug(s) [2]	0	-4	7	+6	7	
Glycemic status						
normal glucose tolerance	5	+5	0	0	-5	
dysglycemia	7	+7	2	+2	-5	0.0010
diabetes	10	-12	20	-2	10	
Fasting biochemistry						
glucose (mmol/l)	6.0 [5.2, 7.4]	-1.4 (-2.0 to -0.9)	8.8 [7.5, 9.8]	0.1 (-1.7 to 2.5)	2.7 (1.4 to 3.4)	0.0054
HbA1c (%)	6.0 [5.6, 6.7]	-0.7 (-1.5 to -0.4)	7.1 [6.3, 7.9]	-0.4 (-1.1 to +0.5)	1.1 (0.5 to 1.7)	0.0010
HbA1c (mmol/mol)	42 [37, 50]	-7.7 (-16.4 to -4.4)	54 [45, 63]	-4.4 (-12.0 to +5.5)	12 (5 to 19)	0.0010
insulin (pmol/l)	47 [18, 70]	-34 (-63 to -17)	101 [47, 175]	-11 (-44 to 20)	54 (9 to 85)	0.0124
C-peptide (nmol/l)	0.64 [0.49, 0.82]	-0.25 (-0.50 to -0.08)	1.04 [0.61, 1.45]	-0.01 (-0.14 to 0.26)	0.40 (0.09 to 0.68)	0.0047
C-peptide/insulin ratio	13.0 [10.1, 33.1]	2.1 (0.7 to 17.7)	11.2 [9.3, 13.5]	0.6 (-0.4 to 2.8)	-1.8 (-8.4 to 0.4)	0.0946
HOMA-B (%)	80 [64, 98]	6 (-10 to 22)	60 [48, 87]	-8 (-20 to 5)	-23 (-36 to -0.4)	0.0437
HOMA-S_{INS} (%)	92 [57, 249]	47 (10 to 156)	39 [23, 85]	4 (-7 to 29)	-53 (-79 to -11)	0.0057
HOMA-S_{CP} (%)	69 [49, 90]	29 (9 to 40)	34 [26, 65]	-1 (-6 to 12)	-35 (-44 to -11)	0.0006
IVGTT findings						
AUC_{GLUC} ($mmol.min.l^{-1}$)	126 [115, 147]	-6 (-17 to 4)	125 [111, 141]	-6 (-16 to 5)	-1 (-15 to 11)	0.6455
AUC_{INS} ($pmol.min.l^{-1}$)	590 [264, 1695]	7 (-125 to 438)	590 [243, 771]	-21 (-410 to 208)	0 (-896 to 160)	0.5688
AUC_{CP} ($nmol.min.l^{-1}$)	3.60 [1.33, 8.23]	0.71 (-0.25 to 2.96)	2.44 [1.23, 3.87]	0.15 (-2.09 to 1.86)	-1.16 (-5.00 to 0.26)	0.1185

Continuous data are median [Q1, Q3]. For categorical data describing diabetes treatment intensity and glycemic status, significance was determined using chi-square test for trend. AUC: area under the curve from 0 to 15 minutes.

1. Oral drugs were metformin, sulfonylurea or sitagliptin

2: Injectables were insulin and/or exenatide.

Table 3
Baseline characteristics and weight outcomes of LAGB participants according to diabetes status at 2 years

	Diabetes remission (n=12)	Persistent diabetes (n=10)
Age (years)	53 [46, 58]	53 [52, 56]
M/F (n)	7/5	4/6
Duration of diabetes (months)	17 [7, 48]	30 [15, 54]
Weight (kg)	80.7 [77.5, 86.1]	80.8 [69, 93.4]
Height (m)	1.65 [1.63, 1.72]	1.66 [1.54, 1.78]
BMI (kg/m^2)	29.4 [29.3, 29.7]	29.4 [27.7, 29.7]
Waist circumference (cm)	100 [94, 102]	101 [97, 106]
Systolic blood pressure (mmHg)	133 [120, 140]	137 [114, 155]
Diastolic blood pressure (mmHg)	80 [73, 89]	83 [78, 95]
Smoker (n)	2	2
Albuminuria (n)	1	1
Diabetes regimen		
no drugs	3	2
oral drug(s) [1]	7	6
injectables±oral drug(s) [2]	2	2
Fasting biochemistry		
glucose (mmol/l)	6.9 [5.8, 7.5]	8.1 [7.5, 10.1]**
HbA1c (%)	6.6 [6.2, 7.2]	7.3 [6.5, 8.3]
HbA1c (mmol/mol)	49 [45, 55]	56 [48, 67]
insulin (pmol/l) [3]	108 [73, 153]	75 [48, 88]
C-peptide (nmol/l)	1.08 [0.8, 1.24]	0.84 [0.73, 1]
creatinine (μmol/l)	79.5 [61.25, 89.5]	58.5 [55.5, 77.25]*
cholesterol (mmol/l)	4.5 [4.1, 6.2]	4.3 [4.2, 5.3]
triglyceride (mmol/l)	1.4 [1, 1.7]	1.4 [0.9, 2.3]
HDL cholesterol (mmol/l)	1.10 [0.98, 1.42]	1.29 [1.07, 1.66]
HOMA-B (%)	95 [87, 131]	62 [45, 71]***
HOMA-S_{INS} (%) [3]	42 [28, 59]	53 [42, 85]
HOMA-S_{CP} (%)	40 [32, 52]	47 [37, 52]
IVGTT findings		
AUC_{GLUC} ($mmol.min.l^{-1}$)	132 [121, 152]	130 [122, 158]
AUC_{INS} ($pmol.min.l^{-1}$)	792 [424, 2007]	229 [132, 569]*
AUC_{CP} ($nmol.min.l^{-1}$)	3.49 [1.31, 7.83]	1.30 [0.33, 2.18]*
Percent weight loss at 2 years	15.4 [13.0, 18.3]	10.4 [6.9, 20.1]

Continuous data are median [Q1, Q3]. AUC: area under the curve from 0 to 15 minutes. Significant differences between the groups are indicated by *, ** and ***, which represent $p<0.05$, <0.01 and <0.001 respectively.
1. Oral drugs were metformin, sulfonylurea or sitagliptin
2: Injectables were insulin and/or exenatide.
3. Excluding data from one remitter with insulin allergy

Table 4 Two-year outcomes for LAGB remitters and non-remitters.

	Diabetes remission (n=12)		Persistent diabetes (n=10)			
	2 year value	**Change from baseline (96% CI)**	**2 year value**	**Change from baseline (98% CI)**	**Difference between groups (96% CI)**	**p-value**
Weight (kg)	68.3 [61.7, 76.5]	-12.0 (-16.5 to -10.0)	69.5 [62, 81]	-9.5 (-17.7 to -4.5)	1.3 (-7.5 to 13.5)	0.7103
Percent weight loss (%)	15 [13, 18]	n/a	10 [7, 20]	n/a	-5 (-9 to 3)	0.1542
BMI (kg/m^2)	24.8 [23.4, 25.9]	-4.5 (-5.3 to -3.7)	25.7 [23.4, 27]	-3.1 (-6.0 to -1.9)	0.9 (-1.2 to 2.6)	0.3428
Waist circumference (cm)	90 [82, 92]	-13 (-16 to -8)	93 [87, 96]	-8 (-17 to -1)	3 (-2 to 12)	0.1256
Diabetes treatment intensity						
no drugs	6	+3	4	+2	-1	
oral drug(s) [1]	6	-1	6	0	+1	0.639
injectables±oral drug(s) [1,2]	0	-2	0	-2	0	
Fasting biochemistry						
glucose (mmol/l)	5.6 [4.9, 6.3]	-1.3 (-1.8 to -0.5)	7.2 [5.9, 7.6]	-1.7 (-2.6 to -0.7)	1.6 (0.1 to 2.2)	0.0257
HbA1c (%)	5.8 [5.5, 6.3]	-0.7 (-1.5 to -0.3)	6.6 [6, 7]	-0.9 (-1.6 to -0.3)	0.8 (0.1 to 1.3)	0.0128
HbA1c (mmol/mol)	40 [37, 45]	-7 (-16 to -3)	49 [42, 52]	-9 (-18 to -3)	9 (1 to 14)	0.0128
insulin (pmol/l) [3]	58 [17, 153]	-42 (-73 to 49)	42 [31, 59]	-28 (-44 to -11)	-15 (-108 to 19)	0.2823
C-peptide (nmol/l)	0.66 [0.45, 1.18]	-0.38 (-0.56 to -0.00)	0.62 [0.5, 0.82]	-0.22 (-0.38 to -0.08)	-0.03 (-0.47 to 0.20)	0.9022
HOMA-B (%)	97 [76, 133]	4 (-53 to 24)	74 [51, 84]	8 (4 to 23)	-23 (-56 to -4)	0.0137
HOMA-S_{INS} (%) [3]	80 [29, 250]	47 (-2 to 191)	97 [73, 154]	47 (10 to 159)	17 (-128 to 71)	0.3683
HOMA-S_{CP} (%)	70 [39, 103]	34 (3 to 53)	66 [49, 87]	18.4 (9.300 to 48.10)	-4 (-33 to 27)	0.6592
IVGTT findings						
AUC_{GLUC} ($mmol.min.l^{-1}$)	125 [117, 140]	-2 (-27 to 5)	126 [112, 161]	-8 (-23 to 29)	1 (-15 to 32)	0.7604
AUC_{INS} ($pmol.min.l^{-1}$)	1549 [451, 2757]	7 (-243 to 1590)	451 [146, 597]	42 (-257 to 688)	-1097 (-2271 to -132)	0.0205
AUC_{CP} ($nmol.min.l^{-1}$)	7.61 [2.07, 14.97]	0.71 (0.44 to 5.21)	2.29 [0.9, 4.23]	0.58 (-0.53 to 3.21)	-5.32 (-10.8 to -0.3)	0.0248

1. Oral drugs were metformin, sulfonylurea or sitagliptin
2: Injectables were insulin and/or exenatide.
3. Excluding data from one remitter with insulin allergy

Supplementary Table Two-year outcomes according to weight loss tertile.

	Weight loss tertile						
	Bottom (n=14)		Middle (n=15)		Top (n=15)		
	2 year value	Median of differences BL v 2y (98% CI)	2 year value	Median of differences BL v 2y (96% CI)	2 year value	Median of differences BL v 2y (96% CI)	p-value for significant difference in medians (ANOVA)
Weight loss (%)	-2.0 [-3.3, 0.2]	-2.0 (-3.4 to 0.6)	6.9 [3.9, 10.5]	6.9 (3.9 to 10.5)	16.8 [15.1, 21.3]	16.8 (15.1 to 21.3)	<0.0001
Weight (kg)	86 [74.4, 93.1]	1.6 (-0.5 to 3.0)	72.3 [68, 79.2]	-5.8 (-8.5 to -3.0)	67.0 [60.3, 78.5]	-14.3 (-17.7 to -12.0)	0.0056
BMI (kg/m^2)	29.4 [27.7, 30.5]	0.58 (-1.8 to 1.0)	27 [26.2, 28.2]	-2.0 (-2.9 to -1.1)	24.2 [23.1, 24.9]	-5.0 (-6.0 to -4.5)	<0.0001
Fasting biochemistry							
glucose (mmol/l)	8.9 [8.2, 10]	1.0 (-2.4 to 2.9)	7.4 [6.1, 8.3]	-1.4 (-2.0 to -0.2)	6 [5.3, 7.4]	-1.3 (-2.3 to -0.5)	0.0008
HbA1c (%)	7.4 [6.5, 8.0]	-0.4 (-1.6 to 0.7)	6.7 [6.0, 7.4]	-0.4 (-1.0 to 0)	5.9 [5.6, 6.4]	-0.7 (-1.5 to -0.5)	0.0012
HbA1c (mmol/mol)	56.8 [47, 63.4]	-4.4 (-17.5 to 7.7)	49.7 [42.1, 57.4]	-4.4 (-10.9 to 0)	41.0 [37.7, 46.5]	-7.7 (-16.4 to -5.5)	0.0012
insulin (pmol/l)	110.7 [52.6, 175.2]	-4.5 (-17.0 to 62.5)	56.9 [46, 109]	-38.5 (-85.9 to -17.2)	42.3 [16.3, 78.3]	-39.2 (-72.6 to 2.8)	0.0416
C-peptide (nmol/l)	1.3 [0.9, 1.5]	0 (-0.1 to 0.5)	0.7 [0.6, 1.0]	-0.2 (-0.6 to -0.1)	0.6 [0.4, 0.7]	-0.4 (-0.5 to -0.1)	0.0004
C-peptide/insulin ratio	10.1 [7.5, 12.8]	0.4 (-3.3 to 3.5)	15.8 [10.2, 22.1]	4.1 (1.9 to 12.4)	27.0 [14.1, 60.7]	15.4 (-0.2 to 55.0)	0.0043
IVGTT findings							
AUC_{GLUC} ($mmol.min.l^{-1}$)	120.7 [111, 130.7]	-1.8 (-15.7 to 22.2)	141 [123.4, 152.3]	-8.1 (-20.2 to 9.1)	120.7 [106.4, 142.2]	-4.9 (-10.3 to 3.5)	0.1005
AUC_{INS} ($pmol.min.l^{-1}$)	589 [244, 717]	-27 (-648 to 231)	600 [243, 1307]	100 (-96 to 458)	551 [284, 2017	-31 (-399 to 319)	0.9619
AUC_{CP} ($nmol.min.l^{-1}$)	2.5 [1.2, 3.1]	-1.0 (-3.1 to 0.8)	2.7 [1.1, 7.1]	2.3 (-0.5 to 3.0)	3.0 [1.4, 10]	0.7 (0.2 to 1.9)	0.4572

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