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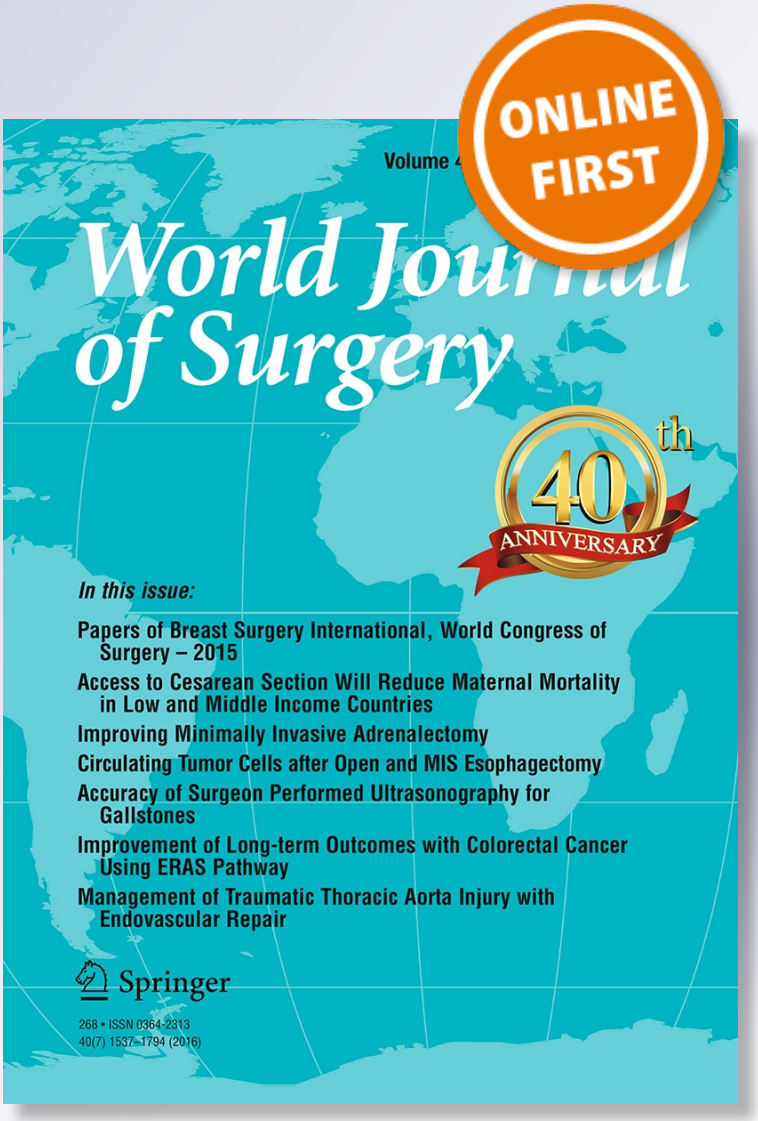

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ORIGINAL SCIENTIFIC REPORT

Mid-Term Remission of Type 2 Diabetes Mellitus After Laparoscopic Roux En-Y Gastric Bypass

Peter Vasas[1] · Waleed Al-Khyatt[2] · Iskandar Idris[2,3] · Paul C. Leeder[2] · Altaf K. Awan[2] · Sherif Awad[2,3] · Javed Ahmed[2,4]

Abstract

Background Laparoscopic Roux en-Y gastric bypass (LRYGB) is an established therapeutic modality for type 2 diabetes mellitus (T2DM). However, there is paucity of data on the outcomes of LRYGB on T2DM beyond 2 years. This study aimed to examine the medium-term effects of LRYGB on T2DM and determine the predictors of T2DM resolution.

Methods Prospective data were collected for all consecutive LRYGB performed from September 2009 to November 2010. The American Diabetes Association guidelines were used to define complete (CR) or partial (PR) remission of diabetes. Diabetes status was considered improved when there was >50 % reduction in the dose of medications or when glycaemic control was achieved after stopping insulin. The effects of baseline characteristics, diabetes data and weight loss data at 4 years on T2DM remission were studied.

Results Forty-six patients with T2DM underwent LRYGB with mean ± SD age and body mass index (BMI) of 48.6 ± 9.6 years and 50.4 ± 6.5 kg/m^2, respectively. Median (IQR, interquartile range) duration of T2DM preoperatively was 60 (36–126) months. Median (IQR) follow-up was 52 (50–57) months. T2DM remission was achieved in 64 % of patients (44 % CR, 20 % PR), and a further 28 % of patients had improvement in their diabetes status. Multivariate analyses demonstrated significant excess weight loss (EWL) [P = 0.008] and lower BMI [P = 0.04] at 4 years to be the only independent predictors of T2DM medium-term outcomes.

Conclusion The medium-term effects of LRYGB on T2DM remission/improvement were maintained in 92 % of patients. EWL and lower BMI at 4 years were independent predictors of T2DM remission.

Introduction

The present epidemic of type 2 diabetes mellitus (T2DM) is largely driven by the increased prevalence of obesity. In 2014, diabetes affected 387 million people with a global incidence rate of 8.3 % [1]. Europe has a prevalence rate of 7.5 % with almost 52 million people diagnosed with diabetes. In the United Kingdom, approximately 10 % of the annual National Health Service budget is spent on diabetes; mostly on pharmaceutical agents and treatment of diabetes-related complications [2] resulting in a significant burden on healthcare resources. Moreover, the costs of treating diabetes and associated complications are predicted to

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increase by 70 % [3, 4]. Bariatric (metabolic) surgery, in particular, the laparoscopic Roux en-Y gastric bypass (LRYGB), has emerged as a key therapeutic modality in patients with T2DM. Data on short-term remission rates following LRYGB range from 40 to 86 % depending on the benchmark used to define T2DM remission [5–9]. In addition, LRYGB has been shown as a cost-effective treatment to reverse the adverse long-term effects of T2DM [2]. In recognition of the increasing data in support of earlier surgical intervention in patients with diabetes, recent guidelines have advised reduced body mass index (BMI) eligibility thresholds for surgical intervention [10]. Whilst there exist sufficient data on the effects of surgery on short-term T2DM remission, there remains a paucity of data on the effects of LRYGB beyond 2 years. This study aimed to analyse the medium-term effects on T2DM of LRYGB and determine the predictors of resolution and remission of T2DM.

Materials and methods

Study population

Prospective data were collected for consecutive LRYGB performed from September 2009 to November 2010 in a regional bariatric centre in the United Kingdom. Review of all LRYGB patients with diabetes was performed in November 2014 permitting collection of follow-up outcomes at 4 years. Exclusion criteria were type 1 diabetes, revisional surgery and patients with secondary diabetes due to glucocorticoid therapy. Data on clinical, anthropometric and laboratory parameters were collected before and annually after surgery; and included age, height, weight, BMI, ideal and excess body weight, BMI change, percentage excess weight loss (%EWL), use of glucose-lowering therapy, lipid profile, fasting glucose, and glycosylated haemoglobin (HbA1c) level.

Surgical procedures

All patients received multi-disciplinary team assessment by a bariatric dietician, physician, surgeon, anaesthetist and psychologist before they were approved for surgery. LRYGB was performed using the 'Higa technique' with slight modification [11–14], utilising a vertical lesser curve-based gastric pouch (30 ml), 100 cm retro-colic Roux limb and 30 cm biliopancreatic limb [12–14]. The gastrojejunostomy was fashioned using a fully hand-sewn technique as previously described. Mesenteric defects were closed using non-absorbable sutures [12–14].

Study endpoints and definitions

The primary end-point of this study was remission of T2DM which was defined according to the American Diabetes Association (ADA) guidelines about the long-term glycaemic target [15, 16]: Complete remission (CR)—HbA1c <42 mmol/mol (6.0 %) and no active anti-diabetes medication; partial remission (PR)—HbA1c 43–48 mmol/mol (up to 6.5 %) and no active anti-diabetes medication; alongside with normal fasting plasma glucose levels. We defined 'improved' status of T2DM when there was a >50 % reduction in diabetes medication or when glycaemic control was achieved after stopping insulin. Patients who did not fulfil these criteria were allocated to the 'no change' category.

Data analyses

Data were analysed using IBM SPSS Statistics for windows v21 software (IBM SPSS Statistics, Feltham, UK) and GraphPad Prism (San Diego, CA, USA). Data were presented as mean ± SD and median (interquartile range [IQR]) as appropriate. The Chi-square test, unpaired *t*-test, Mann–Whitney or Fisher's exact tests were used, as appropriate, to compare differences between study groups, to evaluate group differences in diabetes outcomes and to assess independent associations between baseline variables and diabetes outcomes at 48 months. Multiple regression analyses were used to estimate individual contributions of independent variables to the variance in EWL at 48 months. Variables considered were age, gender, duration of diabetes, baseline BMI, baseline HbA1C, use of insulin, BMI and %EWL at 48 months. Differences were considered significant at $P < 0.05$.

Result

Patient characteristics

Of 185 LRYGB performed during the study period, 65 (35 %) patients had T2DM and met the inclusion criteria. However, a complete dataset was available for 46 (71 %) of these patients as 19 (29 %) were lost to follow-up or refused to provide data. Baseline demographic data are summarised in Table 1. The mean ± SD duration of diabetes was 7.3 ± 6.3 years. The mean ± SD preoperative HbA1c level was 71.5 ± 21.8 mmol/mol (8.7 %). The method of preoperative glycaemic control is described in Table 2. Sixty-one percent of the patients were on oral hypoglycaemic therapy, while 30 % of patients required additional insulin treatment. The median (IQR) postoperative follow-up period was 52 (50–57) months. At 48-month

Table 1 Characteristics of patients with type 2 diabetes mellitus who underwent primary laparoscopic Roux en-Y gastric bypass for morbid obesity

Number of patients	46
Age, mean ± SD (years)	48.6 ± 9.6
Female gender, *N* (%)	27 (59 %)
Body mass index, mean ± SD (kg/m^2)	50.4 ± 6.5
Preoperative weight, mean ± SD (kg)	147.9 ± 20.6
Excess weight, mean ± SD (kg)	74.9 ± 18.4
Follow-up, median (IQR), months	52 (50–57)

Table 2 Method of glycaemic control at baseline in patients with type 2 diabetes mellitus before undergoing laparoscopic Roux en-Y gastric bypass

Diabetes treatment	Number (%)
Diet-controlled	4 (9 %)
Tablet-controlled	28 (61 %)
Monotherapy	14 (30 %)
Dual therapy	11 (24 %)
Triple therapy	3 (6.5 %)
Insulin	14 (30 %)

follow-up, the mean ± SD of weight, BMI, percent total weight loss (%TWL) and total BMI loss (TBL) were, respectively, 103.7 ± 18.5 kg, 35.5 ± 6.5 kg/m^2, 29.5 ± 10 %, 15.5 ± 5.7 kg/m^2, and 60 ± 20 % (Fig. 1).

Outcomes of T2DM

The outcomes T2DM after LRYGB are demonstrated in Table 3 and Fig. 2. 12 months after surgery, 65 % of patients achieved diabetes remission (CR = 54 %, PR = 11 %), while 28 % of patients had improved glycaemic control. Only 4 (7 %) patients had no improvement in their diabetes status. At 48 months, diabetes remission was observed in 64 % (CR = 44 %, PR = 20 %), improved glycaemic control was achieved in 28 %, and only 8 % of patients had no change in their diabetes status. In comparison to preoperative HbA1c levels, there was a significant reduction in HbA1c to mean ± SD 44.1 ± 9.4 mmol/mol and 47.2 ± 10.1 mmol/mol at 1 and 4 years postoperatively, respectively (Fig. 3).

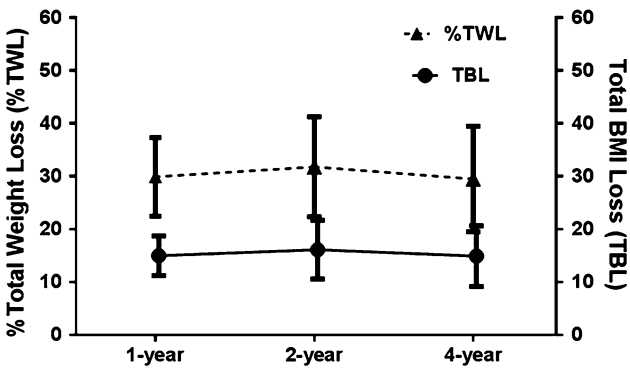

Fig. 1 Weight and BMI changes following laparoscopic Roux en-Y gastric bypass at 1-, 2- and 4-year follow-up. After 4 years, the mean ± SD weight was 103.7 ± 18.5 kg, BMI 35.5 ± 6.5 kg/m^2, percent total weight loss (%TWL) was 30 %, total BMI loss (TBL) was 15.5 kg/m^2 and %EWL was 60 %. *BMI* body mass index, *%TWL* percent total weight loss, *TBL* total body mass index loss

Table 3 Postoperative status of type 2 diabetes mellitus in patients at 4 years post laparoscopic Roux en-Y gastric bypass

Postoperative diabetes outcomes[a]	Number (%)
Remission	29 (64 %)
Complete	20 (44 %)
Partial	9 (20 %)
Improvement	13 (28 %)
No change	4 (8 %)

[a] Remission: no active anti-diabetes medication and HbA1c does not exceed the following limit: Complete—42 mmol/mol (6.0 %), Partial—48 mmol/mol (6.5 %). Improvement—50 % reduction in anti-diabetes medication or stopped insulin treatment

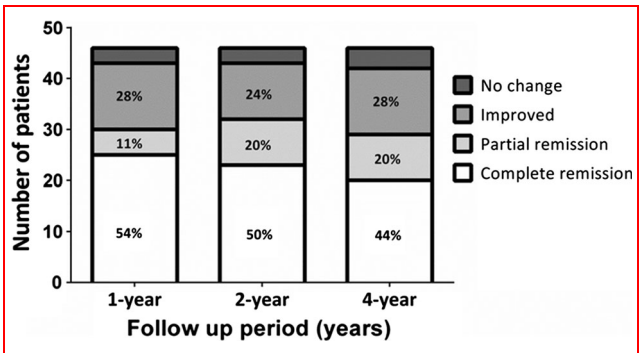

Fig. 2 Mid-term outcomes of type 2 diabetes mellitus in morbidly obese patients after laparoscopic Roux en-Y gastric bypass

Clinical variables influencing T2DM outcomes

A subgroup analysis was performed to examine the effect of various variables on diabetes remission. On univariate and multivariate analyses, significant %EWL (P = 0.008) and lower BMI (P = 0.04) were the only independent clinical predictors of T2DM outcomes at 48 months postoperatively (Tables 4, 5).

Discussion

This study examined the mid-term outcomes of T2DM following consecutive LRYGB for morbidly obese patients. At a median follow-up of 52 months, LRYGB

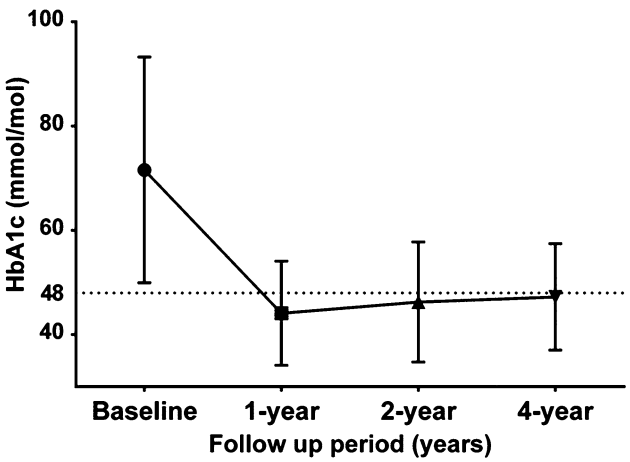

Fig. 3 Postoperative HbA1c levels in patients with type 2 diabetes mellitus following laparoscopic Roux en-Y gastric bypass for morbid obesity

was associated with a 64 % remission rate of T2DM. Moreover, a further one-third of patients had improved glycaemic control postoperatively. Overall, 92 % of patients experienced clinical improvement in the T2DM status. The remission rate described in the present study was higher than the previously published series (36–52 %) [7, 8, 17–20]. Our findings were, however, in keeping with the data from previous meta-analyses that reported 78 % diabetes resolution and a further 8.5 % improvement in clinical status of T2DM patients [21]. Although some patients still required glucose-lowering therapies to manage their hyperglycaemia postoperatively, there was a significant improvement in glycaemic control (as determined by HbA1c measurements) which was sustained at 4 years postoperatively (mean HbA1c <48 mmol/mol).

After surgery, remission of T2DM was associated with higher weight loss (68 %EWL) compared with the non-remission group (43 %, P = 0.002). Univariate and multivariate analyses demonstrated the only predictors of postoperative diabetes remission to be postoperative weight loss and subsequent lower BMI, findings in keeping with another study [6]. In contrast to a previous study which reported that diabetes duration may influence the improved glycaemic response to surgery [17], we did not observe statistical significance in preoperative duration of diabetes between patients who achieved remission and those who did not. However, this may be due to the relatively small sample size in our study. There are data, however, that suggest remission in patients with a preoperative duration of T2DM less than 5 years, to be less dependent on weight loss or incretin effects, and more dependant on enhanced beta-cell function postoperatively [22]. In this series, 24 % of patients in the remission group were insulin-dependent preoperatively compared to 41 % in the non-remission group (P = 0.23). Requirement for insulin to treat diabetes is a progressive sign of beta cells' (relative or absolute) functional insufficiency. Other authors have demonstrated that preoperative insulin usage is an important but statistically insignificant predictor of diabetes remission [17].

Numerous mechanisms may underlie the rapid improvement in glycaemic control after bariatric surgery. The sudden negative energy balance and consequent reduction in pancreatic and hepatic triacylglycerol accumulation have been shown to restore beta-cell function and normalize first-phase insulin secretion in response to a carbohydrate meal [23]. The rise in GLP-1 secretion may also partially explain the rapid improvement in glycaemic control after bariatric procedures, and this is independent of weight loss [23–25]. In addition, improvements in postoperative insulin sensitivity, insulin disposition [26] and obesity-related comorbidities have also been proposed to be a mechanism underlying improved glucose control in patients with T2DM. Other unidentified mechanisms are likely to be of importance in improved glucose control,

Table 4 Variables examined for association with status of type 2 diabetes mellitus 4 years post laparoscopic Roux en-Y gastric bypass

Variable	Remission $N = 29$ (63%)	Non-remission $N = 17$ (37%)	P value
Age, mean ± SD (years)	48.2 ± 9.2	49.5 ± 9.3	0.66
Sex, % Female	59 %	59 %	1
Preoperative weight, mean ± SD (kg)	146.4 ± 22.2	150.7 ± 19.2	0.17
Excess weight, mean ± SD (kg)	74 ± 18.5	76.0 ± 18.7	0.07
Pre-op BMI, mean ± SD (kg/m^2)	51.2 ± 6.7	50.7 ± 7	0.22
Weight loss, mean ± SD (kg)	49 ± 17.4	35.2 ± 14.9	0.016
Excess weight loss, mean ± SD (%)	67.6 ± 15.5	43.3 ± 22.0	0.002
Postoperative BMI, mean ± SD (kg/m^2)	33.6 ± 5.7	38.3 ± 6.7	0.027
Duration of diabetes, mean ± SD (months)	72.2 ± 64	122.2 ± 91	0.084
Insulin-treated (%)	24 %	41.2 %	0.23
Preoperative HbA1c, mean ± SD (mmol/mol)	73.5 ± 20.8	68.8 ± 23.5	0.42

Table 5 Logistic regression model of independent clinical predictors of T2DM outcome 48 months following laparoscopic Roux en-Y gastric bypass

Variable	Odd ratio (95% CI)	P value
Gender	1.01 (0.30–3.40)	0.99
Age	1.02 (0.95–1.09)	0.65
Initial BMI	0.99 (0.91–1.02)	0.84
Preoperative %EWL	1.01 (0.97–1.04)	0.75
Duration Of T2DM	1.01 (0.99–1.02)	0.10
Baseline HbA1C	0.99 (0.96–1.02)	0.41
Preoperative insulin treatment	0.46 (0.13–1.65)	0.23
BMI (48 months)	1.31 (1.01–1.27)	0.04
%EWL (48 months)	0.94 (0.89–0.98)	0.008

however, as evidenced in patients with type I diabetes. In the latter group, there is a significant improvement in insulin sensitivity after bariatric surgery, resulting in improved glycaemic control which persists 4 years post-operatively, in the absence of improved insulin production and disposition [27]. In patients with T2DM, dramatic increases in GLP-1 concentrations were reported 1-year post bariatric surgery. These were associated with improvements in insulin sensitivity and beta-cell function [25]. Interestingly, the effects of incretin-mediated improvement in glycaemic control have not been characterised beyond 12 months.

Observational clinical studies demonstrated the high diabetes remission seen in the early postoperative period (<2 years) to reduce with longer-term follow-up. In the STAMPEDE Trial, the 12-month diabetes remission rate was 42 %, [8] and this decreased to 35 % at 3 years [19]. A recently published randomised controlled trial showed 37 % diabetes remission 5 years post RYGB [28], however, their diabetes remission rate was 75 % at 2 years [7]. The exact underlying mechanism for the reduced long-term remission rate is likely to be multifactorial. Weight regain is likely a contributory factor to reduced medium-term remission rates [19, 28]. In our study, a mild reduction in diabetes remission was also observed, as the highest remission rate was 70 % (at 2 years) and this diminished to 64 % at 4.5 years (three patients had diabetes recurrence and moved from "remission" to "improved" category); however, the weight regain during this time period was insignificant.

The rate of mid-term diabetes remission, based on multiple reports, reduces with time. Therefore, a higher level of diabetes surveillance may need to be employed during the postoperative follow-up, and more aggressive glycaemic control strategies are required to achieve sustained long-term diabetes control.

Limited longer-term (10-year) data on the metabolic response to LRYGB have been published [29]. The latter study utilised a similar operative technique and cohort of patients (baseline BMI 48, 57 %EWL at 10 years postoperatively) to the present study and reported T2DM remission rate to be 83 %, albeit with a 74 % patient attrition rate at 10 years. A less favourable but more recently published data reported a 38 % T2DM remission rate 3 years following LRYGB [19]. Such inconsistencies are likely related to the more stringent ADA criteria regarding diabetes remission. These consensus criteria suggest the use of HbA1c <6.0 % (and fasting plasma glucose level <100 mg/dl), while non-surgically treated diabetic subjects' cut-off rate is <7.0 %, and this may contribute to the lower rates of remission published in recent studies [5]. This contrasts with previously published reports that used less tight definitions of diabetes remission (Buchwald criteria) [6, 30].

Patients in the non-remission group remained clinically obese after surgery (BMI approximately 40), and given that postoperative long-term beta-cell recovery is highly dependent on the degree of weight loss [31], the latter could be one reason why this group did not achieve

Table 6 Mid- and long-term diabetes remissions (calculated)

Study (year)	Number of patients	Follow-up (months)	Preoperative BMI	T2DM duration (years)	%EWL (%)	Remission rate (%)	Follow-up rate (%)
Sjostrom et al. (2004) [18]	34	120	41.3	NK	NK	36	75.3
Buchwald et al. (2009) [21]	110	24	49.5	NA	NA	70.9	NK
Higa et al. (2011) [29]	63	120	48	NK	NK	83	26
Mingrone et al. (2012) [7]	20	24	44.85	6.03	68	75	95
Ikramuddin et al. (2013) [6]	60	12	34.9	8.9	NK	49	95
Brethauer et al. (2013) [20]	162	72	48.8	5	60.5	50	73
Schauer et al. (2014) [19]	48	36	36	8.2	84.9	35	96
Dogan et al. (2014) [17]	52	83	46.6	6.1	60	52	58
This study	46	52	51	7.37	65.8	64	71

NA not applicable, *NK* not known, *preop* preoperative, *T2DM* type 2 diabetes mellitus

remission. Review of previously published data (Table 6) demonstrated these to be confounded by the definitions used, inclusion of lower BMI patients and short duration of follow-up. The reported % of patients achieving remission varied between 35 and 83 % (Table 6). Implementing the more stringent ADA definitions reduces the mean remission rates from 57.5 to 40.6 % [5] or 92.7 to 43.6 % [30].

The main limitation of the present study is the relatively small number of patients studied, however, this is in keeping with the numbers of diabetic patients enrolled at previously reported randomised controlled trials [19, 28] and observational studies [30, 32]. Our data are derived from a single institution, and 29 % of our patients were lost to follow-up, which is comparable to previously published studies with reported attrition rate between 5 and 74 % (Table 6). That said, our patients demonstrated some of the best diabetes remission rates reported in the literature even when using stringent ADA criteria.

Conclusions

This study demonstrated the improvement in diabetes status following LRYGB to persist in over 90 % of the patients at 4 years postoperatively. At 4 years, there was a 64 % remission rate that was independently associated with sustained long-term weight loss. The mean HbA1c level was <6 % 4 years after the procedure. These findings should aid patient counselling and help motivate T2DM patients undergoing bariatric surgery to adhere to dietary and lifestyle modifications necessary to maintain sustained long-term weight loss.

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Compliance with ethical standards

Conflict of interest S Awad has no direct conflicts of interest to declare. He has received unrestricted educational and travel grants from Fresenius Kabi, Nestle Nutrition, Medtronic, Ethicon Endo-Surgery, Merck Sharp & Dohme, Fischer & Paykel Healthcare Ltd, and BBraun. He has received honoraria and consultancy fees from Apollo Endosurgery, Merck Sharp & Dohme and Fischer & Paykel Healthcare Ltd. He has also completed a bariatric fellowship funded via an educational grant from Ethicon EndoSurgery (paid to the institution). The other authors have no conflict of interest.

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