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### **Paper:**

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# **Effect of laparoscopic sleeve gastrectomy on static and dynamic measures of glucose homeostasis and incretin hormone response 4 years post-operatively**

**Min T, Prior SL, Churm R, Dunseath GJ, Barry JD, Stephens JW**

## **Abstract**

There is limited literature available on the long-term effect of bariatric surgery especially laparoscopic sleeve gastrectomy (LSG) on the incretin hormone response.

Our primary aim was to investigate changes in glucose metabolism and incretin hormone responses in participants with impaired glucose regulation approximately 4 years after LSG.

The secondary aim was to examine the long-term incretin hormone changes of biliopancreatic diversion (BPD).

A non-randomized prospective study comprising of 10 participants undergoing LSG and 6 participants undergoing BPD. Serial measurements of glucose, insulin, C-peptide, glucagon like peptide -1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) were performed during an oral glucose tolerance test pre-operatively and 1 month, 6 months and at approximately 4-7 years post-operatively. Area under the curve (AUC) were examined at 60 and 120 minutes.

In the LSG group, a significant reduction in 2-hr plasma glucose (2hr PG), HbA1c, and HOMA-IR was observed at 4 years. Compared with pre-operative levels, significant increases in post-glucose GLP-1 secretion were observed at 1 and 6 months, but not maintained at 4 years. A linear increase was seen in post-glucose GIP response at 1-month and 6-months and 4-years. Within the BPD group, a reduction in HbA1c along with an increase GLP-1 response was observed at 7 years.

An increase in GLP-1 response was not preserved at 4 years, but a significant increase in GIP response was observed along with improved glycaemic control following LSG.

**Key Words:** Bariatric surgery, sleeve gastrectomy, incretin hormone changes, diabetes

## Introduction

Recent years have seen a marked increase in the number of laparoscopic sleeve gastrectomy (LSG) operations performed for obesity and obesity associated type 2 diabetes (T2DM) [1, 2]. Previous studies have shown that LSG produces weight loss and an improvement in metabolic outcomes comparable to Biliopancreatic Diversion (BPD) and Roux-en-Y Gastric Bypass (RYGB). A meta-analysis of 11 randomised clinical trials (RCTs), comprising of 765 participants, comparing at least 2 of 3 bariatric surgical procedures (LSG, RYGB and LAGB) concluded that RYGB and LSG results in similar weight loss, both of which were superior to LAGB [3]. Tsoli et al, demonstrated that LSG (n=12) was comparable to BPD (n=12) in % Excess weight loss (%EWL), diabetes remission and enhanced postprandial Glucagon-like peptide-1 (GLP-1) response at 1 year in patients with obesity associated T2DM [4]. Similarly, Nosso et al reported that LSG (n=19) was comparable to RYGB (n=14) in weight loss and diabetes remission rate, but the improvement in the postoperative postprandial GLP-1 response was more pronounced in the RYGB group at 1 year. [5]. While the observations on the effect of LSG on GLP-1 response were consistent with previous studies, the data on GIP response remains inconclusive. Some studies have described no changes in GIP response [6] while others have reported a decrease [5]. It is important to note that in all the published studies relating to LSG, the follow-up period was up to 1 year. There is limited literature on the long-term effect of LSG on glucose homeostasis, GLP-1 and GIP response in individuals with T2DM or impaired glucose tolerance.

Previously we have demonstrated that LSG was associated with an improvement in glucose homeostasis and an increased GLP-1 response at 1- and 6-months and these results were comparable to the BPD group [6]. We hypothesise that these improvements would be preserved in the longer term (approximately 4 years). The primary aim of this current study

was to examine static and dynamic changes in glucose, insulin, C-peptide, GLP-1 and GIP in participants with T2DM and impaired glucose regulation at a mean follow-up period of 4 years after LSG. The secondary aim was to examine long-term incretin hormone changes in participants who underwent BPD.

## **Methods**

### ***Study participants***

Approval for the study was obtained from the Local Research Ethics Committee (LREC reference 06/WMW02/7). Participants (n=40) who took part in a previously published initial study [6] (pre-operative, 1-month and 6-month post-operative) were invited (by post, email or telephone call) to return at a mean follow-up of 4 years (range: 2-7 years). There were 26 participants in the LSG group and 14 in the BPD group. Ten participants in the LSG group and 6 in the BPD group agreed to participate. Sixteen participants in LSG group and 2 in the BPD group were lost to follow-up or declined to participate in the follow-up study. Six participants were deceased in the BPD group. The study sample has been previously described [6, 7]. In brief, the inclusion criteria at the outset included: - both gender, age between 20 and 60 years and BMI  $\geq 40$  kg/m<sup>2</sup>. All participants had previously diagnosed T2DM or diagnosed during an Oral Glucose Tolerance Test (OGTT) at the start of the study or impaired glucose regulation according to the American Diabetes Association (ADA) criteria [8]. Buse's consensus (2009) criteria was used to define diabetes remission [9]. Complete remission is defined as HbA1c <6% and fasting plasma glucose (FPG) <5.6 mmol/L and off medication and partial remission is defined as HbA1c 6.0-6.4% and FPG 5.6-6.9 mmol/L and off medication for 1 year.

### ***Study design***

The study was a non-randomised prospective study. All the participants underwent a standardised 75 g OGTT (122 mls of Polycal 61.9 g/ 100 ml of glucose, Nutricia Clinical Care, Trowbridge, UK) pre-operatively and post-operatively at 1 month, 6 months and 4 years. Pre-operative tests were performed 1 month prior to the surgery. All participants were asked to fast from the midnight before the test and all diabetes related medications were omitted for 24 hours before OGTT. During the OGTT, blood samples were collected for measurements of glucose, insulin, C-peptide, GLP-1 and GIP at time 0, 15, 30, 45, 60 and 120 minutes. All samples were collected on ice, centrifuged within one hour of collection and stored at -80°C until analysis. At the time of the pre-operative and post-operative OGTT, clinical and biochemical information were obtained. Clinical measurements included weight, height, body mass index (BMI), waist circumference and blood pressure. Biochemical data such as HbA1c and lipid profile were analysed within the local hospital accredited laboratory.

### ***Measurement of insulin, C-peptide, insulin sensitivity and beta cell function***

Insulin was measured using an Invitron Insulin ELISA kit. The analytical sensitivity of the Invitron insulin assay was 0.02 mU/L and the dynamic range of this assay is 0.02 – 250 mU/L. The inter-assay coefficient of variation was  $\leq 7.1$ . Cross reactivities (CR) of related proteins were as follow: - CR 1.2% with intact proinsulin; and 0% with C-peptide. C-peptide was measured with an Invitron C-peptide kit. The analytical sensitivity of the Invitron C-peptide assay was 5.0 pmol/L. The dynamic range of this assay is 5.0-5,000 pmol/L. There was 2% cross reactivity with intact proinsulin but no cross reactivity with insulin.

Insulin sensitivity and beta cell function was measured with Homeostasis Model Assessment (HOMA) by using measurements of fasting glucose and C-peptide concentrations. These were calculated by using the Oxford University online calculator (<https://www.dtu.ox.ac.uk/homacalculator/> accessed 01 June 2015). HOMA was first developed by Matthews and colleagues in 1985 [10] and updated to a HOMA2 computer model in 1996 [11]. HOMA provides three measures: HOMA-%B (estimated steady state beta cell function), HOMA-%S (insulin sensitivity) and HOMA-IR (insulin resistance). These measures have been validated and shown to correlate with clamp-derived studies [11].

#### ***Measurement of total GLP-1 and total GIP***

Total GLP-1 was quantitatively measured using the EMD Millipore Total GLP-1 ELISA Kit. The antibody pair used in this assay measures GLP-1 (7-36) and (9-36) and has no significant cross-reactivity with GLP-2, GIP, Glucagon and Oxyntomodulin. The sensitivity of this assay was 1.5 pM and the approximate range of this assay was 4.1 to 1,000 pM. The intra- and inter-assay coefficients of variation were  $\leq 2\%$  and  $\leq 12\%$  respectively. Total GIP was measured using the EMD Millipore Human GIP (total) ELISA Kit, which reacts fully with intact GIP (1-42) and the NH<sub>2</sub>-terminally truncated metabolite GIP (3-42). The assay does not significantly cross-react with Glucagon, Oxyntomodulin, GLP-1 and GLP-2. The sensitivity of this assay was 4.2 pg/mL (20  $\mu$ L sample size). The appropriate range of this assay is 4.2 pg/mL to 2,000 pg/mL. The intra- and inter-assay coefficients of variation were  $\leq 8.8\%$  and  $\leq 6.1\%$  respectively.

#### ***Statistical analysis***

Statistical analysis was performed using SPSS (version 22, SPSS Inc., Chicago). The normality of data was assessed by the Shapiro-Wilk test. Continuous data with a normal distribution are presented as mean and standard deviation, and data that did not have a normal distribution are described as median and interquartile range. We used ANOVA with post-hoc analyses for data with a normal distribution and Friedman test for data without a normal distribution. In all cases,  $p < 0.05$  is considered to be significant.

## **Results**

### **Participants' characteristics**

There were 10 participants (6 Females, a mean age of  $52 \pm 6$  years) in the LSG group and 6 (5 Females, a mean age of  $48 \pm 7$  years) in the BPD group with follow-up data available for analysis. The mean duration of follow-up for the LSG group was  $4.0 \pm 1.5$  years and for the BPD group  $7.2 \pm 0.6$  years. The baseline and follow-up characteristics of both groups are shown in Table 1. Eight participants had T2DM in the LSG group and all 6 participants in the BPD group. The median duration of T2DM was 19 months in the LSG group and 41 months in the BPD group.

### **Changes in weight, blood pressure and lipid profile**

In both the LSG and BPD groups, an initial improvement in clinical measures of obesity at 1 and 6 months were maintained at long-term follow-up (Table 1). A reduction in both systolic and diastolic blood pressure was noted at 4 years in the LSG group. There was a significant increase in total cholesterol and LDL-cholesterol along with HDL-cholesterol following LSG whereas a reduction in total cholesterol, LDL-cholesterol and HDL-cholesterol was observed

following BPD. However, triglyceride level in both groups did not show any significant changes.

### **Changes in glucose-insulin homeostasis**

#### LSG group

FPG level was lower at 4 years compared to baseline but the result did not reach statistical significance. 2-hour plasma glucose (2hr PG) and HbA1c were significantly lowered at 4 years compared to baseline. Four participants (50%) (1 complete +3 partial) achieved remission of T2DM at 4 years. Preoperatively, two participants were treated with insulin and three treated with oral diabetes agents/ GLP-1 agonist. Postoperatively, one received insulin and two received oral diabetes agents. None of these participants were on long-acting oral diabetes agents. Fasting insulin, 2hr insulin, fasting C-peptide and 2hr C-peptide levels were lower at 4 years but did not reach statistical significance. A significant reduction in HOMA-IR and HOMA-%B and a significant increase in HOMA-%S were observed (Table 2).

#### BPD group

There was no change in FPG at 7 years. However, a reduction in 2hr PG and HbA1c were observed. Two participants (33%) achieved complete diabetes remission. Two out of 6 participants were on oral agents postoperatively, whereas all received oral diabetes agents preoperatively. A numerical but non-significant reduction in fasting insulin, 2 hr insulin and HOMA-%IR and a non-significant increase in HOMA-%B and HOMA-%S were observed at 7 years. There was no change in fasting C-peptide and 2-hour C-peptide at 7 years (Table 2).

### **Dynamic measurements of glucose, insulin and C-peptide**

#### LSG group

At 4 years, there was a significant reduction in the mean plasma glucose at 120 minutes but not at 0, 15, 30, 45, and 60 minutes. The peak glucose response was shifted to the left (peak at 45 minutes at 4 years and at 60 minutes at baseline) (Figure 1). The median AUC measurements for glucose did not show any significant changes compared to baseline (Table 3). With respect to dynamic insulin changes, there were no significant changes in the mean insulin at all 6 time points as well as the AUC measurements (AUC<sub>0-60</sub>, AUC<sub>0-120</sub>). The median AUC measurements for C-peptide also did not show any changes at 4 years from the baseline.

#### BPD group

At 7 years, there was a significant reduction in the mean plasma glucose at 120 minutes but not at the remaining time points. The peak glucose response was shifted to the left (peak at 30 minutes at 7 years, and at 60 minutes at baseline) (Figure 1). The median AUC measurements of glucose did not show any significant changes compared to baseline. There were also no changes in AUC measurements of insulin and C-peptide at 7 years. The BPD group had significant lower C-peptide AUC measurements compared to the LSG group pre-operatively, 1 and 6 month and 7 years post-operatively (Table 3).

### **Changes in incretin hormones**

#### LSG group

Fasting GLP-1 concentrations were not different at 4 years compared to baseline (Table 2). A significant increase in postprandial GLP-1 responses achieved at 1 and 6 months was not observed at 4 years. There were no changes in the GLP-1 AUC<sub>0-60</sub> and AUC<sub>0-120</sub> at 4 years postoperatively (Table 3). On the other hand, a non-significant increase in fasting GIP and

postprandial GIP responses were observed at 4 years. There was a significant increase in the mean GIP concentrations at all postprandial sampling time points at 4 years, in contrast to 1- and 6-months (Figure 1). In line with this, there were significant increase in the GIP AUC<sub>0-60</sub> and non-significant increase in the GIP AUC<sub>0-120</sub> at 4 years postoperatively.

### BPD group

There was a significant increase in fasting GLP-1 at 7 years but there was no change in fasting GIP (Table 2). A significant increase in postprandial GLP-1 response was observed at 7 years compared to baseline. However, there was no significant changes in GIP response (Table 3 and Figure 1).

### **Discussion**

LSG has become a popular bariatric surgical procedure due to its comparable effectiveness and safety profile. In line with previous studies [3, 12-15], we observed significant improvements in markers of glycaemia as well as a significant weight loss at 4 years. There was a significant reduction in HbA1c and 2hr PG levels. One of eight participants achieved complete diabetes remission. The complete remission rate in our study is comparable to other published studies using ADA criteria. Mingrone et al, reported 0% complete remission rate 5 years after RYGB (n=19) and BPD (n=19) [16]. Previous studies have shown that LSG has no significant impact on lowering total cholesterol and LDL-C but is associated with an increase in HDL-C [17-19]. Van Osdal et al, showed that the proportion of participants with a total cholesterol concentration [ $\geq 200$  mg/dL (5.2 mmol/L)] and LDL-C concentration values [ $\geq 130$  mg/dL (3.4 mmol/L)] was greater in the LSG group than the RYGB group (30% vs 10%,  $p < 0.001$  for total cholesterol; 24% vs 4%,  $p, 0.001$  for LDL-C). They also observed that the LSG

group had higher proportion of patients with the recommended HDL-C values than the RYGB group (57% vs 52%,  $p=0.68$ ) [19]. In our study, there was a significant increase in LDL-C and HDL-C at 4 years. Regarding triglyceride level, which is related to the degree of weight loss, we did not find any significant changes despite a significant weight loss at 4 years. Along with a significant weight loss, we observed a non-significant reduction in fasting C-peptide and fasting insulin. Of note, elevated levels of fasting insulin and C-peptide are a key feature of individuals with insulin resistance [11]. Previous studies have demonstrated that LSG is associated with a reduction in insulin resistance [20]. In line with this, we observed a significant improvement in insulin sensitivity (reduction in insulin resistance) at 1 and 6 months. At 4 years, insulin sensitivity (HOMA%-S) decreased compared to the 1- and 6-month's values but was still greater than the baseline level. Similarly, insulin resistance as measured by HOMA-IR increased by 4 years but remained lower than the baseline value. These observations might be explained by weight regained at 4 years (mean BMI was 36.9 kg/m<sup>2</sup> at 6 months and 39.1 kg/m<sup>2</sup> at 4 years). With respect to the effect of bariatric surgery on beta cell function, previous studies have demonstrated an improvement in beta cell function in the early post-operative period [21] but limited improvement in the long-term [22]. In line with this, we observed a significant increase in HOMA-%B at 1 and 6 months, but a significant decrease at 4 years and a downward trend of HOMA-%B from 1-month post-operatively to 4-year post-operatively.

With respect to BPD, our observations of improvement in measures of obesity, glycaemic control, fasting GLP-1 and postprandial GLP-1 responses were in line with previous published literature. Since BPD is a malabsorptive procedure, it is associated with a significant improvement in lipid profile. In line with this, we observed a significant decrease

in total cholesterol at 1 month, 6 months, 7 years and LDL-cholesterol at 1 month and 6 months.

While there is abundant evidence on the metabolic outcomes of LSG, there is limited literature available on the detailed examination of long-term effect of LSG on glucose metabolism and incretin hormone response. Most clinical studies have follow-up periods between 6 weeks and 12 months [4, 13, 23]. Our previous study described a significant improvement in static and dynamic measurements of glucose at 1 and 6 months in 22 participants with impaired glucose regulation [6]. In the current study, we observed a reduction in 2hr PG and HbA1c but no significant changes in glucose AUC measurements in both groups. The mean plasma glucose concentrations at all postprandial sampling time points except 120 minutes were not different at 4 years compared to baseline. The AUC measurements for glucose (0-60min) (0-120min) did not show any significant changes, suggesting that the glucose intolerance state of the participants at 4 years was similar to baseline. Time related relapse of T2DM following bariatric surgery is inevitable [24]. This study's observations raised the questions of whether the glucose AUC measurements are better than static glucose measurements to detect impaired glucose regulation? Of interest, published studies have suggested that the 2hr PG alone cannot predict the full picture of glucose intolerance and the glucose AUC measures are better than 2hr PG [25].

Both LSG and BPD are associated with an accelerated gastric emptying [26]. Studies have suggested that gastric emptying time has an impact on glucose homeostasis and is related to the peak circulation glucose contraction after an oral glucose load. The higher initial gastric emptying rate is positively correlated with the peak postprandial glucose

concentration [27]. In line with this, we observed that the peak glucose response was shifted to the left in both LSG and BPD group. The time to reach peak glucose concentration after an oral glucose load was 60 minutes in both groups at baseline and 45 minutes in the LSG group and 30 minutes in the BPD group at long-term follow-up visit.

An enhanced GLP-1 response is thought to be one of the mechanisms responsible for the resolution of T2DM following bariatric surgery [28, 29]. Previous studies demonstrated that LSG results in an increased GLP-1 response and a T2DM complete remission rate comparable to BPD [4] and RYGB [12]. Tsoli et al, reported that both BPD and LSG are associated with an increase GLP-1 response at 1 month, 3 month and 12 months in 24 participants with T2DM [4]. Papamargaritis et al, reported that the postprandial GLP-1 responses were significantly increased at 6 weeks following LSG and remained at this level at 1 year [30]. In contrast to previous observations of studies with short-term follow-up, there were no significant changes in fasting and postprandial GLP-1 responses in the LSG group at 4 years. One of the possible explanations for our findings is a type 2 error. The other possible explanation is the use of an OGTT instead of a mixed meal tolerance test. The majority of previous published studies have measured a meal-stimulated GLP-1 [5, 12, 13], while others have examined glucose-stimulated GLP-1 [4, 6] Of interest, Nannipieri and colleagues reported an increased GLP-1 response at 15 days but an attenuated GLP-1 response at 1 year following RYGB (n=23) and LSG (n=12) in patients with T2DM [13]. This study used a mixed meal test. Our findings question the role of GLP-1 in the mechanism of long-term diabetes remission. Of note, Steven and colleagues reported that calorie restriction but not GLP-1 explains the acute improvement in glycaemic control following RYGB in subjects with T2DM [31].

With regard to GIP, an increase in fasting GIP as well as postprandial GIP response was observed in the LSG group at 4 years. However, there was no significant changes in GIP response at 1 month and 6 months. Previous studies have described conflicting observations on the GIP response following LSG. Some studies have described no changes in GIP response [6] while others have reported a decrease [5]. On note, these studies examining GIP response have follow-up period of up to 12 months only. The findings of our current study suggest that GIP might play a role in the long-term diabetes outcome.

Although GLP-1 and GIP are derived from the intestine, they have different sites of secretion within the gut: GLP-1 is mainly secreted from ileal L-cells, while GIP is secreted from the K-cells of the duodenum and jejunum. There might be differences in GLP-1 and GIP responses relating to changes in gut anatomy following different bariatric procedures [29]. Our study showed that the BPD group maintained the improvement in GLP-1 response at 7 years, while the LSG group showed no change at 4 years from baseline. Of importance, BPD involves considerable alteration in the anatomy of the gut, which may result in direct exposure of nutrients to the ileal L-cells and would therefore produce a greater postprandial GLP-1 response compared to LSG. On the other hand, LSG would produce a greater post-prandial GIP response because of the expedited delivery of nutrient to the duodenum and the jejunum where K-cells are populated. In line with this, a greater GIP response was observed in the LSG group at 4 years.

To our knowledge, our study is the first to examine the glucose, incretin hormone response 4 years after LSG in participants with impaired glucose regulation. We describe the novel

findings of no change in GLP-1 response but an exaggerated GIP response along with an improvement in glycaemic control at 4 years following LSG. These observations require replication in other bariatric cohorts with longer follow-up.

There are limitations to the current study. Firstly, our study had a small sample size, particularly for the BPD group. The second limitation was that there was a considerable drop-out rate at long-term follow-up with 22.5% (18/40) of participants declining to take part or being lost to follow-up, and 15% (6/40) were deceased. We have examined whether the pre-operative clinical and biochemical characteristics of the participants were related to their long-term follow-up attendance and survival status. There were no differences in baseline weight, blood pressure, HbA1c and lipid profile (except triglyceride level) amongst those who participated in the study, compared to those who were lost-to-follow-up and deceased. All 6 deceased participants underwent BPD, had a significant higher level of triglyceride and lower fasting C-peptide. The causes of death were infection (n=3), suicide (n=1) and unknown (n=2). The third limitation was a variation in follow-up duration in two groups. The BPD group had longer follow-up than the LSG group. Despite this, we observed that the BPD group had a significant increase in GLP-1 level compared to baseline, whereas the LSG group had no change in GLP-1 level. The fourth limitation was the study design, which was a nonrandomised prospective study. At the time of initial study, participants who had BMI >50 kg/m<sup>2</sup> were usually offered BPD as per local protocol. Within the current study we did not plan at the outset to measure glucagon and other gut hormones such as ghrelin, neuropeptide Y.

## **Conclusion**

The current study supports the role of LSG in the management of obesity associated T2DM in the long-term. Despite a non-significant weight regain, increase in HbA1c and a decline in HOMA measures compared to the 6-month values, the study observed that LSG was associated with a significant reduction in weight and glycaemic measures compared to baseline values. This work also provides new insight relating to the long-term effect of LSG on incretin hormone responses, which requires further evaluation.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

**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.

**Informed consent:** Informed consent was obtained from all individual participants included in the study.

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**Table 1: Weight, blood pressure and lipid profile pre-operatively and 1, 6 months and 4-7 years after LSG and BPD**

	Baseline	1 month	6 months	4 years (LSG) 7 years (BPD)	P
<b>Weight (kg)</b>					
LSG	135 ±29	118 ±27	102 ±20	107 ±28	0.001
BPD	184 ±36	162 ±28	143 ±26	134 ±16	0.003
<b>BMI (kg/m<sup>2</sup>)</b>					
LSG	48.4 ±7.2	42.7 ±7.1	36.9 ±6.8	39.1 ±9.6	0.001
BPD	69.5 ±15.0	60.8 ±11.5	54.7 ±9.0	52.9 ±10.0	0.024
<b>%EWL</b>					
LSG		27 ±10	50 ±19	46 ±28	
BPD		19 ±7	35 ±9	40 ±12	
<b>SBP (mmHg)</b>					
LSG	143 ±31	122 ±17	129 ±20	130 ±26	NS
BPD	127 ±17	127 ±10	135 ±9	131 ±14	NS
<b>DBP (mmHg)</b>					
LSG	83 ±19	72 ±10	75 ±9	78 ±15	NS
BPD	80 ±3	67 ±5	78 ±5	68 ±10	NS
<b>TC (mmol/L)</b>					
LSG	4.1 ±0.6	4.3 ±1.2	4.9 ±1.3	5.4 ±1.1	0.009
BPD	4.4 ±1.2	3.1 ±0.6	3.1 ±0.5	3.3 ±0.3	0.005
<b>LDL-C (mmol/L)</b>					
LSG	2.2 ±0.5	2.5 ±0.9	3.0 ±1.0	3.1 ±0.9	0.027
BPD	2.4 ±1.0	1.4 ±0.6	1.3 ±0.4	1.5 ±0.4	0.029
<b>HDL-C (mmol/L)</b>					
LSG	1.3 ±0.4	1.2 ±0.3	1.3 ±0.4	1.7 ±0.6	0.007
BPD	1.4 ±0.2	1.1 ±0.2	1.1 ±0.1	1.3 ±0.2	0.001
<b>TG (mmol/L)</b>					
LSG	1.5 ±0.6	1.5 ±0.6	1.4 ±0.5	1.5 ±0.6	NS
BPD	1.5 ±0.6	1.5 ±0.3	1.4 ±0.4	1.1 ±0.3	NS

Data are presented as mean ±SD. LSG: Laparoscopic sleeve gastrectomy; BPD: Biliopancreatic diversion; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; NS: non-significance.

P value calculated from ANOVA.

**Table 2: Static measurements of glucose-insulin homeostasis and incretin hormones in the LSG and BPD groups**

	Baseline	1 month	6 months	4 years (LSG) 7 years (BPD)	P
<b>FPG (mmol/L)</b>					
LSG	7.9 ±3.2	5.5 ±0.8	5.5 ±1.4	6.8 ±1.9	0.034
BPD	7.0 ±1.7	6.1 ±1.5	7.6 ±5.2	7.2 ±3.0	NS
<b>2hr PG (mmol/L)</b>					
LSG	12.2 ±6.1	8.3 ±4.7	7.5 ±6.8	9.0 ±4.2	0.050
BPD	11.4 ±3.1	9.5 ±3.4	12.0 ±8.0	9.0 ±4.6	NS
<b>HbA<sub>1c</sub> (mmol/mol)</b>					
LSG	55.2 ±19.5	48.9 ±14.1	40.1 ±8.7	45.1 ±9.5	0.050
BPD	53 ±9	43 ±8	48 ±21	40 ±12	0.001
<b>Fasting insulin (mU/L)<sup>^</sup></b>					
LSG	26 (21-31)	10 (6-18)	10 (5-18)	20 (5-42)	NS
BPD	22 (12-36)	18 (13-27)	14 (7-20)	11 (6-18)	NS
<b>2hr Insulin (mU/L)<sup>^</sup></b>					
LSG	105 (44-162)	42 (24-153)	22 (12-170)	55 (22-137)	NS
BPD	55 (25-60)	36 (25-67)	50 (33-76)	41 (23-49)	NS
<b>Fasting C-Peptide (nmol/L)</b>					
LSG	1.5 ±0.2	1.3 ±0.4	1.2 ±0.6	0.7 ±0.4	NS
BPD	0.8 ±0.6	0.9 ±0.3	0.6 ±0.2	0.7 ±0.7	NS
<b>2hr C-Peptide (nmol/L)</b>					
LSG	3.8 ±1.5	4.1 ±1.7	3.7 ±2.1	2.5 ±1.6	NS
BPD	1.9 ±1.0	1.5 ±1.0	1.8 ±0.0	1.1 ±0.2	NS
<b>HOMA-%B</b>					
LSG	117 ±17	175 ±19	155 ±25	83 ±15	0.001
BPD	79 ±36	116 ±61	93 ±38	94 ±90	NS
<b>HOMA-%S<sup>^</sup></b>					
LSG	31 (22-41)	72 (45-131)	87 (49-200)	43 (21-179)	0.019
BPD	41 (26-64)	51 (39-62)	80 (43-125)	89 (54-133)	NS
<b>HOMA-IR<sup>^</sup></b>					
LSG	3.3 (2.5-4.4)	1.4 (0.8-2.2)	1.2 (0.5-2.0)	2.4 (0.6-5.0)	0.019
BPD	2.7 (1.5-4.0)	2.0 (1.6-2.9)	1.6 (0.8-2.4)	1.4 (0.7-1.9)	NS

<b>Fasting GLP-1 (pmol/L)</b>					
LSG	1.9 ±1.7	0.6 ±0.3	0.7 ±0.6	1.3 ±1.3	NS
BPD	1.1 ±0.8	2.2 ±1.7	1.1 ±1.5	2.9 ±0.9	0.044
<b>Fasting GIP (pg/mL)</b>					
LSG	71 ±36	85 ±36	64 ±41	115 ±37	NS
BPD	94 ±38	93 ±48	74 ±39	108 ±55	NS

Data are presented as mean ±SD unless otherwise stated. ^Data are presented as median and interquartile range. FPG: Fasting plasma glucose; 2hr PG: 2-hour plasma glucose; HbA<sub>1c</sub>: Haemoglobin A<sub>1c</sub>; HOMA-%S: homeostatic model assessment (insulin sensitivity); HOMA-IR: homeostatic model assessment (insulin resistance); HOMA-%B: homeostatic model assessment (beta cell function); GLP-1: glucagon like peptide-1; GIP: glucose dependent insulintropic polypeptide.

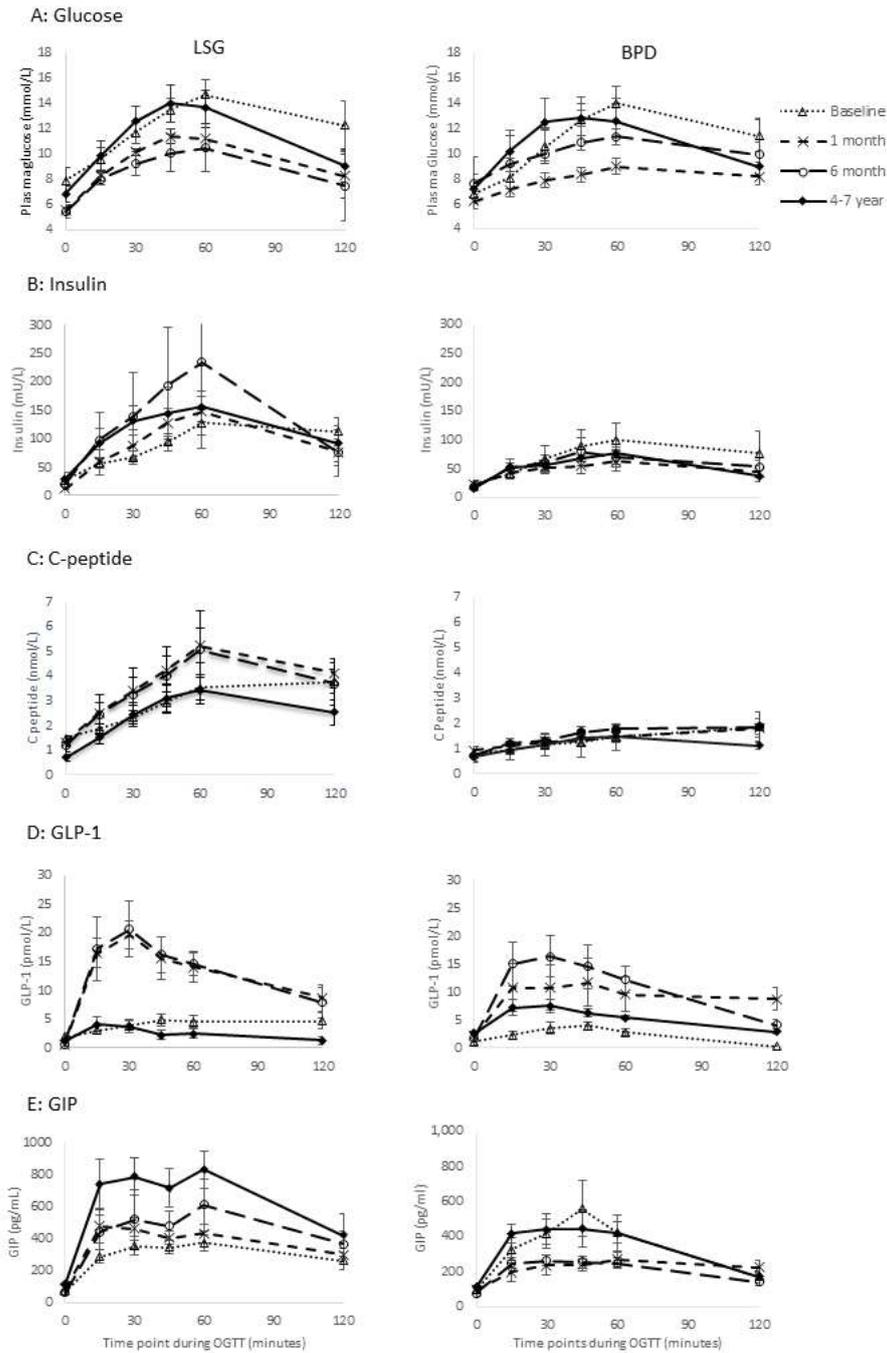
p value calculated from ANOVA or Friedman test. NS: non-significance.

**Table 3: Dynamic measurements of glucose, insulin, C-peptide, GLP-1 and GIP within LSG and BPD groups**

	Baseline	1 month	6 months	4 years (LSG) 7 years (BPD)	P
<b>Glucose AUC<sub>0-60</sub> (mmol/L/hr)</b>					
LSG	11.5 ±2.9	9.6 ±0.7	8.8 ±2.5	11.7 ±3.5	NS
BPD	10.4 ±2.7	7.5 ±1.6*	9.5 ±5.8	10.8 ±3.6	NS
<b>Glucose AUC<sub>0-120</sub> (mmol/L/hr)</b>					
LSG	16.2 ±3.5	13.5 ±2.4	12.7 ±4.6	15.6 ±4.5	NS
BPD	23.1 ±5.6*	15.3 ±3.9	20.1 ±12.4	21.6 ±7.5	NS
<b>Insulin AUC<sub>0-60</sub> (mU/L/hr)<sup>^</sup></b>					
LSG	72 (39-93)	81 (46-104)	61 (44-119)	83 (64-114)	NS
BPD	61 (25-88)	50 (19-69)	50 (23-80)	40 (32-63)	NS
<b>Insulin AUC<sub>0-120</sub> (mU/L/hr)<sup>^</sup></b>					
LSG	107 (64-150)	133 (66-155)	67 (59-159)	111 (85-149)	NS
BPD	79 (50-195)	108 (25-134)	74 (34-159)	78 (64-120)	NS
<b>C-peptide AUC<sub>0-60</sub> (nmol/L/hr)<sup>^</sup></b>					
LSG	2.4 (1.6-3.0)	3.6 (2.0-4.4)	2.2 (1.6-3.1)	2.0 (1.6-3.1)	NS
BPD	0.9 (0.4-2.0)*	1.2 (0.3-1.7)*	1.3 (0.9-1.7)*	1.2 (0.8-1.5)*	NS
<b>C-peptide AUC<sub>0-120</sub> (nmol/L/hr)<sup>^</sup></b>					
LSG	3.4 (2.9-4.5)	5.3 (3.1-6.2)	3.3 (2.2-4.3)	2.8 (2.3-4.1)	NS
BPD	2.0 (0.9-2.8)*	2.3 (0.6-3.2)*	2.1 (1.9-3.0)*	2.2 (1.9-3.0)	NS
<b>GLP-1 AUC<sub>0-60</sub> (pmol/L/hr)</b>					
LSG	3.7 ±2.7	14.1 ±6.4	15.4 ±8.2	3.0 ±2.8	NS
BPD	2.9 ±1.6	13.2 ±7.7	9.0 ±7.1	6.2 ±1.6	0.001
<b>GLP-1 AUC<sub>0-120</sub> (pmol/L/hr)</b>					
LSG	4.8 ±1.3	18.0 ±8	21.4 ±12.3	4.2 ±4.8	NS
BPD	4.3 ±2.4	21.0 ±10.6	17.2 ±10.9	10.4 ±2.4*	0.001
<b>GIP AUC<sub>0-60</sub> (pg/mL/hr)</b>					
LSG	302 ±112	399 ±145	444 ±128	678 ±358	0.020
BPD	389 ±206	205 ±98*	230 ±58	388 ±180*	NS
<b>GIP AUC<sub>0-120</sub> (pg/mL/hr)</b>					
LSG	463 ±307	603 ±366	743 ±654	952 ±591	NS
BPD	983 ±290	424 ±185	411 ±91	681 ±336	NS

Data are presented as mean ±SD unless otherwise stated. <sup>^</sup>Data are presented as median and interquartile range. GLP-1: glucagon like peptide-1; GIP: glucose dependent insulinotropic polypeptide; AUC: area under the curve.

p value calculated from ANOVA or Friedman test. NS: non-significance.



**Figure 1: Changes in glucose, insulin, C-peptide, GLP-1 and GIP during the OGTT before and 1 month, 6 months and 4-7 years after LSG and BPD**

Value represents mean  $\pm$  Standard error. GLP-1: glucagon like peptide-1; GIP: glucose dependent insulinotropic polypeptide; LSG: laparoscopic sleeve gastrectomy; BPD: biliopancreatic diversion.