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

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Summary

Background Randomised controlled trials have shown that bariatric surgery is more effective than conventional treatment for the short-term control of type-2 diabetes. However, published studies are characterised by a relatively short follow-up. We aimed to assess 5 year outcomes from our randomised trial designed to compare surgery with conventional medical treatment for the treatment of type 2 diabetes in obese patients.

Methods We did our open-label, randomised controlled trial at one diabetes centre in Italy. Patients aged 30–60 years with a body-mass index of 35 kg/m² or more and a history of type 2 diabetes lasting at least 5 years were randomly assigned (1:1:1), via a computer-generated randomisation procedure, to receive either medical treatment or surgery by Roux-en-Y gastric bypass or biliopancreatic diversion. Participants were aware of treatment allocation before the operation and study investigators were aware from the point of randomisation. The primary endpoint was the rate of diabetes remission at 2 years, defined as a glycated haemaglobin A_{1c} (HbA_{1c}) concentration of 6·5% or less (≤47·5 mmol/mol) and a fasting glucose concentration of 5·6 mmol/L or less without active pharmacological treatment for 1 year. Here we analyse glycaemic and metabolic control, cardiovascular risk, medication use, quality of life, and long-term complications 5 years after randomisation. Analysis was by intention to treat for the primary endpoint and by per protocol for the 5 year follow-up. This study is registered with ClinicalTrials.gov, number NCT00888836.

Findings Between April 27, 2009, and Oct 31, 2009, we randomly assigned 60 patients to receive either medical treatment (n=20) or surgery by gastric bypass (n=20) or biliopancreatic diversion (n=20); 53 (88%) patients completed 5 years' follow-up. Overall, 19 (50%) of the 38 surgical patients (seven [37%] of 19 in the gastric bypass group and 12 [63%] of 19 in the bilipancreatic diversion group) maintained diabetes remission at 5 years, compared with none of the 15 medically treated patients (p=0·0007). We recorded relapse of hyperglycaemia in eight (53%) of the 15 patients who achieved 2 year remission in the gastric bypass group and seven (37%) of the 19 patients who achieved 2 year remission in the biliopancreatic diversion group. Eight (42%) patients who underwent gastric bypass and 13 (68%) patients who underwent biliopancreatic diversion had an HbA_{1c} concentration of 6·5% or less (≤47·5 mmol/mol) with or without medication, compared with four (27%) medically treated patients (p=0·0457). Surgical patients lost more weight than medically treated patients, but weight changes did not predict diabetes remission or relapse after surgery. Both surgical procedures were associated with significantly lower plasma lipids, cardiovascular risk, and medication use. Five major complications of diabetes (including one fatal myocardial infarction) arose in four (27%) patients in the medical group compared with only one complication in the gastric bypass group and no complications in the biliopancreatic diversion group. No late complications or deaths occurred in the surgery groups. Nutritional side-effects were noted mainly after biliopancreatic diversion.

Interpretation Surgery is more effective than medical treatment for the long-term control of obese patients with type 2 diabetes and should be considered in the treatment algorithm of this disease. However, continued monitoring of glycaemic control is warranted because of potential relapse of hyperglycaemia.

Funding Catholic University of Rome.

Introduction

Bariatric surgery is emerging as a valuable treatment option for patients with type 2 diabetes. The rationale for this concept is based on the substantial clinical improvement of type 2 diabetes after bariatric surgery,[1] and on the growing body of evidence that gastrointestinal operations can directly affect glucose metabolism, independently of weight loss.[2,3]

Intensive lifestyle modification strategies can improve glycaemic and metabolic control in patients with type 2 diabetes, but they do not reduce cardiovascular risk and mortality compared with standard diabetes treatment.[4]

Research in context

Evidence before this study

We searched MEDLINE, Embase, and The Cochrane Library between Jan 1, 2015, and May 15, 2015, for randomised controlled trials comparing bariatric surgery with medical treatment for type 2 diabetes. Our search terms were “bariatric surgery”, “diabetes”, “remission”, “Roux-en-Y gastric bypass” and “bilio-pancreatic diversion”. Randomised trials were included for evidence of glycaemic outcomes; long-term case-control studies were also used to assess evidence of cardiovascular risk and cardiovascular disease reduction after bariatric or metabolic surgery. Only randomised trials with previously published protocols in official sites were considered. Findings from previous trials have shown that bariatric surgery is more effective than conventional treatments for the short-term control of type 2 diabetes. Case-control studies suggest that bariatric surgery might reduce cardiovascular risk and mortality in obese patients with type 2 diabetes.

Added value of this study

Published randomised controlled trials are characterised by a relatively short follow-up time (1–3 years). This is the first report of 5 year outcomes from a trial designed to compare surgery with medical treatment specifically for the treatment of type 2 diabetes. Our findings show that bariatric surgery is more effective than medical treatment for the long-term control of obese patients with type 2 diabetes. Compared with medical treatment, surgery resulted in sustained remission of diabetes in a significant number of patients and in a greater reduction of cardiovascular risk, diabetes-related complications, and medication use, including use of insulin and cardiovascular drugs. Up to 50% of patients who had initial diabetes remission had a relapse of mild hyperglycaemia 5 years after surgery. However, more than 80% of surgically treated patients maintained the American Diabetes Association treatment goal of a glycated haemoglobin A_{1c} concentration less than 7·0% (<53 mmol/mol), despite little or no need for antidiabetic drugs.

Implications of all the available evidence

The available evidence supports consideration of surgery in the treatment algorithm of type 2 diabetes. The ability of surgery to greatly reduce use of diabetes and cardiovascular drugs suggests that surgical treatment of diabetes is a cost-efficient therapeutic approach for this disease. The results of our study also add to a growing body of evidence showing that the gastrointestinal tract is a rational biological target for antidiabetic interventions and support further research into the mechanisms of action of surgery as a way to identify new, less invasive approaches of curative intent.

By contrast, long-term case-control studies show that, compared with usual care, bariatric surgery can lead to major reductions in hyperglycaemia or to diabetes remission, and can reduce cardiovascular disease and death,[4–7] especially in patients with type 2 diabetes.

Several short-term to medium-term (1–3 year) randomised controlled trials comparing bariatric surgery with conventional diabetes management have shown that various surgical procedures, including Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion, and gastric banding, improve type 2 diabetes more effectively than do drugs and lifestyle interventions.[8–13] In one of these trials,[10] our group compared biliopancreatic diversion and Roux-en-Y gastric bypass with standard medical treatment in patients with severe obesity and diabetes (body-mass index [BMI] >35 kg/m²). As many as 95% of patients who underwent biliopancreatic diversion, and 75% of those who underwent Roux-en-Y gastric bypass, achieved the primary endpoint of diabetes remission at 2 years, compared with none of the patients in the medical treatment group. Despite these findings, published trials, including our previous study, are characterised by a relatively short follow-up time (1–3 years).

Here we present the 5 year follow-up data from our randomised controlled trial.[10] We assessed durability of diabetes remission, overall glycaemic and metabolic control, cardiovascular risk, medication use, quality of life, diabetes-related complications, and long-term surgical complications.

Methods

Study design and patients

The study design and methods have been previously described.[10] Briefly, we did a three-group, open-label, randomised controlled trial at the Catholic University diabetes centre in Rome, Italy. Inclusion criteria were an age of 30–60 years, a BMI of 35 kg/m² or more, a history of type 2 diabetes lasting at least 5 years, glycated haemoglobin A_{1c} (HbA_{1c}) concentration of ≥7·0% or more (≥53 mmol/mol), and ability to understand and comply with the study protocol. Exclusion criteria were a history of type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid treatment, previous bariatric surgery, pregnancy, other medical disorders requiring short-term hospital admission, severe diabetes complications, other severe medical disorders, and geographical inaccessibility.

The study was approved by the institutional human ethics committee of the Catholic University of Rome. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1), via a computer-generated randomisation procedure, to receive either medical treatment or surgery by Roux-en-Y gastric bypass or biliopancreatic diversion. Because patients undergoing surgery had to sign informed consent and be fully aware of the specific risks of procedures, masking of patients to treatment allocation was deemed inappropriate. Study investigators were aware of treatment allocation from the point of randomisation.

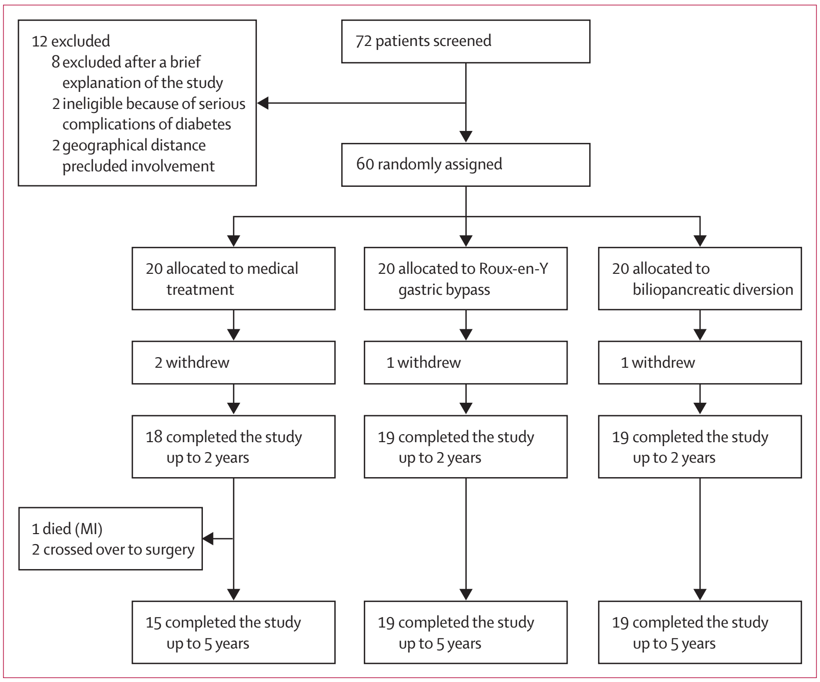


Figure 1: **Trial profile**
MI=myocardial infarction.

	Medical treatment group (n=15)	Roux-en-Y gastric bypass group (n=19)	Biliopancreatic diversion group (n=19)	p value*
ADA partial remission at 2 years	0	15 (75%)	19 (95%)	<0·0001
ADA partial remission at 5 years	0	7 (37%)	12 (63%)	0·0007
ADA complete remission at 5 years	0	0	0	··
HbA_{1c} ≤6% (≤42·1 mmol/mol) and FPG ≤5·6 mmol/L without glucose-lowering drugs	0	1 (5%)	7 (37%)	0·0039
HbA_{1c} ≤6·5% (≤47·5 mmol/mol) without glucose-lowering drugs	0	8 (42%)	13 (68%)	0·0003
HbA_{1c} ≤6·5% (≤47·5 mmol/mol) with or without glucose-lowering drugs	4 (27%)	8 (42%)	13 (68%)	0·0457
Relapse	··	8/15 (53%)	7/19 (37%)	··
ADA treatment goals†	0	2 (11%)	6 (32%)	0·0332

Data are n (%) or n/N (%), unless otherwise indicated. The table shows the number of diabetes remissions according to the criterion used in this study (FPG ≤5·6 mmol/L and HbA_{1c} ≤6·5% [≤47.5 mmol/mol] for at least 1 year without treatment) and the number of partial (FPG 5·6–6·9 mmol/L and HbA_{1c} <6·5% for at least 1 year without treatment) and complete (FPG 5·6 mmol/L and HbA_{1c} <6·0% for at least 1 year without treatment) remissions according to both the ADA expert group definition[17] and one of its variants. Because no patients had remissions in the medical treatment group, risk ratios were computed on the assumption that remission had occurred in the two patients in the medical treatment group who crossed over to surgery. On the basis of this hypothesis, the relative risk of diabetes remission was 7·5 (95% CI 2·0–28·6; p<0·0001) in the gastric bypass group and 9·5 (2·5–35·5; p<0·0001) in the biliopancreatic diversion group, compared with the medical treatment. ADA=American Diabetes Association. HBA_{1c}=glycated haemoglobin A_{1c}. FPG=fasting plasma glucose. *From χ^2 test. †HbA_{1c} less than 7%, systolic blood pressure of 140 mmHg or less, diastolic blood pressure of 80 mm Hg or less, and LDL cholesterol less than 2·6 mmol/L.[14]

Table 1: **Diabetes remission and relapse and glycaemic control at 5 year follow-up**

Procedures

Roux-en-Y gastric bypass and biliopancreatic diversion were done in accordance with standard surgical techniques as previously described.[10] For conventional medical treatment and lifestyle intervention, patients were assessed and managed by a multidisciplinary team (diabetologists [GM, AI, and CG], dietitians, and nurses). Study participants had visits at baseline and at months 1, 3, 6, 9, and 12, and then every 6 months until month 60, or more often, as clinically necessary for diabetes control. All patients complied with follow-up visits and self-reported compliance with the drug regimen.

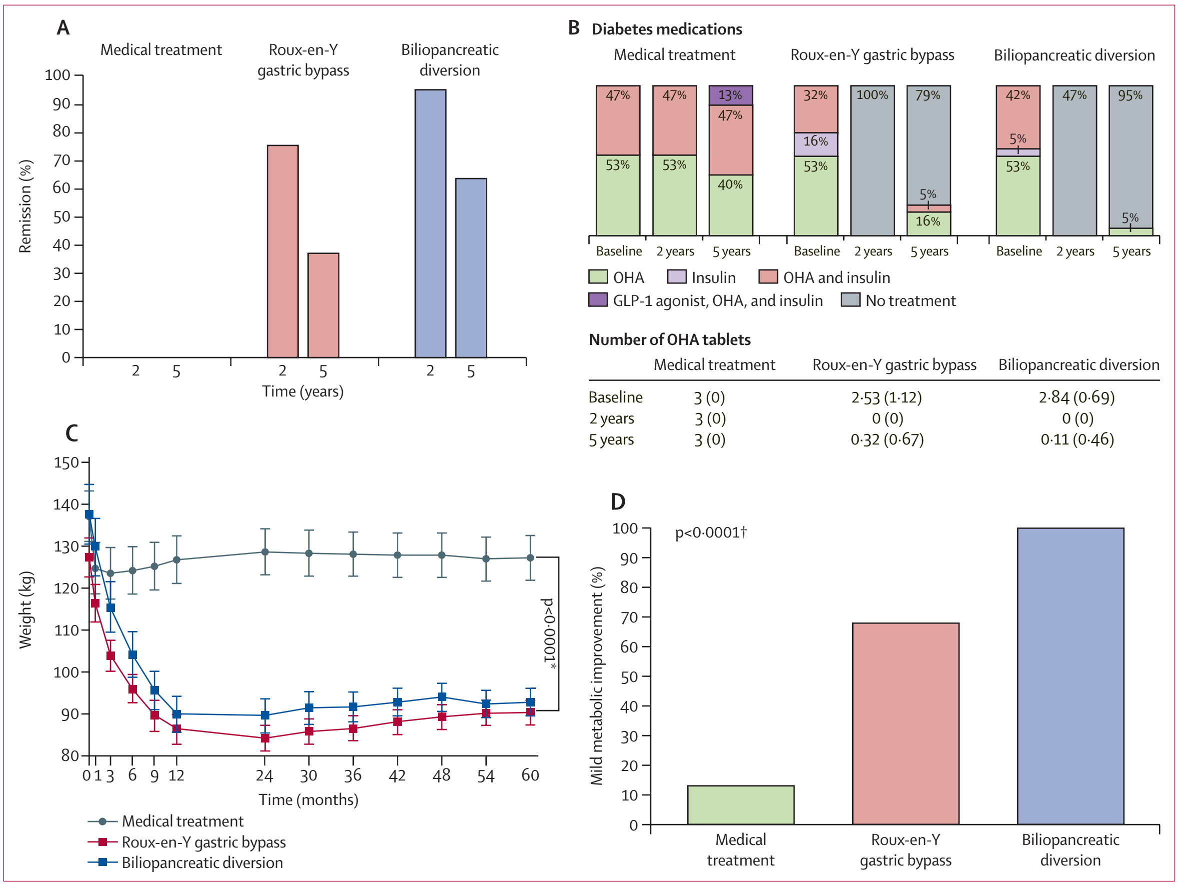
Screening for diabetes-related complications was done by yearly fundus examination, which was followed by intravenous fluorescein angiography when necessary. Neuropathy screening included tests of vibration sense and superficial pain sensation once a year, integrated, when appropriate, by nerve conduction measurements. Renal function was monitored by yearly assessment of the albumin to creatinine ratio and by plasma creatinine and blood urea nitrogen every 6 months. Screening for cardiovascular complications included routine electrocardiograph and echocardiogram once a year, and carotid or peripheral arterial ultrasound examination if clinically indicated.

Diet and lifestyle modification and dosage of glucose-lowering drugs, insulin, and glucagon-like peptide-1 (GLP-1) analogues were optimised on an individual basis with the aim of reaching adequate glycaemic control (HbA_{1c} <7·0% [<53·0 mmol/mol]) in all groups and as per standard diabetes guidelines.[14] Fasting glucose was measured with the glucose-oxidase method (Beckman Glucose Analyzer, Fullerton, CA, USA) and plasma insulin by microparticle enzyme immunoassay (Abbott Laboratories, Abbot Park, IL, USA), with a sensitivity of 1 μU/mL and an intra-assay coefficient of variation of 6·6%. We measured serum HbA_{1c} concentrations with high-performance liquid chromatography (normal range 3·5–6·5%), and total cholesterol, HDL cholesterol, and triglycerides with standard enzymatic assays. LDL cholesterol was calculated with the Friedewald formula.[15] The concentration of HDL cholesterol was defined as low if it was less than 1·0 mmol/L in men or less than 1·3 mmol/L in women. Insulin resistance was measured with the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).[16]

Outcomes

The primary endpoint was the rate of diabetes remission at 2 years, defined as a fasting glucose concentration of 5·6 mmol/L or less and an HbA_{1c} concentration of 6·5% or less (≤47·5 mmol/mol) without active pharmacological treatment for at least 1 year, consistent with criteria recommended by an American Diabetes Association expert group.[17] After completion of the analysis for the primary endpoint, patients with poorly controlled diabetes who requested surgical treatment were allowed to crossover to surgery.

At 5 year follow-up, we assessed various secondary outcome measures including durability of diabetes remission and relapse of hyperglycaemia, overall glycaemic control (HbA_{1c} ≤6·5% [≤47·5 mmol/mol]



Number of OHA tablets

	Medical treatment	Roux-en-Y gastric bypass	Biliopancreatic diversion
Baseline	3 (0)	2·53 (1·12)	2·84 (0·69)
2 years	3 (0)	0 (0)	0 (0)
5 years	3 (0)	0·32 (0·67)	0·11 (0·46)

***Figure 2*: Diabetes remission, medication use, changes in weight, and metabolic improvement over 5 years' follow-up**
(A) Proportion of patients with diabetes remission. (B) Diabetes medications and mean (SD) number of glucose-lowering drugs used. (C) Mean (SD) changes in weight. (D) Proportion of patients who achieved metabolic improvement (glycaemic, blood pressure, and lipidaemic control). OHA=oral hypoglycaemic drugs. GLP-1=glucagon-like peptide-1. *From ANOVA comparison. †From χ^2 test.

with or without medication), changes in bodyweight, BMI, waist circumference, arterial blood pressure, plasma total cholesterol, HDL cholesterol and triglycerides, cardiovascular risk, medication use, quality of life, adverse effects of surgery, and diabetes-related complications. To assess the clinical effect of interventions on cardiometabolic risk, we assessed a composite endpoint of metabolic control, defined as the presence of at least two parameters: a reduction of diabetes or cardiovascular drugs in addition to a reduction of 20% or more in HbA_{1c} from baseline, LDL cholesterol less than 2·3 mmol/L, systolic blood-pressure less than 135 mm Hg, or diastolic blood pressure less than 85 mm Hg. These thresholds were proposed in a position statement on bariatric surgery for obese patients with type 2 diabetes from the International Diabetes Federation.[18]

We measured quality of life at 5 years by administration of the RAND 36-Item Health Survey[19] after amendment of the original protocol on July 28, 2014, to include quality-of-life measures. 10 year predicted probability for cardiovascular disease risk was computed at baseline and at each of the scheduled visits during the follow-up with a validated model,[20] thus the risk was estimated up to 15 years from the study beginning.

Statistical analysis

We used a χ^2 test to study the association between treatment type and diabetes remission. All secondary analyses, including quality of life, have an exploratory scope, and have therefore not been corrected for simultaneous inference. 5 year changes in continuous variables are expressed in absolute values and as a proportion of basal values, and were tested with ANOVA. We did post-hoc analyses to compare treatment levels with the Bonferroni correction method for multiple testing.

We applied logistic regression with stepwise elimination to identify possible predictors of diabetes remission. Each predictor was initially entered in a univariate logistic regression to study its ability to independently predict diabetes remission. Only predictors that were significantly associated with remission (p=0·10) in a univariate analysis were entered

	Medical treatment group (n=15)	Roux-en-Y gastric bypass group (n=19)	Biliopancreatic diversion group (n=19)	p value*
Fasting glucose (mmol/L)				
Baseline	9·9 (3·5)	9·8 (3·3)	9·6 (3·5)	0·96
5 years	5·8 (1·3)	5·5 (1·1)	4·8 (0·4)	0·0150
Absolute change	–4·1 (4·1)	–4·3 (3·1)	–4·8 (3·3)	0·84
Percent change (%)	–34·5 (23·6)	–38·9 (20·8)	–45·6 (14·3)	0·25
HbA_{1c} (%)				
Baseline	8·5 (1·3)	8·7 (1·4)	8·9 (1·8)	0·66
5 years	6·9 (0·6)	6·7 (0·5)	6·4 (0·4)	0·0280
Absolute change	–1·6 (1·0)	–2·0 (1·5)	–2·5 (1·8)	0·21
Percent change (%)	–17·9 (8·1)	–21·4 (12·8)	–25·9 (13·8)	0·17
HOMA-IR				
Baseline	9·6 (7·7)	9·6 (5·7)	7·4 (4·4)	0·38
5 years	3·9 (2·4)	2·0 (1·1)	1·4 (0·6)	<0·0001
Absolute change	–5·7 (5·9)	–7·5 (5·8)	–6·1 (4·1)	0·65
Percent change (%)	–49·3 (21·8)	–76·7 (9·6)	–78·0 (9·1)	<0·0001
Weight (kg)				
Baseline	137·1 (23·5)	127·2 (20·6)	137·5 (31·2)	0·39
5 years	127·1 (20·5)	90·3 (12·7)	92·8 (14·0)	<0·0001
Absolute change	–10·0 (12·2)	–37·0 (13·8)	–44·7 (22·4)	<0·0001
Percent change (%)	–6·9 (8·4)	–28·4 (7·4)	–31·1 (9·3)	<0·0001
Waist circumference (cm)				
Baseline	127·7 (16·2)	123·9 (15·4)	131·2 (19·9)	0·40
5 years	113·9 (14·2)	101·5 (12·8)	102·4 (12·6)	0·0170
Absolute change	–13·8 (12·3)	–22·4 (12·5)	–28·8 (14·1)	0·0065
Percent change (%)	–10·3 (9·1)	–17·6 (8·5)	–21·2 (8·2)	0·0023
BMI (kg/m^2)				
Baseline	45·4 (6·5)	44·0 (4·6)	44·7 (7·7)	0·89
5 years	42·1 (5·8)	31·3 (2·5)	30·3 (4·0)	<0·0001
Absolute change	–3·3 (4·1)	–12·7 (4·4)	–14·3 (6·3)	<0·0001
Percent change (%)	–6·9 (8·4)	–28·4 (7·4)	–31·1 (9·3)	<0·0001
Total cholesterol (mmol/L)				
Baseline	6·3 (1·4)	4·7 (1·1)	5·6 (1·5)	0·0020
5 years	4·7 (0·4)	4·4 (0·6)	3·0 (0·5)	<0·0001
Absolute change	–1·6 (1·1)	–0·3 (1·3)	–2·6 (1·4)	<0·0001
Percent change (%)	–23·2 (14·2)	0·02 (32·4)	–43·0 (12·6)	<0·0001
HDL cholesterol (mmol/L)				
Baseline	0·98 (0·19)	1·08 (0·2)	0·99 (0·21)	0·14
5 years	1·05 (0·13)	1·37 (0·25)	1·13 (0·11)	<0·0001
Absolute change	0·06 (0·09)	0·28 (0·17)	0·14 (0·19)	0·0009
Percent change (%)	8·0 (10·6)	27·6 (17·5)	19·2 (25·2)	0·0200
LDL cholesterol (mmol/L)				
Baseline	4·1 (1·3)	2·8 (1·0)	3·6 (1·3)	0·0051
5 years	2·8 (0·4)	2·4 (0·5)	1·4 (0·5)	<0·0001
Absolute change	–1·4 (1·0)	–0·4 (1·2)	–2·2 (1·1)	<0·0001
Percent change (%)	–28·1 (19·3)	0·02 (49·7)	–58·3 (12·5)	<0·0001
Triglycerides (mmol/L)				
Baseline	2·6 (0·7)	1·7 (0·9)	2·3 (0·9)	0·0061
5 years	1·9 (0·3)	1·3 (0·3)	1·1 (0·1)	<0·0001
Absolute change	–0·7 (0·5)	–0·4 (0·8)	–1·2 (0·9)	0·0160
Percent change (%)	–23·3 (20·0)	–11·1 (38·1)	–42·4 (31·5)	0·0130

(Table 2 continues on next page)

into the multivariate model. We investigated possible 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. We also compared changes from baseline in bodyweight and waist circumference between the two surgical groups.

Continuous variables are reported as mean (SD), whereas categorical variables are reported as numbers and percentages. $p<0·05$ was regarded as significant. Analysis was by intention to treat for the primary endpoint and by per protocol for the 5 year follow-up. We did analyses with R (version 2.13.2).[21] This study is registered with ClinicalTrials.gov, number NCT00888836.

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. GM, FR, SP, and ADG had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between April 27, 2009, and Oct 31, 2009, we randomly assigned 60 patients to receive either medical treatment (n=20) or surgery by gastric bypass (n=20) or biliopancreatic diversion (n=20); 53 (88%) patients completed 5 years' follow-up (figure 1). After completion of the 2 year analysis, two (3%) patients in the medical treatment group crossed over to surgery due to inadequate glycaemic control: one patient underwent gastric bypass at month 30 after randomisation and one patient underwent biliopancreatic diversion at month 36 (figure 1). Outcomes for these patients are not included in the 5 year analysis and are presented separately here. There were no differences at baseline in terms of glycaemic control, duration of diabetes, and use of glucose-lowering drugs.[10]

At 5 years, none of the 15 patients in the medical treatment group and 19 (50%) of the 38 patients in the surgery group had achieved diabetes remission (table 1, figure 2). Specifically, seven (37%) of 19 patients in the gastric bypass group and 12 (63%) of 19 patients in the biliopancreatic diversion group had durable remission at 5 years (table 1, figure 1). Irrespective of remission, eight (42%) patients given gastric bypass and 13 (68%) patients given biliopancreatic diversion had HbA_{1c} concentrations of 6·5% or lower (≤47·5 mmol/mol) with or without medications, compared with four (27%) medically treated patients (table 1).

Hyperglycaemia relapsed in 15 (44%) of the 34 surgery patients who achieved 2 year diabetes remission (table 1). However, patients with relapse maintained a mean HbA_{1c} of 6·7% (SD 0·24; 49·7 mmol/mol [SD 2·39]) at 5 years with just diet and either metformin or no medication, whereas seven (47%) of these patients were taking insulin, and all of them were taking various glucose-lowering drugs before surgery. Overall, 31 (82%) of all 38 surgical patients were able to maintain HbA_{1c} less than 7·0% (<53·0 mmol/mol) despite little or no use of glucose-lowering drugs.

Patients who did not achieve diabetes remission by year 2 after surgery did not improve their glycaemic control by year 5. Only baseline concentrations of triglycerides and HOMA-IR were associated with diabetes remission at year 5 in the univariate analysis (appendix). However, after mutual adjustment in the multivariable model with stepwise elimination, only triglycerides predicted remission (β coefficient 0·93, p=0·0290), whereas HOMA-IR was no longer significant. Weight changes did not predict diabetes remission or relapse after surgery (appendix). Mean fasting glucose and HbA_{1c} concentrations at 5 years were significantly lower in the biliopancreatic diversion group than in the gastric bypass and treatment medical groups (tables 1, 2).

Patients in the surgical group used substantially fewer diabetes medications than did medically treated patients at year 5 and throughout the study (figure 2). Overall, 33 (87%) surgery patients required no medication for hyperglycaemia for the duration of the study. 18 (47%) surgery patients required insulin at baseline, alone or in combination with other drugs; all but one of those patients were no longer taking insulin at year 5 (figure 2). By contrast, insulin use increased in the medical group (figure 2).

The two patients who crossed over to surgery had inadequate control of diabetes (HbA_{1c} >7·5% [>58·5 mmol/mol]) despite medical treatment including both oral drugs and insulin. Both surgical techniques induced remission of diabetes in these patients and eliminated the need for insulin and glucose-lowering drugs at the time of the last follow-up in the study (2 years from conversion).

Surgery caused more weight loss and greater changes in BMI and waist circumference than did medical treatment (table 2, figure 2). There were no significant differences in weight changes between the gastric bypass and the biliopancreatic diversion groups (figure 2). Changes in weight were reflected by similar changes in BMI and waist circumference (table 2). We noted modest weight regain between years 2 and 5 in both surgical groups (6·09 kg [SD 2·51] in the gastric bypass group and 4·56 kg [5·49] in the biliopancreatic diversion group), whereas weight remained stable in the medical treatment group (–1·05 kg [5·49]).

At 5 years, criteria for the composite metabolic endpoint was met by two (13%) medically treated patients compared with 13 (68%) patients who had gastric bypass and all patients who had biliopancreatic diversion (figure 2). By contrast, at 2 years, no medically treated patients met the metabolic endpoint compared with all surgically treated patients (p<0·0001).

	Medical treatment group (n=15)	Roux-en-Y gastric bypass group (n=19)	Biliopancreatic diversion group (n=19)	p value*
(Continued from previous page)				
Diastolic blood pressure (mm Hg)				
Baseline	97·3 (19·2)	92·5 (14·6)	96·0 (13·2)	0·59
5 years	84·0 (2·8)	84·2 (3·5)	83·5 (3·0)	0·81
Absolute change	–13·3 (19·0)	–8·3 (13·5)	–12·4 (11·9)	0·58
Percent change (%)	–10·7 (16·5)	–7·4 (11·7)	–11·7 (10·2)	0·57
Systolic blood pressure (mm Hg)				
Baseline	157·5 (37·7)	147·5 (21·0)	155·3 (30·3)	0·52
5 years	132·3 (4·2)	132·5 (6·2)	129·2 (5·8)	0·14
Absolute change	–25·2 (35·9)	–15·0 (18·6)	–26·1 (27·6)	0·42
Percent change (%)	–12·0 (18·3)	–8·9 (10·3)	–14·2 (14·2)	0·53
Risk of coronary heart disease (%)				
Baseline	0·19 (0·11)	0·12 (0·09)	0·16 (0·11)	0·12
5 years	0·13 (0·06)	0·08 (0·07)	0·05 (0·04)	0·0009
Absolute change	–0·06 (0·07)	–0·04 (0·06)	–0·11 (0·09)	0·0100
Percent change (%)	–22·2 (24·2)	–8·3 (75·7)	–67·3 (15·3)	0·0016
Quality of life (SF-36)				
Physical functioning	22·0 (23·9)	77·4 (19·0)	89·5 (16·0)	<0·0001
Physical role	46·7 (41·0)	94·7 (22·9)	76·3 (39·5)	0·0010
Bodily pain	57·8 (30·5)	89·8 (14·8)	89·5 (17·0)	<0·0001
Vitality	40·3 (10·8)	63·7 (10·4)	49·2 (8·0)	<0·0001
Emotional role	46·7 (48·5)	94·7 (22·9)	79·0 (37·2)	0·0016
General health	30·8 (27·1)	87·7 (19·3)	82·3 (24·0)	<0·0001
Social functioning	46·7 (14·5)	96·7 (23·5)	95·4 (21·3)	<0·0001
Mental health	45·6 (24·4)	79·8 (18·9)	59·2 (7·8)	<0·0001
Physical component score	32·8 (8·4)	52·5 (6·3)	55·4 (9·2)	<0·0001
Mental component score	39·4 (9·9)	54·5 (7·8)	44·6 (4·9)	<0·0001
Total score	42·1 (20·9)	85·6 (17·4)	77·5 (19·0)	<0·0001

Data are mean (SD), unless otherwise indicated. We obtained the percent change in each patient and then calculated the mean and SD. HbA_{1c}=glycated haemoglobin A_{1c}. HOMA-IR=Homeostasis Model Assessment of Insulin Resistance. BMI=body-mass index. SF-36=36-Item Short Form Health Survey. *From ANOVA comparisons.

Table 2: **Secondary outcome measures**

Cardiovascular risk was reduced from baseline in all study groups (table 2, figure 3). The estimated cardiovascular risk at year 5 for surgical patients was roughly half that of patients receiving medical treatment (table 2, figure 3). Over the course of the study, surgical patients used significantly fewer cardiovascular drugs (lipid-lowering or blood-pressure drugs) than medically treated patients (figure 3).

See Online for appendix

Surgically treated patients, particularly those undergoing biliopancreatic diversion, had significantly lower plasma concentrations of total cholesterol, LDL cholesterol, and triglycerides than medically treated patients at 5 years (table 2). HDL cholesterol increased in all three groups, with the largest increase in patients in the gastric bypass group (table 2, figure 3).

Systolic and diastolic blood pressure decreased in all groups from baseline to year 5, albeit not significantly (table 2). Although there were no differences in blood pressure at year 5 year between groups, medically

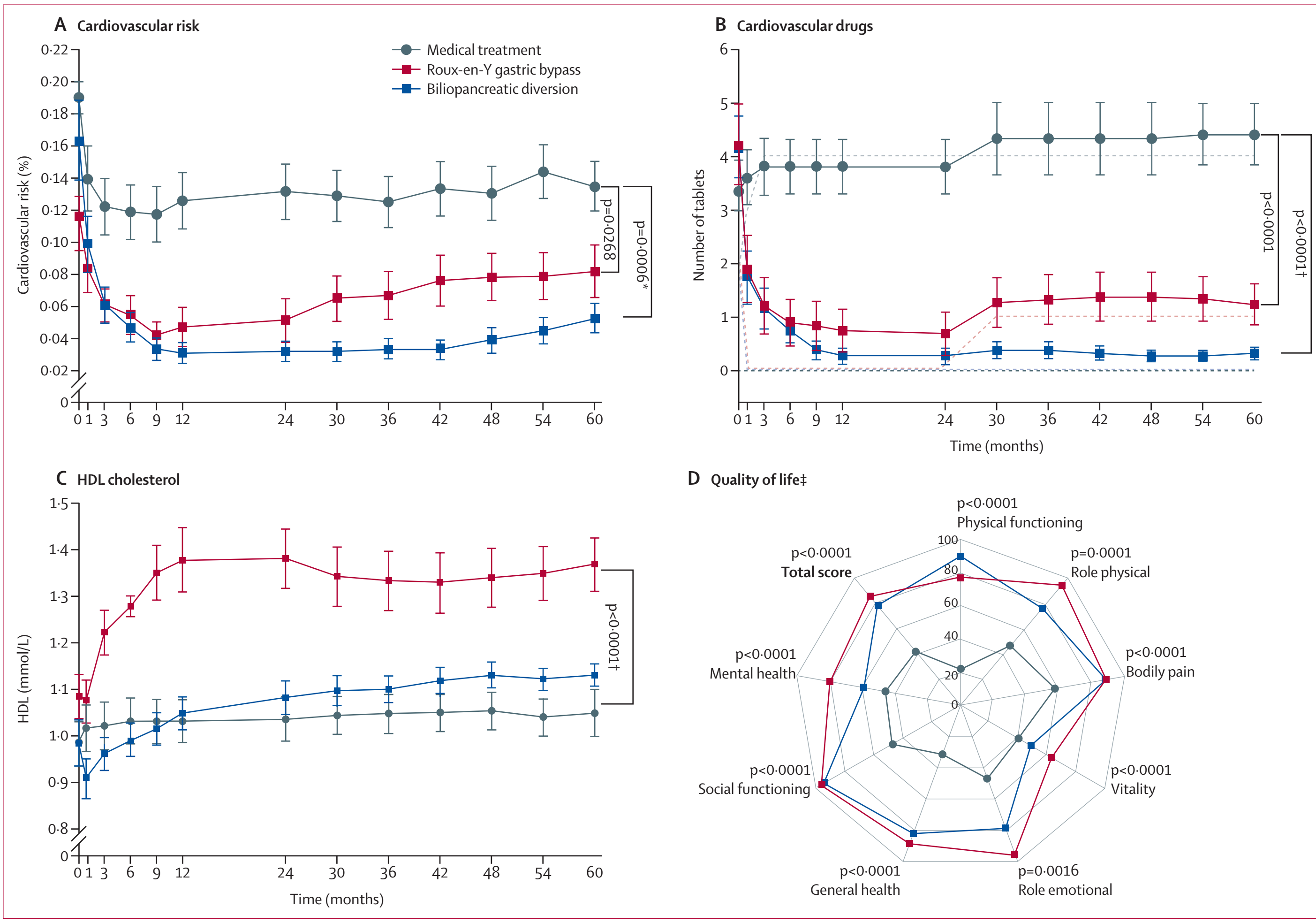


***Figure 3*: Cardiovascular risk, cardiovascular drugs, HDL cholesterol, and quality of life over 5 years' follow-up**
Error bars show SDs. (A) Coronary heart disease probability. (B) Mean number of cardiovascular drugs (including blood pressure and lipid-lowering drugs); dotted lines represent median values. (C) Changes in HDL cholesterol. (D) Values obtained in each domain, and the total scores, of the 36-Item Short Form Health Survey. *From ANOVA post-hoc comparisons. †From non-parametric tests. ‡p values from ANOVA comparisons.

treated patients required more antihypertensive drugs than did patients undergoing either gastric bypass or biliopancreatic diversion (11 [73%] *vs* 11 [58%] and six [32%] patients, respectively; p=0·0498). The appendix reports comparisons between medical treatment and surgery for all the recorded outcomes. HbA_{1c} was significantly lower in the combined surgical group than in the medical group after 5 years (p=0·0359; appendix)

Surgical patients scored significantly better than medically treated patients for all subdomains of quality of life and for the total score domains (table 2, figure 3). Additionally, patients who underwent gastric bypass had significantly higher scores for the domains of vitality and mental health than did those who underwent biliopancreatic diversion (table 2, figure 3). The mental component score was likewise significantly higher in the gastric bypass group than in the biliopancreatic diversion group (p=0·0004; table 2).

Five major complications of diabetes (including one fatal myocardial infarction) arose in four (27%) patients in the medical group during the 5 year study compared with only one complication in the gastric bypass group and no complications in the biliopancreatic group (table 3). No patients died in the surgery groups and there were no late surgical complications in patients undergoing either technique. Early surgical complications included one incisional hernia requiring reoperation (9 months after biliopancreatic diversion), and one intestinal obstruction requiring reoperation (6 months after gastric bypass; table 3). Two (13%) patients who underwent medical treatment had persistent diarrhoea associated with metformin, a side-effect that resolved when the drug was replaced with another oral hypoglycaemic drug (table 3). The incidence of metabolic adverse events was higher in the surgical groups than in the medical treatment groups (table 3).

	Medical treatment group (n=15)	Roux-en-Y gastric bypass group (n=19)	Biliopancreatic diversion group (n=19)
Surgical complications			
Intestinal occlusion	0	1 (5%)	0
Incisional hernia	0	0	1 (5%)
Metabolic complications			
Iron-deficiency anaemia	0	3 (16%)	5 (26%)
Hypoalbuminaemia (albumin <35 g/L)	0	0	3 (16%)
Osteopenia (BMD T-score of −2*)	1 (7%)	1 (5%)	3 (16%)
Osteoporosis (BMD T-score of −2·7*)	0	0	1 (5%)
Transient nyctalopia	0	0	1 (5%)
Renal calculus	0	1 (5%)	2 (11%)
Coronary heart disease			
Myocardial infarction†	1 (7%)	0	0
Retinopathy	1 (7%)‡	0	0
Nephropathy (proteinuria >0·5 g/24 h)	1 (7%)	1 (5%)	0
Neuropathy	2 (13%)§	0	0
Symptomatic hypoglycaemia	0	2 (11%)¶	0
Albumin to creatinine ratio >30 mg/g pre-treatment	4 (27%)	3	2 (11%)
Albumin to creatinine ratio >30 mg/g at 5 years follow-up‖	4 (27%)	0	0

Data are n (%), unless otherwise indicated. BMD=bone mineral density. *BMD at the femoral neck tested with dual-energy X-ray absorptiometry. †Fatal myocardial infarction that led to the death of the patient. ‡Moderate non-proliferative retinopathy according to the International Clinical Disease Severity Scale for diabetic retinopathy.[22] Retinopathy was not present before surgery. §One patient had grade 2b (nerve conduction abnormality with signs and typical neuropathic symptoms) neuropathy according to Dyck classification,[23] and another patient had neuropathic foot ulcer. ¶Symptomatic or severe hypoglycaemia is defined, according to American Diabetes Association definitions,[24] as a hypoglycaemia requiring the assistance of another individual. One patient had three symptomatic hypoglycaemic episodes (blood glucose reported ≥2·5 mmol/L) in 5 years, and the other patient had four episodes (blood glucose reported ≥2·2 mmol/L) in that time. No hospital admission was necessary. ‖One of the patients with an albumin to creatinine ratio greater than 30 mg/g at baseline died of myocardial infarction and one other patient developed albuminuria after enrolment.

Table 3: **Early and long-term complications**

Discussion

Roux-en-Y gastric bypass and biliopancreatic diversion were both more effective than standard medical treatment for the long-term control of hyperglycaemia and for patients' overall metabolic profile. Surgery also resulted in a greater reduction of cardiovascular risk, diabetes-related complications, and medication use, including glucose-lowering drugs, insulin, and cardiovascular drugs. Furthermore, surgical patients had a better quality of life than medically treated patients. The medical group had fewer intervention-related complications than the surgical group; however, early surgical complications were relatively benign with both procedures. No late complications or deaths occurred after surgery, and long-term significant nutritional side-effects were noted mostly after biliopancreatic diversion.

This study has several limitations that stem mainly from its relatively small sample size. We also acknowledge that the choice of diabetes remission as the primary endpoint might have favoured surgery in this study because remission is defined by an absence of ongoing pharmaceutical treatment, it is a rare event with conventional treatment and common after bariatric surgery. However, compared with the medical group, twice as many surgical patients maintained HbA_{1c} concentrations of 6·5% or less (≤47·5 mmol/mol) at 5 years with or without glucose-lowering drugs, showing that the study was robust enough to document differences in other measures of glycaemic control, beyond remission of hyperglycaemia. Diet and medical treatment resulted in substantial and durable improvement of glycaemia and weight loss, meaning that the conventional treatment of diabetes used in this study was a robust comparator to assess the relative potency of surgical treatment.

Overall, half of surgically treated patients were able to maintain long-term remission of diabetes, confirming that remission of diabetes can be a durable event in many patients. The ability of surgery to induce remission even in the two patients for whom medical treatment proved ineffective provides further evidence of the powerful antidiabetic effect of surgical treatment. However, relapse of hyperglycaemia occurred in 37% of biliopancreatic diversion patients and 53% of gastric bypass patients who had achieved 2 year remission, which underscores the need for continued long-term monitoring of glycaemia in all patients after surgery.

Although some patients had relapse of hyperglycaemia after initial remission, roughly 80% of all surgical patients were able to maintain HbA_{1c} at less than 7·0%

(<53·0 mmol/mol) at 5 years, despite little or no use of glucose-lowering drugs. Notably, all but one of the surgically treated patients receiving insulin at baseline did not require insulin in the following 5 years. A long period of remission might have substantial health benefits even in patients who eventually experience relapse of mild hyperglycaemia. Furthermore, substantial reduction of insulin requirement or discontinuation of insulin treatment might have favourable implications for quality of life and overall costs of diabetes treatment.

Remission rates of diabetes after gastric bypass in this study are similar to those reported in other similar randomised controlled trials.[9,11] Although our study was not designed to compare surgical procedures head to head, biliopancreatic diversion resulted in a significantly higher rate of diabetes remission and a lower risk of disease recurrence than gastric bypass. However, gastric bypass induced optimum glycaemic and metabolic control, but with fewer nutritional side-effects and a better quality of life than did biliopancreatic diversion. This finding suggests that Roux-en-Y gastric bypass might have a more favourable risk to benefit ratio than biliopancreatic diversion, whereas biliopancreatic diversion might be a potent alternative in patients with more advanced disease.

The mechanisms responsible for the effects of surgery on diabetes are not completely understood. In this study, weight changes were not associated with either remission or relapse of diabetes; furthermore, despite differences in glycaemic control, weight loss and changes in BMI did not differ significantly between patients in either surgery group. This finding supports the notion that gastrointestinal surgery might activate weight-independent mechanisms of diabetes control and suggests that differences in surgical anatomy might explain variance in clinical effectiveness of surgical procedures. It is important to note that the biliopancreatic diversion technique used in this study involves a partial, horizontal gastrectomy, and patients who underwent the procedure had a much larger gastric reservoir than did those who underwent gastric bypass. This point suggests that intestinal mechanisms might exert more important antidiabetic effects than would changes in gastric volume and gastric physiology. One hypothesis is that a longer bypass of the small intestine as with biliopancreatic diversion might be more effective in reducing putative diabetogenic mechanisms from the proximal bowel.[2,25,26] This hypothesis is supported by several studies, including experiments in rodents[27] and studies in human beings, in which longer biliopancreatic limb gastric bypass improved diabetes more than standard-length gastric bypass.[28] Mechanistic studies specifically designed to investigate this hypothesis could provide important clues for the future design of surgical procedures, and new targets for novel devices and pharmaceutical interventions.

Intriguingly, patients in the gastric bypass group had extremely high plasma concentrations of HDL cholesterol, suggesting that differences in gastrointestinal anatomy might also induce distinct effects on lipid metabolism. Understanding of the mechanism responsible for the effects of gastric bypass on HDL cholesterol could identify new targets for the development of lipid-lowering drugs.

The greater incidence of diabetes-related complications in this study, including a fatal myocardial infarction in medically treated patients, suggests that surgery could also reduce risk of diabetes complications. This finding is consistent with results from a large, non-randomised, case-control study showing that bariatric surgery is associated with reduced incidence of heart attacks, stroke, and microvascular complications compared with usual care.[29] We will continue to follow-up patients in this study with the intent to verify whether the differences in cardiovascular risk between surgery and medical treatment will translate into actual reductions of cardiovascular adverse events and mortality.

In summary, surgery is more effective than medical treatment for the long-term control of obese patients with type 2 diabetes. This evidence supports consideration of surgery in the treatment algorithm of type 2 diabetes. However, continued monitoring of glycaemic control is warranted because of potential relapse of hyperglycaemia in some patients.

Contributors

GM and SP contributed equally to the report and share first authorship. GM, FR, MC conceived the study. GM, FR, MC, and GN designed the study. FR, GN, and MC performed the surgical procedures. CG and AI were responsible for data acquisition. SP and ADG did the analysis. GM, SP, ADG, and FR have access to the data. GM, FR, and SP interpreted the data. GM, FR, SP, and SB drafted the Article. ADG, MC, GN, and SB critically reviewed the manuscript for important intellectual content. All authors agree 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.

Declaration of interests

We declare no competing interests.

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