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DOI:  
[10.1111/dom.13131](https://doi.org/10.1111/dom.13131)

*Document Version*  
Peer reviewed version

*Citation for published version (Harvard):*

Tang, T, Abbott, S, le Roux, CW, Wilson, V, Singhal, R, Bellary, S & Tahrani, AA 2017, 'Preoperative weight loss with glucagon-like peptide-1 receptor agonist treatment predicts greater weight loss achieved by the combination of medical weight management and bariatric surgery in patients with type 2 diabetes: A longitudinal analysis', *Diabetes, Obesity and Metabolism*. <https://doi.org/10.1111/dom.13131>

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Checked for eligibility: 10/01/2018

Supplementary Material

This is the peer reviewed version of the following article:

Tang T, Abbott S, CW le Roux, et al. Preoperative weight loss with glucagon-like peptide-1 receptor agonist treatment predicts greater weight loss achieved by the combination of medical weight management and bariatric surgery in patients with type 2 diabetes: A longitudinal analysis. *Diabetes Obes Metab*. 2017;1–4., which has been published in final form at <https://doi.org/10.1111/dom.13131>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

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# Preoperative Weight Loss With GLP-1 Receptor Agonist Treatment Predicts Greater Weight Loss Achieved by the Combination of Medical Weight Management And Bariatric Surgery In Patients With Type 2 Diabetes: A Longitudinal Analysis

## Supplementary Appendix

### Supplementary Background

Bariatric surgery is currently the most effective method to achieve long-term substantial sustainable weight loss in patients with obesity.<sup>1</sup> The weight loss following bariatric surgery varies considerably amongst individuals with Laparoscopic Adjustable Gastric Banding (LAGB) resulting in 15-25% weight loss compared to Roux-en-Y Gastric Bypass (RYGB) and Laparoscopic Sleeve Gastrectomy (LSG) both resulting in 25-35% weight loss respectively over 10 years period.<sup>2-4</sup>

We hypothesized that greater weight change achieved by GLP-1 RA before surgery predicts greater post-surgical weight loss and greater weight loss from the start of MWM to 12 months post-surgery. A secondary aim of our study was to assess the relationship between weight changes following preoperative GLP-1 RA treatment and surgically-induced weight changes at 12 months after bariatric surgery.

### Supplementary Methods

#### Patient inclusion and exclusion criteria

Patients with T2DM who underwent bariatric surgery were identified from the bariatric surgery database at our centre. To be included in the analysis, patients had to be adults with T2DM, who underwent preoperative GLP-1RA treatment under the care of our centre and then underwent bariatric surgery between the years 2011 and 2014. Receiving GLP-1 RA was at the discretion of the treating physician.

Only patients who attended at least 12 months post-bariatric surgery follow-up were included. Data regarding the preoperative treatment and the details of GLP-1 RA treatment were obtained from the patients' electronic hospital records at our centre. The titration, stopping or continuation of GLP-1 RA treatment were made based on clinical grounds by the treating physicians. As per our clinic protocols, GLP-1 RA treatment was continued to the time of surgery when possible and stopped before surgery. GLP-1 RA treatment were only used after surgery for glycaemic control at the discretion of the treating physician.

### Clinical Setting

Patients were referred to the Tier 3 MWM at our centre if they had a body mass index (BMI)  $\geq 35$  kg/m<sup>2</sup> with at least one obesity-related comorbidity or BMI  $\geq 40$  kg/m<sup>2</sup> with or without comorbidities. The Tier 3 MWM provides input from bariatric physicians, specialist dieticians, a psychologist, and a specialist nurse. Patients generally spend 12-24 months in the Tier 3 services before being referred to the surgical team for the consideration of bariatric surgery.<sup>5</sup> Whilst in the Tier 3 services, patients receive a combination of lifestyle and behavioural intervention delivered in group sessions and in 1-to-1 appointments. These interventions are coupled with pharmacotherapy where deemed appropriate at the discretion of the health care professionals at any time point during the MWM. All patients in our service received medical weight management regardless whether pharmacotherapy was used or not.

### Data Collected

The following data were collected: Start and end dates of Tier 3 MWM; Start and end dates of GLP-1 RA treatment; name of the GLP-1 RA; type of bariatric procedure; weight (kg) and BMI (kg/m<sup>2</sup>) at the start and end of MWM, the start and end of GLP-1 RA treatment, from the day of surgery and 12 months post-bariatric surgery. These values were used to calculate the weight changes in kilograms and percentages as follows (**Figure S1**):

- Total weight change (TWC) in Kg: weight measured at start of MWM – weight at 12 months post-bariatric surgery
- Pre-GLP-1 RA weight change in Kg: MWM Baseline weight – Weight at the start of GLP-1 RA treatment
- Percentage weight change before GLP-1 RA treatment (%): Point 2/ MWM baseline weight

GLP-1 RA induced weight change in Kg: Weight at the start of GLP-1 RA – weight at the end of GLP-1

RA

- Percentage GLP-1 RA induced weight change: weight calculated from point 4/ weight at the start of GLP-1 RA
- Weight change induced by surgery in Kg: weight day of surgery – weight at 12 months post-surgery
- Percentage weight change induced by surgery: weight calculated from Point 6/ weight day of surgery
- Proportion of total weight change attributed to weight change before GLP-1 RA treatment (%): point 2/ point 1
- Proportion of total weight change attributed to GLP-1 RA treatment (%): weight calculated from point 4/ weight calculated from point 1
- Proportion of total weight change attributed to surgery (%): weight change calculated from point 6/ weight change from point 1

In this brief report and based on the methods of calculation detailed above, positive weight change values denoted weight loss, whilst negative values denoted weight gain. In this study, we defined a lack of weight loss (i.e. weight maintenance or weight gain) as weight loss < 3% of total body weight or weight gain as used in previous studies.<sup>6</sup>

## Ethical considerations

The project was registered and approved as a clinical audit/health service evaluation at the department of diabetes and endocrinology at Birmingham Heartlands Hospital and carried out as part of a health service evaluation to assess weight loss predictors and outcomes of patients undergoing bariatric surgery at our centre. All data collected was part of routine care, and only anonymized data were used in this analysis.

## Statistical Analysis

Data analysis was performed using SPSS Statistics 23 (IBM). Depending on data distribution, the data was presented as either frequencies, mean  $\pm$  SD, or median  $\pm$  IQR. Data distribution was assessed using the Shapiro-Wilco test. The relationship between continuous variables (such as weight changes) were assessed using either Pearson's or Spearman's test depending on data distribution. Differences between variables were performed using the Chi-square test in the case of categorical variables and the independent t-test or the Mann-Whitney U test in the case of continuous variables depending on data distribution.

Predictors of post-operative weight change and TWC were assessed using multiple linear regression. Variables included in the regression models were based on their relevance biologically and epidemiologically to the outcome of interest. Assumptions of linear regression were examined and adhered to.

Due to the different mechanisms of action between different types of bariatric surgery, the data analysis was performed in two subgroups: LAGB and RYGB/LSG. The RYGB and LSG were combined due to the limited sample size. A  $p < 0.05$  was considered statistically significant throughout the brief report.

## Supplementary Results

Forty-five patients were included in this analysis (26 gastric band, 16 RYGB and 3 LSG). The study population was mostly composed of middle age women with grade III obesity (**Table S1**). Liraglutide once-daily was used in 35 patients, while 10 patients received Exenatide twice-daily. Eight patients received GLP-1 RA treatment post-operatively to improve glycaemic control at the discretion of the treating physician.

### Weight changes during the study

GLP-1 RA and bariatric surgery resulted in significant weight loss (**Table S2**). Overall, LAGB resulted in 7.3 (2.9 to 9.9) % weight loss and RYGB/LSG resulted in 24.7 (19.5 to 25.9) % weight loss calculated from the day of surgery till 12 months post-bariatric surgery (**Table S2**). Calculating the weight loss from the start of Tier 3 MWM showed that patients who had LAGB lost 13.8 (6.9 to 17.6) % and those who had RYGB/LSG lost 29.3 (23.1 to 34.3) % (**Table S2**).

### The relationships between pre- and post-operative weight changes

There was no relationship between GLP-1 RA induced weight change and the weight change induced by bariatric surgery over 12 months, regardless of the type of the surgical procedure (**Tables S3 and S4**). Comparing the weight changes at multiple timepoints before and after surgery in patients who lost  $\geq 3\%$ , 5% or 8% of their weight on GLP-1 RA treatment vs. those who lost  $< 3\%$ , 5% or 8% body weight respectively can be found in **Table S4**. There was no differences in % weight loss from day of surgery to 12 months post-surgery in patients who lost  $\geq 3$ , 5 or 8% of their weight following GLP-1 RA vs. those who lost  $< 3$ , 5 or 8% respectively regardless of the type of procedure. However, the % body weight loss between start of MWM and 12 months post-operatively was greater, albeit not statistically significant, in LAGB patients who lost  $\geq 3\%$  body weight following GLP-1 RA treatment and was significantly greater in patients who received LSG/RYGB who lost  $\geq 8\%$  body weight following GLP-1 RA treatment.

Using multiple linear regression and after adjusting for % weight change from baseline to the start of GLP-1 RA, the % weight change induced by GLP-1 RA, baseline weight, gender, age and type of surgery (for the model:  $R = 0.761$ ,  $R^2 = 0.580$ ); % weight change from the day of surgery to 12 months post-operatively was predicted by having RYGB/LSG ( $B = 0.168$ ,  $p < 0.001$ ) and % weight change from baseline MWM to the start of GLP-1 RA ( $B = -0.587$ ,  $p = 0.03$ ). Percentage weight change because of GLP-1 RA treatment did not predict 12 months post-operative weight loss ( $B = -0.15$ ,  $p = 0.5$ ). These results suggest that having LSG/RYGB predicted greater weight loss after surgery. However, greater % weight loss before starting GLP-1 RA predicted lower % weight loss after bariatric surgery.

Similarly, following adjustments for age, sex, surgical procedure, baseline weight (kg), weight change before starting GLP-1 RA (in Kg) and weight change after starting GLP-1 RA (Kg) (for the model:  $R = 0.793$ ,  $R^2 = 0.630$ ); predictors of weight change from preoperative weight to 12 months post-surgery weight in kg were: age ( $B = 0.337$ ,  $p = 0.023$ ), baseline weight ( $B = 0.217$ ,  $p = 0.004$ ) and weight change from baseline MWM to starting GLP-1 RA ( $B = -0.9$ ,  $p < 0.001$ ). Weight change due to GLP-1 RA treatment was not a predictor of the weight change post-operatively ( $B = -0.301$ ,  $p = 0.169$ ). The results suggest that higher baseline weight (in kg) and older patients had greater weight loss (in kg) after surgery, while patients who lost more weight (in kg) before starting the GLP-1 RA treatment lost less weight (in kg) after surgery.

## Supplementary Discussion

### Evaluation of secondary aim and study

Our secondary aim was to assess the relationship between weight loss achieved through preoperative GLP-1 RA treatment and weight loss 12 months after bariatric surgery. Our data have shown that the impact of GLP-1 RA treatment before bariatric surgery does not predict the weight loss achieved following bariatric surgery. There was no difference in post-bariatric surgery weight loss in those who lost weight following GLP-1 RA treatment and those who did not lose weight.

While this might be understandable in patients undergoing LAGB, as the weight loss mechanism is not believed to be related to GLP-1, the findings are surprising in patients who underwent RYGB or LSG.

### Limitations and Strengths

Our study has several limitations. Our sample size is small and the duration and timing of treatment of GLP-1 RA varied considerably amongst patients depending on the clinical care. Despite this, the correlation coefficients do not show any trend towards a positive association between weight loss following GLP-1 RA and weight loss following bariatric surgery. Another limitation is the possibility of confounding by indication. Most patients with T2DM in the MWM did not receive GLP-1 RA treatment and hence the indication for starting the GLP-1 RA treatment by the treating clinician might have confounded our findings. Our study was limited to patients with T2DM as GLP-1 RA was not licensed and was not available to treatment of obesity outside the context of T2DM.

Our study also has its strengths: it is the first to examine the relationship between dynamic weight changes due to GLP-1 RA treatment and post-surgery weight loss and our patients received intensive life style intervention by an experienced team before and after bariatric surgery.



## Supplementary Tables and Figures

Table S1. Patient Demographics and baseline characteristics. Data presented as median (IQR) or percentages. MWM: Medical Weight Management Services; BMI: Body Mass Index; GLP-1 RA: Glucagon-like peptide -1 receptor agonist LAGB: Laparoscopic Adjustable Gastric Band; RYGB: Roux-en-Y Gastric Bypass; LSG: Laparoscopic Sleeve Gastrectomy.

	Total Study Population	LAGB	RYGB/ LSG
<i>N</i>	45	26	19
Age at time of surgery	49 (45 to 60)	52.5 (45 to 60)	47 (45 to 58)
Baseline Weight at MWM (kg)	136 (119.1 to 132.4)	137.7 (120.5 to 155.2)	125.7 (113.6 to 140.4)
Baseline BMI at MWM (kg/m <sup>2</sup> )	46.2 (43.1 to 53.9)	48.3 (44.8 to 55.5)	44 (42.9 to 48.2)
Women (% , N)	64.4%, N=29	65.4%, N=17	63.2%, N=12
Length of GLP-1 RA treatment (days)	454 (206.5 to 644)	416.5 (213.25 to 643.5)	455 (177 to 788)
Time in MWM before initiating GLP-1 RA treatment (days)	118 (11.5 to 320)	193.5 (74.25 to 392)	45 (0 to 195)

Table S2. Summary of weight changes (in Kg and %) during the different stage of the study. Data presented as median (IQR). Negative values indicate weight gain. GLP-1 RA: Glucagon-like peptide-1 receptor agonist; MWM: Medical Weight Management Services; TWC: Total Weight Change; LAGB: Laparoscopic Adjustable Gastric Band; RYGB: Roux-en-Y Gastric Bypass; LSG: Laparoscopic Sleeve Gastrectomy.

Weight Change	Total study population Weight Change (Kg and %)	LAGB Weight Change (Kg and %)	RYGB/LSG Weight Change (Kg and %)
Prior to GLP-1 RA treatment	1.1 (0 to 5.3) kg 0.7 (0 to 3.6) %	1.7 (-0.1 to 6.15) kg 1.3 (-0.1 to 3.9) %	0.4 (0 to 3.8) kg 3.3 (0 to 3.5) %
During GLP-1 RA treatment	6.1 (2.6 to 13.0) kg 5.0 (1.9 to 7.7) %	7.4 (1.6 to 11.4) kg 5.7 (1.3 to 7.8) %	5.8 (3.2 to 13.4) kg 4.8 (2.1 to 7.8) %
From day of surgery to 6 months Postoperative	14.9 (10.1 to 22.5) kg 12.4 (7.3 to 21.3) %	11.5 (2.6 to 14.5) kg 8.8 (2.4 to 12.2) %	22.1 (19.6 to 26.8) kg 21.4 (14.7 to 23.2) %
From day of surgery to 12 months Postoperative	14.3 (7.0 to 26.8) kg 10.7 (5.6 to 25.0) %	9.3 (2.9 to 13.5) kg 7.3 (2.9 to 9.9) %	26.3 (19.9 to 29.2) kg 24.7 (19.5 to 25.9) %
Weight change from start of MWM to 12 months after surgery (TWC)	28.3 (17.2 to 40.1) kg 17.9 (13.0 to 29.3) %	18.6 (9.0 to 25.4) kg 13.8 (6.9 to 17.6) %	40 (32.3 to 43.8) kg 29.3 (23.1 to 34.3) %

Table S3. The relationship between weight change during GLP-1 treatment and weight change from day of surgery till 12 months postoperative. GLP-1 RA: Glucagon-like peptide-1 receptor agonist; LAGB: Laparoscopic Adjustable Gastric Band; RYGB: Roux-en-Y Gastric Bypass; LSG: Laparoscopic Sleeve Gastrectomy

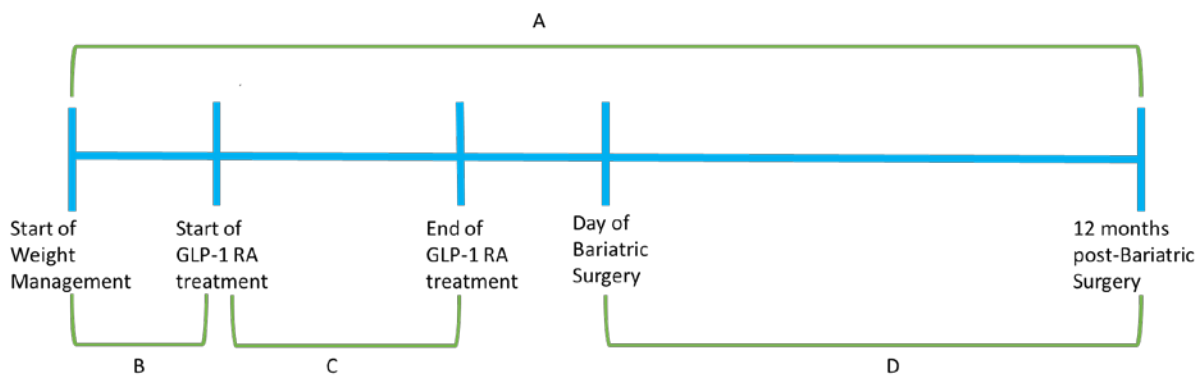
	r value	p-value
<b>Total Study Population (n=45)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and Weight change induced by surgery in Kg	0.021	0.892
Correlations between Percentage GLP-1 RA induced weight change, and Percentage weight change induced by surgery	0.028	0.857
<b>LAGB (n= 26)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and Weight change induced by surgery in Kg	0.024	0.909
Correlations between Percentage GLP-1 RA induced weight change, and Percentage weight change induced by surgery	-0.086	0.677
<b>RYGB/LSG (n= 19)</b>		
Correlations between GLP-1 RA induced weight change in Kg, and Weight change induced by surgery in Kg	-0.313	0.193
Correlations between Percentage GLP-1 RA induced weight change, and Percentage weight change induced by surgery	-0.025	0.92

Table S4. Comparison of percentage weight loss post operatively between patients who lost < 3, 5 and 8% weight on GLP-1 RA treatment and those who lost ≥ 3, 5, and 8%. A negative value indicates weight gain. Data presented as median (IQR). GLP-1 RA: Glucagon-like peptide-1 receptor agonist; LAGB: Laparoscopic Adjustable Gastric Band; RYGB: Roux-en-Y Gastric Bypass; LSG: Laparoscopic Sleeve Gastrectomy

	Weight loss following GLP-1 RA (>= 3%)	Weight maintenance or weight gain following GLP1 RA (< 3%)	p-value
<b>Total Study Population (n=45)</b>	<b>N=30</b>	<b>N=15</b>	
% body weight loss between day of surgery and 12 months post operatively	11.9% (6.8 to 24.1)	9.9% (5.1 to 25.3)	0.866
% body weight loss prior to GLP-1 RA	0.2% (0 to 3.2)	1.8% (0 to 7.5)	0.17
% body weight loss between start of medical weight management and 12 months post operatively	21.2% (13.3 to 29.6)	14.6% (6.1 to 29.3)	0.30
<b>LAGB (n= 26)</b>	<b>N=17</b>	<b>N=9</b>	
% body weight loss between day of surgery and 12 months post operatively	7.3% (3.4 to 9.4)	6.9% (-2.8 to 10.8)	0.916
% body weight loss prior to GLP-1 RA	0.0% (-0.7 to 3.1)	4.3% (0.0 to 8.8%)	0.58
% body weight loss between start of medical weight management and 12 months post operatively	16.3% (11.7 to 17.9)	7.2% (0.1 to 16.1)	0.15
<b>RYGB/LSG (n= 19)</b>	<b>N=13</b>	<b>N=6</b>	
% body weight loss between day of surgery and 12 months post operatively	23.8% (17.3 to 25.7)	25.6% (17.4 to 28.4)	0.521
% body weight loss prior to GLP-1 RA	0.3% (0 to 4.5)	0.4% (-0.2 to 4.6)	0.90
% body weight loss between start of medical weight management and 12 months post operatively	32.9% (24.0 to 37.7)	29.3% (20.7 to 32.9)	0.52
	≥ 5% weight loss	<5% weight loss following	p-

	following GLP-1 RA	GLP1 RA	value
<i>Total Study Population (n=45)</i>	<b>N=23</b>	<b>N=22</b>	
% body weight loss between day of surgery and 12 months post operatively	9.9% (5.0 to 23.6)	15.6% (5.7 to 25.4)	0.4
% body weight loss prior to GLP-1 RA	0% (0 to 3.4)	12.9% (0 to 5.1)	0.5
% body weight loss between start of medical weight management and 12 months post operatively	17.9% (13.0 to 28.2)	20.1% (9.7 to 32.4)	0.9
<i>LAGB (n= 26)</i>	<b>N=15</b>	<b>N=11</b>	
% body weight loss between day of surgery and 12 months post operatively	7.3% (3.3 to 9.9)	6.9% (0.4 to 9.9)	0.9
% body weight loss prior to GLP-1 RA	0 (-0.4 to 3)	4.3% (0 to 7.5)	0.09
% body weight loss between start of medical weight management and 12 months post operatively	16.8% (12.8 to 17.9)	10.6% (1.7 to 16.3)	0.134
<i>RYGB/LSG (n= 19)</i>	<b>N=8</b>	<b>N=11</b>	
% body weight loss between day of surgery and 12 months post operatively	23.7% (13.7 to 25.4)	25.3% (21.3 to 28.1)	0.3
% body weight loss prior to GLP-1 RA	1.8% (0 to 6.5)	0.3% (0 to 2.5)	0.4
% body weight loss between start of medical weight management and 12 months post operatively	30.9% (23 to 41.2)	29.3% (23.1 to 32.9)	0.6
	>= 8% weight loss following GLP-1 RA	<8% weight loss following GLP1 RA	p-value
<i>Total Study Population (n=45)</i>	<b>N=10</b>	<b>N=35</b>	
% body weight loss between day of surgery and 12 months post operatively	13.9% (2.9 to 24.9)	10.7% (5.8 to 25.3)	0.8
% body weight loss prior to GLP-1 RA	0% (-0.1 to 3.6)	4.3% (1.8 to 7.9)	0.6
% body weight loss between start of medical weight management and 12 months post operatively	23.1% (16.1 to 41.2)	17.6% (12.8 to 28.5)	0.2
<i>LAGB (n= 26)</i>	<b>N=6</b>	<b>N=20</b>	
% body weight loss between day of surgery and 12 months post operatively	5.3% (-1.7 to 11.4)	7.8% (3.9 to 9.9)	0.5
% body weight loss prior to GLP-1 RA	0% (-0.3 to 1.5)	2% (-0.3 to 4.8)	0.4
% body weight loss between start of medical weight management and 12 months post operatively	17.5% (10.6 to 20.5)	13.2% (6.4 to 17.2)	0.2
<i>RYGB/LSG (n= 19)</i>	<b>N=4</b>	<b>N=15</b>	
% body weight loss between day of surgery and 12 months post operatively	25.2% (24.1 to 27.6)	23.6% (15.1 to 25.9)	0.4
% body weight loss prior to GLP-1 RA	1.8% (-0.1 to 9.6)	3.3% (0 to 3.3)	0.7
% body weight loss between start of medical weight management and 12 months post operatively	41.2% (35.3 to 42.2)	28.5% (22.8 to 32.9)	0.002

Figure 1. A schematic representation of a patient's journey from the start of Weight Management to 12 months after bariatric surgery. A refers to the Total Weight Change (kg) which is calculated by Weight taken at the Start of Weight Management (kg; WMS Baseline Weight) minus weight measured 12 months post-Bariatric Surgery (kg). B refers to Pre-GLP-1 RA weight change (kg) as calculated by WMS Baseline Weight minus weight at start of GLP-1 RA treatment. C refers to GLP-1RA induced weight change (kg) as calculated by weight measured at the start of GLP-1 RA treatment minus the weight measured at the end of GLP-1 RA treatment. D refers to weight change induced by Bariatric surgery (kg) as calculated by weight measured pre-operatively minus the weight measured 12 months post-Bariatric Surgery.



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