Gastric bypass *versus* best medical treatment for diabetic kidney disease: 5 years follow up of a single-centre open label randomised controlled trial

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eClinicalMedicine
2022;53: 101725

Published Online 11 November 2022
https://doi.org/10.1016/j.eclinm.2022.101725

Summary

Background We compared the albuminuria-lowering effects of Roux-en-Y gastric bypass (RYGB) to best medical treatment in patients with diabetic kidney disease and obesity to determine which treatment is better.

Methods A 5 year, open-label, single-centre, randomised trial studied patients with diabetic kidney disease and class I obesity after 1:1 randomization to best medical treatment (n = 49) or RYGB (n = 51). The primary outcome was the proportion of patients achieving remission of microalbuminuria after 5 years. Secondary outcomes included improvements in diabetic kidney disease, glycemic control, quality of life, and safety. For efficacy outcomes, we performed an intention-to-treat (ITT) analysis. This study was registered with ClinicalTrials.gov, NCT01821508.

Findings 88% of patients (44 per arm) completed 5-year follow-up. Remission of albuminuria occurred in 59.6% (95% CI = 45.5–73.8) after best medical treatment and 69.7% (95% CI = 59.6–79.8) after RYGB (risk difference: 10%, 95% CI, –7 to 27, P = 0.25). Patients after RYGB were twice as likely to achieve an HbA1c ≤ 6.5% (60.2% versus 25.4%, risk difference, 34.9%; 95% CI = 15.8–53.9, P < 0.001). Quality of life after five years measured by the 36-Item Short Form Survey questionnaire (standardized to a 0-to-100 scale) was higher in the RYGB group than in the best medical treatment group for several domains. The mean differences were 13.5 (95% CI, 5.5–21.6, P = 0.001) for general health, 19.7 (95% CI, 9.1–30.3, P < 0.001) for pain, 6.1 (95% CI, –4.8 to 17.0, P = 0.27) for social functioning, 8.3 (95% CI, 0.23 to 16.3, P = 0.04) for emotional well-being, 12.2 (95% CI, 3.9–20.4, P = 0.004) for vitality, 16.8 (95% CI, –0.75 to 34.4, P = 0.06) for mental health, 21.8 (95% CI, 4.8–38.7, P = 0.01) for physical health and 11.1 (95% CI, 2.24–19.9, P = 0.01) for physical functioning. Serious adverse events were experienced in 7/46 (15.2%) after best medical treatment and 11/46 patients (24%) after RYGB (P = 0.80).

Interpretation Albuminuria remission was not statistically different between best medical treatment and RYGB after 5 years in participants with diabetic kidney disease and class 1 obesity, with 6–7 in ten patients achieving remission of microalbuminuria (uACR <30 mg/g) in both groups. RYGB was superior in improving glycemia, diastolic blood pressure, lipids, body weight, and quality of life.

Funding The study was supported by research grants from Johnson & Johnson Brasil, Oswaldo Cruz German Hospital, and by grant 12/YI/B2480 from Science Foundation Ireland (Dr le Roux) and grant 2015-02733 from the

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Swedish Medical Research Council (Dr le Roux). Dr Pereira was funded by the Chevening Scholarship Programme (Foreign and Commonwealth Office, UK).

Keywords: Bariatric surgery; Type 2 diabetes; Diabetic kidney disease; Obesity

Research in context

Evidence before this study

We searched MEDLINE from January 1, 2000, to March 30, 2022, for randomised clinical trials, case–control studies, and observational series reporting on the renal effects of Roux-en-Y gastric bypass surgery for patients with type 2 diabetes, obesity and diabetic kidney disease. Keywords included "bariatric surgery", "metabolic surgery", "type 2 diabetes", "diabetic kidney disease", and "Roux-en-Y gastric bypass". All non-randomised studies showed that bariatric surgery has renal protective effects. However, those case–control and observational studies may have overestimated the effects of surgery on kidney outcomes. We were prompted to conduct this study as all previous randomised controlled trials of metabolic surgery only focused on glycaemic outcomes and not on the complications of diabetes. Moreover, previous trials did not benefit from the latest medications now in routine use to treat diabetic kidney disease.

Added value of this study

We report the 5 years follow-up of a randomised controlled trial comparing Roux-en-Y gastric bypass with the best current medical treatment for patients with, diabetes and chronic kidney disease. RYGB was as effective as the best medical treatment for achieving remission of albuminuria (urine albumin creatinine ratio below 30 mg/g) and chronic kidney disease (remission of albuminuria (<30 mg/g) with an eGFR >60 mL/min). Surgery was, however, better at achieving weight loss, glycemic control, and quality of life. Surgery had a similar safety profile to the best medical care.

Implications of all the available evidence

This data contributes to the evolving clinical management of diabetic kidney disease. Best medical therapy was an effective strategy for many patients with diabetes, obesity and kidney disease. This is a potentially disruptive finding because, until now, metabolic surgery substantially outperformed the best medical care on all the relevant clinical outcomes. Our 5 years data may be used to support the best medical therapy as the first option for patients and clinicians. However, Roux-en-Y gastric bypass was also safe and effective in remission of albuminuria and diabetic kidney disease, offering several extra-renal benefits. Thus, clinicians should not be hesitant to refer patients to surgery, as people with diabetes complications do not carry higher surgical risks. A subsequent question that remains to be answered is the relative and additive benefits of best medical therapy and RYGB in slowing the progression of more advanced diabetic kidney disease.

Introduction

Diabetic kidney disease is a significant cause of early mortality in patients with type 2 diabetes.[1] The Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease (CKD) working group classification, $CKD_{G1\text{-}3a;\ A2\text{-}3}$ identifies patients with a urine albumin creatinine ratio (uACR) above 30 mg/g in combination with an estimated glomerular filtration rate above 45 mL/min.[2] Around 30–40% of patients with type 2 diabetes are in $CKD_{G1\text{-}3a;\ A2\text{-}3,}$ which predicts other micro and macrovascular complications.[3] Albuminuria is a major clinical biomarker of diabetic kidney disease, and contemporary advances in pharmacotherapy have significantly reduced albuminuria in patients with diabetes.[4–6] Unfortunately, diabetic kidney disease remains a chronic progressive condition despite the best medical care.[7]

The American Diabetes Association and International Diabetes Federation suggest metabolic surgery as rescue therapy to treat hyperglycemia in patients with obesity and difficult-to-control type 2 diabetes.[8] These patients continue to pose a clinical challenge, and despite optimized non-surgical therapeutic regimens, a substantial residual morbidity and mortality risk persist.[9,10] Roux-en-Y gastric bypass (RYGB) was superior in 13 randomised controlled trials to medical care for glycemic control, weight loss, blood pressure, dyslipidemia, and quality of life. Nevertheless, the complications of diabetes have not been a focus of these trials,[11–15] except in one where the interim results

showed that RYGB after 2 years was better than the best medical treatment in patients with diabetic kidney disease and class 1 obesity (body mass index [BMI] 30–35 kg/m^2).[16]

Modest increases in albuminuria have been associated with incident chronic kidney disease, risk of myocardial infarction, and all-cause mortality.[17,18] Hence, lowering albuminuria may further reduce the risk of end-organ damage, including a reduction in function.[19] Observational studies and our interim analysis of a randomised controlled trial suggest that metabolic surgery reduces albuminuria in patients with type 2 diabetes,[16,20–22] but we conducted this study because evidence from definitive randomised controlled trials is needed to change clinical practice.

We aimed to assess if RYGB was more effective than the best medical treatment in achieving remission of albuminuria after 5 years in patients with diabetic kidney disease and class 1 obesity.

Methods

Study design

A detailed description of the Microvascular Outcomes after Metabolic Surgery (MOMS) trial protocol[23] and the results of the 2-year follow-up were published previously.[16] All participants provided written informed consent, and the study was approved by the Institutional Research Ethics Committee of Hospital Alemão Oswaldo Cruz, São Paulo, Brazil. We recruited patients between 2013 and 2016 into a single-center, randomised trial with a five-year follow-up (NCT01821508). The study compared the impact of best medical treatment and RYGB on renal outcomes and other cardiovascular risk factors in patients with diabetic kidney disease and a BMI of 30–35 kg/m^2. Using a computer-generated (Stata 14), centrally concealed, and stratified 1:1 randomization sequence, we assigned 100 eligible patients to the best medical treatment or RYGB (Fig. 1). Randomization was stratified by sex. The study sponsors were not involved in the study design, conduct, or analysis. Detailed information on the randomization procedure and database structure can be found in our previous publications.[16,23] The trial protocol (original, amendments, and final version) is available in the supplementary appendix.

Participants

Eligibility criteria at screening included uACR >30 mg/g, but <300 mg/g, type 2 diabetes with glycated hemoglobin (HbA1c) <12%, eGFR >60 mL/min, age 18–65 years, and a BMI of 30–35 kg/m^2. Study eligibility criteria for MOMS have been described previously.[23]

Study treatments

All patients were treated using the best medical treatment defined by American Diabetes Association guidelines.[24] Best medical treatment continued to evolve, and our protocol was generally consistent with the updated 2021 ADA guidelines.[25] The core pharmacological armamentarium has been described previously.[16,23] Drugs with a beneficial effect on microvascular and macrovascular outcomes, such as angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, sodium-glucose co-transporter 2 inhibitors (empagliflozin), glucagon peptide 1 analog (liraglutide), and statins, were continued in the best medical treatment arm even when metabolic targets were met, and albuminuria remission had occurred. Angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and statins were continued in the RYGB arm even if albuminuria had remitted, and sodium-glucose co-transporter 2 inhibitors, glucagon peptide 1 analog were added to RYGB in rare cases of weight regain or relapse of diabetes remission. Glucose-lowering drugs, including insulin, had their dose adjusted depending on patients' glycemic control. Metformin was maintained in all patients; however, doses were reduced or stopped when HbA1c was <5.7%, fasting plasma glucose <100 mg/dL, and/or metformin caused gastrointestinal side effects. Except for the post-operative visit (PO7) for the surgical arm, all patients had the same follow-up with the study team throughout these five years. All efforts were done by a specialized and totally dedicated research team to ensure patients' adherence to protocol visits (and their respective procedures).

RYGB was performed laparoscopically by a single surgeon and consisted of a 30 mL gastric pouch, a 150 cm alimentary limb, and an 80 cm biliopancreatic limb (Supplementary Fig. S1).

The operative technique used in this study is very standard and thus can be performed by any trained bariatric surgeon. The RYGB group received standard supplementation and was assessed for nutritional deficiencies at 6, 12, 18, 24, 36, 48, and 60 months.

Outcomes

The primary outcome was the proportion of patients achieving remission of microalbuminuria (uACR <30 mg/g; <3.39 mg/mmol) after 5 years. A non-prespecified analysis included remission of diabetic kidney disease, defined as remission of albuminuria (<30 mg/g) with an eGFR >60 mL/min. Pre-specified secondary outcomes included albuminuria, metabolic control (glycemia, blood pressure, lipid profiles, weight loss), medication usage, quality of life (validated Brazilian-Portuguese language version of the SF-36 questionnaire[26]), and adverse events. Supplementary Table S1 describes detailed trial outcomes, Supplementary Table S2 summarizes all non-prespecified outcomes.

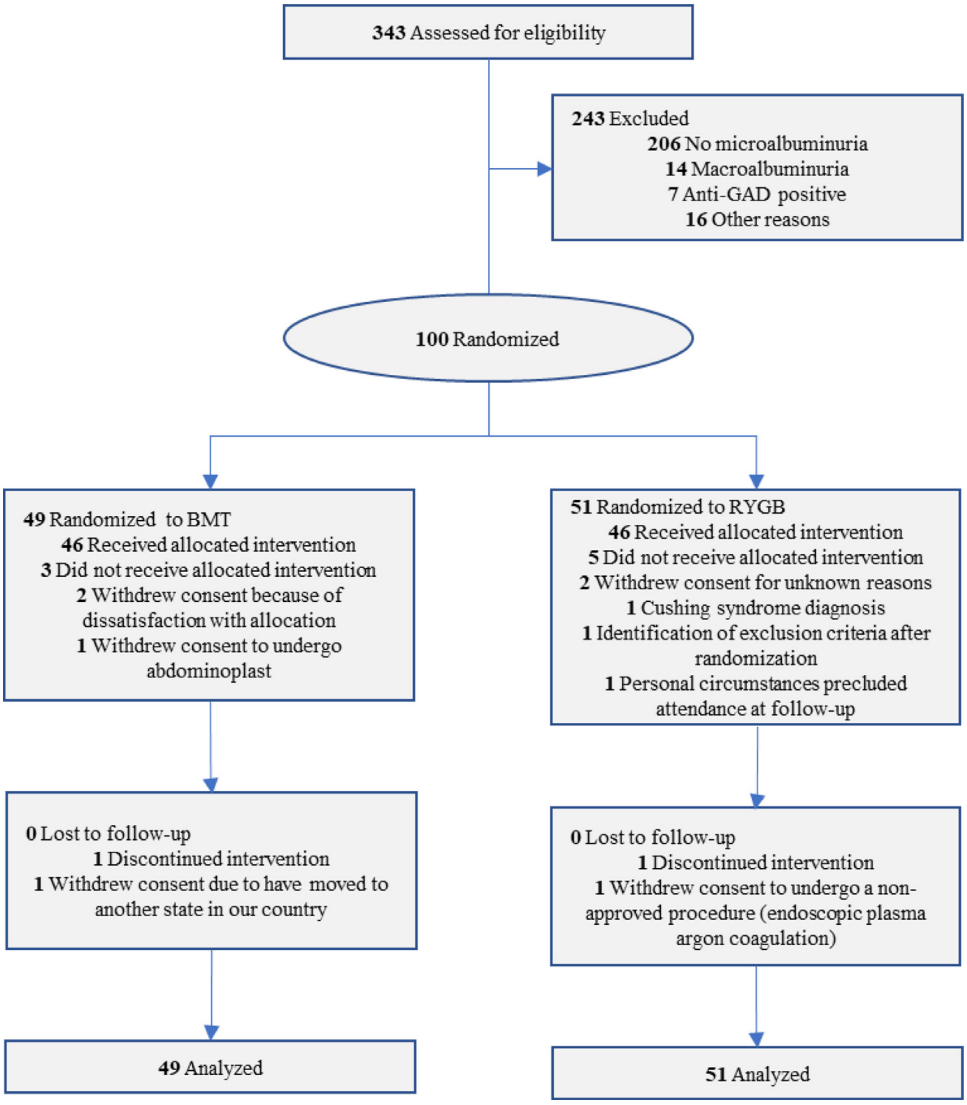

Fig. 1: CONSORT diagram of screening, enrollment and 60-month follow-up in the Microvascular Outcomes after Metabolic Surgery (MOMS) Trial. The intention-to-treat population included 49 patients in the best medical treatment (BMT) group and 51 patients in the Roux-en-Y gastric bypass (RYGB) group, whereas the safety population included 46 patients in each group. GAD, glutamic acid decarboxylase.

We coded adverse events according to the preferred terms and system organ classes in the *Medical Dictionary for Regulatory Activities (MedDRA)*, version 23.1. We summarized those events according to severity (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening or disabling and then assessed the relationship to the intervention (best medical treatment or RYGB).

Data collection

We assessed uACR, eGFR, HbA1c, fasting plasma glucose, blood pressure, lipid profiles, body weight, and waist circumference at baseline, 6,12, 24, 36, 48, and 60 months. Information on adverse events was collected continuously.

Sample size

Fifty participants per treatment group provided ≥90% power at the 1.7% significance level (two-sided) for detecting a five-fold relative difference in achieving the primary outcome after 5 years between groups (10% vs. 50%).[23] In 2012, before the advent of recent antidiabetic drugs, this was the realistic predicted difference between RYGB and the best medical treatment based on

available evidence and clinical experience.[23] Sample size calculations assumed a 20% loss of follow-up rate. The α level was pre-specified[23] and reflected the Bonferroni correction for multiple testing (three assessments made at 12, 24, and 60 months, $0.05/3 \approx 0.017$). The DELTA2 checklist is provided in Supplementary Table S3. Further details on the sample size calculation are reported in the trial protocol.[23]

Statistical analyses

Continuous outcomes were presented as means (standard deviation, SD), median (interquartile range, IQR), or mean (95% confidence interval [95% CI]). Binary outcomes were presented as numbers (percentage), and treatment effects were summarized as risk differences (95% CI) or odds ratio (OR) (95% CI). We present results as odds ratios (95% CIs) for safety outcomes, given model non-convergence for rare outcomes and the necessity of using exact logistic regression models.

For efficacy outcomes, we performed an intention-to-treat (ITT) analysis, in which all randomised participants were included and contributed to the analysis – regardless of protocol deviations or intervention received. For comparison, complete-case (per protocol) analyses were also conducted. The safety population was defined as all randomised participants who received the intended intervention (best medical treatment or RYGB) - regardless of follow-up time and withdrawals.

Changes in the statistical analysis plan are described in the Supplementary Table S4. We analysed continuous efficacy outcomes with linear mixed-effects regression models and binary efficacy outcomes with logistic mixed-effects models. Ordered categorical outcomes were analysed by mixed-effects ordered logistic regression models. All models accounted for the repeated measures over time and were estimated via restricted maximum likelihood using the identity variance-covariance structure. Missing data were inherently accounted for in the mixed-effects models - assuming that data were missing at random. In the fixed-effect part of the models, we included a dummy variable denoting the treatment group, time (as a categorical variable), and the interaction between time and treatment group. The random-effects part of the model included a random intercept for each participant ("random intercept only" model). To facilitate the interpretation, we converted mixed-effects models' results to mean differences and risk differences (percentage-point differences). We fitted exact logistic regression models with the treatment group as an independent variable for safety binary outcomes, given the mixed-effect models' sparse data and non-convergence problems. A two-sided P-value <0.017 indicated statistical significance for the primary outcome. A P-value <0.05 was considered statistically significant for all the remaining outcomes. We used no adjustment for multiple comparisons in secondary outcomes, and the results are considered exploratory. All analyses were performed in Stata 14.0 (StataCorp, Texas, USA).

Role of the funder

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

Results

Patients were recruited from a single center and randomised between April 1, 2013, through March 31, 2016. After 5 years, 88 patients (44 per group) completed the follow-up with no crossovers. As shown in Fig. 1, eight patients did not receive the assigned interventions: 3 in the best medical treatment arm and 5 in the RYGB arm. The efficacy population (ITT analysis) comprised 100 participants, whereas the safety population comprised 92 patients (46 in each arm).

Primary end-point

In the ITT analysis, remission of microalbuminuria (uACR <30 mg/g) was achieved in 59.6% (95% CI = 45.5–73.8) of patients after best medical treatment and 69.7% (95% CI = 59.6–79.8) after RYGB (P = 0.25) (Table 2 and Fig. 2, panel A).

Secondary endpoints

Albuminuria levels and diabetic kidney disease

The geometric mean for albuminuria levels was 46% lower after RYGB (P = 0.001) (Fig. 2, panel B). Changes in albuminuria occurred within 6 months and remained stable between 2 and 5 years. A non-pre specified outcome, remission of diabetic kidney disease, occurred in 52.8% (95% CI = 37.9–67.6) of patients after best medical treatment and 63.1% (95% CI = 49.5–76.7) after RYGB (P = 0.32).

Metabolic control

ADA criteria. After 5 years, the ADA composite target[25] was achieved by 7.3% after best medical treatment and 22% after RYGB (risk difference, 14.9%, 95% CI = –0.1 to 29.9, P = 0.06) (Table 2). Mean HbA1c reduced by –1.2% points after best medical treatment and –2.3% points after RYGB, with a mean difference of –1.3% (95% CI = –11.8 to –0.7, P < 0.001) (Table 2 and Fig. 2, panel C). The ADA target of HbA1c ≤ 6.5% was achieved by 25.4% after best medical treatment and 60.2% after RYGB (risk difference, 34.9%; 95% CI = 15.8–53.9, P < 0.001) (Table 2).

Blood pressure. At baseline, 78% of patients were either treated for hypertension or had blood pressures in the

Characteristic	BMT (N = 49)	RYGB (N = 51)
Age – yr, Mean (SD)	50.2 (7.5)	52.5 (7.6)
Diabetes duration – years, Median (IQR)	9 (5–13)	10 (6–12)
Male sex, no. (%)	27 (55)	28 (55)
Race[a], no (%)		
White	34 (69)	46 (90)
Black	2 (4.1)	0
Asian	3 (6.2)	1 (2)
Mixed	8 (16)	4 (7.8)
Undeclared	2 (4.1)	0
Waist circumference – cm, Mean (SD)	111.1 (8.1)	112.2 (8.01)
BMI[b], Mean (SD)	32.6 (2.1)	32.5 (1.9)
Creatinine – mg/dL, Median (IQR)	0.80 (0.65–0.95)	0.78 (0.64–0.98)
Urinary creatinine –g/dL, Median (IQR)	0.95 (0.64–1.12)	0.95 (0.71–1.33)
Albuminuria – mg/g of creatinine		
Median (IQR)	73 (52–168)	72 (53–143)
eGFR stages[a]		
Stage 1, No. (%)	36 (73.5)	36 (70.1)
Stage 2, No. (%)	10 (20.4)	13 (25.5)
Stage 3, No. (%)	3 (6.1)	2 (3.9)
Retinopathy status, No. (%)		
Not available or undetermined	6 (12)	3 (6)
None	29 (59)	31 (61)
NPDR	9 (18)	11 (22)
PDR	5 (10)	6 (12)
Neuropathy Status, no. (%)		
Not available	1 (2)	3 (6)
None	25 (51)	25 (49)
Any	23 (47)	23 (45)
Glycemia		
HbA1c – %, Mean (SD)	8.94 (1.96)	8.80 (1.86)
Fasting plasma glucose – mg/dL, median (IQR)	174 (142–232)	167 (145–208)
Lipids		
Total Cholesterol – mg/dL, Mean (SD)	192.8 (46.6)	185.2 (38.4)
HDL – mg/dL, Mean (SD)	39.0 (11.4)	41.1 (12.4)
LDL – mg/dL, Mean (SD)	108.6 (41.1)	102 (36.5)
Proportion of patients LDL <100 mg/dL, no.(%)	22 (45)	24 (47)
Triglycerides – mg/dL, Median (IQR)	214 (150–334)	195 (145–293)
Blood pressure		
Systolic – mmHg, Mean (SD)	137.3 (15.5)	141.5 (17.2)
Diastolic – mmHg, Mean (SD)	85.7 (8.0)	88.1 (12.7)
Medications		
Biguanides, no. (%)	45 (91.8)	40 (78.4)
Thiazolidinediones, no. (%)	4 (8.2)	2 (3.9)
GLP-1 analog/receptor agonists, no (%)	13 (26.5)	23 (45)
SGLT2 inhibitors, no. (%)	2 (4.1)	2 (3.9)
Secretagogues, no. (%)	20 (40.8)	21 (41.2)
Insulin, no. (%)	12 (24.5)	20 (39.2)
Lipid lowering agents, no. (%)	18 (36.7)	30 (58.8)
Beta-blockers, no. (%)	6 (12.2)	8 (15.7)
Calcium channel blockers, no. (%)	7 (14.3)	13 (25.5)
ACE-inhibitors or ARBs, no. (%)	30 (61.2)	37 (72.5)
Diuretics, no. (%)	17 (34.7)	15 (29.4)
Anticoagulants, no. (%)	16 (32.7)	17 (33.3)

The median (IQR) age was 50 years (45–55) for the best medical treatment group and 54 years (48–58) for the RYGB group. The median (IQR) body mass index was 33 kg/m^2 (31–34) for the best medical treatment group and 33 kg/m^2 (31–34) for the RYGB. BMT - best medical treatment; RYGB - Roux-en-Y gastric bypass; SD - standard deviation; IQR-inter-quartile range; NPDR-non-proliferative diabetic retinopathy; PDR-proliferative diabetic retinopathy; GLP-1- glucagon-like peptide 1; SGLT2-sodium-coupled glucose transporter 2; ACE inhibitor-angiotensin-converting enzyme inhibitor; ARB-angiotensin-receptor blocker. [a]Race was self-reported. [b]BMI - body mass index, is weight (kg) divided by the square of the height (m).

Table 1: **Baseline characteristics of the trial participants (ITT population,n = 100).**

Outcome	BMT (N = 49)	RYGB (N = 51)	Difference [a](95% CI)	P value
Primary outcome				
ITT analysis, %	59.6 (45.5–73.8)	69.7 (59.6–79.8)	10.1 (−7.1 to 27.3)	0.25
Complete case analysis (no missing data)[b], no. (%)	26 (59.1)	30 (68.2)	9.1 (−10.9 to 29.1)	0.38
Secondary outcomes				
Albuminuria – mg/g of creatinine[c]	30.2 (21.6–42.2)	13.9 (9.9–19.3)	0.46 (0.29–0.74)[c]	0.001
eGFR ml/min/1.73 m^2	88.8 (83.7–93.9)	89.6 (84.5–94.6)	0.75 (−6.4 to 7.9)	0.84
eGFR stages				
Estimated proportion (%), Stage 1	70.7 (65–76)	67.5 (59–76)	−3.3 (−13.1 to 6.5)	0.51
Estimated proportion (%), Stage 2	24 (19.8–28.2)	25.5 (18.6–32.5)	1.5 (−3.7 to 6.6)	0.58
Estimated proportion (%), Stage 3	5.2 (1.6–8.8)	7.1 (1.4–12.7)	1.9 (−3.7 to 7.4)	0.51
HbA1c – %	7.75 (7.38–8.1)	6.48 (6.11– 6.85)	−1.26 (−1.78 to −0.74)	<0.001
Estimated proportion (%) of patients ≤7·0%	38.6 (24.7–52.5)	79.3 (67.9–90.7)	40.6 (22.7–58.7)	<0.001
Estimated proportion (%) of patients ≤6·5%	25.4 (12.7– 38.0)	60.2 (45.9–74.5)	34.9 (15.8–53.9)	0.001
Estimated proportion (%) of patients ≤6·0%	11.4 (2.1–20.6)	20.0 (8.4–31.4)	8.5 (−6.0 to 23.0)	0.25
Fasting glucose – mg/dL	145.4 (132.4–158.4)	112.7 (99.8–125.7)	−32.6 (−51.0 to −14.3)	<0.001
Estimated proportion (%) of patients <100 mg/dL	13.7 (3.8–23.6)	34.8 (20.5–49.0)	21.1 (3.8–38.4)	0.02
SBP – mmHg	135.9 (130.9–141.0)	131.1 (126.2–136.1)	−4.81 (−11.9 to 2.25)	0.18
DBP – mmHg	86.0 (82.9–89.1)	78.9 (75.8– 82.0)	−7.12 (−11.5 to −2.7)	0.001
Estimated proportion (%) – SBP <130 mmHg	16.6 (4.8–28.3)	38.8 (23.8–53.8)	22.3 (3.2–41.3)	0.03
Estimated proportion (%) – DBP <80 mmHg	8.5 (0.01–17.5)	38.7 (23.6–53.8)	30.3 (12.6 to 47.7)	0.003
Body-mass index[d]	31.1 (30.3–31.9)	24.89 (24.1–25.7)	−6.21 (−7.35 to −5.07)	<0.001
Waist circumference – cm	105.4 (102.3–108.5)	93.3 (90.2–96.4)	−12.09 (−16.5 to −7.68)	<0.001
Total cholesterol – mg/dL	174.3 (163.5–185.0)	164.7 (154.0–175.4)	−9.58 (−24.7 to 5.58)	0.22
LDL cholesterol – mg/dL	98.6 (89.5–107.7)	85.4 (76.3–94.4)	−13.2 (−26.1 to −0.41)	0.04
Estimated proportion (%) of patients <100 mg/dL	61.8 (47.6–76.0)	64.8 (50.9–78.6)	2.96 (−16.9 to 22.8)	0.77
HDL cholesterol – mg/dL	43.9 (39.7–48.1)	59.3 (55.1–63.5)	15.4 (9.5–21.4)	<0.001
Estimated proportion (%) of patients >50 mg/dL	24.1 (11.8–36.3)	55.0 (41.0–69.0)	31.0 (12.3–49.6)	0.001
Triglycerides – mg/dL	212.1 (187.1–237.1)	109.5 (84.6–134.5)	−102.5 (−137.8 to −67.3)	<0.001
Estimated proportion (%) of patients <150 mg/dL	28.7 (15.8–41.6)	86.8 (76.7– 96.8)	58.1 (41.7–74.5)	<0.001
CKD remission[e]				
Estimated proportion (%) of CKD remission	52.8 (37.9–67.6)	63.1 (49.5–76.7)	10.3 (−9.8 to 30.5)	0.32
Metabolic control (ADA composite criteria)				
ITT analysis, Estimated proportion (%)	7.3 (0.0–15.2)	22.2 (9.4–49.9)	14.9 (−0.1 to 29.9)	0.06
Complete cases analysis, no. (%)[f]	3 (7.7)	9 (22.5)	14.8 (−0.6 to 30.2)	0.08
Neuropathy– Estimated proportion (%)	17.2 (6.2–28.2)	17.8 (5.9–29.6)	0.55 (−15.1 to 16.2)	0.95

BMT-best medical treatment; RYGB- Roux-en-Y gastric bypass; HbA1c - glycated hemoglobin; SBP - systolic blood pressure; DBP -diastolic blood pressure. TBWL-total body weight loss. ADA composite criteria-the American Diabetes Association 2012 composite criteria for metabolic control, defined as glycated hemoglobin <7% + LDL <100 mg/dL + systolic blood pressure <130 mmHg + diastolic blood pressure <80 mmHg. ITT - intention-to-treat analysis. [a]Data were presented as means (95% confidence interval [95% CI]) or risk differences (95% CI) in percentage points - unless otherwise indicated. For the primary outcome (ITT analysis), the risk difference (in percentage points) for a 98.3% level (i.e., α adjusted for multiple testing; three tests) was 10.1 (−10.9 to 31.1). This interval does not include the difference of 40 percentage points anticipated in the sample size calculations (50% for the RYGB group vs 10% for the best medical treatment group). [b]Fixed-effect model (ignoring repeated measurements, single time point). 44 participants in the BMT arm and 44 participants in the RYGB arm. [c]The difference between the groups is given by the ratio of geometric means (95% CI). [d]The body-mass index is the weight in kilograms divided by the square of the height in meters. [e]CKD remission was defined as uACR<30 mg/g of creatinine and eGFR >60 mL/min/1.73 m^2. [f]Fixed-effect model (ignoring repeated measurements, single time point). 39 participants in the BMT arm and 40 participants in the Medical GB arm. [g]Voiding dysfunction was listed in the protocol as a pre specified secondary outcome. However, during the follow-up, it was not assessed.

Table 2: **Primary and secondary[g] outcomes at 5 years[a]. (ITT analysis, n = 100).**

hypertensive range. After five years, there was no difference in systolic blood pressure, but diastolic blood pressure was significantly lower after RYGB (Table 2).

Lipids. For LDL-cholesterol, 55% of patients in each group were above the ADA target of 100 mg/dL at baseline (Table 1). After 5 years, there was no difference between the groups in the proportion reaching LDL-cholesterol targets (61.8% vs. 64.8 for best medical treatment and RYGB groups, respectively, P = 0.77), but the mean LDL-cholesterol was higher after best medical treatment than RYGB (98.6 vs. 85.4 mg/dL, P = 0.04) (Table 2 and Fig. 2, panel D). The triglyceride target of 150 mg/dL was achieved by 28.7% of patients after best medical treatment and 86.8% after RYGB (risk difference, 58.1, 95% CI: 41.7–74.5, P < 0.001). Over 5 years, HDL cholesterol levels increased linearly in both groups, but the increase was greater in the RYGB group,

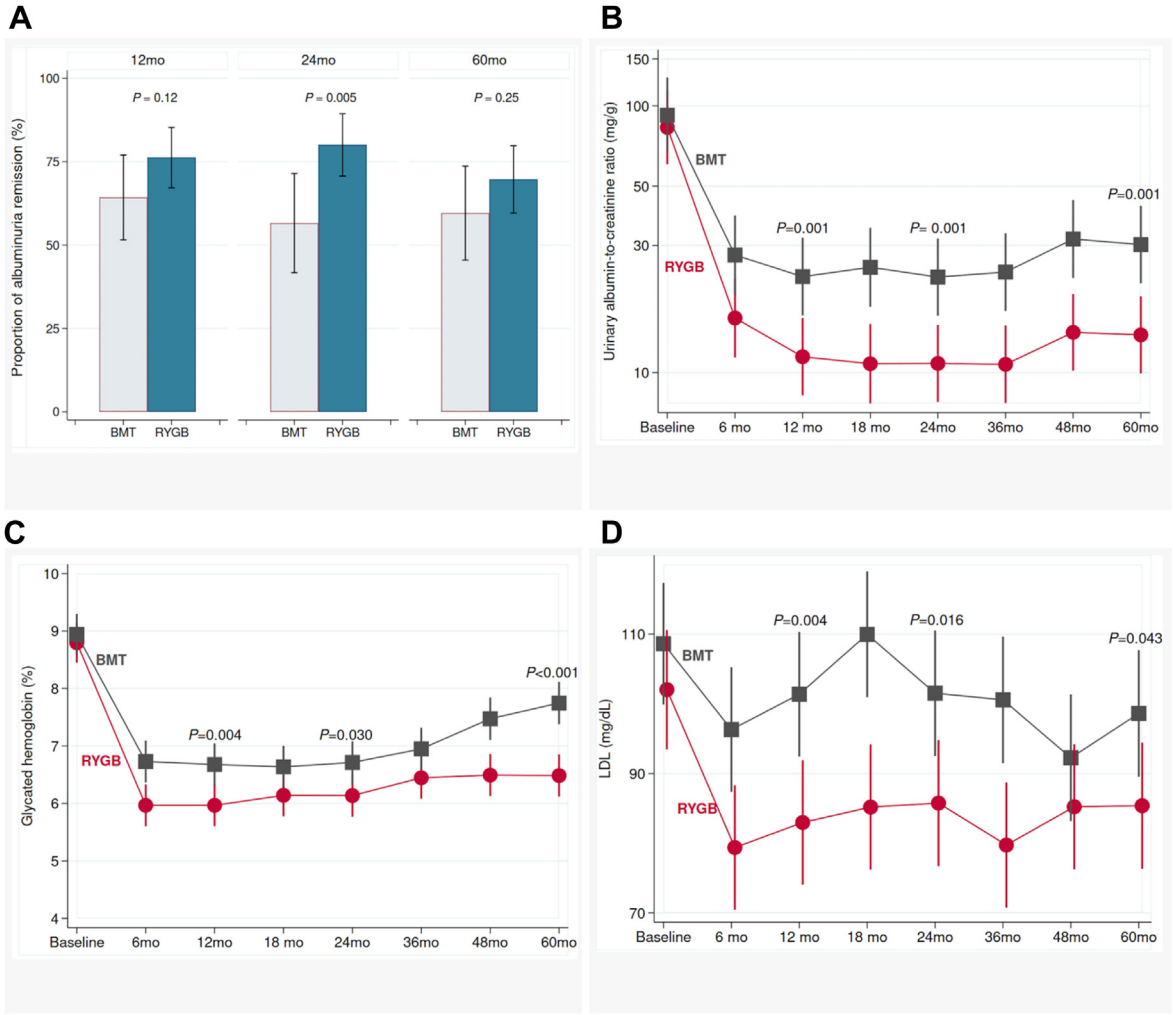

Fig. 2: Albuminuria remission rates at 12, 24, and 60 months of follow-up and longitudinal biochemical measures of urinary albumin creatinine ratio (uACR) and metabolic control. (A) Rates of albuminuria remission (uACR <30 mg/g) at 12-, 24- and 60 months follow-up. B-D, Longitudinal trajectories of uACR (B), glycated hemoglobin (to convert to proportion of total hemoglobin, multiply by 0.01) (C), and low-density lipoprotein cholesterol (LDL-C) (to convert to millimoles per liter, multiply by 0.0259) (D) from baseline to 60-months follow-up. Error bars indicated 95% confidence intervals. BMT indicates best medical treatment; RYGB indicates Roux-en-Y gastric bypass. All analyses are based on the intention-to-treat principle (n = 100 participants).

with a mean difference of 15.4 mg/dL favoring RYGB at 5 years (95% CI: 9.5–21.4 mg/dL, P < 0.001) (Table 2 and Supplementary Fig. S2).

Body weight. The mean BMI of patients after best medical treatment was 31.1 (SD: 3.2, IQR: 29–34) kg/m^{2,} and after RYGB was 24.9 (SD: 3.0, IQR: 23–27) kg/m^2 (P < 0.001) (Table 2). Only 22.5% of patients after best medical treatment achieved >15% body weight loss, while 90% of patients after RYGB lost >15% body weight (Supplementary Fig. S3). A BMI in the normal range was achieved in 0% of patients after best medical treatment and 53% after RYGB (P < 0.001).

Medication usage

Medication profiles are detailed in Supplementary Table S5. Considering all diabetes, blood pressure, and cardiovascular drugs, the median number of pharmacological agents after 5 years was 8 (IQR 6–10) in the best medical treatment and 5 (IQR 3–6) in the RYGB group (P < 0.001). For blood pressure medications, the median was 1 (IQR: 0–2) in best medical treatment and 1 (0–2) in the RYGB group (P = 0.32). Although the same American Diabetes Association guidelines and classes of medications were used for both arms of the study, patients in the best medical treatment needed more antidiabetic medications than patients in the RYGB group (5 [4–6] vs. 3 [2–4], P < 0.001) to achieve metabolic control.

Quality of life

Baseline SF-36 pain and social functioning scores differed between groups (P = 0.03 and P = 0.02, respectively) (Supplementary Table S6 and Fig. S4). After 5 years, both arms observed better scores for general health. However, patients allocated to RYGB had more significant improvements in their general health (P = 0.001), pain (P < 0.001), emotional well-being (P = 0.04), vitality (P = 0.004), physical health (P = 0.01), and physical role functioning (P = 0.01) than patients after best medical care (Supplementary Table S6).

Safety

Supplementary Table S7 shows all adverse events occurring during the 5-year follow-up. There were no differences between the best medical treatment and RYGB groups in the incidence of treatment-emergent adverse events (Table 3). Serious adverse events (SAEs) occurred in 7 of 46 participants after best medical treatment (15.2%) and 11 of 46 participants after RYGB (24%). In the best medical treatment group, there were 9 SAEs, which mainly occurred later on during follow-up (2–4 years of follow-up): 1 case each of nephrolithiasis, chest pain, anaphylactic shock, erysipelas, septic shock due to foot infection, diabetic foot infection, osteomyelitis, enterocolitis and a cerebrovascular accident (which evolved to death). In the RYGB group, there were 16 SAEs: 2 endoscopic interventions (1 to correct an anastomotic stricture [day 28; Clavien-Dido grade IIIb] and 1 to contain a gastric pouch leak [day 2; Clavien-Dido grade IIIa]), 1 case of enterorrhagia (day 10; Clavien-Dindo grade II24), 2 cases of pressure ulcers and 1 case of sepsis due to osteomyelitis unrelated to surgery at 2 years of follow-up, 1 case of sepsis with abdominal focus unrelated to surgery, 1 case of appendicitis, 1 case of cholelithiasis, 1 case of right facial abscess due to mandible osteochondroma, 1 ischemic stroke, 1 case of gastric ulcer, 1 case of weakness and 1 case of organic mental disorder; 2 cases of epigastric pain. No cases of acute kidney injury, nephrolithiasis, or oxalate nephropathy occurred in the RYGB group.

Sensitivity analysis

The complete-case (per protocol) analysis furnished qualitatively identical results compared to the ITT analysis for all efficacy outcomes (Supplementary Table S8).

Discussion

We found that the long-term rates of albuminuria remission were not statistically different between best medical treatment and RYGB in patients with diabetic kidney disease and class 1 obesity. A non-pre-specified analysis also confirmed no difference in diabetic kidney disease between the groups, although more than half of patients in both groups achieved remission of diabetic kidney disease. The superior benefits of RYGB achieving remission of albuminuria and remission of diabetic kidney disease we identified after 2 years[16] did not persist after 5 years of follow-up. The treatments were equally safe, but RYGB improved glycemia, diastolic blood pressure, lipids, body weight, and quality of life with 40% fewer medications, consistent with previous randomised trials.[27] Whether improved long-term control of these risk factors, which are associated with the progression of diabetic kidney disease, can potentially halt the evolution of chronic kidney disease from early to more advanced stages remains to be studied.[27]

The strengths of our study included the focus on diabetic kidney disease as a primary outcome, the inclusion of patients with class 1 obesity, and the use of current state-of-the-art pharmacotherapy, with more than 90% of patients in the best medical treatment group receiving sodium-coupled glucose transporter 2 inhibitors (SGLT2 inhibitors).[11–15] Our results confirm observational data that RYGB substantially reduces urine albumin creatinine ratios in patients with type 2 diabetes beyond what could be achieved with the best medical treatment.[28,29] Our best medical therapy protocol

Safety outcomes	RYGB (n = 46)	BMT (n = 46)	OR (95% CI)	P
Serious adverse events	11 (24)	7 (15)	1.74 (0.55–5.92)	0.80
Grade I	46 (100)	45 (98)	1.00 (0.03, +inf)	>0.99
Grade II	28 (61)	36 (78)	0.44 (0.15–1.18)	0.11
Grade III	5 (11)	2 (4.3)	2.66 (0.41–29.3)	0.43
Grade IV	2 (4.3)	2 (4.3)	1.00 (0.07, 14.4)	>0.99

Summary of treatment-emergent adverse events (safety population, 46 participants per treatment group) after 5 years of follow-up. BMT - best medical treatment; RYGB -Roux-en-Y gastric bypass.; OR - odds ratio. 95% CI denotes a 95% confidence interval. *P* values refer to two-sided tests based on exact logistic regression models. Grades I to IV refers to Clavien-Dindo for grading adverse events. +inf denotes that the upper bound cannot be computed (+infinity).

Table 3: **Safety outcomes (safety population, n = 92).**

also successfully reduced mean urine albumin creatinine ratios, but not as much as RYGB. The magnitude of improvements we observed in metabolic parameters and quality of life was consistent with our two-year interim analysis[16] and other randomised trials of metabolic surgery in patients with type 2 diabetes.[27]

Our study has several limitations, including the relatively small sample size and the inherent open-label design. The single-center, single surgeon, nature of our trial is a strength that increases internal validity, albeit it limits the generalizability of our findings; our institution is a tertiary care center accredited by the Joint International Committee since 2009. Thus, the complexity of the intervention, the influence of care providers, and the center's expertise allow this study's results to be generalizable within similar centers around the world (external validation).

Durability and long-term tolerability remain uncertain, but the consistency of most parameters between the 2 and 5-year follow-up data is reassuring. Another limitation is that when the trial was designed,[23] there was no scientific evidence that newer agents such as SGLT2 inhibitors or glucagon-like peptide 1 analogs offered renoprotection. Thus, the clinical effectiveness of the best medical treatment arm was underestimated.

In clinical practice, patients with diabetic kidney disease are often not referred for RYGB because of the perceived increased risks of surgical complications. However, our data support previous observational reports showing that RYBG is well tolerated, even in persons with diabetic kidney disease.[30] In our higher-risk surgical population, there were no deaths related to surgery. Serious adverse events following surgery were also easily managed without any sequelae. Most early adverse events after RYGB are related to discrete, self-limiting, or readily resolvable postoperative factors within the expected range for the first 5 postoperative years. No hypoglycemic events required third-party assistance, and the down-titration of glucose-lowering drugs corrected biochemically detected hypoglycemia.

Our study contributes to the evolving clinical management of diabetic kidney disease. Best medical therapy was an effective strategy for many patients. For individuals with multiple diabetes complications, RYGB offered additional metabolic and quality-of-life benefits. Our data support the best medical therapy to remain an important treatment option for many patients and clinicians. We expect that as the number of patients treated with the best medical therapy increases over time, there will be an increasing number of non-responders to medications, and our data would suggest that these patients could benefit from RYGB. A subsequent question that needs addressing in the future will be the relative and additive benefits of the best medical therapy and RYGB in slowing the progression of more advanced diabetic kidney disease.

In conclusion, although RYGB offered additional extra-renal benefits, the results of the best medical treatment were not statistically different from RYGB for efficacy and safety in remitting albuminuria in patients with diabetic kidney disease.

Contributors

RVC and CWL conceived and designed the study. RVC performed all laparoscopic Roux-en-Y gastric bypass procedures. CMA collected the data. TVP performed the statistical analysis. RVC, CWL, ANF, FLJC,BCM and TBZP interpreted the data. RVC, CWL, TVP, and ANF wrote the first draft of the manuscript. CEP, FNQP, LPCS, CAS, PPC, HH, JLLC, ACCS and RK critically reviewed the manuscript for important intellectual content. All authors gave crucial feedback on the revised report and approved the final version of the manuscript. CMA, TVP and RVC accessed the raw data.

Data sharing statement

Anonymised patient data are available for use in collaborative studies to researchers upon reasonable request to the corresponding author (ricardo.cohen@haoc.com.br). 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 RVC, TVP and CWL.

Declaration of interests

During the study, Dr Cohen reported receiving grants from Johnson & Johnson Medical Brasil. Dr Petry reported receiving grants from Johnson &Johnson Medical Brasil during the study. Dr Schiavon reported receiving grants from Ethicon and personal fees from Johnson & Johnson Brasil outside the submitted work. During the study, Dr Pompilio reported receiving grants from Johnson & Johnson Medical Brasil. Dr Sarian reported receiving grants from Johnson & Johnson

Medical Brasil. Dr Nogueira Pechy reported receiving grants from Johnson & Johnson Medical Brasil and honoraria for lectures, Johnson&Johnson and Medtronic. Dr Porto da Silveira reported receiving grants from Johnson & Johnson Medical Brasil and honoraria for lectures, Johnson&Johnson and Medtronic. Dr Friedman reported partciating on a Data.

Safety Monitoring Board or Advisory Board for Gila Therapeutics and GI Dynamics, leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for the International Society of Renal Nutrition and Metabolism and Editorial board- Journal of Renal Nutrition Dr le Roux reported receiving grants from Science Foundation Ireland, Health Research Board, European Federation for Study of Diabetes, and the Swedish Research Council during the conduct of the study and receiving an honorarium for lectures and scientific advisory board from Novo Nordisk, GI Dynamics, Sanofi, Johnson & Johnson Brasil, Keyron, Herbalife, and Boehringer Ingelheim outside the submitted work. Dr. Pereira reported receiving consulting fees from Novartis unrelated to the study. All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101725.

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