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

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Scientific summary

The LONG LIMB RCT

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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.

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