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4 **Original Contribution**

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

9 *Secondary outcomes of a randomized controlled trial*  
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45 Beta-cell recovery after LAGB  
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4 **ABSTRACT**  
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7 **Introduction**  
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9 We aimed to determine the effects of LAGB on beta-cell function in overweight people  
10 with type 2 diabetes and to assess the relationship between baseline beta-cell function and  
11 glycemic outcomes.  
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14 **Methods**  
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16 We studied 44 overweight but not obese people with type 2 diabetes who participated in a  
17 randomized trial whose primary outcome was the rate of diabetes remission after 2 years  
18 of multidisciplinary diabetes care (MDC group) or multidisciplinary care combined with  
19 LAGB. Dynamic beta-cell function was assessed by intravenous glucose challenge and  
20 basal beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) were determined  
21 using the homeostatic model.  
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27 **Results**  
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29 Twelve and 2 participants in the LAGB and MDC groups respectively were in diabetes  
30 remission at 2 years. The C-peptide response to intravenous glucose and HOMA-S  
31 increased significantly in LAGB but not in MDC participants. The insulin response to  
32 glucose did not change in LAGB participants whereas their fasting C-peptide/insulin ratio  
33 increased. Baseline measures of beta-cell function correlated with diabetes remission but  
34 not with reduction in HbA1c following LAGB.  
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40 **Conclusions**  
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42 In overweight people with diabetes, LAGB improves endogenous beta-cell function after  
43 2 years. Baseline beta-cell function correlated with diabetes remission, but not with  
44 HbA1c change following LAGB.  
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4 **INTRODUCTION**  
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6 Randomized trials have shown that bariatric surgery for obese people with type 2  
7 diabetes achieves diabetes remission more frequently than medical care <sup>1-4</sup>. We recently  
8 reported outcomes of a randomized trial of laparoscopic adjustable gastric band surgery  
9 (LAGB) in people with diabetes and body mass index (BMI) between 25 and 30kg/m<sup>2</sup>  
10 that showed similar surgical benefits <sup>5</sup>. In these studies it was not clear why a substantial  
11 proportion of surgical participants did not achieve diabetes remission, and factors  
12 associated with reductions in HbA1c after bariatric surgery were not reported.  
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20 Type 2 diabetes occurs when the chronically increased demands for insulin due to insulin  
21 resistance, which is aggravated by obesity, cannot be compensated by the genetically  
22 defective  $\beta$ -cell <sup>6</sup>. Improved glycemic control following weight loss is therefore  
23 dependent on increased insulin sensitivity, improved beta-cell function, or a combination  
24 of the two. Retrospective analyses of cohorts undergoing bariatric surgery have shown  
25 that weight loss is strongly associated with diabetes remission <sup>7,8</sup>, arguing that improved  
26 insulin sensitivity is a key driver of remission. In addition, several studies of obese people  
27 with type 2 diabetes have shown the beta-cell response to *oral* glucose increases  
28 following gastric bypass or biliopancreatic diversion (reviewed in <sup>9</sup>). This improvement is  
29 primarily due to incretin effects rather than increased endogenous beta-cell function  
30 because the C-peptide response to parenteral glucose does not appear to change <sup>10,11</sup>.  
31 Whilst these findings suggest that dynamic beta-cell function in people with type 2  
32 diabetes would not change after LAGB, this assumption has not been tested by prior  
33 studies.  
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48 Identifying baseline predictors of diabetes remission and of reduced HbA1c following  
49 bariatric surgery may help target this expensive and at times dangerous therapy to those  
50 most likely to benefit <sup>12</sup>. Current evidence, mostly derived from retrospective analyses,  
51 suggests diabetes duration <sup>7,8,13-15</sup>, baseline levels of C-peptide <sup>13,14</sup> and beta-cell  
52 responsiveness to glucose <sup>16</sup> predict diabetes remission. This suggests baseline pancreatic  
53 beta-cell function is a key determinant of glycemic outcome following surgery. To date,  
54 no studies have tested this hypothesis in the LAGB context.  
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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.

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4 **METHODS**

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6 *Participants*

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

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32 Clinical data were collected as previously described<sup>5</sup> by study nurses (JP and CL), who  
33 were not blinded to treatment group. HbA1c, lipid and OGTT glucose levels, and urine  
34 albumin/creatinine ratio were performed by Melbourne Pathology (Abbotsford,  
35 Australia).  
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41 *Intravenous glucose tolerance test*

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43 Participants withheld glucose-lowering drugs for 24h prior to the test, which was  
44 performed between 9am and 11am in the fasting state. A cannula was inserted into a  
45 cubital vein and baseline venous samples collected at 5, 3 and 1 minute prior to injection  
46 of 50mL 50% w/v glucose over 1 minute followed by 10ml saline over 10 seconds. Then,  
47 5mL of venous blood was withdrawn from the same cannula over the next 2 minutes and  
48 discarded, followed by sample collection at 4, 6, 8, 10, 12 and 15 minutes after the start  
49 of the glucose injection. Blood samples were collected into 4.7ml serum tubes  
50 (*Monovette*, Starstedt, Germany) and allowed to clot on ice for up to 30 minutes. The  
51 tubes were then centrifuged and serum stored at -70°C. Levels of glucose, insulin and C-  
52 peptide were determined in one batch by Melbourne Health Pathology (Parkville,  
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4 Australia), using a 2700 Autoanalyser (Olympus, USA) for glucose assays (CV<2%) and  
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6 the Immulite 2000 assay (Siemens, Germany) for insulin and C-peptide (CVs <9% and  
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8 <8% respectively). Beta-cell function was defined as the trapezoidal area under the curve  
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10 (AUC) of the incremental insulin (AUC<sub>INS</sub>) or C-peptide (AUC<sub>CP</sub>) responses to  
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12 intravenous glucose. The HOMA2 calculator version 2.2.3<sup>17</sup> was used to impute beta-  
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14 cell function from the mean baseline levels of glucose and C-peptide (HOMA-B). Insulin  
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16 sensitivity was calculated using the baseline levels of glucose and insulin (HOMA-S<sub>INS</sub>)  
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18 or glucose and C-peptide (HOMA-S<sub>CP</sub>). Two methods were used because whilst HOMA-  
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20 S<sub>INS</sub> is generally a better measure of systemic insulin sensitivity<sup>17</sup>, we anticipated that  
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22 HOMA-S<sub>CP</sub> would be a better measure of insulin sensitivity after LAGB because weight  
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24 loss increases hepatic insulin clearance<sup>18</sup>. Insulin concentrations could not be assessed at  
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26 baseline in one LAGB participant with allergy to exogenous insulin and serum levels of  
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28 more than 1800pmol/l.

### 29 30 ***Definition of diabetes remission***

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32 Diabetes status was assessed 2 years after randomization in people whose HbA1c was  
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34 less than 7.0% by 75g oral glucose tolerance test, which was performed a week prior to  
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36 IVGTT and at least 2 days after stopping diabetes medication. Participants were  
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38 categorized as having diabetes if the fasting value was 7.0mmol/l or greater and/or the 2-  
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40 hour value was more than 11.0mmol/l. Dysglycemia was defined as a fasting level  
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42 between 5.6 and 7.0mmol/l and/or a 2h level ranging from 7.8 to 11.0mmol/l. Six of the  
43  
44 12 LAGB participants who achieved diabetes remission were taking metformin  
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46 monotherapy and the other six had not been taking diabetes medication for at least six  
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48 months prior to the glucose tolerance test.

### 49 50 ***Statistical analyses***

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52 We did analyses with Prism software (version 6.0b) and included only patients who  
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54 underwent IVGTT. We compared categorical data with the Fisher's exact test and Chi  
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56 square test for trend. Because few variables were normally distributed according to the  
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58 Shapiro-Wilk test, continuous data are presented as median [Q1, Q3], and we used the  
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60 Wilcoxon matched-pairs signed rank test and the Mann-Whitney U test to compare paired  
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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<sub>INS</sub> and HOMA-S<sub>CP</sub>) 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<sub>INS</sub> not changing significantly in either patient group. However, the median [Q1, Q3] AUC<sub>CP</sub> in the LAGB group increased significantly ( $p=0.0059$ ) from 2.11 [0.89, 5.19] nmol.min.l<sup>-1</sup> at baseline to 3.60 [1.33, 8.23] nmol.min.l<sup>-1</sup> at 2 years, whereas AUC<sub>CP</sub> did not change significantly in MDC participants. AUC<sub>INS</sub> 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<sub>CP</sub> 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<sub>CP</sub> 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

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4 loss tertile. An increased C-peptide response over the latter half of the IVGTT was seen  
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6 in participants belonging to the middle and top tertiles.  
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10 To determine the association between of beta-cell function and diabetes remission, we  
11 compared the twelve LAGB participants who entered diabetes remission (five with  
12 normoglycemia and seven with dysglycemia at two years) to the ten who did not. Their  
13 baseline characteristics are presented in Table 3, which shows that, compared to non-  
14 remitters, the remitters had significantly higher levels of HOMA-B, lower levels of  
15 fasting glucose and higher serum creatinine concentrations. Two-year outcomes for these  
16 groups are presented in Table 4, which describes similar weight loss in both groups. The  
17 IVGTT analysis shows that both groups had a similar glucose excursion, with remitters  
18 characterized by higher insulin and C-peptide responses at both baseline and at 2 years.  
19 Furthermore, only remitters showed improved C-peptide responses, evident at 8, 12 and  
20 15 minutes after the intravenous glucose challenge (Figure 1b), which was reflected by an  
21 increase in  $AUC_{CP}$  at 2 years (Table 4). Thus, compared to non-remitters, remitters had  
22 greater baseline beta-cell function that improved after 2 years.  
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35 Finally, among the LAGB participants, we examined the relationship between baseline  
36 beta cell function (as either HOMA-B or as  $AUC_{CP}$ ) and absolute reduction in HbA1c at  
37 2 years, and found no significant correlation. This finding accorded with the similar  
38 HbA1c reductions of 7mmol/mol in remitters and 9mmol/mol in non-remitters despite  
39 similar treatment intensities (Table 4).  
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4 **DISCUSSION**  
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6 These randomized trial outcomes show that, in overweight but not obese people who had  
7 diabetes for less than five years and received multidisciplinary diabetes care, LAGB  
8 improved insulin sensitivity and increased the amount of C-peptide released in response  
9 to intravenous glucose. In addition, beta-cell function correlated with diabetes remission  
10 but not with improved glucose control following LAGB.  
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17 In the LAGB group but not the MDC group, insulin sensitivity (HOMA-S) improved at 2  
18 years, but did not reach ‘normal’ levels of 100% seen in healthy people <sup>19</sup>. We described  
19 similar LAGB outcomes in obese people with type 2 diabetes <sup>1,20</sup>, which accord with  
20 those reported following other bariatric procedures (reviewed in <sup>9</sup>). Weight loss was the  
21 predominant predictor of diabetes remission in the entire group of LAGB and MDC  
22 participants <sup>5</sup>, which together with the HOMA-S data argues that improved insulin  
23 sensitivity from weight loss contributed to improved glycaemia in the LAGB group.  
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31 The C-peptide response to intravenous glucose, a marker of dynamic beta-cell function <sup>21</sup>,  
32 also improved following LAGB. This novel finding reflects intrinsic beta-cell recovery  
33 following LAGB-induced weight loss. However, it is at odds with two recent studies of  
34 obese people with type 2 diabetes that described no effect of gastric bypass surgery on C-  
35 peptide release following intravenous glucose. In one study, a combined  
36 glucose/glucagon challenge was performed a year after bypass surgery in 10 people  
37 whose diabetes duration varied between 1 and 11 years <sup>11</sup>. Possibly the stronger beta-cell  
38 stimulus provided by the glucose/glucagon combination together with the use of a smaller,  
39 more heterogeneous study population introduced type 2 error into this study. The other <sup>10</sup>  
40 reported outcomes of 14 people with type 2 diabetes who were given a varying infusion  
41 of intravenous glucose to match glucose excursions observed after oral glucose challenge.  
42 The authors modeled data from eight samples collected over 3 hours to calculate C-  
43 peptide secretion rate, which did not change despite substantial weight loss up to three  
44 years after surgery. Again, methodological differences and patient heterogeneity may  
45 have prevented detection of improved endogenous beta-cell function after bariatric  
46 surgery. Long-term outcomes of intravenous glucose testing have not previously been  
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4 reported in the context of LAGB or sleeve gastrectomy. However, a small study reported  
5 no change in the C-peptide response to a glucose increment of ~7mmol/l in 7 people (3  
6 LAGB and 4 sleeve gastrectomy) who lost around 7% body weight four weeks after  
7 restrictive surgery<sup>22</sup>. Taken with our findings, these results suggest that beta-cell  
8 recovery following LAGB or sleeve gastrectomy may require more substantial and  
9 prolonged weight loss. We did not elucidate the mechanism underlying beta-cell  
10 recovery after LAGB, but its correlation with weight loss suggests weight loss as a potential  
11 mechanism, perhaps via sustained reductions in circulating glucose, lipid, leptin or other  
12 inflammatory factors that are associated with obesity and known to adversely affect beta-  
13 cell function and survival<sup>23</sup>.  
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24 In contrast to the improved C-peptide response, LAGB had minimal effect on the insulin  
25 response to intravenous glucose, with only the eight-minute value different between the  
26 LAGB and MDC groups at 2 years and no significant change over time. This paradox is  
27 probably explained by increased hepatic insulin clearance after LAGB, reflected by a  
28 significant increase in the fasting C-peptide/insulin ratio. Weight loss is the likely reason  
29 for this because we found this to correlate with increased C-peptide/insulin ratio, and  
30 because similar changes were seen in obese people with diabetes who underwent weight  
31 loss through a very low calorie diet<sup>18</sup> or gastric bypass surgery<sup>11</sup>. Nonetheless, it is  
32 notable that the first phase of insulin release, occurring from baseline up to 8 minutes in  
33 our study, did not change significantly in LAGB participants. This finding is at odds with  
34 prior reports of dramatically improved first phase insulin release in severely obese people  
35 after gastric bypass or biliopancreatic diversion<sup>24,25</sup>. The reason for this discrepancy is  
36 not clear, but may relate to differences in study populations or to greater weight loss and  
37 its associated metabolic improvements observed in these two studies. Nonetheless, the  
38 unchanged acute insulin response coupled with improved insulin sensitivity observed in  
39 our study implies LAGB improved the disposition index to intravenous glucose<sup>21</sup>,  
40 consistent with similar outcomes for people with diabetes who lose weight through diet<sup>18</sup>  
41 or gastric bypass surgery<sup>10,11,24</sup>.  
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4 Our subgroup analysis of LAGB participants revealed an association between the 2-year  
5 values for HOMA-B, AUC<sub>INS</sub> and AUC<sub>CP</sub> and diabetes remission, consistent with the  
6 prevailing view that beta-cell function is a key determinant of type 2 diabetes <sup>6</sup>. More  
7 striking was the finding that baseline beta-cell function derived from fasting glucose and  
8 C-peptide levels (HOMA-B) was most strongly associated with diabetes remission 2  
9 years after LAGB, with a HOMA-B threshold of 80% predicting diabetes remission with  
10 a sensitivity of 83% and specificity of 90%. Further study is needed to confirm this  
11 finding and to assess its generalizability to obese patients and those with longer-standing  
12 diabetes. It is also important to note that baseline beta-cell function was not associated  
13 with the absolute reduction in HbA1c among the LAGB participants. Thus, people with  
14 low levels of beta-cell function may still derive significant glycaemic benefit from LAGB,  
15 even if diabetes remission is not achieved.  
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28 This study was limited by relatively small patient numbers and there was a high degree of  
29 inter-individual variability in glucose, insulin and C-peptide excursion following the  
30 intravenous glucose challenge. These features limited our ability to detect differences  
31 between the groups studied. The use of HOMA-S to assess insulin sensitivity may also  
32 have introduced error because, although HOMA-S has been shown to correlate well with  
33 euglycaemic clamp-derived measures of insulin sensitivity <sup>19</sup>, it has not been validated  
34 following substantial weight loss. Because we find evidence for increased hepatic insulin  
35 clearance after LAGB and marked discrepancy between HOMA-S<sub>CP</sub> and HOMA-S<sub>INS</sub>  
36 values after LAGB, it seems HOMA-S<sub>CP</sub> is the better of the two measures of insulin  
37 sensitivity in this context. Finally, it is not known if our findings are relevant to obese  
38 populations with type 2 diabetes. However, the metabolic effects of weight loss observed  
39 in this study <sup>5</sup> were comparable to those observed in obese cohorts <sup>1-4</sup>, consistent with a  
40 similar mechanism of disease remission across the BMI spectrum from 25kg/m<sup>2</sup> to over  
41 40kg/m<sup>2</sup>. It is also important to note that although the insulin and C-peptide responses to  
42 intravenous glucose improved after LAGB, their incremental responses remained much  
43 lower than those observed in people with normal glucose tolerance <sup>26</sup>. In addition,  
44 because these improvements occurred during the second and not the first phase of the  
45 IVGTT, they may not have contributed to diabetes remission.  
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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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26 **STATEMENT OF ETHICAL APPROVAL**  
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28 All procedures performed in studies involving human participants were in accordance  
29 with the ethical standards of the institutional and/or national research committee and with  
30 the 1964 Helsinki declaration and its later amendments or comparable ethical standards.  
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35 **CONFLICT OF INTEREST**  
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37 Paul Burton has received an honorarium, to speak at an education conference, from  
38 Covidien Australia, manufacturer of surgical stapling devices that are used in procedures  
39 designed to treat obesity. No other author reports a conflict of interest.  
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44 **AUTHOR CONTRIBUTIONS**  
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46 PEO and JMW designed the study, analysed the data and prepared the manuscript. PEO,  
47 WAB and PB did the LAGB surgery. JMW, CL and JP performed the IVGTTs. All  
48 authors contributed to, reviewed and approved the manuscript. JMW and PEO had full  
49 access to all of the data in the study and take responsibility for the integrity of the data  
50 and the accuracy of the data analysis.  
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4 **FIGURE LEGEND**  
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7 **Figure 1.** *IVGTT outcomes at baseline and 2 years.*

8 **a** Median glucose, insulin and C-peptide responses to intravenous glucose in MDC and  
9 LAGB participants.

10 **b** LAGB outcomes stratified according to diabetes remission at 2 years.

11 Statistical comparisons at each timepoint were performed by t-test as indicated with 1, 2  
12 and 3 symbols representing  $p < 0.05$ ,  $P < 0.01$  and  $P < 0.001$  respectively. Median [Q1, Q3]  
13 AUC data for each curve are provided in Tables 1 to 4.  
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17 **Supplementary Figure.** *IVGTT outcomes according to weight loss at 2 years*

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

	<b>LAGB Group (n=22)</b>	<b>MDC Group (n=22)</b>
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 <sup>2</sup> )	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
<i>Diabetes regimen</i>		
no drugs	5	4
oral drug(s) <sup>1</sup>	13	17
injectables±oral drug(s) <sup>2</sup>	4	1
<i>Fasting biochemistry</i>		
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) <sup>3</sup>	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 <sub>INS</sub> (%) <sup>3</sup>	47 [32, 72]	39 [25, 53]
HOMA-S <sub>CP</sub> (%)	46 [33, 52]	35 [26, 51]
<i>IVGTT findings</i>		
AUC <sub>GLUC</sub> (mmol.min.l <sup>-1</sup> )	132 [122, 157]	127 [106, 150]
AUC <sub>INS</sub> (pmol.min.l <sup>-1</sup> )	543 [150, 1036]	538 [297, 1072]
AUC <sub>CP</sub> (nmol.min.l <sup>-1</sup> )	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)		Difference between groups (95% CI)	p-value
	2 year value	Change from baseline (98% CI)	2 year value	Change from baseline (98% CI)		
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 <sup>2</sup> )	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
<i>Diabetes treatment intensity</i>						
no drugs	10	+5	2	-2	-8	
oral drug(s) <sup>1</sup>	12	-1	13	-4	1	0.0005
injectables±oral drug(s) <sup>2</sup>	0	-4	7	+6	7	
<i>Glycemic status</i>						
normal glucose tolerance	5	+5	0	0	-5	
dysglycemia	7	+7	2	+2	-5	0.0010
diabetes	10	-12	20	-2	10	
<i>Fasting biochemistry</i>						
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 <sub>INS</sub> (%)	92 [57, 249]	47 (10 to 156)	39 [23, 85]	4 (-7 to 29)	-53 (-79 to -11)	0.0057
HOMA-S <sub>CP</sub> (%)	69 [49, 90]	29 (9 to 40)	34 [26, 65]	-1 (-6 to 12)	-35 (-44 to -11)	0.0006
<i>IVGTT findings</i>						
AUC <sub>GLUC</sub> (mmol.min.l <sup>-1</sup> )	126 [115, 147]	-6 (-17 to 4)	125 [111, 141]	-6 (-16 to 5)	-1 (-15 to 11)	0.6455
AUC <sub>INS</sub> (pmol.min.l <sup>-1</sup> )	590 [264, 1695]	7 (-125 to 438)	590 [243, 771]	-21 (-410 to 208)	0 (-896 to 160)	0.5688
AUC <sub>CP</sub> (nmol.min.l <sup>-1</sup> )	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 <sup>2</sup> )	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
<i>Diabetes regimen</i>		
no drugs	3	2
oral drug(s) <sup>1</sup>	7	6
injectables±oral drug(s) <sup>2</sup>	2	2
<i>Fasting biochemistry</i>		
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) <sup>3</sup>	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 <sub>INS</sub> (%) <sup>3</sup>	42 [28, 59]	53 [42, 85]
HOMA-S <sub>CP</sub> (%)	40 [32, 52]	47 [37, 52]
<i>IVGTT findings</i>		
AUC <sub>GLUC</sub> (mmol.min.l <sup>-1</sup> )	132 [121, 152]	130 [122, 158]
AUC <sub>INS</sub> (pmol.min.l <sup>-1</sup> )	792 [424, 2007]	229 [132, 569]*
AUC <sub>CP</sub> (nmol.min.l <sup>-1</sup> )	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)		Difference between groups (96% CI)	p-value
	2 year value	Change from baseline (96% CI)	2 year value	Change from baseline (98% CI)		
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 <sup>2</sup> )	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
<i>Diabetes treatment intensity</i>						
no drugs	6	+3	4	+2	-1	
oral drug(s) <sup>1</sup>	6	-1	6	0	+1	0.639
injectables±oral drug(s) <sup>1,2</sup>	0	-2	0	-2	0	
<i>Fasting biochemistry</i>						
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) <sup>3</sup>	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 <sub>INS</sub> (%) <sup>3</sup>	80 [29, 250]	47 (-2 to 191)	97 [73, 154]	47 (10 to 159)	17 (-128 to 71)	0.3683
HOMA-S <sub>CP</sub> (%)	70 [39, 103]	34 (3 to 53)	66 [49, 87]	18.4 (9.300 to 48.10)	-4 (-33 to 27)	0.6592
<i>IVGTT findings</i>						
AUC <sub>GLUC</sub> (mmol.min.l <sup>-1</sup> )	125 [117, 140]	-2 (-27 to 5)	126 [112, 161]	-8 (-23 to 29)	1 (-15 to 32)	0.7604
AUC <sub>INS</sub> (pmol.min.l <sup>-1</sup> )	1549 [451, 2757]	7 (-243 to 1590)	451 [146, 597]	42 (-257 to 688)	-1097 (-2271 to -132)	0.0205
AUC <sub>CP</sub> (nmol.min.l <sup>-1</sup> )	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						p-value for significant difference in medians (ANOVA)
	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)	
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 <sup>2</sup> )	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
<i>Fasting biochemistry</i>							
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
<i>IVGTT findings</i>							
AUC <sub>GLUC</sub> (mmol.min.l <sup>-1</sup> )	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 <sub>INS</sub> (pmol.min.l <sup>-1</sup> )	589 [244, 717]	-27 (-648 to 231)	600 [243, 1307]	100 (-96 to 458)	551 [284, 2017]	-31 (-399 to 319)	0.9619
AUC <sub>CP</sub> (nmol.min.l <sup>-1</sup> )	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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