Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

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Summary

Background No data from randomised controlled trials of metabolic surgery for diabetes are available beyond 5 years of follow-up. We aimed to assess 10-year follow-up after surgery compared with medical therapy for the treatment of type 2 diabetes.

Methods We did a 10-year follow-up study of an open-label, single-centre (tertiary hospital in Rome, Italy), randomised controlled trial, in which patients with type 2 diabetes (baseline duration >5 years; glycated haemoglobin [HbA_{1c}] >7·0%, and body-mass index ≥35 kg/m²) were randomly assigned (1:1:1) to medical therapy, Roux-en-Y gastric bypass (RYGB), or biliopancreatic diversion (BPD) by a computerised system. The primary endpoint of the study was diabetes remission at 2 years (HbA_{1c} <6·5% and fasting glycaemia <5·55 mmol/L without ongoing medication for at least 1 year). In the 10-year analysis, durability of diabetes remission was analysed by intention to treat (ITT). This study is registered with ClinicalTrials.gov, NCT00888836.

Findings Between April 30, 2009, and Oct 31, 2011, of 72 patients assessed for eligibility, 60 were included. The 10-year follow-up rate was 95·0% (57 of 60). Of all patients who were surgically treated, 15 (37·5%) maintained diabetes remission throughout the 10-year period. Specifically, 10-year remission rates in the ITT population were 5·5% for medical therapy (95% CI 1·0–25·7; one participant went into remission after crossover to surgery), 50·0% for BPD (29·9–70·1), and 25·0% for RYGB (11·2–46·9; p=0·0082). 20 (58·8%) of 34 participants who were observed to be in remission at 2 years had a relapse of hyperglycaemia during the follow-up period (BPD 52·6% [95% CI 31·7–72·7]; RYGB 66·7% [41·7–84·8]). All individuals with relapse, however, maintained adequate glycaemic control at 10 years (mean HbA_{1c} 6·7% [SD 0·2]). Participants in the RYGB and BPD groups had fewer diabetes-related complications than those in the medical therapy group (relative risk 0·07 [95% CI 0·01–0·48] for both comparisons). Serious adverse events occurred more frequently among participants in the BPD group (odds ratio [OR] for BPD *vs* medical therapy 2·7 [95% CI 1·3–5·6]; OR for RYGB *vs* medical therapy 0·7 [0·3–1·9]).

Interpretation Metabolic surgery is more effective than conventional medical therapy in the long-term control of type 2 diabetes. Clinicians and policy makers should ensure that metabolic surgery is appropriately considered in the management of patients with obesity and type 2 diabetes.

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Introduction

A large body of evidence accumulated over the past two decades has led to the repurposing of bariatric surgery as a treatment for type 2 diabetes, a practice referred to as metabolic surgery.[1,2] Several randomised controlled trials[2–7] comparing surgery and conventional medical therapy specifically for the treatment of type 2 diabetes show that metabolic surgery results in major short-term to mid-term improvements in hyperglycaemia, prolonged disease remission, reduced cardiometabolic risk, reduced hypertension,[8] and lower incidence of chronic kidney disease.[9]

The ability of metabolic surgery to induce prolonged remission of diabetes, defined as non-diabetic glycaemia without the need for ongoing pharmacological treatment,[10] makes surgery a potentially curative approach to type 2 diabetes.[11] In 2009, a consensus statement by the American Diabetes Association operationally defined cure of type 2 diabetes as the maintenance of stable remission of hyperglycaemia for at least 5 years.[10]

Although observational studies of traditional bariatric surgery suggest that diabetes remission can persist long term,[12,13] it is difficult to extrapolate these findings to the broader population of patients with type 2 diabetes. Patients seeking traditional bariatric surgery are typically younger, and have a shorter duration of diabetes and lower prevalence of insulin dependency and cardiovascular disease at baseline when compared with patients who seek metabolic surgery specifically to treat type 2 diabetes.[14] Since duration of diabetes and insulin use are

Research in context

Evidence before this study

We searched MEDLINE from Jan 1, 2000, to Nov 30, 2020, for randomised clinical trials, case-control studies, and observational series reporting on diabetes remission or comparisons of medical and surgical treatment for type 2 diabetes. Keywords included "bariatric surgery", "metabolic surgery", "type 2 diabetes", "remission", and "very-low-calorie diet". Observational studies of traditional bariatric surgery suggest that surgically induced remission of type 2 diabetes can persist long term. However, such studies might overestimate durability of disease remission and other benefits of surgery in type 2 diabetes given that the vast majority of patients seeking bariatric surgery are typically younger and have early or milder disease than the broader population of people with type 2 diabetes. To our knowledge, there are no data from randomised controlled trials specifically comparing metabolic surgery and conventional diabetes therapy in patients with advanced type 2 diabetes, beyond 5 years of follow-up.

Added value of this study

Here, we report for the first time to our knowledge, the 10-year outcomes of a randomised controlled trial comparing surgery with medical therapy plus lifestyle interventions for type 2 diabetes. Surgery induced continued 10-year remission of diabetes—defined as non-diabetic glycaemia (glycated haemoglobin <6·5%) without the need for ongoing pharmacological treatment—in 37% of patients with advanced type 2 diabetes at baseline. Compared with medical therapy, surgery was associated with greater weight loss, reduced medication use, lower cardiovascular risk, better quality of life, and a lower incidence of diabetes-related complications.

Implications of all the available evidence

These data show that type 2 diabetes is a potentially curable disease. Metabolic surgery is more effective than medical therapy in the long-term control of advanced type 2 diabetes. Clinicians and policy makers should ensure that metabolic surgery is appropriately considered in the management of patients with obesity and type 2 diabetes.

inversely associated with diabetes remission and positively associated with diabetes relapse,[15–17] observational studies of traditional bariatric surgery might overestimate durability of diabetes remission and other benefits of surgery in patients with type 2 diabetes.

To date, there are no data beyond 5 years from randomised controlled trials specifically designed to investigate the efficacy of metabolic surgery for type 2 diabetes.[3–5] We aimed to report the 10-year outcomes of our randomised controlled trial to compare metabolic surgery by Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) with medical therapy plus lifestyle interventions for the treatment of advanced type 2 diabetes. The 2-year[3] and 5-year[18] outcomes of the study were previously reported and we continued to follow up patients for evaluation of durability of diabetes remission and secondary endpoints.

Methods

Study design and participants

Briefly, we did a 10-year follow-up of a three-group, open-label, single-centre (tertiary hospital in Rome, Italy), randomised controlled trial comparing metabolic surgery, by either RYGB or BPD, with conventional medical therapy plus lifestyle interventions for type 2 diabetes. Participants were included if they were aged 30–60 years, had a body-mass index (BMI) of 35 kg/m² or greater, a history of type 2 diabetes lasting at least 5 years, and a glycated haemoglobin (HbA_{1c}) concentration of 7·0% or more (for HbA_{1c} SI units see appendix p 7). Exclusion criteria were a history of type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, pregnancy, other medical conditions requiring short-term hospital admission, severe diabetes complications, other severe medical conditions, and geographical inaccessibility.

See Online for appendix

All participants provided written informed consent. The study was approved by the Ethical Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Rome, Italy). Study design, methods, and analysis of the primary endpoint and 5-year outcomes have been previously reported.[3,18]

Randomisation and masking

This study was open label. Participants were randomly assigned (1:1:1) to medical therapy, RYGB, or BPD by a computerised system. Masking of treatment allocation was not possible due to the nature of the intervention.

Procedures

RYGB and BPD were done according to standard surgical techniques (details previously reported).[18] In brief, RYGB was done laparoscopically in all patients whereas BPD was through an open-surgery approach using the Scopinaro procedure. Of note, the Scopinaro procedure involves a horizontal gastrectomy rather than a sleeve gastrectomy as in the BPD-duodenal switch variant. Thus, the BPD used in this study leaves behind a larger gastric remnant and has a lesser effect on restriction of calorie intake than the duodenal switch variant.

For medical and lifestyle treatment, patients were assessed and managed by a multidisciplinary team of

diabetologists, dietitians, and nurses. Participants in the study had scheduled visits at baseline and at 1, 3, 6, 9, and 12 months, every 6 months until 60 months, and every year thereafter. Diet and lifestyle modifications and pharmacological treatment were optimised on an individual basis with the aim of weight loss and a target of glycaemic control of HbA_{1c} less than 7·0% in all groups. Programmes for diet and lifestyle modifications were designed and administered by experienced diabetologists and dietitians (all with more than 15 years of clinical practice) and patients were advised to reduce overall energy and fat intake (<30% total fat, <10% saturated fat, and high fibre content) and increase physical exercise (≥30 min of brisk walking every day, possibly associated with moderate-intensity aerobic activity twice a week).

Medical therapy options were updated throughout the 10-year period to reflect the most current standards of care.[19] Drugs used in this trial included various oral antihyperglycaemic agents, insulin, GLP-1 analogues, and SGLT2 inhibitors (appendix pp 4–5).

After completion of the 2-year analysis for the primary endpoint,[18] patients with poorly controlled diabetes who requested surgical treatment were allowed to cross over to the surgery group.

Outcomes

The primary outcome of this follow-up study was durability of diabetes remission at 10 years among patients undergoing surgery (either RYGB or BPD), as compared with medical therapy and lifestyle interventions assessed in the intention-to-treat and per-protocol populations. Remission of diabetes was defined as the combination of fasting plasma glucose less than 100 mg/dL (5·6 mmol/L) and HbA_{1c} less than 6·5% without ongoing pharmacological therapy for at least 1 year, consistent with established criteria.[10]

The secondary outcomes of the 10-year analysis comprised relapse of hyperglycaemia, overall glycaemic control, achievement of target glycaemia of HbA_{1c} less than 7·0% with or without medications, changes in bodyweight, BMI, waist circumference, insulin resistance, arterial blood pressure, plasma total cholesterol, HDL cholesterol and triglycerides, coronary heart disease risk score, glomerular filtration rate (GFR), medication use, quality of life (QOL), major surgical complications (30-day and long term), nutritional and metabolic adverse events, and diabetes-related complications. QOL was measured with the RAND 36-Item Health Survey.[20] GFR[21] and coronary heart disease score[22] were computed using validated models. 10-year predicted probability for coronary heart disease was computed at baseline and at each of the scheduled visits during the follow-up using a validated model.[22] This score system includes the following criteria: gender, age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, and presence or absence of diabetes.

Insulin resistance was measured with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).[23] Methods of laboratory tests are described in the appendix (pp 1–2).

Participants underwent screening for diabetes-related complications. They had a fundus examination every year, followed, where necessary, by intravenous fluorescein angiography. Neuropathy screening included determination of the foot deformity score for both feet,[24] passive range of motion measurements (eg, hallux, ankle), tests of vibration and superficial pain sensation once a year, integrated, when necessary, by nerve conduction measurements. Possible diabetes foot complications were also assessed by a diabetes nurse specialist or endocrinologist and patients were then referred to our podiatry clinic for further specialised consultation if necessary. Screening for possible renal complications of diabetes was done by yearly assessment of the albumin to creatinine ratio and plasma creatinine and blood urea nitrogen. Screening for cardiovascular complications included routine electrocardiogram and echocardiogram once a year, and carotid or peripheral arterial ultrasonography if clinically indicated. For the assessment of surgical safety, we recorded all (30-day and late [beyond 30 days]) major adverse events, defined as complications requiring prolonged hospital stay, re-admission, or unplanned care.[25] Patients' reported frequency of bowel movements and other gastrointestinal symptoms (ie, abdominal pain and gastro-oesophageal reflux disease, among others) were recorded. Recurrent or chronic gastrointestinal symptoms (ie, diarrhoea and abdominal pain) were included in major surgical adverse events.

Statistical analysis

The study was powered to detect an absolute difference of 65 percentage points in the rate of diabetes remission between RYGB and the medical therapy group (assuming a remission rate of 15% for medical therapy and of 80% for RYGB) and a difference of 75 percentage points in the rate of remission between BPD and the medical therapy group (on the basis of a remission rate of up to 90% for BPD), with a statistical power of 90% at a two-sided p value of 0·025. Because the study was not powered to assess differences among treatments for all the analysed variables, results that were not related to the primary outcome should be considered as merely indicative. On the basis of the above assumptions, 15 patients would be needed for the medical therapy group, 15 for the RYGB group, and 11 for the BPD group. Assuming an attrition rate of 25% over the course of the study, we calculated a sample size of 60 patients (20 per study group) for this study.

Data collection was at baseline and after 1, 3, 6, 9, 12, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 108, and 120 months. A long format database was used. For each patient, 18 records were allocated and missing data were coded

with Not a Number in JavaScript. The database structure was designed by two independent statisticians in collaboration with the principal investigator and in accordance with the study protocol. Data were doubly entered into csv files by two physicians trained for the purpose and independently of each other. All data were checked for discrepancies. In cases in which data discrepancies occurred, they were resolved with recourse to the original sources. After data were entered in the database, patients were anonymised and associated with a unique identification number. Lists of the correspondences between database identification codes and patient identities were securely stored and managed only by authorised investigators, according to general data protection regulation compliant standard operating procedures. Data were analysed by two independent statisticians (SP and ADG), who designed the database. Reliability of values were checked by means of their relative acceptability ranges. Queries, when necessary, were made to the investigators using the patient's identification code.

Changes at 10 years from baseline are expressed both as absolute values and as absolute changes of basal values. Outcome variables were analysed using ANOVA with the baseline value as a covariate. Differences between treatments were reported together with 95% CIs. Fisher's exact test was used to study the association between the type of surgical procedure and diabetes remission and between surgical procedure and all the considered categorical variables (presence or absence of severe adverse events, presence or absence of diabetes complications). Because the treatment effect of metabolic surgery on diabetes is so large, there was no allowance for the effect of the operating surgeon.

Logistic regression with stepwise elimination was used to identify predictors of diabetes remission. Each predictor was initially tested with univariate logistic regression. Only predictors individually associated with remission (p=0·10) were entered into the multivariate model. We identified predictors of diabetes remission with *t* tests or Mann-Whitney *U* tests when appropriate to check for possible differences between remission and non-remission. Variables tested as possible predictors were all those recorded at baseline.

A survival analysis, with the Kaplan-Meier method, was used to estimate the diabetes-free survival time curves. Observed cumulative risk of relapse was fitted by a Hill function and the time at which 95% of maximal cumulative risk occured was computed by the estimated parameters. Continuous variables are reported as mean and SD, whereas categorical variables are reported as numbers and percentages. 95% CIs for binomial proportions are also reported and computed with the Wilson method. For the subgroup of patients who had a relapse, a paired *t* test was used to evaluate the possible improvements in diabetes and metabolic control at 10 years compared with baseline. All p values for secondary outcomes, including QOL, had an exploratory scope and should be considered as purely indicative of a possible difference among treatments. All tests were done at a nominal α error of 0·05 and no correction for multiple comparisons was done.

The primary analysis for the 10-year follow-up was per protocol; we also present results of the intention-to-treat analysis for the primary endpoint. All analyses were done with the statistical package R, version 3.6.1. This study is registered with ClinicalTrials.gov, NCT00888836.

	Medical therapy group (n=20)	BPD group (n=20)	RYGB group (n=20)
Age, years	43·5 (7·3)	43·6 (8·2)	43·9 (7·6)
Gender			
Men	10 (50·0%)	10 (50·0%)	8 (40·0%)
Women	10 (50·0%)	10 (50·0%)	12 (60·0%)
Weight, kg	137·0 (120·5–144·25)	128·0 (118·0–154·0)	128·7 (117·3–144·1)
Body-mass index, kg/m²	44·6 (41·6–48·8)	44·4 (39·2–50·6)	44·2 (41·2–47·8)
Waist circumference, cm	127 (119·0–136·25)	139·5 (117·5–145·5)	129·0 (114·3–133·0)
Diabetes duration, years	6·0 (5·0–7·0)	5·5 (5·0–7·0)	6·0 (5·0–7·0)
Fasting glucose, mmol/L	9·9 (3·4)	9·7 (3·4)	9·5 (3·3)
Glycated haemoglobin, %	8·5 (1·2)	8·9 (1·7)	8·6 (1·4)
HOMA-IR	11·0 (10·1)	7·7 (4·4)	9·7 (5·7)
Total cholesterol, mmol/L	6·1 (1·6)	5·5 (1·5)	4·6 (1·0)
HDL cholesterol, mmol/L	1·0 (0·2)	1·0 (0·2)	1·1 (0·2)
LDL cholesterol, mmol/L	4·0 (1·4)	3·5 (1·3)	2·8 (0·9)
Triglycerides, mmol/L	2·5 (0·8)	2·2 (0·9)	1·7 (0·9)
Diastolic blood pressure, mm Hg	96·0 (17·5)	95·9 (12·9)	91·5 (14·2)
Systolic blood pressure, mm Hg	155·2 (34·2)	154·5 (29·7)	145·8 (20·5)
Risk of coronary heart disease	0·2 (0·1)	0·2 (0·1)	0·1 (0·1)
Glomerular filtration rate, mL/min per 1·73 m²	82·9 (12·3)	90·6 (25·1)	85·3 (24·2)
Total number of diabetes medications	2·6 (0·5)	2·4 (0·6)	2·2 (0·7)
Insulin use	11 (55·0%)	10 (50·0%)	9 (45·0%)

Data are mean (SD), n (%), or median (IQR). BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass. HOMA-IR=Homeostatic Model Assessment of Insulin Resistance.

Table 1: **Baseline characteristics**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and GM and FR had final responsibility for the decision to submit for publication.

Results

Between April 30, 2009, and Oct 31, 2011, of 72 patients assessed for eligibility, 60 were randomly assigned to the conventional medical therapy (n=20), RYGB (n=20), or BPD (n=20) groups. Demographic data at baseline are reported in table 1.

In the medical therapy group, two patients were lost to follow up shortly after random assignment, one patient

died of myocardial infarction, and two crossed over to metabolic surgery after completion of the assessment for the primary endpoint (2 years after random assignment). Two patients who underwent surgery dropped out in the first year after surgery but re-entered the study later on (one patient re-entered at month 72 and one at month 84) and were included in the 10-year follow-up analysis. Therefore, 57 patients (95·0%) completed the 10-year follow-up. The outcomes for the medically treated patients who died (one patient) and crossed over to surgery (two patients) are not included in the per-protocol analysis (n=15 medical therapy, n=20 RYGB, n=20 BPD), but are included in the intention-to-treat analysis for diabetes remission (n=18 medical therapy, n=20 BPD, and n=20 RYGB; figure 1).

Table 2 shows the per-protocol statistics for anthropometric measures and major biochemical variables at baseline and 10 years together with their corresponding absolute and percentage differences. There were no differences at baseline in terms of age, gender, glycaemic control, duration of diabetes, bodyweight or BMI, use of insulin, and glucose-lowering medications (table 1).

No patient was shown to be in diabetes remission after medical therapy. At the per-protocol analysis, 15 (37·5%) patients among all surgically treated patients maintained diabetes remission throughout the 10-year period of the study. Specifically, 10-year remission persisted in ten patients after BPD (50·0% [95% CI 30·0–70·1), and five after RYGB (25·0% [11·2–46·9]; p=0·19, Fisher's exact test between surgical procedures). The corresponding 10-year remission rates in the intention-to-treat analysis were 5·5% for medical therapy (95% CI 1·0–25·7; one participant went into remission after crossover to surgery), 50·0% for BPD (29·9–70·1), and 25·0% for RYGB (11·2–49·9; p=0·0082). Relative risks were 9·0 (95% CI 1·3–63·5) for BPD versus medical therapy and 4·5 (0·58–35·0) for RYGB versus medical therapy.

None of the patients who did not go into remission in the first 2 years after surgery went into remission thereafter. Among patients who did go into remission at 2 years, 20 (58·8%) of 34 had a relapse of hyperglycaemia during follow-up (ten [52·6%] of 19 in the BPD group and ten [66·7%] of 15 in the RYGB group; table 2).

Figure 2A shows the estimated diabetes-free survival time curves for the surgical procedures. The median diabetes-free survival time was 5 years (95% CI 4 to infinite value) in RYGB and 9 years (5 to infinite value) in BPD; the log-rank test (p=0·25) indicated no difference between the two surgical groups.

The cumulative risk of relapse during the 10-year follow-up study, computed on data from patients who remitted from diabetes at 2 years, showed that the highest risk of relapse occurred within the first 5 years after surgery (appendix p 9).

All patients who had a relapse of hyperglycaemia, however, maintained good glycaemic control at 10 years (mean 10-year HbA_{1c} was 6·7 [SD 0·2]; all but one patient had HbA_{1c} <7·0%) despite drastically reduced use of diabetes medications. Both patients who crossed over to surgery from the medical therapy group had diabetes remission postoperatively and one of them maintained remission at 10 years.

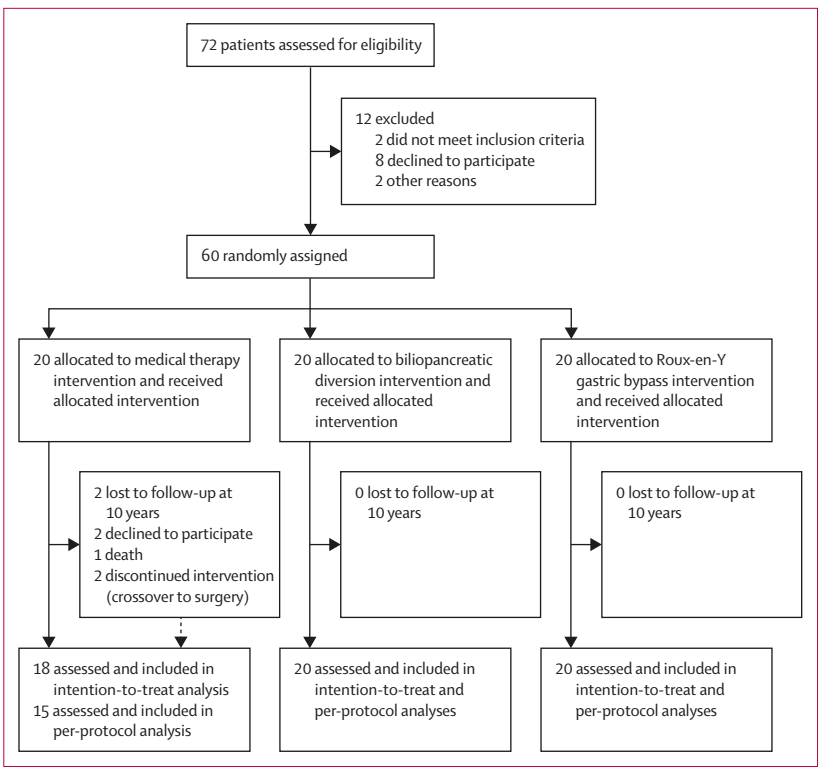

Figure 1: **Trial profile**

The mean HbA_{1c} at 10 years was 6·4% (SD 0·3) in the BPD group, 6·7% (0·3) in the RYGB group, and 7·6% (0·5) in the medical therapy group (–1·2% [95% CI –1·5 to –0·9] for BPD *vs* medical therapy and –0·9% [–1·2 to –0·6] for RYGB *vs* medical therapy). Patients in the medical therapy group had better glycaemic control at 10 years than at baseline (table 2); however, surgical treatment resulted in a significantly greater HbA_{1c} percentage reduction from baseline than medical therapy (–0·8% [SD 1·0] for medical therapy *vs* –2·4% [1·6] for BPD *vs* 1·9% [1·6%] for RYGB; p<0·0097). The target of HbA_{1c} less than 7·0% was met in 87·5% of the patients who underwent metabolic surgery and in none of the patients in the medical therapy group at 10 years. The time course of HbA_{1c} is reported in figure 2B.

Surgery resulted in significantly lower bodyweight (figure 2C), BMI, and waist circumference than medical therapy (table 2). 10-year percentage weight loss was –4·2% (SD 8·8) after medical therapy, –29·2% (8·9) for BPD, and –28·0% (8·0) for RYGB. Surgically treated patients had modest weight regain after the second postoperative year (6·6 kg [SD 3·0] in the RYGB group

and 5·4 kg [7·6] in the BPD group). Weight changes, however, did not predict diabetes remission or relapse among patients who underwent surgery. Weight regain at 10 years was 7·1% (SD 6·9) among patients who maintained remission versus 8·2% (6·2) for those who had a diabetes relapse.

Both surgical procedures were associated with significant lower HOMA-IR scores than medical therapy, indicating better insulin sensitivity (table 2). HOMA-IR score was lower among patients with persistent remission versus those with disease relapse (mean score 1·3 [SD 0·4] *vs* 1·8 [0·9]); p=0·034).

	Medical therapy group (n=15)	BPD group (n=20)	RYGB group (n =20)	BPD *vs* medical therapy	RYGB *vs* medical therapy	p value
Fasting glucose, mmol/L						
Baseline	9·9 (3·5)	9·7 (3·4)	9·5 (3·3)	..	..	..
10 years	7·2 (0·7)	5·1 (0·3)	5·6 (0·8)	−2·1 (−2·6 to −1·6)	−1·6 (−2·1 to −1·1)	<0·0001
Absolute change	−2·7 (3·5)	−4·6 (3·4)	−3·9 (3·2)	−1·9 (−4·7 to 0·8)	−1·3 (−4 to 1·5)	0·24
Glycated haemoglobin, %						
Baseline	8·5 (1·3)	8·9 (1·7)	8·6 (1·4)	..	..	..
10 years	7·6 (0·5)	6·4 (0·3)	6·7 (0·3)	−1·2 (−1·5 to −0·9)	−0·9 (−1·2 to −0·6)	<0·0001
Absolute change	−0·8 (1·0)	−2·4 (1·6)	−1·9 (1·6)	−1·6 (−2·8 to −0·4)	−1·0 (−2·2 to 0·2)	0·0097
HOMA-IR						
Baseline	9·6 (7·7)	7·7 (4·4)	9·7 (5·7)	..	..	..
10 years	5·1 (2·1)	1·5 (0·6)	2·0 (1·2)	−3·4 (−4·3 to −2·4)	−3·1 (−4 to −2·1)	<0·0001
Absolute change	−4·4 (6·3)	−6·2 (4·3)	−7·7 (5·7)	−1·7 (−6·2 to 2·7)	−3·2 (−7·6 to 1·2)	0·22
Weight, kg						
Baseline	137·1 (23·5)	137·8 (30·3)	129·8 (22·6)	..	..	..
10 years	130·6 (20·2)	95·7 (13·9)	92·6 (14·3)	−35·3 (−43·8 to −26·8)	−34·4 (−42·9 to −25·9)	<0·0001
Absolute change	−6·5 (12·9)	−42·2 (21·5)	−37·3 (14·5)	−35·7 (−49·7 to −21·6)	−30·8 (−44·8 to −16·7)	<0·0001
Waist circumference, cm						
Baseline	127·7 (16·2)	130·4 (19·7)	125·4 (16·6)	..	..	..
10 years	116·2 (14·9)	103·0 (12·3)	102·5 (13·3)	−14·6 (−22·6 to −6·6)	−12·5 (−20·5 to −4·5)	0·0001
Absolute change	−11·5 (12·1)	−27·4 (13·8)	−22·9 (11·9)	−15·9 (−26·4 to −5·5)	−11·4 (−21·9 to −1)	0·0021
Body-mass index, kg/m²						
Baseline	45·4 (6·5)	45·1 (7·8)	44·9 (5·2)	..	..	..
10 years	43·3 (5·7)	31·5 (4·3)	32·0 (2·9)	−11·6 (−14·5 to −8·8)	−11·0 (−13·8 to −8·2)	<0·0001
Absolute change	−2·1 (4·3)	−13·6 (6·0)	−12·8 (4·8)	−11·5 (−15·7 to −7·3)	−10·7 (−15·0 to −6·5)	<0·0001
Total cholesterol, mmol/L						
Baseline	6·3 (1·4)	5·5 (1·5)	4·6 (1·0)	..	..	..
10 years	4·8 (0·4)	3·1 (0·4)	4·4 (0·6)	−1·5 (−1·9 to −1·2)	−0·2 (−0·5 to 0·2)	<0·0001
Absolute change	−1·6 (1·2)	−2·4 (1·3)	−0·2 (1·2)	−0·8 (−1·8 to 0·2)	1·3 (0·3 to 2·4)	<0·0001
HDL cholesterol, mmol/L						
Baseline	1·0 (0·2)	1·0 (0·2)	1·1 (0·2)	..	..	..
10 years	1·1 (0·1)	1·2 (0·1)	1·4 (0·2)	0·1 (0·0 to 0·2)	0·2 (0·1 to 0·3)	<0·0001
Absolute change	0·1 (0·2)	0·2 (0·2)	0·2 (0·3)	0·1 (−0·1 to 0·3)	0·1 (0·0 to 0·3)	0·1960
LDL cholesterol, mmol/L						
Baseline	4·1 (1·2)	3·5 (1·3)	2·8 (0·9)	..	..	..
10 years	2·8 (0·4)	1·5 (0·4)	2·4 (0·5)	−1·2 (−1·6 to −0·9)	−0·2 (−0·5 to 0·2)	<0·0001
Absolute change	−1·4 (1·1)	−2·1 (1·0)	−0·3 (1·1)	−0·7 (−1·6 to 0·2)	1·0 (0·2 to 1·9)	<0·0001
Triglycerides, mmol/L						
Baseline	2·6 (0·7)	2·2 (0·9)	1·7 (0·9)	..	..	..
10 years	1·9 (0·2)	1·1 (0·1)	1·3 (0·3)	−0·8 (−0·9 to −0·6)	−0·4 (−0·6 to −0·3)	<0·0001
Absolute change	−0·7 (0·6)	−1·2 (0·9)	−0·4 (0·7)	−0·5 (−1·1 to 0·1)	0·4 (−0·3 to 1·0)	0·0047
Diastolic blood pressure, mm Hg						
Baseline	97·3 (19·2)	95·9 (12·9)	91·5 (14·2)	..	..	..
10 years	88·7 (4·8)	82·8 (3)	85·5 (3·2)	−5·8 (−8·7 to −2·9)	−2·7 (−5·6 to 0·2)	<0·0001
Absolute change	−8·7 (18·8)	−13·2 (12·0)	−6·0 (13·4)	−4·5 (−16·5 to 7·5)	2·7 (−9·4 to 14·7)	0·30

(Table 2 continues on next page)

	Medical therapy group (n=15)	BPD group (n=20)	RYGB group (n =20)	BPD *vs* medical therapy	RYGB *vs* medical therapy	p value
(Continued from previous page)						
Systolic blood pressure, mm Hg						
Baseline	157·5 (37·7)	154·5 (29·7)	145·8 (20·5)	..	..	..
10 years	140·3 (5·5)	131·3 (5·3)	134·5 (4·8)	−8·9 (−12·9 to −4·8)	−5 (−9·1 to −1·0)	<0·0001
Absolute change	−17·2 (36·2)	−23·3 (28·1)	−11·3 (19·3)	−6·1 (−29 to 16·9)	6 (−17 to 28·9)	0·40
Cardiovascular risk, %						
Baseline	0·2 (0·1)	0·2 (0·1)	0·1 (0·1)	..	..	..
10 years	0·2 (0·1)	0·1 (0·0)	0·1 (0·1)	−0·1 (−0·1 to −0·1)	0·0 (−0·1 to 0·0)	<0·0001
Absolute change	0·0 (0·1)	−0·1 (0·1)	0·0 (0·1)	−0·1 (−0·1 to 0·0)	0·0 (−0·1 to 0·1)	0·0009
Glomerular filtration rate, mL/min per 1·73 m²						
Baseline	82·1 (12)	90·6 (25·1)	85·3 (24·2)	..	..	..
10 years	64·0 (18·3)	70·1 (17·5)	81·0 (16·5)	1·6 (−8·7 to 11·8)	15·5 (5·4 to 25·7)	0·0004
Absolute change	−18·8 (17·9)	−20·9 (12·2)	−4·4 (16·3)	−2·1 (−15·3 to 11·0)	14·4 (1·4 to 27·4)	0·0031
Diabetes medication, total number of medications						
Baseline	2·5 (0·5)	2·4 (0·6)	2·2 (0·7)	−0·1 (−0·6 to 0·4)	−0·3 (−0·8 to 0·2)	0·31
10 years	2·9 (0·8)	0·7 (0·9)	1·4 (0·9)	−2·2 (−2·9 to −1·5)	−1·5 (−2·2 to −0·7)	<0·0010
Percentage change, %	17·8 (35·3)	−73·3 (36·4)	−27·5 (61·2)	−91·1 (−129·7 to −52·5)	−45·3 (−83·9 to −6·7)	<0·0010
Insulin use						
Baseline	7·0 (46·7%, 24·8 to 69·9)	10·0 (50·0%, 29·9 to 70·1)	9·0 (45%, 25·8 to 65·8)	1·1 (0·2 to 5·4)	0·9 (0·2 to 3·7)	0·95
10 years	8·0 (53·3%, 30·1 to 75·2)	0·0 (0·0%, 0·0 to 16·1)	1·0 (5%, 0·9 to 23·6)	0·0 (0·0 to 0·28)	0·1 (0·0 to 0·5)	<0·0001
Diabetes remission						
10 years	0·0 (0·0%, 0·0 to 20·4)	10·0 (50·0%, 30·0 to 70·1)	5·0 (25·0%, 11·2 to 46·9)	7·5 (1·1 to 52·4)*	3·8 (0·5 to 28·8)*	0·0020
Diabetes relapse†						
10 years	..	10·0 (52·6%, 31·7 to 72·7)	10·0 (66·7%, 41·7 to 84·8)	..	..	..

Data are mean (SD), mean difference (95% CI), or n (%, 95% CI). BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass. HOMA-IR=Homeostatic Model Assessment of Insulin Resistance. *Relative risk computed by adding one remission to the medical therapy group. †Computed on data from patients who were in remission at 2 years.

Table 2: **Baseline and 10-year follow-up variables, and absolute and percentage variations**

At 10 years, patients in the medical therapy group had significantly higher cardiovascular risk than patients in the BPD group (mean 0·06 [SD 0·03]) and patients in the RYGB group (mean 0·10 [0·07], table 2, appendix p 10).

Surgically treated patients had significantly lower concentrations of plasma triglycerides than patients in the medical therapy group (table 2). Patients in the BPD group had significantly lower plasma concentrations of total cholesterol and LDL cholesterol than both patients in the RYGB and medical therapy groups. HDL cholesterol increased in all groups, with the largest increase seen in patients who underwent RYGB (table 2).

There were no differences in blood pressure among groups but patients in the medical therapy group required more anti-hypertensive medications than patients who underwent surgery (3·2 [SD 2·0] tablets in the medical therapy group, 1·6 [1·5] tablets in the RYGB group, and 0·6 [0·8] tablets in the BPD group; appendix p 4). Estimated GFR declined in all three groups over time but surgically treated patients had significantly better estimated GFR at 10 years than patients in the medical therapy group (table 2, appendix p 11).

Patients who underwent surgery had better QOL at 10 years than patients treated medically as shown by significantly higher total scores and higher scores for all QOL subdomains (figure 3A). Patients in the RYGB group had significantly higher scores than patients in the BPD group for the domains vitality, physical role, and mental health (appendix p 6).

Medically treated patients had a significantly higher incidence of diabetes-related complications than surgically treated patients (72·2% [95% CI 49·1–87·5] *vs* 5·0% [0·9–23·6]; figure 3B, table 3, appendix p 13). Participants in both the RYGB and the BPD group had less diabetes-related complications throughout the 10-year study than participants in the medical therapy group (relative risk 0·07 [95% CI 0·01–0·48] for both comparisons). Participants in the medical therapy group had both macrovascular (two myocardial infarctions, one fatal) and microvascular diabetic complications (retinopathy [n=2], nephropathy [n=5], and neuropathy [n=4]). Only two patients among surgically treated patients developed diabetic complications (one case of macro-albuminuria in each surgical group).

At baseline, patients used a mean of 2·3 (SD 0·6) anti-diabetes drugs with no differences in the types of drugs used between groups (figure 4). At 10 years (and throughout the study period) surgically treated patients used significantly less diabetes medications than patients in the medical therapy group (mean number of

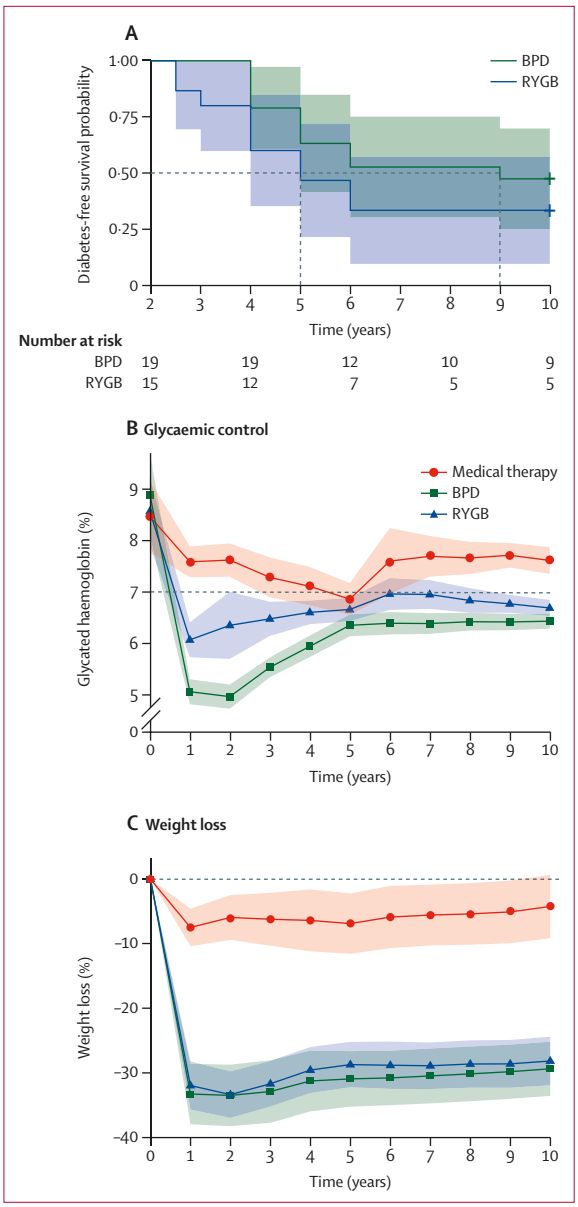

Figure 2: **Remission, glycaemic control, and weight loss**
(A) Estimated diabetes-free survival time curves with CIs for the surgical procedures (BPD and RYGB). The median diabetes-free survival time was 5 years (4 to infinite value in RYGB and 9 years (5 to infinite value) in BPD; the log-rank test (p=0·25) indicated no difference between the two surgical groups. Patients in the medical therapy group who crossed over, one to RYGB and one to BPD, are censored and so are not included in the figure. (B) Time course of glycaemic control expressed as glycated haemoglobin (%). The dotted line indicates the target concentration of 7·0% considered to be adequate glycaemic control and the shaded area represents the SD. (C) Weight loss (percentage weight loss from baseline). Time course of bodyweight over the 10-year follow-up by treatment. The shaded area represents the SD. BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass.

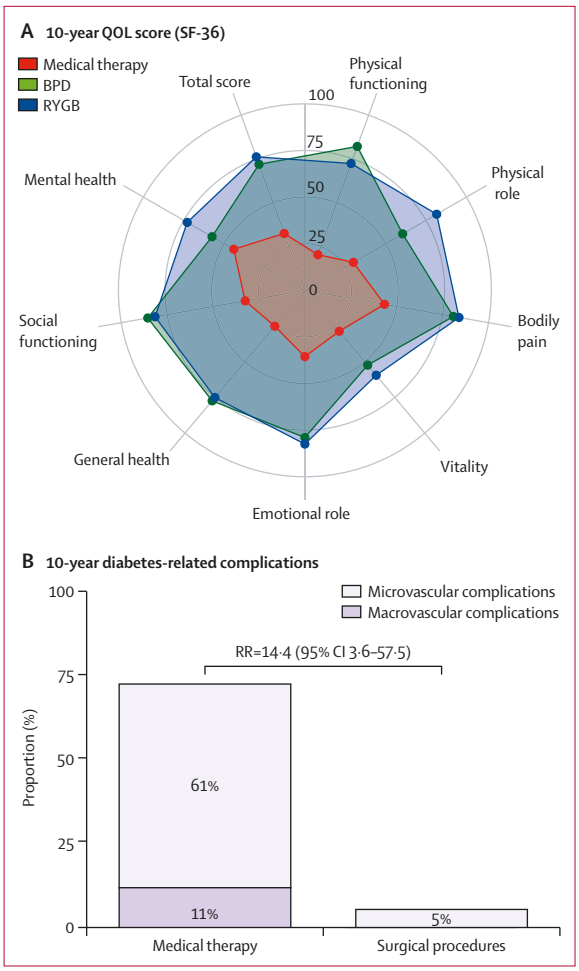

Figure 3: **QOL and diabetes-related complications**
(A) QOL as assessed by the SF-36. Patients who underwent surgery had better QOL total scores and scores for all QOL subdomains. Patients in the RYGB group had higher scores than patients in the BPD group for the domain mental health. (B) Percentage of diabetes-related complications across the 10-year duration of the study in patients who were medically treated versus patients who were surgically treated (RYGB and BPD combined). QOL=quality of life. BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass. SF-36= RAND 36-Item Health Survey (Short Form). RR=relative risk.

anti-diabetes drugs at 10 years 0·7 [SD 0·9] in the BPD group, 1·4 [0·9] in the RYGB group, and 2·9 [0·8] in the medical therapy group; p<0·0001; table 2). At baseline, about half of all patients in the study were on insulin. At 10 years, 53·3% of the patients in the medical therapy group required insulin therapy compared with only 2·5% among patients who underwent surgery (none for BPD and one for RYGB, table 2, figure 4). Patients in the medical therapy group used significantly more injectable drugs (insulin or GLP-1 analogues, figure 3, appendix p 4) and significantly more cardiovascular medications (lipid-lowering and blood pressure-lowering medications) than patients in both surgical groups (p<0·0001; appendix p 4). Medication use increased over time in the medical therapy group. Use of GLP-1 analogues, SGLT2 inhibitors, and insulin further increased after year 5 (appendix p 12).

Serious adverse events recorded during the study, including 30-day major surgical complications, late surgical

	BPD group				RYGB group				Medical therapy group			
	0–2 years	2–5 years	5–10 years	10–year total	0–2 years	2–5 years	5–10 years	10–year total	0–2 years	2–5 years	5–10 years	10–year total
Major 30-day postoperative complications												
Deep vein thrombosis or pulmonary embolism	1	0	0	1	1	0	0	1	0	0	0	0
Atrial fibrillation episode	1	0	0	1	0	0	0	0	0	0	0	0
Late surgical complications												
Intestinal occlusion	0	0	0	0	1	0	0	1	0	0	0	0
Incisional hernia	1	0	0	1	0	0	0	0	0	0	0	0
Recurrent or chronic diarrhoea	12	10	8	30	0	0	0	0	0	0	0	0
Nutritional or metabolic complications												
Iron-deficiency anaemia	0	5	3	8	0	3	2	5	0	0	0	0
Hypoalbuminaemia, plasma albumin <3·5 mg/dL	0	3	2	5	0	0	0	0	0	0	0	0
Osteopenia*	0	3	3	6	0	1	1	2	0	1	2	0
Osteoporosis†	0	1	2	3	0	0	0	0	0	0	0	0
Transient nyctalopia	0	1	2	3	0	0	0	0	0	0	0	0
Renal calculus	0	2	1	3	0	0	0	0	0	0	0	0
Symptomatic hypoglycaemia‡	0	0	0	0	0	2§	0	2	0	0	0	0
Diabetes-related complications												
Myocardial infarction	0	0	0	0	0	0	0	0	0	1¶	1	2
Retinopathy	0	0	0	0	0	0	0	0	0	1	1	2
Albumin to creatinine ratio >30 mg/mmol	0	0	1	1	0	1	0	1	0	4	1	5
Neuropathy	0	0	0	0	0	0	0	0	0	2	2	4

BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass. *Osteopenia defined by bone mineral density T score measured by dual-energy x-ray absorptiometry. †Osteoporosis defined by BMD T score –2·5. ‡Symptomatic or severe hypoglycaemia is defined according to the American Diabetes Association Workgroup on Hypoglycemia as hypoglycaemia requiring the assistance of another individual. §There were seven episodes in two patients who underwent RYGB (all with blood glucose reported ≥40 mg/dL). However, no hospital admission was necessary. All episodes occurred between 3 years to 5 years after surgery. No further episodes beyond 5 years were observed. ¶The myocardial infarction was severe and resulted in the death of the patient.

Table 3: **Major surgical and medical complications**

complications (after 30 days), and metabolic, nutritional, and diabetes complications are reported in table 3. Serious adverse events occurred more frequently among participants in the BPD group than in the medical therapy group (odds ratio 2·7 [95% CI 1·3–5·6]). Participants in the medical therapy group, however, had a higher incidence of adverse events than patients who underwent RYGB (odds ratio RYGB *vs* medical therapy 0·7 [95% CI 0·3–1·9]). There were no late surgical complications. Iron deficiency and mild osteopenia occurred in both surgical groups but they were more common in patients who underwent BPD. Osteoporosis, transient nyctalopia as a consequence of vitamin A deficiency, and kidney stones were observed only in the BPD group (table 3).

Discussion

The results of our study showed that metabolic surgery is more effective than medical and lifestyle interventions in the long-term control of type 2 diabetes. Surgery resulted in durable remission of type 2 diabetes, with more than a third of patients maintaining non-diabetic concentrations of glycaemia without the need for diabetes medications for the entire 10-year study period. Compared with medical therapy, surgery also resulted in a significantly greater reduction in HbA_{1c} concentrations from baseline as well as lower coronary heart disease risk, better kidney function (estimated GFR), better QOL, reduced medication use, and lower incidence of diabetes-related complications.

As a single-centre, open-label, small size trial, this study has several limitations. In particular, the open-label design inherently exposes the study to a risk of bias in both the management and the assessment of study participants. By design, however, clinical management of diabetes-related outcomes and assessment of study outcomes in this trial were done by non-surgeons; thus mitigating the risk of bias toward the intervention that proved most effective in this study. At the time we designed our study, RYGB was done laparoscopically while BPD was still routinely done by an open technique at our institution. In this context, it was not possible to mask patients to the type of operation received. Also, unlike RYGB, BPD has characteristic side-effects like foul-smelling stools that are described to patients as part of the preoperative consent process. Hence, maintaining patient masking to which procedure they had was both ethically and practically problematic.

The small sample size and the consequent low absolute number of major diabetes-related complications means that data for the protective effects of surgery with regard

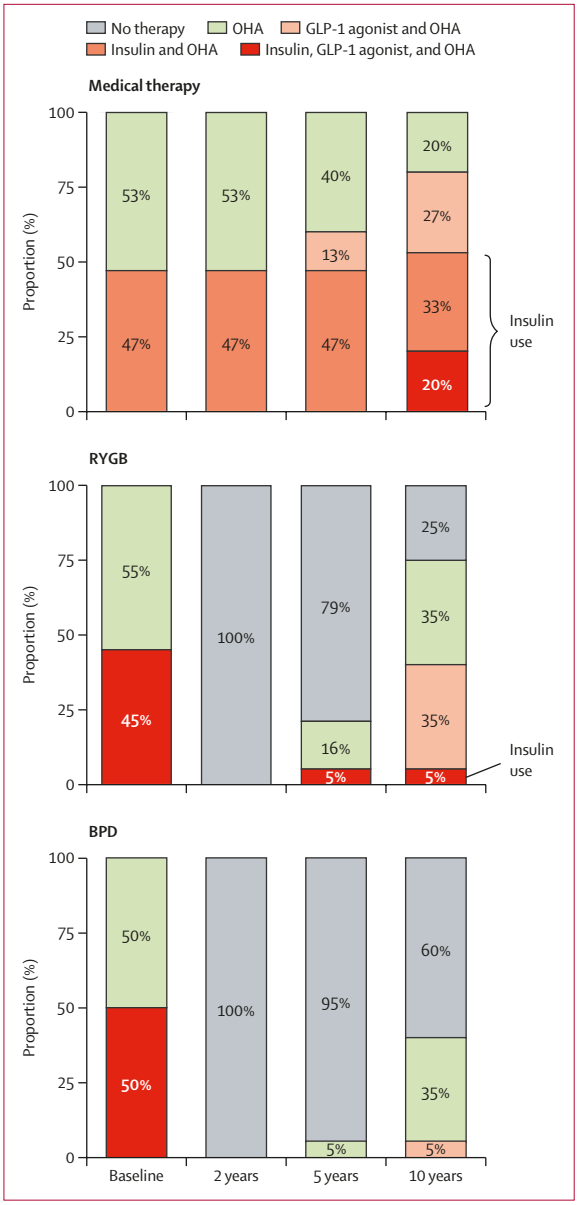

Figure 4: **Medication use**
Medication use in each group at baseline, and at 2, 5, and 10 years after intervention. Bars indicate the percentages of patients using each class of drugs including oral glucose-lowering medications (oral anti-hyperglycaemic agents), GLP-1-receptor agonists (injectables), and insulin, as well as their relative combinations. Insulin use is shown at 10 years. BPD=biliopancreatic diversion. RYGB=Roux-en-Y gastric bypass. OHA=oral anti-hyperglycaemic agents.

to diabetes-related morbidity and mortality should be taken with caution.

The study also has unique strengths that primarily stem from the high follow-up rate (95%) and the very long period of continued follow-up. The availability of all patients who underwent surgery for the 10-year analysis of the study provides robust information about the durability of surgically induced diabetes remission in patients with advanced type 2 diabetes. Furthermore, the good long-term results of medical therapy in this study (4·2% mean weight loss and 0·8% HbA_{1c} reduction from baseline) are consistent with those of larger trials of intensive lifestyle interventions[26] and novel weight-loss-inducing diabetes drugs, such as SGLT2 inhibitors and GLP-1-receptor agonists. This finding means that the medical therapy used in this trial reflects current best medical practice and provides a valid comparator to assess the relative efficacy of metabolic surgery as a therapy for type 2 diabetes. The deterioration of glycaemic control observed in the medical therapy group after 5 years, despite no substantial weight regain and increased use of effective modern drugs (appendix p 12), is a reminder of the progressive nature of type 2 diabetes and, by contrast, attests to the remarkable anti-diabetes potency of metabolic surgery.

The finding that metabolic surgery resulted in continued 10-year disease remission in 37·5% of patients with advanced type 2 diabetes (by design all patients had a >5-year history of disease and 50% of them required insulin at baseline), supports the hypothesis that type 2 diabetes is a potentially curable disease.[11] In fact, more than a third of patients who underwent metabolic surgery in this trial met the American Diabetes Association definition of diabetes cure (ie, persistent remission of hyperglycaemia without need for any pharmacological therapy for more than 5 years).[10]

The choice of diabetes remission as a primary endpoint in this study admittedly favours surgery, given the fact that the definition of remission requires discontinuation of pharmacological therapy. However, when this study was designed, no randomised controlled trial had yet compared medical and surgical therapy specifically for the treatment of diabetes using the then newly established (2009) strict criteria for the definition of diabetes remission. Furthermore, other outcome measures of this study included several objective and clinically meaningful measures of glycaemic control beyond remission of hyperglycaemia, including HbA_{1c} concentrations, fasting glycaemia, percentage change in HbA_{1c} from baseline, use of diabetes medications, and major diabetes-related complications such as microvascular and macrovascular complications. The finding that metabolic surgery outperformed medical therapy on all the above outcomes provides robust evidence of the greater anti-diabetes potency of surgery than the medical and lifestyle interventions used in this trial.

In this study, the risk of diabetes relapse appeared to be highest within the first 5 years after surgery and declined significantly thereafter. Also, relapse of diabetes was characterised by mild hyperglycaemia with all but one such patients maintaining an HbA_{1c} concentration of less than 7·0% at 10 years after surgery with minimal or no medications. Furthermore, none of the patients who went into diabetes remission in this study had diabetes-related complications, whether or not their hyperglycaemia eventually relapsed. Considered together, these findings

suggest that although continued monitoring of glycaemia remains necessary in all patients with surgical remission of diabetes, it could be reasonable to reduce the frequency of glycaemic monitoring and screening for diabetes-related complications in patients that maintain stable disease remission postoperatively beyond 5 years. More data from larger prospective observations, however, are necessary to further corroborate this point and help define the appropriate frequency of surveillance and monitoring in patients with long-lasting diabetes remission after surgery.

The rates of long-term diabetes remission in this study are lower than the 50–80% reported in several retrospective series of RYGB.[12,17] Also, duration of diabetes and insulin use at baseline did not predict remission or relapse of type 2 diabetes in this study, in contrast with reported series of bariatric surgery.[7,13,17] These findings might reflect greater and more homogeneous disease severity at baseline among the patients of this trial than patients in standard bariatric surgery practice.

Rates of diabetes remission and overall diabetes control were better after BPD compared with RYGB, despite identical weight loss trajectories in both surgical groups throughout the study. This finding supports the notion that metabolic surgery induces anti-diabetes mechanisms additional to weight loss[2,27] and suggests that BPD might engage such mechanisms more powerfully than RYGB. The absence of a difference in weight loss between BPD and RYGB in this study might seem surprising given that BPD generally induces greater weight loss than RYGB. However, the BPD variant used in our study (Scopinaro procedure) entails a horizontal gastrectomy and a larger gastric remnant than the more commonly performed duodenal-switch variant of BPD, which involves a sleeve gastrectomy. Furthermore, almost all participants in this trial had a BMI of less than 50 kg/m² and BPD causes greater weight loss than RYGB only in patients with a BMI greater than 50 kg/m².[28]

Despite BPD's greater anti-diabetic potential, patients who underwent this operation had a higher incidence of nutritional complications, overall serious adverse events, and lower QOL than patients who underwent RYGB. This result suggests that RYGB might have a more favourable risk-to-benefit profile than BPD as a standard surgical option for the treatment of type 2 diabetes.

Short-term remission of hyperglycaemia has been reported in 30–40% of people with onset of type 2 diabetes within the past 5 years undergoing a very-low-calorie diet (VLCD).[29] However, rates of diabetes remission after VLCD are not comparable with those associated with surgery in this or other clinical trials as the studies of VLCD so far have used a substantially different definition of remission, involved only patients with early or mild diabetes, and generally had short-term follow-up.[29]

Despite its small sample size, our study shows clear and statistically significant differences in the incidence of diabetes-related complications between medically and surgically treated patients. These findings are plausibly a result of the magnitude and durability of improved glycaemic and metabolic control achieved by surgery over the long-term period of this study. Our study confirms, in the context of a randomised controlled trial, that metabolic surgery is more effective than alternative treatment strategies at delaying disease progression and preventing macrovascular and microvascular complications of type 2 diabetes, as previously suggested in other non-randomised studies.[30]

We acknowledge that reduction of muscle mass after major postoperative weight loss could influence estimated GFR and overestimate renal function after metabolic surgery. Because we did not measure body composition in this study, we cannot rule out such potential confounding. However, this possibility is mitigated by the fact that major postoperative weight loss occurs in the first 6 months to 1 year after surgery and skeletal muscle mass is typically maintained or increases thereafter except in cases of clinical malabsorption. Clinical malabsorption is rare after RYGB but possible after BPD. In this study however, patients in the BPD group had lower, not higher, estimated GFR than patients in the RYGB group, thus suggesting that differences in body compositions are unlikely to account for the differences in estimated GFR measured in the participants of this study.

The evidence that metabolic surgery reduces long-term medication usage, cardiovascular risk factors, and diabetes-related complications in this trial also supports the notion that surgery can be a cost-effective approach to treating type 2 diabetes.

In conclusion, the results of this study show that surgery is more effective than medical therapy in the long-term control of type 2 diabetes. Our findings suggest that it might be possible to reduce the frequency of glycaemic monitoring in patients who maintain at least 5 years of remission of type 2 diabetes although larger studies are needed to confirm this finding. Clinicians and policy makers should ensure that metabolic surgery is appropriately considered in the management of patients with obesity and type 2 diabetes.

Contributors

GM and FR conceived and designed the study. FR did laparoscopic RYGB procedures. CG, AI, and EC collected the data. SP and ADG did the statistical analysis. GM, FR, and SP interpreted the data. GM and FR drafted the Article. GC helped with editing of the manuscript and tables. SRB, ADG, and GC critically reviewed the manuscript for important intellectual content. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the Article are appropriately investigated and resolved. All authors have seen and approved the final text.

Declaration of interests

The authors of this study declare no competing interests concerning this manuscript. GM reports grants and personal fees from Novo Nordisk and Fractyl and personal fees from Johnson & Johnson, outside the submitted work. FR reports receiving research grants from Ethicon and Medtronic; receiving consulting fees from Novo Nordisk, Ethicon, and

Medtronic; and serving on scientific advisory boards for GI Dynamics and Keyron. All other authors declare no competing interests.

Data sharing

Anonymised patient data are available for use in collaborative studies to researchers upon reasonable request to the corresponding author (geltrude.mingrone@unicatt.it). Data will be provided following the review and approval of a research proposal (including a statistical analysis plan) and completion of a data sharing agreement. Responses to the request for the raw data will be judged by a committee including GM, SP, and FR.

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