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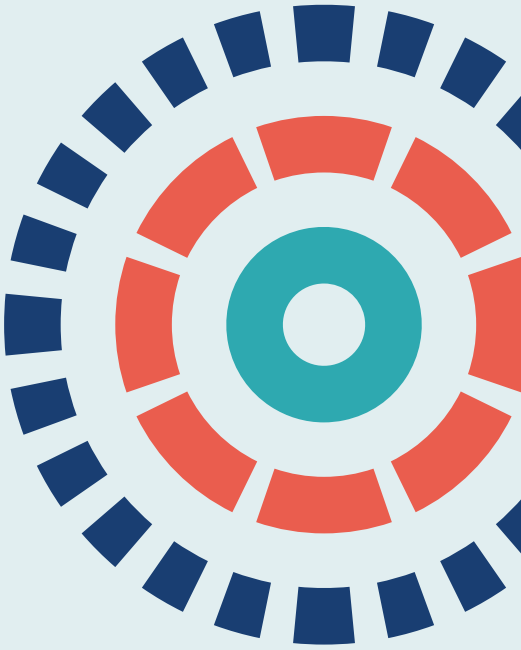

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Abstract

Long limb compared with standard limb Roux-en-Y gastric bypass for type 2 diabetes and obesity: the LONG LIMB RCT

Alexander Dimitri Miras,[1†] Anna Kamocka,[1†] Tricia Tan,[1†] Belén Pérez-Pevida,[1] Harvinder Chahal,[1] Krishna Moorthy,[2] Sanjay Purkayastha,[2] Ameet Patel,[3] Anne Margot Umpleby,[4] Gary Frost,[1] Stephen Robert Bloom,[1*†] Ahmed Rashid Ahmed[1†] and Francesco Rubino[3†]

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Background: Roux-en-Y gastric bypass is recognised as a standard of care in the treatment of diabetes mellitus and obesity. However, the optimal length of the Roux-en-Y gastric bypass limbs remains controversial, with substantial variation in practice. Specifically, a longer biliopancreatic limb length of 150 cm ('long limb') has been hypothesised to be better for the treatment of diabetes mellitus because it increases the postprandial secretion of gut hormones, such as glucagon-like peptide 1, and increases insulin sensitivity, compared with the Roux-en-Y gastric bypass utilising a standard biliopancreatic limb length of 50 cm ('standard limb').

Objective: To evaluate the mechanisms, clinical efficacy and safety of long limb versus the standard limb Roux-en-Y gastric bypass in patients undergoing metabolic surgery for obesity and diabetes mellitus.

Design: A double-blind, mechanistic randomised controlled trial was conducted to evaluate the mechanisms, clinical efficacy and safety of the two interventions.

Setting: Imperial College London, King's College London and their associated NHS trusts.

Participants: Patients with obesity and type 2 diabetes mellitus who were eligible for metabolic surgery.

Interventions: Participants were randomly assigned (1 : 1) to 150-cm (long limb) or 50-cm (standard limb) biliopancreatic limb Roux-en-Y gastric bypass with a fixed alimentary limb of 100 cm. The participants underwent meal tolerance tests to measure glucose excursions, glucagon-like peptide 1 and insulin secretion, and hyperinsulinaemic–euglycaemic clamps with stable isotopes to measure insulin sensitivity preoperatively, at 2 weeks after the surgery and at matched 20% total body weight loss. Clinical follow-up continued up to 1 year.

Main outcome measures: Primary – postprandial peak of active glucagon-like peptide 1 concentration at 2 weeks after intervention. Secondary – fasting and postprandial glucose and insulin concentrations, insulin sensitivity, glycaemic control and weight loss at 12 months after surgery, and safety of participants.

Results: Of the 53 participants randomised, 48 completed the trial. There were statistically significant decreases in fasting and postprandial glucose concentrations, increases in insulin, glucagon-like peptide 1

secretion and insulin sensitivity, and reductions in the levels of glycated haemoglobin (i.e. HbA_{1c}) and weight in both long and standard limb groups. However, there were no significant differences between trial groups in any of these parameters.

Limitations: The main limitations of this trial include the relatively short follow-up of 12 months and elongation of the biliopancreatic limb to a fixed length of 150 cm.

Conclusion: Patients undergoing both types of Roux-en-Y gastric bypass benefited metabolically from the surgery. The results have not demonstrated that elongation of the biliopancreatic limb of the Roux-en-Y gastric bypass from 50 to 150 cm results in superior metabolic outcomes in terms of glucose excursions, insulin and incretin hormone secretion, and insulin sensitivity, when assessed at up to 12 months after surgery.

Future work: Continued longitudinal follow-up of the long and standard limb cohorts will be necessary to evaluate any differential effects of the two surgical procedures on patients' metabolic trajectories.

Trial registration: Current Controlled Trials ISRCTN15283219.

Funding: This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 3. See the NIHR Journals Library website for further project information. The section in the report on endocrinology and investigative medicine is funded by grants from the Medical Research Council, the Biotechnology and Biological Sciences Research Council, NIHR, an Integrative Mammalian Biology Capacity Building Award and a FP7-HEALTH-2009-241592 EuroCHIP grant. This section is also supported by the NIHR Biomedical Research Centre Funding Scheme.

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List of abbreviations

ANCOVA	analysis of covariance
AUC	area under the curve
BMI	body mass index
BOSPA	British Obesity Surgery Patient Association
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EEC	enteroendocrine cell
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
HbA_{1c}	haemoglobin A_{1c} (glycated haemoglobin)
IQR	interquartile range
NIHR	National Institute for Health Research
PPI	public and patient involvement
PYY	peptide YY
Ra	rate of glucose appearance
Rd	rate of glucose disappearance
RCT	randomised controlled trial
RYGB	Roux-en-Y gastric bypass
SD	standard deviation
T2DM	type 2 diabetes mellitus

Plain English summary

Metabolic surgery produces major and sustained weight loss and is being increasingly used to treat patients with obesity and diabetes mellitus. There was initial optimism that these procedures might 'cure all diabetes mellitus'. However, the gold standard operation, standard gastric bypass, effectively results in diabetes mellitus remission in only 4 out of 10 patients.

To design a more successful procedure, an understanding of how metabolic surgery works to improve diabetes mellitus is required. Hormones from the gut are released when food is eaten. It has been discovered that the beneficial effects of surgery on glucose control are mainly due to increased release of these gut hormones. These gut hormones improve blood sugar levels by increasing the release of insulin, and also reduce appetite, leading to weight loss.

In this trial a procedure called long limb gastric bypass was tested. It was designed to be better at improving diabetes mellitus than the 'standard limb' gastric bypass, while being as safe. It was expected that this new procedure would work better than the standard limb gastric bypass by causing an even bigger increase in the release of gut hormones and, thus, of insulin.

Forty-eight people with diabetes mellitus completed the trial. It was found that the standard and long limb operations were equally effective in reducing blood sugar and reducing weight by causing the release of gut hormones. The study did not show that there was a significant difference between the standard and long limb operations.

This trial has taken the first critical step in studying the role of the gut in glucose control after gastric bypass surgery. This trial shows that a long limb gastric bypass does not result in better glucose control and more weight loss than the standard limb operation. Other changes to the surgical procedure to construct a better gastric bypass that is more effective for patients with diabetes mellitus can now be investigated.

Scientific summary

Introduction

Background

At least 11 randomised controlled trials have demonstrated that bariatric surgery, and, in particular, the Roux-en-Y gastric bypass, is substantially more effective than intensive medical care for the treatment of the hyperglycaemia of type 2 diabetes mellitus. The effects of surgery are so profound that approximately 50% of patients achieve 'diabetes mellitus remission' (i.e. euglycaemia) in the absence of glucose-lowering medications.

The anatomical rearrangements of Roux-en-Y gastric bypass result in three intestinal segments or 'limbs': the 'alimentary limb', through which food enters the small intestine; the 'biliopancreatic limb', which includes the bypassed segments of duodenum and proximal jejunum through which the biliopancreatic secretions flow; and the 'common limb', in which food and biliopancreatic secretions mix.

The optimal length of each of these limbs remains controversial, with substantial variation in practice. The reason underlying this inconsistent clinical practice is that the physiological role of each of the limbs on glucose regulation has until recently been unclear.

Although many of the benefits of Roux-en-Y gastric bypass on glucose control can be attributed to weight loss, both early and longer-term substantial improvements in glycaemia also take place independently. Human and rodent studies suggest that the bypass of the proximal intestine might be the component of Roux-en-Y gastric bypass underlying, at least in part, its weight loss-independent effects on glucose regulation. Beta cell function and early postprandial release of insulin are enhanced after Roux-en-Y gastric bypass. The prevailing view is that the dominant mechanism is the early and enhanced secretion of the incretin hormone glucagon-like peptide 1. It is thought that the rapid delivery of nutrients to the enteroendocrine cells of the distal small intestine triggers the exaggerated release of glucagon-like peptide 1 within the gut and the circulation.

Hypothesis

It is hypothesised that a long biliopancreatic limb Roux-en-Y gastric bypass would enable an even *faster* delivery of nutrients to the distal small intestine, resulting in an even *greater* release of glucagon-like peptide 1 and insulin compared with a 'standard' biliopancreatic limb Roux-en-Y gastric bypass.

Methods

Trial design

This was a prospective, double-blind, randomised controlled trial. Both the patient and the clinical/research teams (except the operating surgeon) were blind to treatment disposition.

Trial setting

Imperial College London, King's College London and their associated NHS trusts.

Trial population

Key inclusion criteria were:

- aged 18–70 years
- a diagnosis of type 2 diabetes mellitus treated with at least one glucose-lowering medication
- body mass index of $\geq$ 30 kg/m^2
- eligible for metabolic surgery.

Key exclusion criteria were:

- any surgical, medical or psychological contraindications to metabolic surgery
- pregnancy
- currently breastfeeding.

Interventions and assessments

Patients were randomised at a ratio of 1 : 1 to a laparoscopic Roux-en-Y gastric bypass with biliopancreatic limbs that were either 150 cm (long limb) or 50 cm (standard limb) while keeping the alimentary limb constant at 100 cm. Patients were assessed by the multidisciplinary clinical team as part of routine NHS care. Glycaemic remission was defined based on the American Diabetes Association's criteria. Mechanistic assessments took place at three time points: preoperatively, at 2 weeks after surgery and when 20% total body weight loss was achieved. Participants were admitted to the clinical research facility in the evening and consumed a standardised meal. The next morning they underwent a two-stage hyperinsulinaemic–euglycaemic clamp with the stable isotope [6,6-$^2H_2$]glucose using a validated protocol. On the morning of the third, and final, day of their visit they underwent a mixed-meal tolerance test. Blood samples were obtained before and 180 minutes after a liquid meal.

Follow-up

The participants were followed up for 12 months.

Results

Fifty-three participants were recruited into the study. Twenty-seven participants were randomised to the standard limb and 26 were randomised to the long limb Roux-en-Y gastric bypass. For anatomical reasons one patient in the standard limb group underwent a vertical sleeve gastrectomy and one patient in the long limb group underwent a one-anastomosis gastric bypass. Forty-eight participants completed the trial (24 in the standard limb group and 24 in long limb group).

Baseline characteristics

Characteristics were well balanced between the trial groups at baseline. The majority of the patients were middle-aged, white, European and female. The mean body mass index was 42 kg/m^2 (standard deviation 6 kg/m^2) in the standard limb group and 43 kg/m^2 (standard deviation 8 kg/m^2) in the long limb group. Patients in the standard limb group had a mean glycated haemoglobin level of 73 mmol/mol (standard deviation 17 mmol/mol), a median duration of type 2 diabetes mellitus of 8 years (interquartile range 6–10 years) and were taking a median of three glucose-lowering medications. Patients in the long limb group had a glycated haemoglobin level of 76 mmol/mol (standard deviation 16 mmol/mol), a median duration of type 2 diabetes mellitus of 8 years (interquartile range 6–9 years) and were taking a median of three glucose-lowering medications.

Primary outcome

There were significant increases in the postprandial peak of active glucagon-like peptide 1 concentration in both groups at 2 weeks compared with baseline, but there were no significant differences between the standard and long limb groups. There were significant increases in the postprandial peak of active glucagon-like peptide 1 concentration and area under the curve in both

groups at 20% weight loss compared with baseline, but there were no significant differences between the standard and long limb groups.

Secondary outcomes

Glucose tolerance

Fasting and postprandial glucose secretion during the mixed-meal tolerance test, as judged by area under the curve, was significantly reduced in both groups at 2 weeks [the median area under the curve was 1828 mmol/minute/l (interquartile range 1553–2189 mmol/minute/l) in the standard limb group and 1862 mmol/minute/l (interquartile range 1632–200 mmol/minute/l) in the long limb group] and at matched 20% weight loss after surgery [the area under the curve was 1564 mmol/minute/l (interquartile range 1276–1896 mmol/minute/l) in the standard limb group and 1301 mmol/minute/l (interquartile range 1170–1580 mmol/minute/l) in the long limb group], compared with baseline. However, there were no significant differences between the standard and long limb groups ($p = 0.66$ and $p = 0.38$, respectively).

Insulin secretion

Postprandial insulin secretion during the mixed-meal tolerance test was significantly increased in both trial groups at 2 weeks [the area under the curve was 6259 mU/minute/l (standard deviation 3088 mU/minute/l) in the standard limb group and 6037 mU/minute/l (standard deviation 3481 mU/minute/l) in the long limb group] and at matched 20% weight loss after surgery [the area under the curve was 6433 (standard deviation 3058) mU/minute/l in the standard limb group and 5716 (standard deviation 2879) mU/minute/l in the long limb group], compared with baseline. However, there were no significant differences between the standard and long limb groups ($p = 0.89$ and $p = 0.34$, respectively).

Insulin sensitivity

The rate of glucose appearance during the low-dose insulin phase (i.e. Ra – a measure of hepatic insulin sensitivity) decreased significantly in both groups at 2 weeks [the Ra low was 3.4 µmol/minute/kg (standard deviation 0.9 µmol/minute/kg) in the standard limb group and 3.4 µmol/minute/kg (standard deviation 1.4 µmol/minute/kg) in the long limb group], signifying an early improvement in hepatic insulin sensitivity. A similar observation was made at 20% matched weight loss compared with baseline [the Ra low was 2.8 µmol/minute/kg (standard deviation 1.3 µmol/minute/kg) in the standard limb group and 2.6 µmol/minute/kg (standard deviation 1.7 µmol/minute/kg) in the long limb group], but there were no significant differences between groups ($p = 0.94$ and $p = 0.62$, respectively).

The rate of glucose disappearance during the high-dose insulin phase (i.e. Rd – a measure of peripheral insulin sensitivity) increased significantly compared with baseline in both groups both at 2 weeks [the Rd high was 29 µmol/minute/kg (standard deviation 9.1 µmol/minute/kg) in the standard limb group and 29.8 µmol/minute/kg (standard deviation 9.8 µmol/minute/kg) in the long limb group] and at the point of 20% matched weight loss [the Rd high was 36.1 µmol/minute/kg (standard deviation 8.5 µmol/minute/kg) in the standard limb group and 38.1 µmol/minute/kg (standard deviation 9.2 µmol/minute/kg) in the long limb group]. This change signifies an improvement in peripheral insulin sensitivity. However, there were no significant differences between standard and long limb groups ($p = 0.98$ and $p = 0.47$, respectively).

Glycaemic control and weight loss

There were no significant differences in levels of glycated haemoglobin between the groups at any time point postoperatively, including at 12 months [standard limb group 43 mmol/mol (standard deviation 10 mmol/mol) vs. long limb group 41 mmol/mol (standard deviation 5 mmol/mol); $p = 0.20$]. There were no significant differences in the percentage of patients achieving glycaemic remission at 12 months (standard limb 62% vs. long limb 77%; $p = 0.23$). There were no differences in total body weight loss percentage between the standard and long limb groups at any time point postoperatively, including at 12 months [standard limb 30% (standard deviation 8%) vs. long limb 29% (standard deviation 8%); $p = 0.52$].

Surgical outcomes

The median total small intestinal length was 615 cm (range 320–740 cm) in the standard limb group and 610 cm (range 520–910 cm) in the long limb group. The median common channel length was 465 cm (range 170–590 cm) in the standard group and 360 cm (range 250–660 cm) in the long limb group. The median biliopancreatic limb/total small intestinal length ratio was 8% (range 7–16%) in the standard limb group and 25% (range 16–29%) in the long limb group. There were no differences between the groups in the length of hospital stay at 2 days (standard deviation 0.7 days). The safety profile of the procedures was similar, with no signal for excess malabsorption of macronutrients or micronutrients in the long limb group.

Discussion

This trial has demonstrated that people with obesity and diabetes mellitus benefit metabolically in terms of glucose homeostasis and weight loss from both types of Roux-en-Y gastric bypass and there were no differences in safety profile. The data have shown that a long limb Roux-en-Y gastric bypass with a biliopancreatic limb of 150 cm is not mechanistically superior to a standard limb Roux-en-Y gastric bypass with a biliopancreatic limb of 50 cm with regard to fasting and postprandial glycaemia, glucagon-like peptide 1 secretion, insulin secretion or insulin sensitivity. In line with these mechanistic measurements, there were no differences between the two study groups in terms of levels of glycated haemoglobin or weight reduction at 12 months.

Previous studies have compared Roux-en-Y gastric bypass designs with varying biliopancreatic *and* alimentary limbs, making it challenging to determine which, if any, segment was responsible for any superior clinical benefits. To our knowledge, this is the first double-blinded randomised controlled trial to conduct a systematic head-to-head comparison between these two Roux-en-Y gastric bypass designs with in-depth metabolic phenotyping of its participants. In this trial a reductionist approach was used and the alimentary limb length was kept constant to isolate the contribution of the length of the biliopancreatic limb to glucose control.

In the only other retrospective case–control mechanistic study of long limb Roux-en-Y gastric bypass (Patrício BG, Morais T, Guimarães M, Veedfald S, Hartmann B, Hilsted L, *et al.* Gut hormone release after gastric bypass depends on the length of the biliopancreatic limb. *Int J Obes* 2019;**43**:1009–18), it was found that postprandial glucagon-like peptide 1 concentrations were higher in patients who underwent long limb Roux-en-Y gastric bypass 4 years previously. However, this finding was not replicated in this trial. An explanation for the discrepant results between the two studies could be that, in this trial, glucagon-like peptide 1 responses were measured at 2 weeks and at 20% weight loss, which takes place approximately 4 months after surgery. This may not have been enough time for the full physiological impact of intestinal adaptation that takes place after Roux-en-Y gastric bypass to come into play. In addition, the cohort of patients studied in the other retrospective case–control mechanistic study did not have type 2 diabetes mellitus and the length of the biliopancreatic limb used was 200 cm. It cannot be excluded that the use of a longer biliopancreatic limb and/or longer follow-up period might reveal differences in glucagon-like peptide 1 secretion between the two designs that could drive superior reductions in glycaemia and/or weight.

The absence of either an earlier or a higher peak in postprandial glucagon-like peptide 1 concentrations after the long biliopancreatic limb Roux-en-Y gastric bypass also challenges the hypothesis that the delivery of nutrients to more distal segments of the small intestine, where the density and number of enteroendocrine cells is higher, triggers the enhanced secretion of gut hormones such as glucagon-like peptide 1 and peptide YY. One plausible explanation of this unexpected finding is that there is no linear relationship between glucagon-like peptide 1 secretion and the length of intestine exposed to ingested nutrients, as previously suggested, but a ‘ceiling’ effect, that is the delivery of nutrients beyond a certain critical point in the jejunum does not result in further enhancement of the glucagon-like peptide 1 response.

This study did not observe any differences between the groups in terms of insulin sensitivity at either 2 weeks or 4 months after surgery. Studies in humans and animal models of procedures, including the duodenal–jejunal bypass operation and the duodenal–jejunal bypass liner, in which food bypasses the proximal intestine, have demonstrated reductions in fasting glucose and markers of insulin sensitivity independent of caloric restriction and weight loss. The mechanisms underlying these observations are thought to involve altered glucose sensing in the distal and mid-jejunum and/or the reduction in the secretion of insulin 'desensitising' factors from the duodenum and proximal jejunum. Similar to the glucagon-like peptide 1 story, we postulate that beyond the bypass of a critical length of the duodenum and jejunum, no additional effects on insulin sensitivity take place.

The study's findings are strengthened by key aspects of the trial design. These aspects include (1) the double-blind, randomised approach, (2) the measurement of the entire length of the small intestine during surgery, (3) the robust way of ensuring that the surgical approach used was consistent between surgeons and in line with a pre-agreed standard operating procedure, (4) the use of the gold standard method of measuring insulin sensitivity through the use of hyperinsulinaemic–euglycaemic clamps with stable isotopes, (5) the conduct of the mechanistic studies after washout of diabetes mellitus medications and (6) the longitudinal metabolic phenotyping of participants both early and at matched weight loss after the two interventions.

The main limitations of the trial, including the relatively short follow-up and elongation of the biliopancreatic limb to a fixed length of 150 cm, have already been mentioned. For the purposes of standardisation, the 'standard Roux-en-Y gastric bypass' was defined as a bypass with a biliopancreatic limb of 50 cm and an alimentary limb of 100 cm, based on the popularity of this design in current surgical practice. However, it is appreciated that there is substantial variation in practice around the world and that not all surgeons will agree with this definition.

In conclusion, this trial has not shown a physiological rationale for the elongation of the biliopancreatic limb of the Roux-en-Y gastric bypass to 150 cm to achieve superior metabolic outcomes for patients with type 2 diabetes mellitus and obesity. Confirmation of our findings in larger clinical trials with longer follow-up periods is necessary. It is hoped that the trial design and findings lay the foundation for a new generation of experimental medicine studies that aim to optimise the clinical efficacy of metabolic surgery, or indeed non-surgical interventions, through interrogation of the elusive physiology of the intestine and the impact of its various segments on metabolic regulation.

Trial registration

This trial is registered as ISRCTN15283219.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 3. See the NIHR Journals Library website for further project information. The section in the report on endocrinology and investigative medicine is funded by grants from the Medical Research Council, the Biotechnology and Biological Sciences Research Council, NIHR, an Integrative Mammalian Biology Capacity Building Award and a FP7-HEALTH-2009-241592 EuroCHIP grant. This section is also supported by the NIHR Biomedical Research Centre Funding Scheme.

Chapter 1 Introduction

Background

At least 11 randomised controlled trials (RCTs) have demonstrated that bariatric surgery, and, in particular, the Roux-en-Y gastric bypass (RYGB), is substantially more effective than intensive medical care for the treatment of the hyperglycaemia of type 2 diabetes mellitus (T2DM).[1,2] The effects of surgery are so profound that approximately 50% of patients achieve 'diabetes mellitus remission', (i.e. euglycaemia) in the absence of glucose-lowering medications.[3]

The anatomical rearrangements of RYGB result in three intestinal segments or 'limbs': the 'alimentary limb', through which food enters the small intestine; the 'biliopancreatic limb', which includes the bypassed segments of duodenum and proximal jejunum, through which the biliopancreatic secretions flow; and the 'common limb', in which food and biliopancreatic secretions mix (*Figure 1*).

The profound improvements in glucose control after RYGB have led to the recognition of the intestine as an organ with a major impact on glucose regulation. Thus, surgeons have experimented with different intestinal limb lengths to enhance the clinical effect of RYGB. However, the optimal length of each of these limbs remains controversial, with substantial variation in practice. The reason underlying this inconsistent clinical practice is that the physiological role of each of the limbs in glucose regulation has until recently been unclear. Indeed, it is challenging to determine the precise physiological impact of each of these intestinal segments because changes in the length of one will invariably result in the change in the length of the others. The matter is complicated further by the variability in the total length of the human small intestine.[5]

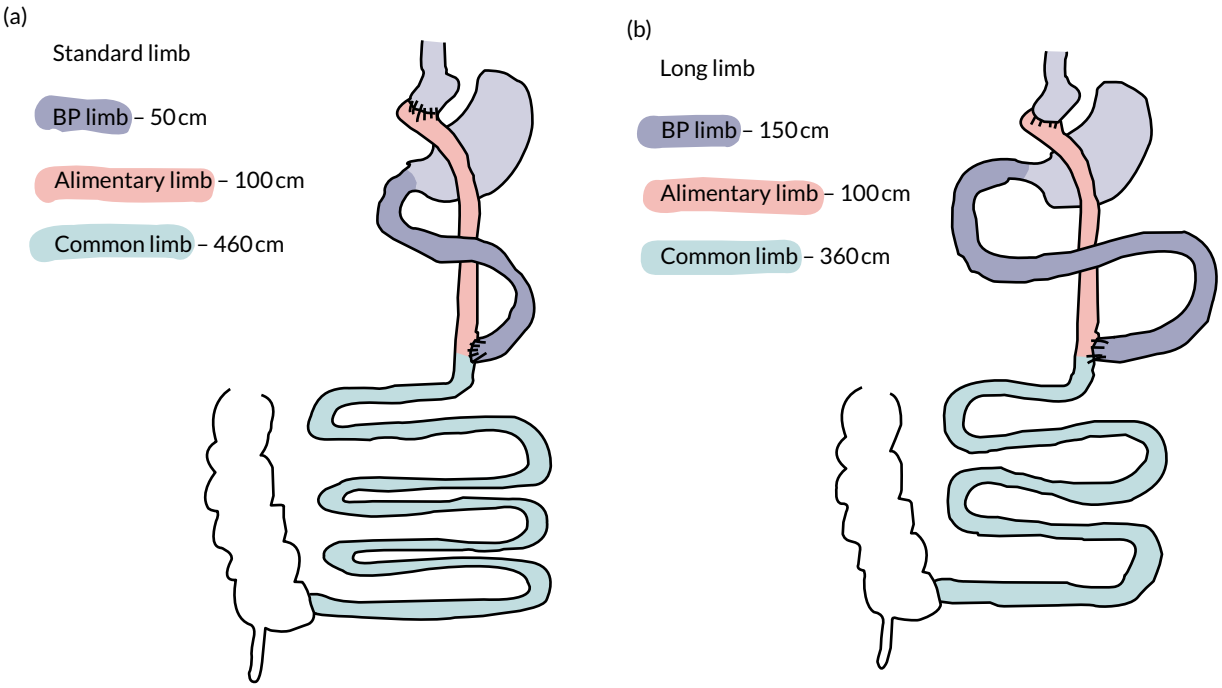

FIGURE 1 Schematic drawing of the standard limb and the long limb RYGB. a, Standard limb; b, long limb. BP limb, biliopancreatic limb. Reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association.[4]

Although many of the benefits of RYGB on glucose control can be attributed to weight loss, both early and longer-term substantial improvements in glycaemia also take place independently. This has led to the concept of 'metabolic surgery'.[6,7] Human and rodent studies suggest that the bypass of the proximal intestine might be the component of RYGB underlying, at least in part, its weight loss-independent effects on glucose regulation.[8] Beta cell function and early postprandial release of insulin are enhanced after RYGB.[9] The prevailing view is that the dominant mechanism underlying this observation is the early and enhanced secretion of the incretin hormone glucagon-like peptide 1 (GLP–1).[10] It is thought that the rapid delivery of nutrients to the enteroendocrine cells (EECs) of the distal small intestine triggers the exaggerated release of GLP-1 within the gut and the circulation.[11] At the same time, the simultaneous postprandial release of other hormones from the EECs, such as peptide YY (PYY) and oxyntomodulin, leads to synergistic effects on increased satiety and, perhaps, increased energy expenditure.[12,13]

Hypothesis

The aim was to address the gap in knowledge with regard to the optimal lengths of the RYGB limbs through the understanding of the physiology of glucose regulation after surgery. Therefore, a reductionist approach was applied to examine the effects of a longer biliopancreatic limb on glucose control in this double-blind, mechanistic RCT. It was hypothesised that a long biliopancreatic limb RYGB would enable an even *faster* delivery of undigested nutrients to the distal small intestine, resulting in an even *greater* release of GLP-1 and insulin, than a 'standard' biliopancreatic limb RYGB.

Chapter 2 Methods

Trial design

This was a prospective, randomised, double-blind RCT. Fifty-three patients with T2DM and obesity due to undergo RYGB surgery were recruited from the Imperial College Healthcare NHS Trust and King's College Hospital NHS Foundation Trust by the clinical and the research team and randomised at a ratio of 1 : 1 to either a 150-cm (long limb) or a 50-cm (standard limb) RYGB while keeping the alimentary limb constant at 100 cm (see *Figure 1*). Both the patient and the clinical/research teams (except the operating surgeon) were blinded to treatment disposition. Participants were randomised to either long limb or standard limb RYGB surgery in a 1 : 1 ratio using an online randomisation program (www.randomisation.com; accessed 1 July 2015) by Dr Victoria Salem, who was not otherwise involved in the trial. No stratification variables were used.

Inclusion and exclusion criteria

Key inclusion criteria were aged 18–70 years, a diagnosis of T2DM treated with at least one glucose-lowering medication, a body mass index (BMI) $\geq$ 30 kg/m^2 and eligible for metabolic surgery based on the UK's National Institute for Health and Care Excellence Clinical Guideline Number 189.[14] Key exclusion criteria were any surgical, medical or psychological contraindications to metabolic surgery, pregnancy and currently breastfeeding.

Ethics approval

The trial was approved by the West London Research Ethics Committee (reference number 15/LO/0813) and registered in the International Standard Randomised Controlled Trial registry (as ISRCTN 15283219). Written informed consent was obtained from all patients prior to participation in the trial.

Intervention and follow-up

Patients were assessed by the multidisciplinary clinical team as part of routine NHS care preoperatively and at 2 weeks, and 3, 6 and 12 months after surgery, unless clinical need dictated more frequent consultations. Operations were performed laparoscopically by four surgeons, who followed a standard operating protocol agreed before the trial commenced (see *Appendix 1*). The procedures were filmed to enable independent assessment of the consistency of the surgical technique among the operating surgeons. The total length of the small intestine was measured from the ligament of Treitz to the ileocaecal valve. This was performed using set distance markers on laparoscopic graspers, running the bowel segment by segment along the antimesenteric border. The management of glucose-lowering medications was performed by a single consultant diabetologist (ADM), who was blind to treatment allocation. Glucose-lowering medications were discontinued during the course of the 12-month follow-up depending on glycated haemoglobin (HbA_{1c}) concentrations and capillary glucose measurements, and when clinically safe. Glycaemic remission was defined based on a variation of the American Diabetes Association's criteria[15] as an HbA_{1c} concentration $<$ 48 mmol/mol and fasting glucose level of $<$ 5.6 mmol/l in the absence of glucose-lowering medication for a minimum of 12 months. Micronutrient supplementation was based on the British Obesity & Metabolic Surgery Society's guidance.[16]

Mechanistic visits

Mechanistic assessments took place at three time points: preoperatively, at 2 weeks after surgery to examine the effects of the interventions before substantial weight loss has taken place and when 20% of weight loss was achieved in order to remove weight loss as a confounding variable. Five days prior to the mechanistic visits, all glucose-lowering medications were discontinued and intermediate-acting insulin used as 'rescue' treatment if necessary. Patients were asked to refrain from consuming alcohol and strenuous physical activity for 48 hours before the visit. The patients were admitted to the Imperial College London or King's College London National Institute for Health Research (NIHR) clinical research facilities in the evening and consumed a standardised meal. The next morning the patients underwent a two-stage hyperinsulinaemic–euglycaemic clamp with the stable isotope [6,6-$^{2}H_{2}$] glucose using a validated protocol.[17] Stage 1 consisted of an insulin infusion at 0.5 mU/kg/minute (low dose) for 120 minutes to measure hepatic insulin sensitivity based on endogenous glucose production; and stage 2 consisted of an insulin infusion at 1.5 mU/kg/minute (high dose) for 120 minutes to measure peripheral insulin sensitivity based on glucose uptake. On the morning of the third, and final, day of their visit the patients underwent a mixed-meal tolerance test. Blood samples were obtained before and at 180 minutes following a liquid meal [Ensure® Compact (Abbott Laboratories, Abbott Park, IL, USA), 300 kcal in 125 ml].

Trial outcomes

Primary outcome

The primary outcome of this trial was postprandial peak of active GLP-1 concentration at 2 weeks after intervention.

Secondary outcomes

The secondary outcomes of this trial were:

- fasting and postprandial glucose and insulin concentrations in the mixed-meal tolerance test and insulin sensitivity in the hyperinsulinaemic–euglycaemic clamp at 2 weeks after the surgery and at the 20% total body weight loss time point
- glycaemic control
- weight loss at 12 months after surgery
- safety of participants
- intra- and perioperative outcomes.

The complete LONG LIMB trial protocol can be accessed an the NIHR project web page [www.journalslibrary.nihr.ac.uk/programmes/eme/1312107 (accessed 1 February 2019)].

Sample analysis

Plasma and serum samples were stored at –80 °C until further analysis. Glucose was measured on the ARCHITECT ci8200 (Abbott Laboratories) platform using a hexokinase method. Insulin was measured using the ARCHITECT i2000SR (Abbott Laboratories) immunoassay. GLP-1, PYY and glucose-dependent insulinotropic polypeptide (GIP) were measured using the MAGPIX® (Luminex Corporation, Austin, TX, USA) assay. Glucose isotopic enrichment was measured by gas chromatography–mass spectrometry on a HP 5971 A mass selective detector (Agilent Technologies, Inc., Santa Clara, CA, USA). Rates of glucose appearance (Ra) and disappearance (Rd) from plasma were calculated using non-steady-state equations proposed by Steele *et al.*[18] and modified for stable isotopes.

Sample size calculations

The majority of published studies have shown that peak active GLP-1 concentrations are approximately twofold greater after standard limb RYGB,[19,20] compared with preoperatively. It was estimated that peak active GLP-1 levels after long limb RYGB will be tripled at 2 weeks after surgery. The trial was powered to detect a minimum clinically significant difference between the groups in mean peak active GLP-1 of 10.0 pmol/l, assuming a standard deviation (SD) of 10.8 pmol/l in each group. With a sample size of 20 completers in each arm, the statistical power was 80% to detect this difference at an alpha of 0.05. Based on the centre's experience, a predicted 20% dropout rate was predicted; therefore, the recruitment target was 25 patients in each arm.

Statistical analyses

A detailed statistical analysis plan is available in *Appendix 2*. In summary, continuous variables were summarised using the number of (non-missing) data points, mean and SD if found to follow a normal distribution. Continuous variables not found to be normally distributed were summarised by the number of data points, median and interquartile range (IQR). Categorical variables were summarised by the frequency and percentage (based on the non-missing sample size) of values in each category. All the analyses presented in this report were based on the full analysis population, which consisted of patients in the groups to which they were randomised, regardless of deviation from the protocol or whether or not they received the allocated surgery. Patients with completely missing data at the outcome time point were excluded from this data set for the particular outcome for which they had missing data.

The analysis of the primary outcome was performed using analysis of covariance (ANCOVA). In the analysis, the peak of active GLP-1 concentration at the early mechanistic postoperative visit at 2 weeks was considered as the outcome measure, whereas the baseline peak of active GLP-1 was included as a covariate. The baseline-adjusted differences in outcome values between groups were reported, along with a corresponding 95% confidence interval (CI). Secondary outcomes were measured on a continuous scale, with a baseline measurement, and were analysed using a similar approach to that outlined for the primary efficacy outcome. The data from each postoperative time point will be analysed in a separate analysis. For continuous secondary outcomes with no baseline measurement, the two groups were compared using the unpaired *t*-test. Alternatively, the Mann–Whitney *U*-test was used if the assumptions of the *t*-test were not met. Binary and nominal outcomes were compared between the two study groups using either the chi-squared test or Fisher's exact test if the number of responses in some categories was low. Ordinal outcomes were analysed using the Mann–Whitney *U*-test to allow for the natural ordering of the response categories. Statistical significance was defined as a p-value of < 0.05. Association between outcomes were performed using Pearson's correlation. Alternatively, Spearman's rank-order correlation was used if the Pearson's correlation assumptions (e.g. non-linear relationship, both variables non-normally distributed) were not met. The data analyses were performed using the statistical software packages Stata® (version 15.1; StataCorp LP, College Station, TX, USA), IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism (version 6; GraphPad Software Inc., CA, USA).

Public and patient involvement

The research and clinical teams engaged closely and formed an active partnership with the following key contacts during the application process: Ms Georgina Hayman, lead of the British Obesity Surgery Patient Association (BOSPA) west-London branch; and Dr Shamil Chandaria, Patron of the National Obesity Forum, an independent charity supporting patients and health-care professionals.

Ms Danielle Neal, the communications and public and patient involvement (PPI) officer, NIHR North West London, approached the Diabetes Research Network PPI group and asked members the following questions:

- What are your initial feelings about the research?
- Do you think the research question is important?
- What issues do you feel will prevent people from taking part in the study?
- Do you feel that the treatment and assessment plan will be acceptable to the participants?

This feedback direct from the patient contact influenced the direction of both the clinical trial and the mechanistic studies in this proposal.

All three PPI representatives contributed to the development of the grant application, starting from its design, and to undertaking the research and the choice of research topics, and will help with dissemination of the study findings through their organisations.

During the course of the project Ms Hayman conducted patient support groups every 2 months. These support groups served to support patients following their operations and acted as an avenue for the patient voice to be heard. The Trial Steering Committee and researchers conducting the day-to-day running of the trial obtained feedback from patients and optimised the conduct of the trial to make it more acceptable. Numerous minor and major modifications were made to the way the clinical and mechanistic assessments and follow-up were performed as a result this feedback. This helped the trial immensely with recruitment and retention. Only one patient dropped out of the trial. Patients were so excited about contributing to this important study that many refused to accept the allocated reimbursement at the end of the trial.

Patients did not take part in the data analyses. However, the above patient support groups will be approached to help disseminate the findings of the trial to the local patient and health-care communities. How this will take place practically is currently being decided on. The contribution of patients has been acknowledged in both the report and the draft manuscripts for publication.

Chapter 3 Results

Trial participants

Fifty-three participants were recruited into the study between August 2015 and November 2017. Twenty-seven participants were randomised to standard limb and 26 to long limb RYGB (*Figure 2*). For anatomical reasons, one patient in the standard limb group underwent a vertical sleeve gastrectomy and one patient in the long limb group underwent a one-anastomosis gastric bypass. The final visit of the last patient took place in December 2018. After dropouts resulting from failure to undergo mechanistic visits and loss to follow-up, 24 participants completed the 12-month mechanistic visit in the long limb group and 24 in the standard limb group.

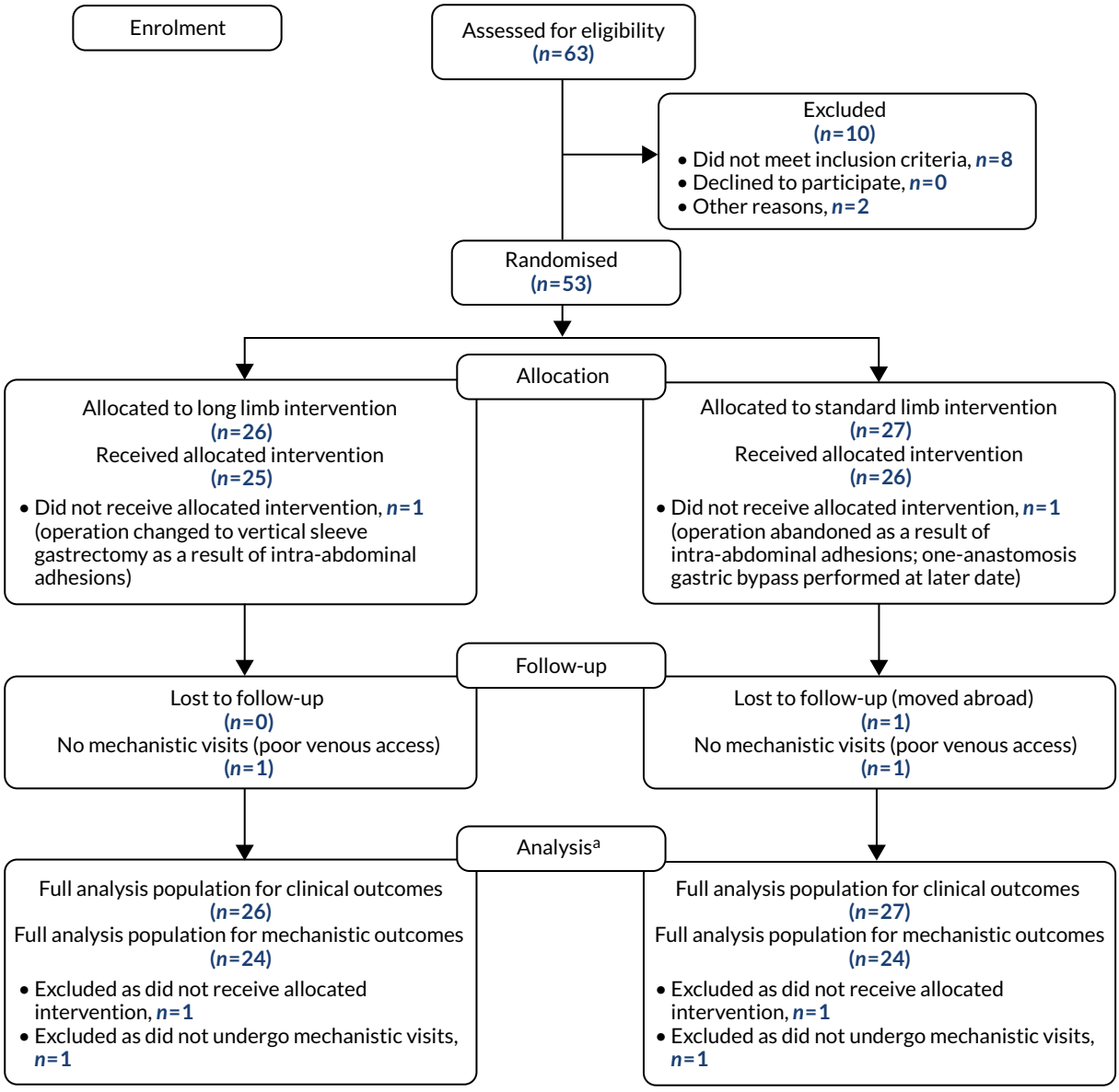

FIGURE 2 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram. a, For more details on the full analysis population see the statistical analysis plan (in *Appendix 2*).

Clinical parameters at baseline

Clinical parameters were well balanced between trial groups at baseline (*Table 1*). The majority of the patients were middle-aged, white, European and female. The mean (SD) BMI was 42 kg/m^2 (6 kg/m^2) in the standard limb group and 43 kg/m^2 (8 kg/m^2) in the long limb group. Patients in the standard limb group had a mean HbA_{1c} level of 73 mmol/mol (SD 17 mmol/mol), a median duration of T2DM of 8 years (IQR 6–10 years) and were taking a median number of three (IQR 2–3) glucose-lowering medications (*Table 2*). Patients in the long limb group had a mean HbA_{1c} level of 76 mmol/mol (SD 16 mmol/mol), a median duration of T2DM of 8 years (SD 6–9 years) and were taking a median of 3 (IQR 2–3) glucose-lowering medications.

TABLE 1 Key clinical parameters at baseline and at 12 months postoperatively

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Baseline	12 months		
HbA_{1c} (mmol/mol)[a]	Standard limb	26	71 (15)	43 (10)	0	0.20
	Long limb	26	76 (16)	41 (5)	−3 (−8 to 2)	
% weight loss[b]	Standard limb	26	–	30 (8)	0	0.52
	Long limb	26	–	29 (8)	−1 (−6 to 3)	
Weight (kg)[a]	Standard limb	26	117 (18)	82 (13)	0	0.36
	Long limb	26	121 (28)	87 (24)	2 (−3 to 8)	
BMI (kg/m^2)[a]	Standard limb	26	41.8 (5.7)	29.2 (4.9)	0	0.43
	Long limb	26	43.4 (7.8)	31.1 (7.0)	0.8 (−1.1 to 2.6)	
Circumference (cm)[a]						
Waist	Standard limb	24	129 (12)	97 (12)	0	0.39
	Long limb	23	128 (14)	99 (16)	3 (−4 to 9)	
Hip	Standard limb	24	129 (9)	105 (7)	0	0.16
	Long limb	23	134 (17)	111 (15)	4 (−1 to 9)	
Neck	Standard limb	24	43.6 (3.7)	37.1 (4.1)	0	0.87
	Long limb	23	43.8 (5.8)	37.2 (4.8)	−0.1 (−1.7 to 1.4)	
Total body fat (%)[a]	Standard limb	21	43.1 (6.5)	26.6 (8.4)	0	0.32
	Long limb	24	44.4 (6.4)	29.8 (9.4)	1.9 (−1.9 to 5.7)	
Fat-free mass (%)[a]	Standard limb	21	63 (13)	55 (9)	0	0.30
	Long limb	24	66 (15)	56 (12)	−1 (−3 to 1)	
Basal metabolic rate (kcal/24 hours)[a]	Standard limb	20	2026 (401)	1680 (292)	0	0.72
	Long limb	20	2194 (548)	1832 (418)	12 (−57 to 82)	
Blood pressure (mmHg)[a]						
Systolic	Standard limb	26	134 (13)	123 (12)	0	0.43
	Long limb	26	135 (14)	126 (16)	3 (−5 to 11)	
Diastolic	Standard limb	26	77 (10)	71 (9)	0	0.03
	Long limb	26	78 (10)	76 (9)	5 (0 to 10)	

TABLE 1 Key clinical parameters at baseline and at 12 months postoperatively (*continued*)

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Baseline	12 months		
King's score[a]	Standard limb	25	11.1 (3.2)	5.3 (2.2)	0	0.08
	Long limb	25	11.6 (4.0)	4.7 (2.2)	−0.8 (−1.7 to 0.1)	
HOMA IR[a]	Standard limb	25	8.1 (5.0)	1.4 (0.8)	0	0.64
	Long limb	25	7.6 (4.4)	1.3 (0.7)	−0.1 (−0.5 to 0.3)	
Cholesterol concentration (mmol/l)[a]						
Total	Standard limb	26	4.5 (0.9)	4.0 (0.8)	0	0.88
	Long limb	26	4.7 (1.2)	4.2 (0.9)	0.0 (−0.4 to 0.5)	
LDL	Standard limb	26	2.4 (0.9)	2.2 (0.7)	0	0.39
	Long limb	24	5.6 (0.9)	2.5 (0.7)	0.1 (−0.2 to 0.5)	
HDL	Standard limb	26	1.1 (0.2)	1.3 (0.3)	0	0.06
	Long limb	26	1.0 (0.3)	1.2 (0.2)	−0.1 (−0.2 to 0.0)	
Glucose concentration (mmol/l)[a]	Standard limb	25	11.2 (3.1)	5.6 (1.4)	0	0.43
	Long limb	26	10.3 (2.7)	5.4 (0.9)	−0.3 (−0.9 to 0.4)	
Haemoglobin concentration (g/l)[a]	Standard limb	26	134 (13)	133 (9)	0	0.27
	Long limb	26	131 (16)	135 (12)	3 (−2 to 8)	
Iron concentration (µmol/l)[a]	Standard limb	23	13.4 (4.8)	17.1 (5.5)	0	0.79
	Long limb	26	13.1 (5.1)	16.5 (6.5)	−0.4 (−3.5 to 2.7)	
Transferrin saturation (%)[a]	Standard limb	24	19 (8)	24 (9)	0	0.96
	Long limb	26	19 (8)	24 (10)	0 (−5 to 5)	
Folate concentration (µg/l)[a]	Standard limb	24	10.5 (5.6)	11.1 (4.8)	0	0.56
	Long limb	24	9.5 (4.8)	10.0 (4.5)	−0.7 (−3.2 to 1.7)	
25-Hydroxyvitamin D concentration (nmol/l)[a]	Standard limb	25	69 (30)	83 (34)	0	0.18
	Long limb	26	61 (27)	126 (16)	−11 (−28 to 6)	
Pulse (beats/minute)[a]	Standard limb	26	86 (15)	66 (8)	0	0.26
	Long limb	26	88 (11)	70 (12)	3 (−2 to 9)	
Oxygen saturation (%)[a]	Standard limb	25	99.3 (1.4)	99.4 (1.1)	0	0.13
	Long limb	23	97.7 (1.6)	98.8 (1.4)	−0.6 (−1.4 to 0.2)	
Outcome	**Trial group**	***n***	**Time point, median (IQR)**		**Ratio of difference (95% CI)**	***p*-value**
			Baseline	**12 months**		
Bowel frequency (per day)[c]	Standard limb	26	–	1 (1–2)	1	0.48
	Long limb	26	–	1 (1–1)	1.07 (0.80 to 1.43)	

continued

TABLE 1 Key clinical parameters at baseline and at 12 months postoperatively (*continued*)

Outcome	Trial group	*n*	Time point, median (IQR)		Odds ratio (95% CI)	*p*-value
			Baseline	12 months		
Vitamin B_{12} concentration (ng/l)[a,d]	Standard limb	25	354 (252–479)	405 (323–608)	1	0.89
	Long limb	25	362 (274–467)	399 (307–620)	0.98 (0.75 to 1.29)	
Triglycerides concentration (mmol/l)[a,d]	Standard limb	26	2.1 (1.2–3.4)	0.9 (0.7–1.1)	1	0.45
	Long limb	26	2.0 (1.3–3.0)	1.2 (0.9–1.4)	1.08 (0.88 to 1.33)	

HDL, high-density lipoprotein; HOMA IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein.
a Analysis using ANCOVA.
b Analysis using the unpaired *t*-test.
c Analysis using Mann–Whitney *U*-test.
d Variable analysed on the log scale.
Notes
Categorical data are presented as a percentage (*n*).
Continuous data are presented as a mean (SD) when normally distributed or a median (IQR) when non-normally distributed except where indicated.
Treatment effect denoted as mean (95% CI).
p-values refer to comparing outcomes of the long limb group with the standard limb group 1 year postoperatively.
Differences adjusted for outcome at baseline.
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TABLE 2 Key diabetes mellitus-related parameters at baseline and at 12 months postoperatively

Characteristic	Time point				
	Baseline		12 months postoperatively		
	Long limb (*n* = 26)	Standard limb (*n* = 27)	Long limb (*n* = 26)	Standard limb (*n* = 26)	*p*-value (95% CI)
Duration of T2DM (years), median (IQR)	8 (6–9)	8 (6–10)			
Number of glucose-lowering medications, median (IQR)	3 (2–3)	3 (2–3)	0 (0–0)	0 (0–0)	0.71
T2DM remission			77% (20)	62% (16)	0.23 (0.62 to 6.96)

Notes
Categorical data are presented as a percentage (*n*).
Continuous data are presented as a mean (SD) when normally distributed or a median (IQR) when non-normally distributed except where indicated.
Statistical tests used were ANCOVA, unpaired *t*-test, logistic regression and Fisher's exact test.
p-values refer to comparing the outcomes of the long limb group with the standard limb group outcomes at 1 year postoperatively.

Primary outcome

There were significant increases compared with baseline in the postprandial peak of active GLP-1 concentration in both trial groups at the 2-week time point, but there were no significant differences between the standard and long limb trial groups (*Table 3* and *Figure 3*). There were significant increases at the point of 20% weight loss compared with baseline in the postprandial peak active GLP-1 concentration and the area under the curve (AUC) in both trial groups; however, there were no significant differences between the trial groups.

TABLE 3 Glucose, insulin and gut hormone responses during the mixed-meal tolerance test preoperatively and postoperatively

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Preoperatively	2 weeks postoperatively		
GLP-1 active peak (pmol/l)	Standard limb	24	24 (33)	78 (41)	0	0.34
	Long limb	24	16 (13)	62 (30)	−8 (−25 to 9)	
GLP-1 active AUC (pmol/l/minute)	Standard limb	19	2574 (4082)	5338 (3968)	0	0.68
	Long limb	21	1384 (1404)	4528 (1764)	215 (−831 to 1261)	
GLP-1 total peak (pmol/l)	Standard limb	24	13 (6)	105 (49)	0	0.48
	Long limb	24	14 (10)	96 (33)	−9 (−34 to 16)	
GLP-1 total AUC (pmol/l/minute)	Standard limb	24	1017 (394)	6190 (2566)	0	0.68
	Long limb	24	1044 (543)	6487 (1987)	278 (−1057 to 1613)	
Insulin peak (mU/l)	Standard limb	24	29 (14)	37 (16)	0	0.93
	Long limb	23	28 (16)	36 (21)	0 (−9 to 8)	
Insulin AUC (mU/l/minute)	Standard limb	24	5281 (2464)	6259 (3088)	0	0.89
	Long limb	23	5128 (2833)	6037 (3481)	−102 (−1623 to 1418)	
Outcome	**Trial group**	***n***	**Time point, median (IQR)**		**Odds ratio (95% CI)**	***p*-value**
			Preoperatively	**2 weeks postoperatively**		
PYY peak (pmol/l)	Standard limb	16	56 (31–75)	125 (106–151)	1	0.26
	Long limb	12	33 (27–69)	115 (90–154)	0.86 (0.65 to 1.13)	
PYY AUC (pmol/l/minute)	Standard limb	10	6012 (5310–10,072)	12,583 (11,336–14,536)	1	0.55
	Long limb	4	7348 (6563–9986)	13,054 (11,073–15,911)	0.92 (0.69 to 1.24)	
GIP peak (pmol/l)	Standard limb	24	75 (39–110)	120 (40–205)	1	0.69
	Long limb	23	101 (31–171)	110 (76–160)	1.11 (0.66 to 1.86)	
GIP AUC (pmol/l/minute)	Standard limb	18	5276 (1219–9671)	4329 (1537–11,941)	1	0.22
	Long limb	15	11,641 (1965–14,666)	9184 (4782–9829)	1.56 (0.75 to 3.25)	
Glucose peak (mmol/l)	Standard limb	24	15.3 (13.2–17.2)	10.3 (8.7–12.6)	1	0.76
	Long limb	24	14.4 (11.4–17.5)	10.5 (8.9–11.1)	1.02 (0.88 to 1.20)	
Glucose AUC (mmol/l/minute)	Standard limb	24	2828 (2450–3172)	1828 (1553–2189)	1	0.66
	Long limb	24	2647 (2103–3221)	1862 (1632–2006)	1.04 (0.88 to 1.22)	

Notes
All data were analysed using ANCOVA, with adjustment of between-group differences (treatment effect or odds ratio) for outcome at baseline.
Continuous data are presented as a mean (SD) when normally distributed or a median (IQR) when non-normally distributed.
Between-group differences denoted as mean (95% CI).
The AUC was calculated from time point 0 to 120 minutes.

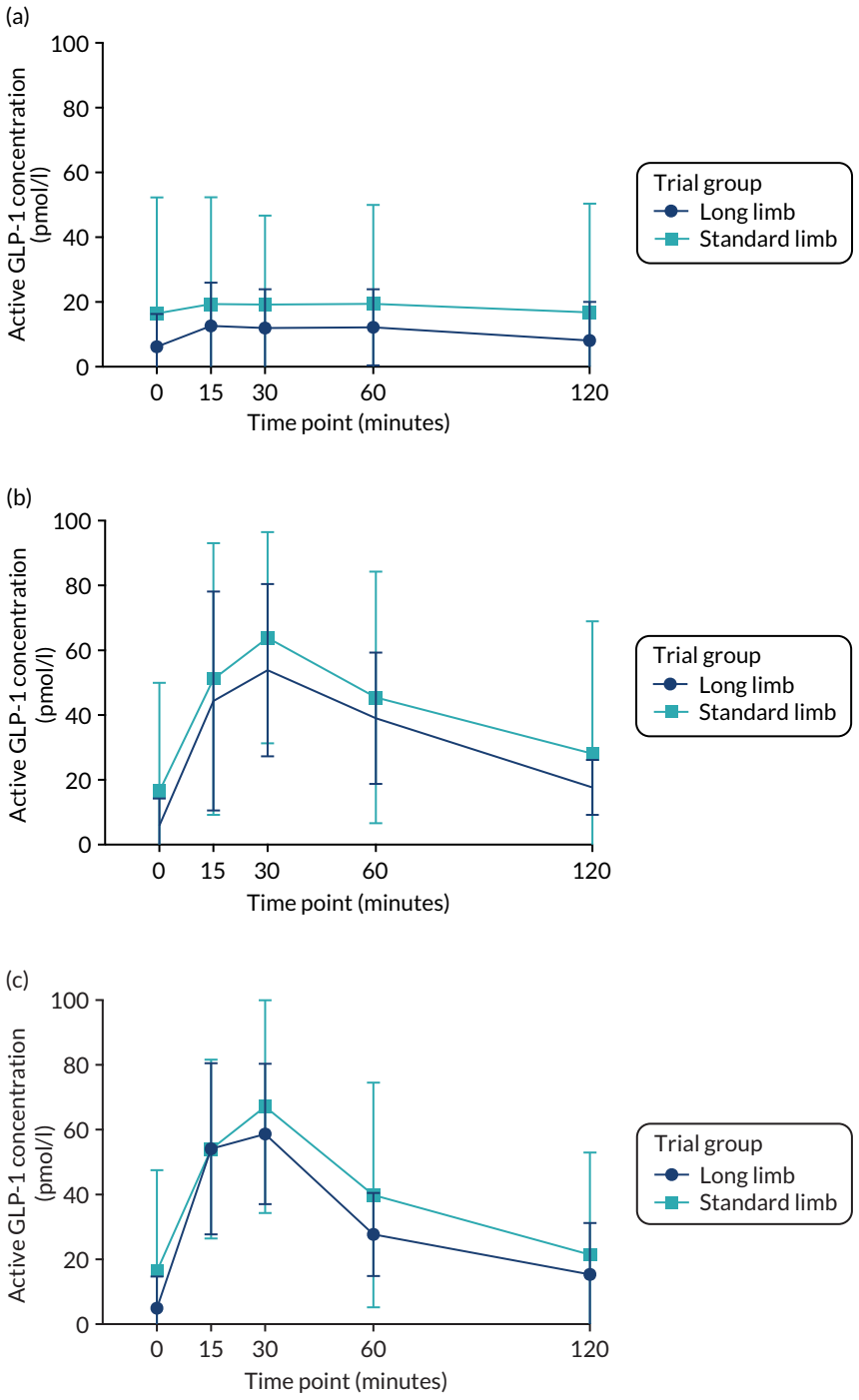

FIGURE 3 Glucagon-like peptide 1 response during the mixed-meal tolerance test. (a) Plasma-active GLP-1 concentration preoperatively; (b) plasma-active GLP-1 concentration at 2 weeks postoperatively; and (c) plasma-active GLP-1 concentration at 20% weight loss time point. Data were plotted as means (SDs). $n = 24$ in each trial group. Reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association.[4]

Secondary outcomes

Glucose tolerance

At the 2-week time point and at the point of matched 20% weight loss, fasting and postprandial glucose concentrations (as assessed via AUCs) during the mixed-meal tolerance test were significantly reduced compared with baseline in both trial groups. However, there were no significant differences between the standard and long limb trial groups (*Tables 3* and *4* and *Figure 4*).

TABLE 4 Glucose, insulin and gut hormone responses during the mixed-meal tolerance test and at the point of matched 20% weight loss

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Preoperatively	20% weight loss		
GLP-1 active peak (pmol/l)	Standard limb	24	24 (33)	70 (32)	0	0.43
	Long limb	23	16 (14)	70 (19)	5 (–8 to 18)	
GLP-1 active AUC (pmol/l/minute)	Standard limb	18	2496 (4219)	5312 (3711)	0	0.18
	Long limb	18	1292 (1497)	3812 (1327)	–529 (–1315 to 256)	
GLP-1 total peak (pmol/l)	Standard limb	24	13 (6)	117 (57)	0	0.68
	Long limb	24	14 (10)	112 (38)	–6 (–35 to 23)	
GLP-1 total AUC (pmol/l/minute)	Standard limb	24	1017 (394)	6281 (2586)	0	0.69
	Long limb	24	1044 (543)	6039 (2555)	–285 (–1726 to 1155)	
Insulin peak (mU/l)	Standard limb	24	29 (14)	42 (20)	0	0.37
	Long limb	23	28 (16)	38 (18)	–3 (–10 to 4)	
Insulin AUC (mU/l/minute)	Standard limb	24	5281 (2464)	6433 (3058)	0	0.34
	Long limb	23	5128 (2833)	5716 (2879)	–594 (–1828 to 641)	
			Time point, median (IQR)			
Outcome	Trial group	*n*	Preoperatively	20% weight loss	Odds ratio (95% CI)	*p*-value
PYY peak (pmol/l)	Standard limb	16	56 (31–75)	104 (85–158)	1	0.29
	Long limb	12	33 (27–69)	101 (74–120)	0.88 (0.68 to 1.13)	
PYY AUC (pmol/l/minute)	Standard limb	8	8163 (5419–10,539)	14,472 (10,444–16,385)	1	0.78
	Long limb	3	5966 (2576–7536)	11,189 (5514–12,851)	0.96 (0.68 to 1.35)	
GIP peak (pmol/l)	Standard limb	24	75 (39–110)	129 (61–259)	1	0.20
	Long limb	23	101 (31–171)	88 (38–181)	0.56 (0.23 to 1.37)	
GIP AUC (pmol/l/minute)	Standard limb	15	5139 (1489–8472)	9185 (4006–15,486)	1	0.69
	Long limb	16	11,203 (2614–13,665)	6041 (4174–11,893)	0.87 (0.44 to 1.74)	
Glucose peak (mmol/l)	Standard limb	24	15.3 (13.2–17.2)	9.3 (7.7–11.0)	1	0.32
	Long limb	24	14.4 (11.4–17.5)	8.0 (6.9–9.3)	0.93 (0.81 to 1.07)	
Glucose peak (mmol/l)	Standard limb	24	2828 (2450–3172)	1564 (1276–1896)	1	0.38
	Long limb	24	2647 (2103–3221)	1301 (1170–1580)	0.94 (0.80 to 1.09)	

Notes
Continuous data are presented as a mean (SD) when normally distributed or a median (IQR) when non-normally distributed.
Between-group differences are denoted as a mean (95% CI).
The statistical test used was ANCOVA.
All data were analysed using ANCOVA, with adjustment of between-group differences (treatment effect or odds ratio) for outcome at baseline.
The AUC was calculated from time point 0 to 120 minutes.

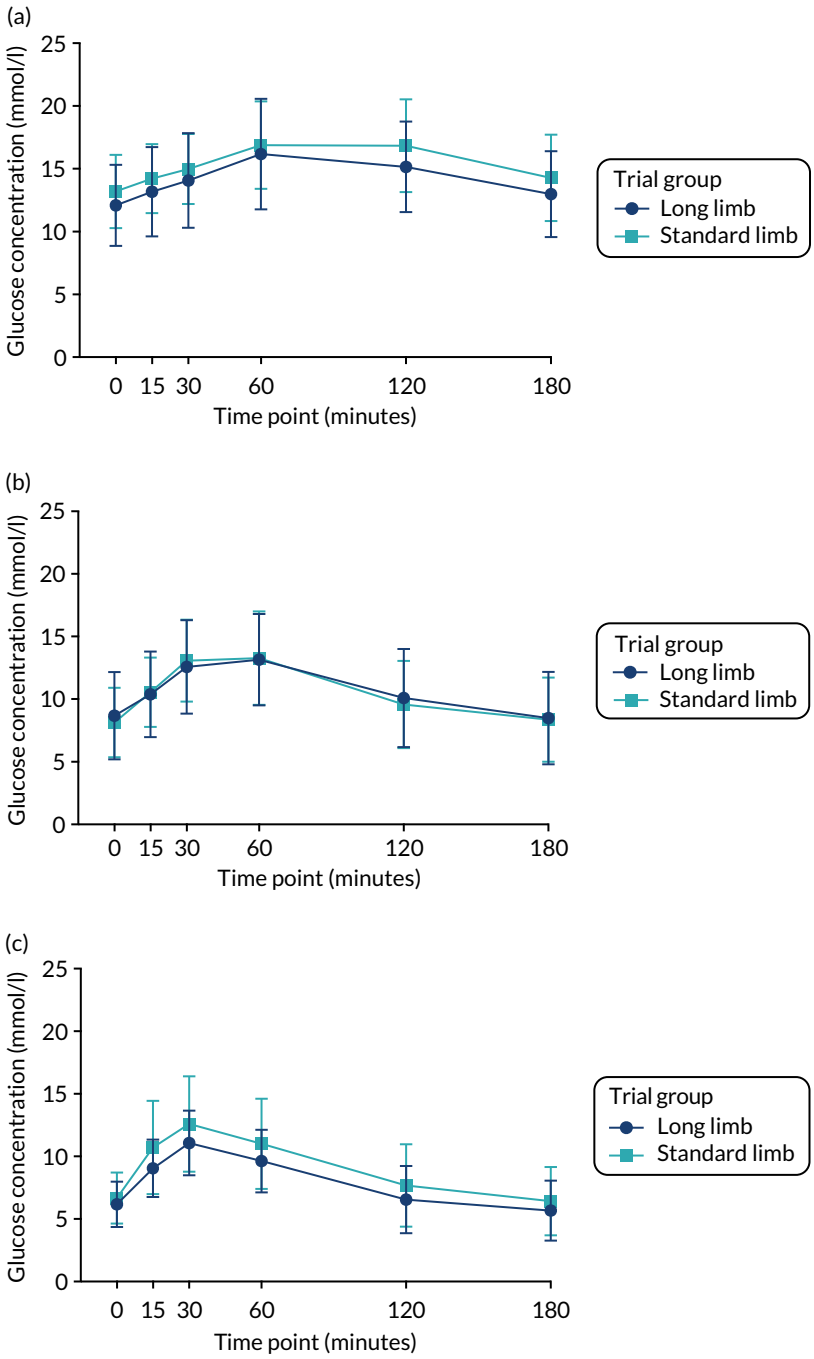

FIGURE 4 Plasma glucose excursion during the mixed-meal tolerance test. (a) Plasma glucose concentrations preoperatively; (b) plasma glucose concentrations 2 weeks postoperatively; and (c) plasma glucose concentrations at the 20% weight loss time point. Data were plotted as means (SDs). $n = 24$ in each trial group. Reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association.[4]

Insulin secretion

At the 2-week time point and at the point of matched 20% weight loss, peak postprandial insulin concentrations during the mixed-meal tolerance test were significantly increased compared with baseline in both trial groups. However, there were no significant differences between the standard and long limb trial groups (see *Tables 3* and *4*; *Figure 5*).

Secretion of other gut hormones

There were no significant differences in the peak concentration or AUC of postprandial PYY or GIP secretion between the standard and long limb trial groups (see *Tables 3* and *4*).

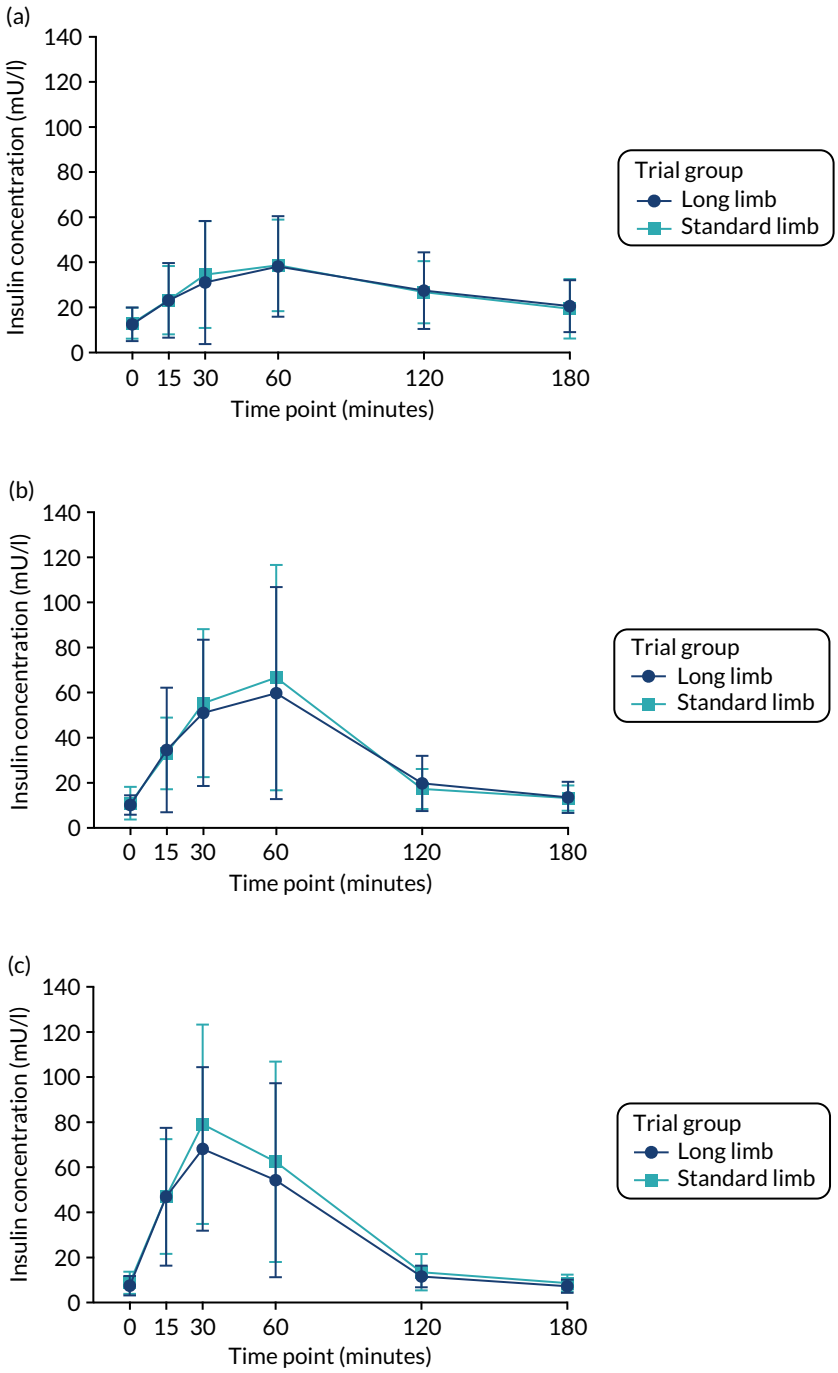

FIGURE 5 Serum insulin excursion during the mixed-meal tolerance test. (a) Serum insulin concentrations preoperatively; (b) serum insulin concentrations 2 weeks postoperatively; and (c) serum insulin concentrations at the 20% weight loss time point. Data were plotted as means (SDs). $n = 24$ in each trial group. Reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association.[4]

Insulin sensitivity

At the 2-week time point and at the point of matched 20% weight loss, the rate of glucose appearance during the low-dose phase of the hyperinsulinaemic–euglycaemic clamp (i.e. Ra), which is a measure of hepatic insulin sensitivity, had decreased significantly compared with baseline in both trial groups. This decrease of Ra denotes an improvement in insulin sensitivity. However, there were no significant differences between the standard and long limb trial groups (*Tables 5* and *6* and *Figure 6*).

At the 2-week time point and at the point of matched 20% weight loss, the rate of glucose disappearance during the high-dose phase of the hyperinsulinaemic–euglycaemic clamp (i.e. Rd), which is a measure of peripheral insulin sensitivity, had increased significantly compared with baseline in both trial groups. This increase in Rd denotes an improvement in insulin sensitivity. However, there were no significant differences between the standard and long limb trial groups (*Tables 5* and *6* and *Figure 6*).

Glycaemic control and weight loss

There were no significant differences in the levels of HbA_{1c} between the standard limb and long limb trial groups at any time point postoperatively. At 3 months postoperatively, the level of HbA_{1c} in the standard limb group was 50 mmol/mol (SD 10 mmol/mol), compared with 48 mmol/mol (SD 10 mmol/mol) in the long limb group ($p = 0.40$). At 6 months postoperatively, the level of HbA_{1c} in the standard limb trial

TABLE 5 Rate of glucose appearance (Ra), disappearance (Rd) and metabolic clearance rate of glucose (MCR) in the hyperinsulinaemic–euglycaemic clamps 2 weeks postoperatively

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Preoperatively	2 weeks postoperatively		
Ra						
Basal	Standard limb	23	11.1 (2.0)	9.6 (1.0)	0	0.23
	Long limb	23	10.9 (1.5)	10.0 (1.5)	0.4 (–0.3 to 1.1)	
Low	Standard limb	23	5.1 (1.7)	3.4 (0.9)	0	0.94
	Long limb	23	5.0 (2.4)	3.4 (1.4)	0.0 (–0.6 to 0.7)	
High	Standard limb	23	1.9 (2.4)	0.6 (1.7)	0	0.86
	Long limb	23	1.1 (2.0)	0.7 (1.7)	0.1 (–0.9 to 1.1)	
Rd						
Basal	Standard limb	23	11.2 (2.0)	9.7 (1.0)	0	0.23
	Long limb	23	10.9 (1.5)	10.1 (1.5)	0.4 (–0.3 to 1.2)	
Low	Standard limb	23	9.8 (1.6)	11.8 (2.9)	0	0.18
	Long limb	23	10.6 (3.6)	13.6 (4.2)	1.3 (–0.6 to 3.2)	
High	Standard limb	23	18.7 (7.6)	29.0 (9.1)	0	0.98
	Long limb	23	19.1 (9.4)	29.2 (9.9)	0.1 (–5.2 to 5.3)	
MCR						
Basal	Standard limb	23	1.9 (0.3)	1.8 (0.2)	0	0.05
	Long limb	23	1.9 (0.3)	1.9 (0.3)	0.1 (0.0 to 0.3)	
Low	Standard limb	23	1.7 (0.3)	2.1 (0.6)	0	0.23
	Long limb	23	1.9 (0.7)	2.4 (0.8)	0.2 (–0.1 to 0.6)	
High	Standard limb	23	3.2 (1.3)	5.3 (1.8)	0	0.89
	Long limb	22	3.6 (2.2)	5.6 (2.0)	0.1 (–1.0 to 1.1)	

High, measured in the phase of high-dose insulin infusion; Low, measured in the phase of low-dose insulin infusion; MCR, metabolic clearance rate of glucose.

Notes

Continuous data are presented as means (SDs) when normally distributed.

Between-group differences are denoted as a mean (95% CI).

All data were analysed using ANCOVA, with adjustment of between-group differences (treatment effect) for outcome at baseline.

TABLE 6 Rate of glucose appearance (Ra), disappearance (Rd) and metabolic clearance rate of glucose (MCR) in the hyperinsulinaemic–euglycaemic clamps at a matched 20% weight loss

Outcome	Trial group	*n*	Time point, mean (SD)		Treatment effect (95% CI)	*p*-value
			Preoperatively	20% weight loss		
Ra						
Basal	Standard limb	24	11.1 (2.0)	10.6 (1.4)	0	0.28
	Long limb	23	10.9 (1.5)	11.0 (2.2)	0.6 (–0.4 to 1.5)	
Low	Standard limb	24	5.2 (1.7)	2.8 (1.3)	0	0.62
	Long limb	23	5.0 (2.4)	2.6 (1.7)	–0.2 (–1.0 to 0.6)	
High	Standard limb	24	2.0 (2.4)	0.0 (1.8)	0	0.09
	Long limb	23	1.2 (2.0)	–1.0 (1.3)	–0.8 (–1.8 to 0.1)	
Rd						
Basal	Standard limb	24	11.2 (2.0)	10.7 (1.4)	0	0.28
	Long limb	23	10.9 (1.5)	11.1 (2.2)	0.5 (–0.4 to 1.5)	
Low	Standard limb	24	9.8 (1.6)	15.2 (2.9)	0	0.36
	Long limb	23	10.6 (3.6)	16.5 (4.1)	0.9 (–1.1 to 2.9)	
High	Standard limb	24	18.5 (7.6)	36.1 (8.5)	0	0.47
	Long limb	23	19.1 (9.4)	38.1 (9.2)	1.8 (–3.2 to 6.9)	
MCR						
Basal	Standard limb	24	1.9 (0.3)	2.1 (0.2)	0	0.17
	Long limb	23	1.9 (0.3)	2.2 (0.5)	0.1 (–0.1 to 0.3)	
Low	Standard limb	24	1.7 (0.3)	2.7 (0.4)	0	0.10
	Long limb	23	1.9 (0.7)	3.1 (0.8)	0.3 (–0.1 to 0.7)	
High	Standard limb	24	3.2 (1.2)	6.7 (1.7)	0	0.57
	Long limb	23	3.6 (2.1)	7.1 (1.7)	0.3 (–0.7 to 1.2)	

High, measured in the phase of high-dose insulin infusion; Low, measured in the phase of low-dose insulin infusion; MCR, metabolic clearance rate of glucose.

Notes

Continuous data are presented as means (SDs) when normally distributed.

Between-group differences are denoted as a mean (95% CI).

All data were analysed using ANCOVA, with adjustment of between-group differences (treatment effect) for outcome at baseline.

group was 44 mmol/mol (SD 8 mmol/mol), compared with 41 mmol/mol (SD 6 mmol/mol) in the long limb trial group ($p = 0.07$). At 12 months postoperatively, the level of HbA_{1c} in the standard limb trial group was 43 mmol/mol (SD 10 mmol/mol), compared with 41 mmol/mol (SD 5 mmol/mol) in the long limb trial group ($p = 0.20$) (see *Table 2* and *Figure 7*). There were no significant differences in the percentage of patients achieving glycaemic remission at 12 months between the trial groups (standard limb 62% vs. long limb 77%; $p = 0.23$).

The usage of glucose-lowering medications decreased in both trial groups (see *Appendix 3*). At baseline, 100% of patients were on pharmacotherapy. At 3 months postoperatively, 38% of standard limb and 24% of long limb trial group participants required medications. At 6 months the corresponding figures were 28% and 24%. Only one participant from the long limb trial group was on glucose-lowering pharmacotherapy at 12 months, with none in the standard limb group.

At 2 weeks postoperatively, patients in both trial groups lost similar percentages of body weight [standard limb 6.2% (SD 2.3%) vs. long limb 6.1% (SD 1.6%); $p = 0.97$]. As per protocol, both trial groups were studied

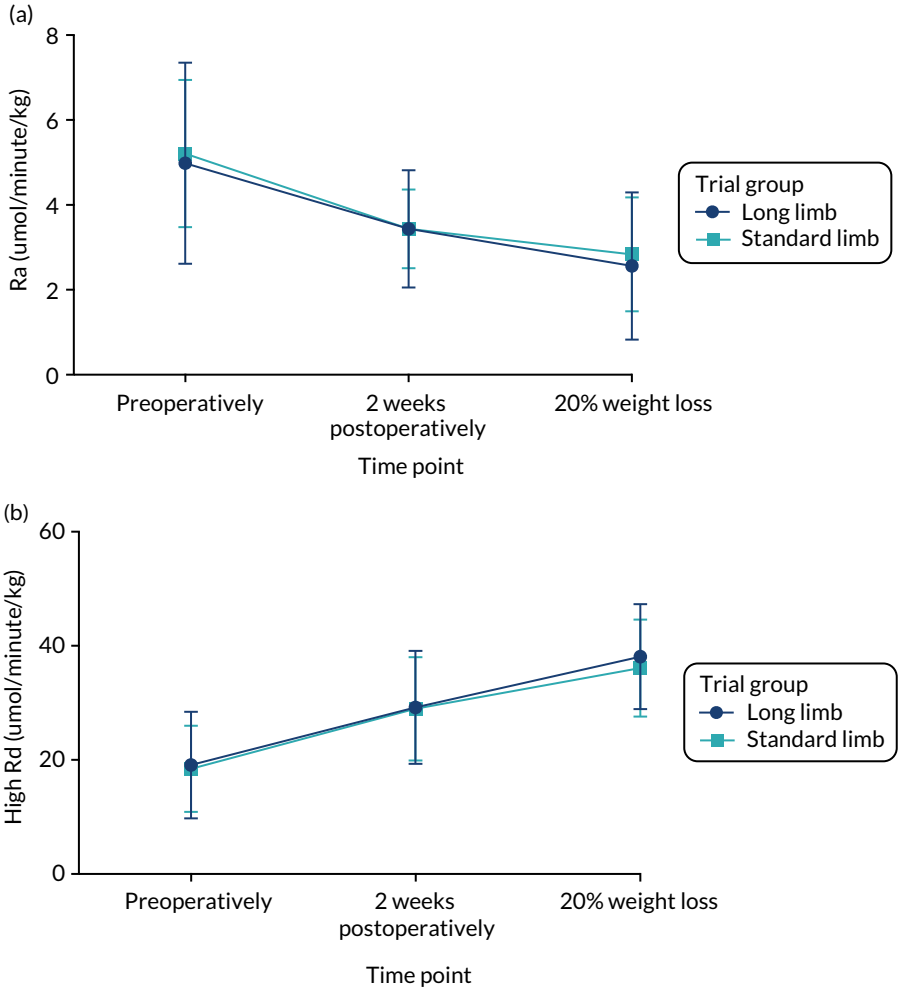

FIGURE 6 (a) Rate of glucose appearance (Ra) at low-dose insulin infusion; and (b) rate of glucose disappearance (Rd) at high-dose insulin infusion. Data are plotted as means (SDs). $n = 23$ in each trial group. Reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association.[4]

again at the point of matched 20% weight loss; this occurred, on average, 4.5 months after surgery. At this time point, mean percentage weight loss was 21.5% (SD 2.8%) in the standard limb group and 20.6% (SD 2.7%) in the long limb trial group. There were no differences in total body weight loss percentage between the trial groups at any time point postoperatively. At 3 months postoperatively, mean weight loss was 19% (SD 4%) in both trial groups ($p = 0.99$). At 6 months postoperatively, mean weight loss was 26% (SD 6%) in the standard limb group and 24% (SD 4%) in the long limb trial group ($p = 0.11$). At 12 months postoperatively, the corresponding figures were 30% (SD 8%) and 29% (SD 8%) ($p = 0.52$) (see *Figure 7*).

Surgical outcomes

The median total small intestinal length was 615 cm (range 320–740 cm; $n = 26$) in the standard limb group and 610 cm (range 520–910 cm; $n = 25$) in the long limb group. The median common channel length was 465 cm (range 170–590 cm) in the standard limb group and 360 cm (range 250–660 cm) in the long limb trial group. The median biliopancreatic limb-to-total small intestinal length ratio was 8% (range 7–16%) in the standard limb group and 25% (range 16–29%) in the long limb trial group (*Table 7*). There were no significant differences in the operative time or length of hospital stay [mean, 2 days (SD 0.7 days)] between the two surgical procedures. The safety profile of the procedures was similar, with no signal for excess malabsorption of macronutrients or micronutrients in the long limb trial group (*Table 8*).

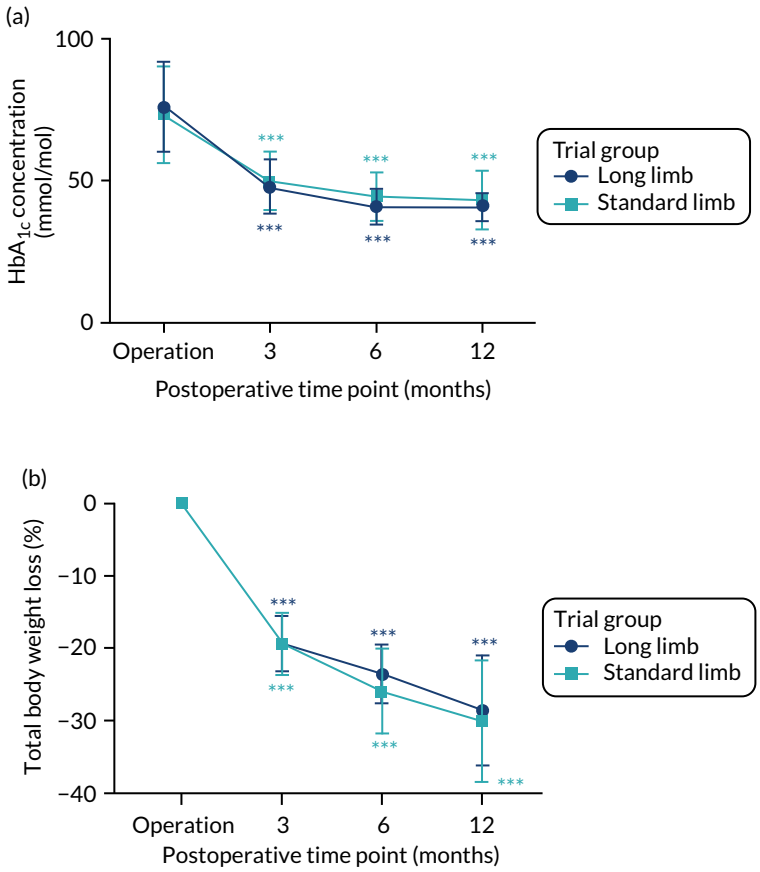

FIGURE 7 Level of (a) glycated haemoglobin and (b) total body weight loss within the first postoperative year. Data are expressed as means (SDs). $n = 26$ in each trial group. Asterisks in aqua and navy compare the values with baseline within each group. ***$p < 0.001$.

TABLE 7 Intraoperative measurements

Measurement	Trial group	
	Long limb ($n = 25$)	Standard limb ($n = 26$)
Common channel length (cm)	360 (IQR 305–435); range 250–660	465 (IQR 320–528); range 170–590
Total small intestinal length (cm)	610 (IQR 555–685); range 520–910	615 (IQR 470–678); range 320–740
Biliopancreatic limb-to-total small intestinal length ratio (%)	25 (IQR 22–27); range 16–29	8 (IQR 7–11); range 7–16
Common channel-to-total small intestinal length ratio (%)	59 (IQR 55–64); range 48–73	76 (IQR 68–78); range 53–80
Operating time (minutes)	164 (SD 51); range 59–241	146 (SD 42); range 79–250

Note
Continuous data are presented as means (SDs) and ranges when normally distributed or medians (IQRs) and ranges when non-normally distributed.

TABLE 8 Postoperative adverse events and complications

Adverse event	Trial group, number of adverse events	
	Long limb ($n = 26$)	Standard limb ($n = 27$)
Cardiovascular	0	0
Gastrointestinal		
Anastomotic stricture	1	0
Anastomotic ulcer	0	1
Perioperative bleeding	2	0
Gallstones	1	0
Abdominal pain	1	0
Laparotomy for purulent peritonitis	1	0
Gastritis	1	0
Diarrhoea	1	2
Constipation	0	1
Infections		
Wound infection	4	2
Pneumonia	4	2
Viral tonsillitis	1	0
Soft tissue and musculoskeletal		
Incisional hernia	1	0
Limb fracture	0	1
Nutritional and metabolic		
Intravenous treatment for dehydration	0	1
Acute kidney injury	0	2
Anaemia	2	2
Vasovagal	1	2
Hypoglycaemic episode	2	4
Adverse events leading to hospitalisation	5 (in three participants)	4 (in four participants)
Clavien–Dindo classification of complications (grades)		
I	6	11
II	14	9
IIIa	1	0
IIIb	1	0
IV	1	0
V	0	0
Total	**23**	**20**

Notes

Clavien–Dindo classification:

- *Grade I*: any deviation from the normal postoperative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside.
- *Grade II*: complications requiring drug treatments other than those allowed for grade I complications; this includes blood transfusion and total parenteral nutrition (TPN).
- *Grade III*: complications requiring surgical, endoscopic or radiological intervention.
  - *Grade IIIa*: intervention not under general anaesthetic.
  - *Grade IIIb*: intervention under general anaesthetic.
- *Grade IV*: life-threatening complications; this includes central nervous system complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) that require intensive care, but excludes transient ischaemic attacks (TIAs).
  - *Grade IVa*: single-organ dysfunction (including dialysis).
  - *Grade IVb*: multiorgan dysfunction.
- *Grade V*: death of the patient.

Correlation between intestinal limb length ratios and key clinical and mechanistic outcomes

No significant correlations were found between the ratio of the biliopancreatic or common limb length to the total small bowel length and total body weight loss, reduction in level of HbA_{1c} and T2DM remission at 1 year. Similarly, no significant correlations were found between the limb length ratios and postprandial active GLP-1, glucose and insulin excursions in the mixed-meal tolerance tests, or in Ra and Rd in the hyperinsulinaemic–euglycaemic clamps, at any time point.

Remission of other comorbidities

The prevalence of hypertension, dyslipidaemia and sleep apnoea at 12 months was reduced at 12 months in both trial groups; however, none of these remission rates was statistically significantly different between the standard and long limb surgery trial groups (*Table 9*).

Secondary outcomes not included in the report

Results on gut microbiota have not been reported in this trial, as the analysis is still ongoing. Samples for metabolomics, bile acids and fibroblast growth factor (FGF) 19 and 21 assays were not processed, as no differences between the study arms were expected based on the available mechanistic and clinical outcomes. Systolic and diastolic blood pressure AUCs and heart rate AUC from the mixed-meal tolerance tests were not analysed as single point measurements from the clinical visits would suffice.

TABLE 9 Remission of other comorbidities

			Time point, *n* (%)			
Outcome	**Trial group**	***N***	**Baseline**	**12 months**	**Odds ratio (95% CI)**	***p*-value**
Hypertension[a]	Standard limb	26	19 (73)	15 (58)	1	0.58
	Long limb	26	18 (69)	13 (50)	0.73 (0.25 to 2.19)	
Dyslipidaemia[a]	Standard limb	26	18 (69)	17 (65)	1	1.00
	Long limb	26	20 (77)	17 (65)	1.00 (0.32 to 3.13)	
Sleep apnoea[b]	Standard limb	26	12 (46)	3 (12)	–	0.24
	Long limb	26	7 (27)	0 (0)	–	

a Analysis using logistic regression. Unable to adjust for baseline, as no cases of the characteristic at 12 months in patients without characteristic at baseline.
b Analysis using Fisher's exact test. Unable to use logistic regression as there were no cases of sleep apnoea at 12 months in one group.

Notes
Continuous data are presented as means (SDs). Odds ratio are presented as means (95% CIs).

Chapter 4 Discussion

This trial has shown that patients with diabetes mellitus and obesity benefit significantly from both standard and long limb RYGB. The trial did not demonstrate that a RYGB with a biliopancreatic limb of 150 cm is superior to a RYGB with a biliopancreatic limb of 50 cm with regard to fasting and postprandial glycaemia, GLP-1 secretion, insulin secretion or insulin sensitivity. In line with these mechanistic measurements, there were no differences between the two trial groups in terms of HbA_{1c} level or weight reduction at 12 months. There was no difference in the safety profile of the two procedures.

Previous studies have compared RYGB designs with varying biliopancreatic and alimentary limbs, making it challenging to determine which segment was responsible for superior clinical benefits, if any.[21–25] To our knowledge, this is the first double-blind RCT to conduct such a systematic head-to-head comparison of these two RYGB designs and an in-depth metabolic phenotyping of its participants. In this trial, a reductionist approach was used and the alimentary limb length was kept constant in an attempt to isolate the contribution of the length of the biliopancreatic limb to glucose control. Owing to the inherent nature of RYGB anatomy, and as per trial design, the length of the common channel was also different between the trial groups. Considering the variability in the length of the human small intestine, we were relieved to observe that this difference was serendipitously 100 cm, thus reducing even further the number of variables that could have confounded the results. The study was powered to detect significant differences in mechanistic, but not clinical, outcomes. It was postulated that the lack of even a trend for a difference in fasting and postprandial glucose concentrations between the study groups makes it unlikely that trials with even bigger sample sizes will find clinically significant differences in HbA_{1c} levels and weight, at least within the first postoperative year.

The findings of the study are in line with several other clinical studies in which a longer biliopancreatic limb showed no additional benefit in terms of reduction in level of HbA_{1c}, T2DM remission or weight loss. Any differences in the weight loss were either only short-lived or not clinically significant.[21–25] In the only other study in the literature that kept the alimentary limb length fixed,[26] patients in the long biliopancreatic limb RYGB achieved higher rates of T2DM remission 2 years postoperatively. However, this study was retrospective in nature and patients were not randomised.[26]

In the only other retrospective case–control mechanistic study of long limb RYGB,[27] it was found that postprandial GLP-1 concentrations were higher in patients who underwent a long limb RYGB 4 years previously; however, this finding was not replicated in this trial. In the report by Patrício *et al.*,[27] the higher concentrations of GLP-1 did not translate to enhanced postprandial insulin secretion or lower concentrations of glucose, which is not consistent with the well-established insulinotropic actions of GLP-1. One explanation for the discrepant results between the two studies could be that in this trial GLP-1 and other mechanistic responses were measured at 2 weeks and at the point of matched 20% weight loss, which occurs approximately 4 months after surgery. This may not have been enough time for the full physiological impact of intestinal adaptation that takes place after RYGB to come into play. In addition, the cohort of patients studied in the report of Patrício *et al.*[27] did not have T2DM and the length of the biliopancreatic limb used was 200 cm. Therefore, it cannot be excluded that the use of a longer biliopancreatic limb and/or a longer follow-up period might reveal differences in GLP-1 concentrations between the two trial designs that could drive superior reductions in glycaemia and/or weight. In addition, although it may be argued that our failure to find any difference in GLP-1 secretion might be due to a type II error, our gut hormone secretion data (which revealed no significant difference between the interventions) and our data on glucose and insulin dynamics (which also revealed no significant difference between the interventions) suggest that our mechanistic conclusions are robust.

The absence of either an earlier or a higher peak in postprandial GLP-1 concentrations after the long biliopancreatic limb RYGB also challenges the hypothesis that the delivery of nutrients to more distal segments of the small intestine, where the density of EECs is higher, triggers the enhanced secretion of incretin and anorexigenic hormones such as GLP-1 and PYY.[28] The study did not observe any differences between the two RYGB designs either within 2 weeks after the operation or after 4 months, at which time at least part of the intestinal adaptation after the RYGB has taken place. One plausible explanation of this unexpected finding is that there is no linear relationship between GLP-1 secretion and the length of intestine exposed to ingested nutrients, as previously suggested, but a 'ceiling' effect such that the delivery of nutrients beyond a certain critical point in the jejunum does not result in further enhancement of the GLP-1 response. A second, alternative, hypothesis is that the regulation of GLP-1 secretion does not take place exclusively through the interaction of nutrients with the distal small intestine. A third possibility is that the difference in biliopancreatic limb length tested in the study (i.e. 50 vs. 150 cm) was not long enough to trigger the enhanced secretion of GLP-1, PYY, etc.; as mentioned in the discussion above, a longer biliopancreatic limb length of 200 cm might be more effective. The similarities in postprandial GLP-1 responses after sleeve gastrectomy and RYGB in both humans and animal models raise the possibility that the secretion of this incretin may, at least in part, be regulated by gastric neural and/or hormonal mechanisms.[29] It should be noted that our findings do not question the substantial impact of enhanced GLP-1 secretion after a RYGB on insulin secretion or appetite regulation, but only challenge commonly held beliefs regarding the regulation of its secretion.

The study did not observe any differences between the groups in terms of insulin sensitivity at 2 weeks or 4 months after surgery. Studies in humans and animal models of procedures, including the duodenal–jejunal bypass operation and the duodenal-jejunal bypass liner, in which food bypasses the proximal intestine, have demonstrated caloric restriction- and weight loss-independent reductions in fasting glucose and markers of insulin sensitivity.[8,30,31] Additional support for this concept comes from elegant studies on patients undergoing the biliopancreatic diversion procedure in which the biliopancreatic limb is at least 200 cm long. These studies demonstrated profound improvements in hepatic and peripheral insulin sensitivity within weeks after the intervention.[32] The mechanisms underlying these observations are thought to involve altered glucose-sensing in the distal and mid-jejunum[33,34] and/or the reduction in the secretion of insulin 'desensitising' factors from the duodenum and the proximal jejunum.[35] Based on these studies it was expected that a RYGB with a 150-cm biliopancreatic limb would be superior to a standard RYGB in terms of insulin sensitivity, but without the potentially severe macronutrient and micronutrient deficiencies associated with the biliopancreatic diversion. Similar to the GLP-1 story, it is postulated that beyond the bypass of a critical length of the duodenum and jejunum, no additional effects on insulin sensitivity take place. The surprising impact of the duodenal mucosal resurfacing intervention, in which only 12 cm of the duodenum is thermally ablated, on glucose regulation and markers of insulin sensitivity[36] provides further support that the key segment of the bypassed intestine, or 'sweet spot', responsible for insulin sensitisation might be confined to the duodenum.[37]

The study's findings are strengthened by key aspects of the trial design. These include (1) the double-blinded, randomised approach, (2) the measurement of the entire length of the small intestine during surgery, (3) the robust way of ensuring that the surgical approach used was consistent between surgeons and in line with a pre-agreed standard operating procedure, (4) the use of the gold standard method of measuring insulin sensitivity through hyperinsulinaemic–euglycaemic clamps with stable isotopes, (5) the conduct of the mechanistic studies after washout of diabetes mellitus medications and (6) the longitudinal metabolic phenotyping of participants both early and at matched weight loss after the two interventions. What the study authors also wanted to demonstrate when designing this trial was that the clinical and scientific communities are now able to rationally optimise the efficacy of metabolic surgery operations through the available knowledge on their mechanisms of action. This represents a paradigm shift in a field in which, until recently, surgical experimentation took place in the absence of mechanistic information to guide it. The study demonstrated that, in certain circumstances, double-blind RCTs are ethical and feasible in the field of surgery and, hopefully, set a precedent for future studies.

The trial has narrowed down the number of intestinal segments that can be manipulated in an attempt to improve the impact of metabolic surgery on glycaemic control. Future physiological and clinical studies could investigate the role of the common channel and explore novel mechanisms through which the intestine regulates glycaemia. Recent findings from humans and animal models have demonstrated that the common channel is the intestinal segment where the majority of ingested glucose uptake takes place after surgery.[38] This process is dependent on the interaction of glucose and the sodium content of bile with the sodium-dependent glucose co-transporter 1. Thus, a RYGB with a common channel short enough to selectively reduce the absorption of glucose, but not other nutrients, could prove to be superior to the standard RYGB design for patients with T2DM. Building on from this trial, such experimentation could involve the use of limb length ratios, rather than absolute lengths, in an attempt to personalise surgery to the patient's total small intestinal length.

The main limitations of this trial, including the relatively short follow-up and elongation of the biliopancreatic limb to a fixed length of 150 cm, have already been mentioned. For the purposes of standardisation, the study defined the 'standard RYGB' as one with a biliopancreatic limb of 50 cm and an alimentary limb of 100 cm based on the popularity of this design in current surgical practice. However, it is appreciated that there is substantial variation in practice around the world and that not all surgeons will agree with this definition.

Recommendations

It is hoped that the trial design and findings lay the foundation for a new generation of experimental medicine studies that aim to optimise the clinical efficacy of metabolic surgery, and indeed non-surgical interventions, through interrogation of the elusive physiology of the intestine and the impact of its various segments on metabolic regulation.

Based on the findings of this trial, an application for a follow-up extension to 5 years has been submitted and successfully secured. It will include a mixed-meal tolerance test 2 years after surgery, followed by yearly clinical follow-ups. This will enable the measurement of any differences in the long-term impact of the long limb compared with the standard limb RYGB.

Should further trials on the biliopancreatic limb length be planned, this study recommends consideration of a longer biliopancreatic limb length and using limb lengths in proportion to the total small bowel length instead of the absolute values. Furthermore, investigating intestinal remodelling and its impact on the postoperative outcomes could be considered by taking intestinal biopsies intraoperatively and then endoscopically at least 12 months after the surgery.

However, it is possible that no further improvement in glucose homeostasis can be achieved with manipulation of the biliopancreatic limb length and, therefore, the research should be directed towards investigating the common limb.

Chapter 5 Conclusions

In conclusion, this trial has demonstrated that people with diabetes mellitus and obesity do benefit metabolically from a RYGB; however, the study did not demonstrate a physiological rationale for the elongation of the biliopancreatic limb of the RYGB to 150 cm to achieve superior metabolic outcomes for patients with T2DM and obesity. Confirmation of the findings in larger clinical trials with longer follow-up is necessary.

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Dr Julian Marchesi and Professor Elaine Holmes are co-investigators. They are currently collaborating on further analysis, which includes the gut microbiota data.

Dr Paul Bassett is the trial statistician and is independent of the study.

Dr Victoria Salemis is an independent researcher from Imperial College London and is responsible for the randomisation of trial patients.

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Publication

Miras AD, Kamocka A, Pérez-Pevida B, Purkayastha S, Moorthy K, Patel A, *et al.* The effect of standard versus longer intestinal bypass on GLP-1 regulation and glucose metabolism in patients with type 2 diabetes undergoing Roux-en-Y gastric bypass: The Long-Limb Study. *Diabetes Care* 2020;**43**:dc20076.

Data-sharing statement

Data are archived at the National Institute for Health Research Imperial Clinical Research Facility. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

References

1. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Nanni G, *et al.* Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015;**386**:964–73. https://doi.org/10.1016/S0140-6736(15)00075-6
2. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, *et al.* Bariatric surgery versus intensive medical therapy for diabetes – 5-year outcomes. *N Engl J Med* 2017;**376**:641–51. https://doi.org/10.1056/NEJMoa1600869
3. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, *et al.* Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. *Diabetes Care* 2016;**39**:861–77. https://doi.org/10.2337/dc16-0236
4. Miras AD, Kamocka A, Pérez-Pevida B, Purkayastha S, Moorthy K, Patel A, *et al.* The effect of standard versus longer intestinal bypass on GLP-1 regulation and glucose metabolism in patients with type 2 diabetes undergoing Roux-en-Y gastric bypass: The Long-Limb Study. *Diabetes Care* 2020;**43**:dc20076. https://doi.org/10.2337/dc20-0762
5. Tacchino RM. Bowel length: measurement, predictors, and impact on bariatric and metabolic surgery. *Surg Obes Relat Dis* 2015;**11**:328–34. https://doi.org/10.1016/j.soard.2014.09.016
6. Gastaldelli A, Iaconelli A, Gaggini M, Magnone MC, Veneziani A, Rubino F, Mingrone G. Short-term effects of laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass. *Diabetes Care* 2016;**39**:1925–31. https://doi.org/10.2337/dc15-2823
7. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, *et al.* Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;**366**:1577–85. https://doi.org/10.1056/NEJMoa1200111
8. Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, *et al.* The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. *Ann Surg* 2006;**244**:741–9. https://doi.org/10.1097/01.sla.0000224726.61448.1b
9. Camastra S, Muscelli E, Gastaldelli A, Holst JJ, Astiarraga B, Baldi S, *et al.* Long-term effects of bariatric surgery on meal disposal and β-cell function in diabetic and nondiabetic patients. *Diabetes* 2013;**62**:3709–17. https://doi.org/10.2337/db13-0321
10. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes* 2011;**60**:2308–14. https://doi.org/10.2337/db11-0203
11. Gribble FM. The gut endocrine system as a coordinator of postprandial nutrient homoeostasis. *Proc Nutr Soc* 2012;**71**:456–62. https://doi.org/10.1017/S0029665112000705
12. Tan T, Behary P, Tharakan G, Minnion J, Al-Najim W, Albrechtsen NJW, *et al.* The effect of a subcutaneous infusion of GLP-1, OXM, and PYY on energy intake and expenditure in obese volunteers. *J Clin Endocrinol Metab* 2017;**102**:2364–72. https://doi.org/10.1210/jc.2017-00469
13. le Roux CW, Batterham RL, Aylwin SJ, Patterson M, Borg CM, Wynne KJ, *et al.* Attenuated peptide YY release in obese subjects is associated with reduced satiety. *Endocrinology* 2006;**147**:3–8. https://doi.org/10.1210/en.2005-0972

14. National Institute for Health and Care Excellence (NICE). *Obesity: Identification, Assessment and Management*. London: NICE; 2014. URL: www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925 (accessed 1 February 2019).
15. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, *et al.* How do we define cure of diabetes? *Diabetes Care* 2009;**32**:2133–5. https://doi.org/10.2337/dc09-9036
16. British Obesity & Metabolic Surgery Society (BOMSS). *BOMSS Guidelines on Peri-operative and Postoperative Biochemical Monitoring and Micronutrient Replacement for Patients Undergoing Bariatric Surgery*. London: BOMSS; 2014. URL: www.bomss.org.uk/wp-content/uploads/2014/09/BOMSS-guidelines-Final-version1Oct14.pdf
17. Shojaee-Moradie F, Baynes KC, Pentecost C, Bell JD, Thomas EL, Jackson NC, *et al.* Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. *Diabetologia* 2007;**50**:404–13. https://doi.org/10.1007/s00125-006-0498-7
18. Steele R, Bishop JS, Dunn A, Altszuler N, Rathbeb I, Debodo RC. Inhibition by insulin of hepatic glucose production in the normal dog. *Am J Physiol* 1965;**208**:301–6. https://doi.org/10.1152/ajplegacy.1965.208.2.301
19. Bradley D, Magkos F, Klein S. Effects of bariatric surgery on glucose homeostasis and type 2 diabetes. *Gastroenterology* 2012;**143**:897–912. https://doi.org/10.1053/j.gastro.2012.07.114
20. Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, *et al.* Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. *Diabetes Care* 2007;**30**:1709–16. https://doi.org/10.2337/dc06-1549
21. Brolin RE, Kenler HA, Gorman JH, Cody RP. Long-limb gastric bypass in the superobese. A prospective randomized study. *Ann Surg* 1992;**215**:387–95. https://doi.org/10.1097/00000658-199204000-00014
22. Homan J, Boerboom A, Aarts E, Dogan K, van Laarhoven C, Janssen I, Berends F. A longer biliopancreatic limb in Roux-en-Y gastric bypass improves weight loss in the first years after surgery: results of a randomized controlled trial. *Obes Surg* 2018;**28**:3744–55. https://doi.org/10.1007/s11695-018-3421-7
23. Inabnet WB, Quinn T, Gagner M, Urban M, Pomp A. Laparoscopic Roux-en-Y gastric bypass in patients with BMI < 50: a prospective randomized trial comparing short and long limb lengths. *Obes Surg* 2005;**15**:51–7. https://doi.org/10.1381/0960892052993468
24. Nergaard BJ, Leifsson BG, Hedenbro J, Gislason H. Gastric bypass with long alimentary limb or long pancreato-biliary limb – long-term results on weight loss, resolution of co-morbidities and metabolic parameters. *Obes Surg* 2014;**24**:1595–602. https://doi.org/10.1007/s11695-014-1245-7
25. Pinheiro JS, Schiavon CA, Pereira PB, Correa JL, Noujaim P, Cohen R. Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. *Surg Obes Relat Dis* 2008;**4**:521–5. https://doi.org/10.1016/j.soard.2007.12.016
26. Kaska L, Kobiela J, Proczko M, Stefaniak T, Sledziński Z. Does the length of the biliary limb influence medium-term laboratory remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass in morbidly obese patients? *Wideochir Inne Tech Maloinwazyjne* 2014;**9**:31–9. https://doi.org/10.5114/wiitm.2014.40383
27. Patrício BG, Morais T, Guimarães M, Veedfald S, Hartmann B, Hilsted L, *et al.* Gut hormone release after gastric bypass depends on the length of the biliopancreatic limb. *Int J Obes* 2018;**43**:1009–18. https://doi.org/10.1038/s41366-018-0117-y
28. Larraufie P, Roberts GP, McGavigan AK, Kay RG, Li J, Leiter A, *et al.* Important role of the GLP-1 Axis for glucose homeostasis after bariatric surgery. *Cell Rep* 2019;**26**:1399–408.e6. https://doi.org/10.1016/j.celrep.2019.01.047

29. Patel RT, Shukla AP, Ahn SM, Moreira M, Rubino F. Surgical control of obesity and diabetes: the role of intestinal vs. gastric mechanisms in the regulation of body weight and glucose homeostasis. *Obesity* 2014;**22**:159–69. https://doi.org/10.1002/oby.20441

30. Klein S, Fabbrini E, Patterson BW, Polonsky KS, Schiavon CA, Correa JL, *et al.* Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes. *Obesity* 2012;**20**:1266–72. https://doi.org/10.1038/oby.2011.377

31. Cohen R, le Roux CW, Papamargaritis D, Salles JE, Petry T, Correa JL, *et al.* Role of proximal gut exclusion from food on glucose homeostasis in patients with type 2 diabetes. *Diabet Med* 2013;**30**:1482–6. https://doi.org/10.1111/dme.12268

32. Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, *et al.* Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* 2006;**55**:2025–31. https://doi.org/10.2337/db06-0068

33. Salinari S, Carr RD, Guidone C, Bertuzzi A, Cercone S, Riccioni ME, *et al.* Nutrient infusion bypassing duodenum-jejunum improves insulin sensitivity in glucose-tolerant and diabetic obese subjects. *Am J Physiol Endocrinol Metab* 2013;**305**:E59–66. https://doi.org/10.1152/ajpendo.00559.2012

34. Breen DM, Rasmussen BA, Kokorovic A, Wang R, Cheung GW, Lam TK. Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. *Nat Med* 2012;**18**:950–5. https://doi.org/10.1038/nm.2745

35. Salinari S, Debard C, Bertuzzi A, Durand C, Zimmet P, Vidal H, Mingrone G. Jejunal proteins secreted by db/db mice or insulin-resistant humans impair the insulin signaling and determine insulin resistance. *PLOS ONE* 2013;**8**:e56258. https://doi.org/10.1371/journal.pone.0056258

36. Rajagopalan H, Cherrington AD, Thompson CC, Kaplan LM, Rubino F, Mingrone G, *et al.* Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. *Diabetes Care* 2016;**39**:2254–61. https://doi.org/10.2337/dc16-0383

37. Rubino F, Amiel SA. Is the gut the 'sweet spot' for the treatment of diabetes? *Diabetes* 2014;**63**:2225–8. https://doi.org/10.2337/db14-0402

38. Baud G, Daoudi M, Hubert T, Raverdy V, Pigeyre M, Hervieux E, *et al.* Bile diversion in Roux-en-Y gastric bypass modulates sodium-dependent glucose intestinal uptake. *Cell Metab* 2016;**23**:547–53. https://doi.org/10.1016/j.cmet.2016.01.018

Appendix 1 The LONG LIMB trial surgical standard operating procedure

Detailed standard operating procedure for the standard and long limb Roux-en-Y gastric bypass operations.

Standard limb RYGB

1. The procedure is performed by a consultant surgeon using Covidien (Dublin, Ireland) instruments
2. The patient is placed on the operating table. General anaesthesia is administered
3. The patient's abdomen is prepped and draped in sterile fashion
4. The abdominal cavity is entered and the pneumoperitoneum is established to a pressure of 15 mmHg of carbon dioxide. The procedure is filmed
5. Laparoscopic bladeless 12-mm trocars are passed obliquely through the abdominal wall, including the left upper quadrant, left flank and umbilical midline
6. The omentum and the transverse colon are then reflected cephalad to expose the ligament of Treitz
7. From this position, the small intestine (jejunum) is measured with 5-cm marks (Steri-Strip™; 3M, Saint Paul, MN, USA) placed on graspers
8. The small bowel is divided 50 cm from the ligament of Treitz with an endostapler. This proximal segment of intestine defines the biliopancreatic limb
9. The distal segment of intestine is then further measured to 100 cm and this is the length of the Roux/ alimentary limb
10. A side-to-side enteroenterostomy is performed by stapling the biliopancreatic limb to the 100-cm mark on the alimentary limb, making parallel antimesenteric enterotomies and firing the endostapler into the lumen of each. The enterotomy is closed
11. All mesenteric defects will be closed
12. A completely isolated proximal gastric pouch 30–40 ml in volume is created using endostaplers. The actual length of the pouch may vary depending on the anatomical conditions seen at the time of surgery, but, in general terms, the horizontal transection of the pouch will be at the level of the second gastric vein, lesser curve side, below the fat pad
13. The previously measured alimentary/Roux limb is taken up to the gastric pouch (antecolic) with the 100-cm alimentary limb on the patient's right and a 50-cm biliopancreatic limb on the patient's left. The antecolic antegastric approach will be used unless during the surgery there is a clinical need to use the retrocolic approach
14. The alimentary limb is anastomosed with a circular or linear stapler to the gastric pouch and a leak test is performed with the Roux loop occluded
15. The pneumoperitoneum is allowed to escape
16. The trocars are withdrawn under laparoscopic vision, ensuring that there is no bleeding from the port site
17. The wound is irrigated with normal saline, infiltrated with 0.25% Marcaine® (Cook-Waite Laboratories, Inc., New York, NY, USA) and closed with staples

Long limb RYGB

1. The procedure is performed by a consultant surgeon using Covidien instruments
2. The patient is placed on the operating table. General anaesthesia is administered
3. The patient's abdomen is prepped and draped in sterile fashion
4. The abdominal cavity is entered and pneumoperitoneum is established to a pressure of 15 mmHg of carbon dioxide. The procedure is filmed
5. Laparoscopic bladeless 12-mm trocars are passed obliquely through the abdominal wall, including the left upper quadrant, left flank and umbilical midline

6.	The omentum and the transverse colon are then reflected cephalad to expose the ligament of Treitz
7.	From this position, the small intestine (jejunum) is measured with 5-cm marks (Steri-Strip) placed on graspers
8.	The small bowel is divided 150 cm from the ligament of Treitz with an endostapler. This proximal segment of intestine defines the biliopancreatic limb
9.	The distal segment of intestine is then further measured to 100 cm and this is the length of the Roux/ alimentary limb
10.	A side-to-side enteroenterostomy is performed by stapling the biliopancreatic limb to the 100-cm mark on the alimentary limb making parallel antimesenteric enterotomies and firing the endostapler into the lumen of each. The enterotomy is closed
11.	All mesenteric defects will be closed
12.	A completely isolated proximal gastric pouch 30–40 ml in volume is created using endostaplers. The actual length of the pouch may vary depending on the anatomical conditions seen at the time of surgery, but, in general terms, the horizontal transection of the pouch will be at the level of the second gastric vein, lesser curve side, below the fat pad
13.	The previously measured alimentary/Roux limb is taken up to the gastric pouch (antecolic) with the 100-cm alimentary limb on the patient's right and a 150-cm biliopancreatic limb on the patient's left. The antecolic antegastric approach will be used unless during the surgery there is a clinical need to use the retrocolic approach
14.	The alimentary limb is anastomosed with a circular or linear stapler to the gastric pouch and a leak test is performed with the Roux loop occluded
15.	The pneumoperitoneum is allowed to escape
16.	The trocars are withdrawn under laparoscopic vision, ensuring there is no bleeding from the port site
17.	The wound is irrigated with normal saline, infiltrated with 0.25% Marcaine and closed with staples

Appendix 2 The LONG LIMB trial statistical analysis plan

Statsconsultancy Ltd

Freelance Statistical Consultancy

[redacted]

Statistical Analysis Plan

TRIAL FULL TITLE	Comparison of the effects of the Long Limb to the Standard Limb gastric bypass on type 2 diabetes mellitus. The LONG LIMB trial.
SAP VERSION	1.3
SAP VERSION DATE	1st May 2019
TRIAL STATISTICIAN	Paul Bassett
SAP AUTHOR	Paul Bassett

Abbreviations and Definitions

AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BMI	Body Mass Index
BMR	Basic Metabolic Rate
LOCF	Last Observation Carried Forward
MCR	Metabolic Clearance rate of Glucose
MMTT	Mixed Meal Tolerance Test
NICE	National Institute for Health and Care Excellence
NMDS	Non-metric MultiDimensional Scaling
PANAS	Positive and Negative Affect Schedule
PERMANOVA	PERmutational Multivariate ANalysis Of Variance
Ra	Rate of glucose appearance
Rd	Rate of glucose disposal
RYGB	Roux-en-Y Gastric Bypass
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T2DM	Type II Diabetes Mellitus
VAS	Visual Analogue Scale
WHO	World Health Organization

Introduction

The most effective and durable treatment for both obesity and type 2 diabetes mellitus (T2DM) remains bariatric surgery. Alternative surgical techniques have been sought to improve the rates of T2DM remission. Standard Limb RYGB and biliopancreatic diversion (BPD) has been showed to lead to a matched total body weight loss of 33% at 2 years post-operatively. Unfortunately, the BPD procedure has the distinct disadvantage of a substantially higher risk of developing severe nutritional complications, and this has limited its use.

To improve the glucose-lowering efficacy of Standard Limb RYGB, whilst avoiding the high risk of complications with the BPD procedure, the Long Limb RYGB has been devised as a hybrid operation that combines the standard design of Standard Limb RYGB, but with a longer biliopancreatic limb. Previous research has suggested that the rates of any complications, including nutritional, were not higher than those reported after Standard Limb RYGB.

The main anatomical difference between Long Limb RYGB and Standard Limb RYGB is that the segment of the bypassed proximal intestine, the biliopancreatic limb, is longer (150 vs. 50cm respectively). This means that in the Long Limb RYGB the common channel is shorter, and as a result nutrients reach the distal small bowel faster and in a less-digested state. The hypothesis is that the Long Limb RYGB is better for treatment of T2DM because:

a) It increases post-prandial secretion of gut hormones, and in particular glucagon-like peptide-1 (GLP-1) which results in the immediate post-prandial insulin secretion significantly higher than the Standard Limb RYGB.
b) It increases insulin sensitivity significantly more than the Standard Limb RYGB, before and after weight loss has taken place.

The trial will evaluate the efficacy on T2DM of the Long Limb RYGB compared to the Standard Limb RYGB, and investigate the mechanisms underlying any potential differences by conducting:

1. Mechanistic assessments with Mixed Meal Tolerance Test (MMTT) and Hyperinsulinaemic Euglycaemic Clamp at: pre-operative, early mechanistic post-operative (at 1-2 weeks after the surgery) and late mechanistic post-operative visits (at 20% total body weight loss after the surgery).
2. Clinical assessment pre-operatively, at the day of surgery and at 3, 6 and 12 months post-operatively.

Study Methods

General Study Design and Plan

The study is a prospective double-blinded randomised controlled parallel group clinical trial. Patients were recruited from the Imperial Weight Centre and the King's College Obesity Clinic and randomised to either the Long Limb or the Standard Limb RYGB surgery.

Inclusion-Exclusion Criteria

Inclusion Criteria

The participants must have met ALL of the following criteria to be considered eligible for the study:

- Male or female participants
- Aged between 18-70 years
- Diagnosed with T2DM according to WHO 2006 and 2011 criteria
- HbA1c ≥7.0% (≥53.0 mmol/mol) on screening
- Body mass index (BMI) ≥ 30 kg/m^2 and eligible for bariatric surgery based on NICE guidance
- On glucose-lowering medications
- Willing to comply with study requirements and able to give informed consent

Exclusion Criteria

Participants were not allowed to enter the study if ANY of the following applied:

- History of any medical, psychological or other condition, or use of any medications, including over-the-counter products, which, in the opinion of the investigators, would either interfere with the study or potentially cause harm to the volunteer.
- Without access at home to a telephone or other factor likely to interfere with ability to participate reliably in the study.
- Specific contraindications to bariatric surgery
- Previous bariatric surgery
- Diagnosed with Type 1 diabetes mellitus
- Donated blood during the preceding 3 months or intention to do so before the end of the study Current pregnancy or breastfeeding
- Inability to maintain adequate contraception

Randomisation and Blinding

Participants were randomised to Long Limb or Standard Limb RYGB surgery in a 1:1 ratio. All patients were randomised in a single stratum.

Study Variables

Summary of study data and timing of measurements

The study measured patients at the following timepoints:

- Screening
- Pre-operative mechanistic visit
- Day of the operation
- Early mechanistic post-operative visit – 1-2 weeks after operation
- Late mechanistic post-operative visit – at 20% total body weight loss of the pre-operative value
- 3 months post-operatively
- 6 months post-operatively
- 12 months post-operatively

Table 1 outlines the key study measurements, and the timing of these measurements.

Table 1. Summary of study measurements

	Screening visit	Pre-op visit	Operation	Early mechanistic post-op visit	Late mechanistic post-op visit	3, 6 months post-op	12 months post-op
Demographics, duration of T2DM	x						
Weight/weight loss, BMI			x			x	x
HbA1c			x			x	x
Other blood tests			x				x
BP/heart rate	x	x		x	x		x
Body composition and measurements, BMR	x	x		x	x		x
Comorbidities and King's Score	x						x
Medications			x			x	x
Food diary		x		x	x		
Rates of T2DM remission							x
Bowel movements							x
GLP-1, GIP, PYY, bile acids, FGFs		x		x	x		
Fasting Plasma Glucose		x	x	x	x		x
Postprandial plasma glucose		x		x	x		
Markers of insulin secretion		x		x	x		
Ra, Rd, MCR from Clamp		x		x	x		
VAS		x		x	x		
Microbiota, metabolomics		x		x	x		
Faecal calories		x					x
Adverse events							x

Sample Size

The sample size was based on the primary outcome, GLP-1 concentration after the Mixed Meal Tolerance Test.

The study was powered to detect a difference in peak of active GLP-1 of 10.0 pmol/L, equating to the previously estimated change in GLP-1 post-surgery in the Standard Limb RYGB group. The standard deviation of the change in outcome values was estimated to be 10.8 pmol/L within each group. It is calculated that, with a 5% significance level and 90% power, a sample size of 20 patients in each arm was required. Based on experience, it was estimated that up to 20% of patients will drop-out of the study. To allow for this, 25 patients in each arm of the trial were planned, 50 patients in total.

Study Objectives and Endpoints

Study Objectives

The study will assess the following research questions:

The primary objective is to compare Long Limb and Standard Limb RYGB in terms of the change in peak of active GLP-1 concentration after the mixed meal tolerance test 1-2 weeks after the surgery.

The secondary objectives are to compare Long Limb and Standard Limb RYGB in terms of a number of other efficacy outcomes, and also to compare surgical methods in terms of their safety.

Demographic and Baseline measurements

The following demographic and baseline characteristics of the study participants will be collected:

- Age
- Gender
- Ethnicity
- Duration of T2DM
- Height

Endpoints

Primary outcome measure

The primary study endpoint is:

- Peak of active GLP-1 concentration after the mixed meal tolerance test 1-2 weeks after the surgery.

Secondary outcome measures

The secondary endpoints are measured at several different timepoints.

Endpoints from mixed meal test at late mechanistic post-operative visit:

- Peak of active GLP-1 concentration

Endpoints from both early and late mechanistic post-operative visits:

a) From the Hyperinsulinaemic Euglycaemic Clamp
   - Rate of glucose appearance (Ra) and disposal (Rd) and metabolic clearance rate of glucose (MCR) - basal, low and high

b) From the MMTT:
   - Active GLP-1 concentration (AUC)
   - Total GLP-1 (peak, AUC)
   - PYY (peak, AUC)
   - GIP (peak, AUC)
   - Markers of insulin secretion (peak, AUC)
   - Plasma glucose (peak, AUC)
   - Bile acids (peak, AUC)
   - FGF-19 and 21 (peak, AUC)
   - Systolic and diastolic blood pressure (AUC)
   - Heart rate (AUC)
   - Appetite ratings (Visual Analogue Scales; AUC)

c) Blood, urine and faecal microbial diversity and metabolomics
d) Total caloric intake and macronutrient composition - % fat, % protein, % carbohydrates
e) Body composition and Basic Metabolic Rate (BMR)

Endpoints at the day of surgery:

- Common channel length
- Total small bowel length
- Proportion of common channel to total small bowel length
- Operating time
- Length of in hospital stay

Endpoints at 3, 6 and 12 months:

- HbA1c
- % of total body weight loss
- Number of glucose lowering medications

Secondary endpoints at 12 months:

- % of total body weight loss
- BMI
- Body composition
- Basic Metabolic Rate (BMR)
- Waist, hips and neck measurements
- T2DM remission
- Comorbidities
- Medications
- King's Obesity Staging Score
- Systolic and diastolic blood pressure

- Heart rate
- Oxygen saturation
- Bowel movements frequency
- Blood tests: fasting plasma lipids concentration, fasting plasma glucose, haematinics, vitamins
- Total caloric intake
- Macronutrient composition - % fat, % protein, % carbohydrates
- Faecal caloric content

Safety outcomes

Safety will be assessed by the recording of adverse events (AEs) and serious adverse events (SAEs) reported during the operation for up to one-year following surgery. This will include medical, surgical, nutritional and psychological complications adverse events.

An SAE will be defined as an adverse event that meets any of the follow criteria:

- Leading to death
- Life-threatening
- Leads to hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect.

Derived values

Peak

For each outcome, the peak will be defined as the maximum post-meal concentration (i.e. from time 15 onwards) per patient, regardless of at which timepoint the peak concentration was achieved.

Area Under the curve (AUC)

A number of outcomes from the mixed-meal tests will be summarised by the Area under the curve values. The AUC will be calculated using the trapezium rule.

For outcomes with measurements at time -30, the first value used in the calculation will be the mean of the -30 and 0 timepoints. When there is no -30 value, the time 0 value will be used as the first measurement in the calculation.

Absolute changes from baseline

Absolute changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the outcome timepoint.

Percentage changes from baseline

Percentage changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the outcome timepoint, dividing this sum by the baseline value and multiplying by 100.

General Considerations

Timing of Analyses

A single analysis will take place at the completion of the study, after all data is collected. No interim analyses will be performed.

Analysis Populations

Full Analysis Population

The Full Analysis Population will consist of patients in the groups to which they were randomised, regardless of deviation from the protocol or whether they received the allocated surgery. Patients with completely missing data at the outcome timepoint will be excluded from this dataset for the particular outcome for which they had missing data.

Per Protocol Population

The Per Protocol patient population will consist of those patients who received the surgery that they were randomised to. Patients receiving surgery different to their allocation will be excluded from this population. Analyses will only be performed using this population if it differs from the Full Analysis Population.

Safety Population

The safety population will consist of all patients recruited into the study who participate for at least one week of the study. This dataset will analyse patients in the groups to which they were randomised, regardless of deviation from the protocol or whether they received the allocated surgery.

Subgroups

All patients will be analysed together, with no subgroup analyses performed.

Missing Data

At any timepoint, if there is no data at all for a given outcome, patients with missing data will be excluded from the analysis, and only observed data will be analysed. Missing data will be assumed to

be Missing At Random. No imputation procedures will be employed to deal with missing data if it is completely missing at a given timepoint.

During the MTTT, data is collected serially over a short time period. For patients with some data collected, but missing information from the final serial measurements, a Last Observation Carried Forward (LOCF) approach will be used to impute missing data.

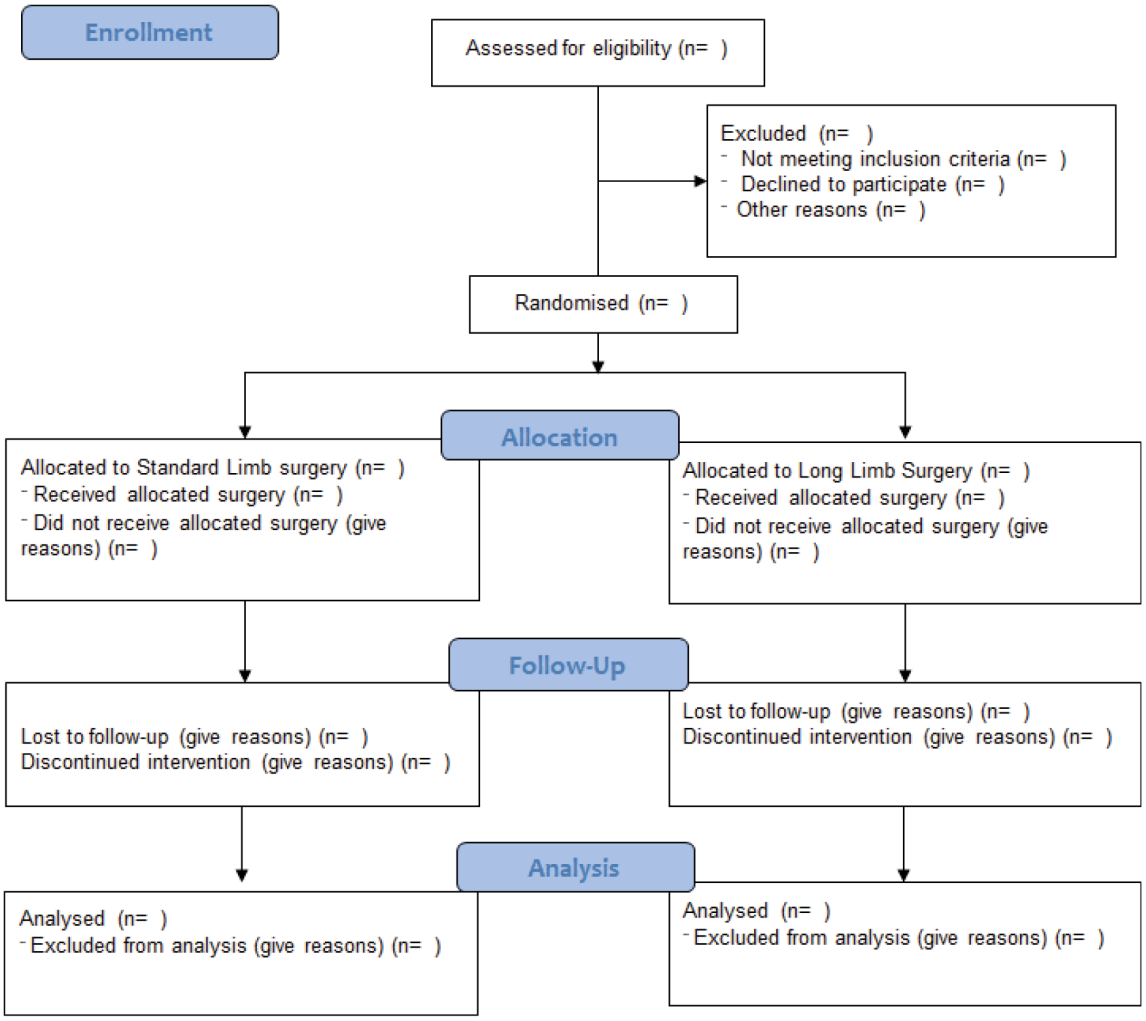
Summary of Study Data

Subject Disposition

A summary of the number of subjects that reached the various stages of the study will be summarised. Reasons for non-participation and withdrawal will be summarised.

A CONSORT diagram will be produced, such as Figure 1, which will illustrate the flow of patients throughout the study.

Figure 1. Outline CONSORT diagram



Descriptive Analysis Methods

Continuous variables will be summarised using the number of (non-missing) datapoints, mean and standard deviation if found to follow a normal distribution. Continuous variables not found to be normally distributed will be summarised by the number of datapoints, median and inter-quartile range. Categorical variables will be summarised by the frequency and percentage (based on the non-missing sample size) of values in each category.

Demographic and Baseline Variables

Baseline values for each parameter are defined as the last value measured before the intervention, i.e. surgery. A summary of patient demographics and baseline measurements are outline in Section 5.4.2.

Descriptive statistics will be produced for these variables for each of the two study arms separately.

The summary statistics will be produced in accordance with section 8.2. No hypothesis tests will be performed to compare the two groups at baseline.

Efficacy Analyses

Primary Efficacy Analysis

The primary endpoint of the study is the peak of active GLP-1 concentration at the early mechanistic post-op visit.

The analysis will be performed using Analysis of Covariance (ANCOVA). In the analysis, the peak of active GLP-1 concentration at the early mechanistic post-operative visit will be considered as the outcome measure, whilst baseline peak of active GLP-1 will be included as a covariate.

If the data does not meet the assumptions of the ANCOVA analysis (e.g. normally distributed residuals, homogeneity of variance), a data transformation of the outcome variable (e.g. log transformation) before analysis will be utilised to ensure that the assumptions are met.

The summary statistics for the outcome variable will be produced in accordance with section 8.2. The baseline adjusted difference in outcome values between groups will be reported, along with a corresponding 95% confidence interval.

The primary study analysis will be performed using the Full Analysis Population (see section 7.2.1).

Secondary Efficacy Analysis

Secondary outcomes measured on a continuous scale, with a baseline measurement, will be analysed using a similar approach to that outline for the primary efficacy outcome. The data from each post-operative timepoint will be analysed in a separate analysis.

For continuous secondary outcomes where there no baseline measurement, the two groups will be compared using the unpaired t-test. Alternatively, the Mann-Whitney test will be used if the assumptions of the t-test are not met.

For the continuous outcomes, the exceptions to the previously described methods are for the blood, urine and faecal microbial diversity and metabolomics outcomes. These will be analysed using non-metric multidimensional scaling (NMDS) plots. Additionally, PERMANOVA p-values will be generated using the UniFrac weighted distance matrix generated from Mothur. Family-level extended error bar plots will be generated, White's non-parametric t-test with Benjamini-Hochberg FDR will be utilised.

Binary and nominal outcomes (e.g. achieving diabetes remission) will be compared between the two study groups using either the Chi-square test, or Fisher's exact test if the number of responses in some categories is low.

Ordinal outcomes will be analysed using the Mann-Whitney test to allow for the natural ordering of the response categories.

The secondary efficacy analyses will be performed using the Full Analysis Population.

Sensitivity Efficacy Analysis

If the Per Protocol Population differs in its membership from the Full Analysis Population, the primary outcome will be additionally analysed using this population. The analysis methods will be equivalent to those described in Section 9.1.

If there is no difference between the Per Protocol Population and Full Analysis Population, no sensitivity analyses will be performed.

Other Analyses

An additional set of analyses will examine the association between the key primary and secondary efficacy outcomes measured on a continuous scale and the proportion of the common channel length to the total small bowel length. The analysis will be performed using Pearson correlation. Alternatively, Spearman's rank correlation will be used if the Pearson correlation assumptions (e.g. non-linear relationship, both variables non-normally distributed) are not met. For each outcome, a single analysis will be performed for all patients, combining the two study arms together.

Safety Analyses

The main safety outcome is the occurrence of adverse events (AEs). For each of the study groups, the number of adverse events in each group and per patient will be summarised. Specific details of the adverse events will be recorded in addition to the number of AEs that are serious and non-serious.

If it is deemed that there are sufficient occurrences of adverse events in total, a formal test of significance will be performed to compare AE occurrence at the patient level between study arms. Fisher's exact test will be used for this analysis. However, it is acknowledged that the study is unlikely to be powered to show a difference between groups for this endpoint.

Technical Details

The data analysis will be primary performed using the statistical software packages Stata (version 15.1), SPSS (version 20 or later), GraphPad PRISM (version 6 or later). Programs recording details of all data manipulation and data analyses will be produced and kept, so that the analyses can be externally inspected and, if necessary, re-run.

The exception is for the analysis of the blood, urine and faecal microbial diversity and metabolomics outcomes, which will be analysed using the Vegan library within the R statistical package and the Statistical Analysis of Metagenomic Profiles software package.

Summary of Changes to the Analysis Plan

Changes from Version 1.0 to 1.1

The following changes were made between the SAP versions:

- Reformatting of the order the sections
- Omission of demographic summaries for both study groups combined
- Addition of further secondary outcomes
- Details of LOCF approach to be used for MMTT data

Changes from Version 1.1 to 1.2

The following changes were made between the SAP versions:

- Change of approach for secondary outcomes from the MMTT to consider all measurements in the analysis, and not summary measures (peak, AUC).
- Change of statistical methods for secondary analysis of MMTT outcomes to reflect the change of approach for these outcomes

Changes from Version 1.2 to 1.3

The following changes were made between the SAP versions:

- Change of approach for secondary outcomes from the MMTT to consider analysing as summary measures (peak, AUC) rather than using all individual measurements in the outcomes.
- Change of statistical methods for secondary analysis of MMTT outcomes to reflect the change of approach for these outcomes

Further changes to the SAP

If there are further revisions to the original proposed analyses, or if any supplementary analyses are planned, these will be documented in a future version of the SAP. The reason for any changes/additions will be documented.

Appendix 3 The LONG LIMB trial supplementary data

Characteristic	Time point			
	Baseline		1 year postoperatively	
	Long limb RYGB ($n = 26$)	Standard limb RYGB ($n = 27$)	Long limb RYGB ($n = 26$)	Standard limb RYGB ($n = 27$)
Number of glucose-lowering medications at baseline (classes)				
1	11% (3)	4% (1)	0	0
2	27% (7)	44% (12)	0	0
3	35% (9)	26% (7)	1	0
4	27% (7)	19% (5)	0	0
5	0% (0)	7% (2)	0	0
Classes of medications				
Biguanides	92% (24)	93% (25)	1	0
SGLT-2 inhibitors	54% (14)	56% (15)	1	0
Sulfonylurea	50% (13)	48% (13)	0	0
GLP-1 agonists	35% (9)	15% (4)	1	0
DPP-4 inhibitors	31% (8)	52% (14)	0	0
Insulin	15% (4)	15% (4)	0	0
Total	72	75		

DPP-4, dipeptidyl peptidase 4; SGLT-2, sodium–glucose transport protein 2.
Note
Categorical data presented as a percentage (*n*).

EME
HS&DR
HTA
PGfAR
PHR

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