ORIGINAL CONTRIBUTIONS



Predictors of Remission of T2DM and Metabolic Effects after Laparoscopic Roux-en-y Gastric Bypass in Obese Indian Diabetics—a 5-Year Study

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Abstract

Background Bariatric surgery has proven results for diabetes remission in obese diabetics. Despite this, a lot of ambiguity exists around patient selection. The objectives of this study are the following: (1) evaluation of results of laparoscopic Rouxen-y gastric bypass (LRYGB) in obese type 2 diabetic (T2DM) Indian patients at 5 years and (2) to define predictors of success after surgery.

Methods This is a prospective observational study. One hundred six Indian patients underwent LRYGB from January 2004 to July 2009. Patients were evaluated for percent excess weight loss (%EWL) and remission of T2DM. Mean age 50.34 ± 9.08 years, mean waist circumference 129.8 ± 20.8 cm, mean weight 119.2 ± 23.6 kg, mean BMI 45.01 ± 7.9 kg/m², and mean duration of diabetes 8.2 ± 6.2 years.

Results At 5 years, mean EWL% was 61.4 ± 20.3 , mean weight regain of 8.6 ± 6.2 kg was seen in 63.6 %, mean glycosylated hemoglobin dropped from 8.7 ± 2.1 to 6.2 ± 01.3 %, mean triglycerides declined by 31 %, and serum high density lipoprotein rose by 18.4 %. Mean low-density lipoprotein levels declined by 6.8 %. Age, BMI, fasting C-peptide levels, duration of T2DM, and pre-op use of insulin

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emerged as significant predictors of success after surgery. One hundred percent remission was seen in patients with T2DM <5 years.

Conclusions LRYGB is safe and efficacious for long-term remission of T2DM (BMI≥35 kg/m²). In a country with the second largest population of type 2 diabetics in the world, predictors of success after surgery can help in prioritizing patients who have a greater chance to benefit from metabolic surgery.

Keywords Laparoscopic Roux-en-Y gastric bypass · Long-term results · Type 2 diabetes mellitus · Bariatric surgery · Predictors of success

Introduction

Over the years, strong evidence of improvement in the diabetic status of obese type 2 diabetics after all types of bariatric/ metabolic surgeries has emerged [1, 2]. In the long term, all-cause mortality has been shown to decrease by 40 % and disease-specific mortality by 92 % after surgery [2–5]. In 2009, the American Diabetes Association included bariatric surgery in the treatment algorithm for the management of obese diabetics [6]. Bariatric surgery was also acknowledged as a component of the chronic disease management of type 2 diabetic (T2DM) and obesity by the International Diabetes Federation in its position statement in 2011 [7]. Despite proven results, there is yet a lot of ambiguity around patient selection and procedure selection. We still lack a system that can serve as a guide to the clinicians to select the right patients and prioritize them for surgery.



The aims of this paper were twofold: to evaluate the results of laparoscopic Roux-en-Y gastric bypass (LRYGB) in Indian obese T2DM patients (body mass index (BMI) \geq 35 kg/m²) in terms of diabetes remission over 5 years and to define the predictors of success after surgery. These predictors can help in patient selection and help the surgeons and clinicians decide which patients will benefit most from surgery.

Material and Methods

This was a prospective observational study conducted at the Center for Obesity and Digestive Surgery, Saifee Hospital, Mumbai, India. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsin-ki declaration and its later amendments or comparable ethical standards.

The study group included Indian patients operated between January 2004 and July 2009. One hundred six obese type 2 diabetic patients were included and studied prospectively. All patients underwent LRYGB. Informed consent was taken from all individual participants included in the study.

The eligibility criteria were age of 18 to 75 years, documented evidence of T2DM (HbA1c>7%), and a BMI≥35 kg/m². Patients with previous bariatric procedures coming for revisional surgery, fasting C-peptide ≤1, inability to take lifelong nutritional supplementation, severe medical illness rendering them unfit for surgery, and those with severe psychiatric disorders were excluded from the study group. Patients with evidence of end-organ damage such as nephropathy, neuropathy, and retinopathy were also excluded from this study.

Demographics

The study group included 106 Indian patients out, of whom, there were 63 females and 43 males. Mean age was 50.3 ± 9.1 years, mean waist circumference was 129.8 ± 20.8 cm, mean weight was 119.2 ± 23.6 kg, and mean BMI was 45 ± 7.8 kg/m². All patients had T2DM from 3 to 30 years from the time of diagnosis. Mean duration of diabetes was 8.2 ± 6.2 years. Table 1 depicts the details of anti-diabetic treatment.

Seventy-eight out of one hundred six (73.5 %) patients in the study group were hypertensive and 48/106 (45.3 %) had LDL levels >100 mg/dl. Mean total cholesterol was 174.9 mg/dl, mean triglyceride levels were 181.4 mg/dl, and mean HDL levels were 38.6±06.6 mg/dl. Follow-up rate at 1, 2, and 5 years was 100, 94.3, and 84.9 % respectively.

All patients were counseled by a team inclusive of the surgeon, nutritionist, endocrinologist, and psychologist. An

extensive pre-operative evaluation was performed for all patients. Apart from the routine investigations, a complete nutritional evaluation, urine for microalbuminuria and fundoscopy, was done in all patients. The patients were put on a strict high protein-low carbohydrate diabetic diet for 7 days pre-operatively. Low molecular weight heparin (LMWH) was given prior and within 12 h of the surgical procedure, and sequential compression stockings and pumps were used for DVT prophylaxis.

The diagnosis and remission of T2DM were as per the ADA criteria. Complete remission after surgery was defined as the achievement of the ADA criteria without any medication for a continuous minimum period of 6 months. Partial remission was defined as the achievement of these results, but with some medication required. No remission was defined as the non-achievement or worsening of the diabetic status despite medication. Weight regain was defined as the percentage of weight regained from the nadir of the percent excess weight loss (%EWL).

Immediate complications were defined as those within 3 days of surgery, early complications were defined as those within 3 weeks, and late complications as those occurring after 3 weeks. A major complication was identified as an event that required hospitalization and interventional management.

Surgical Technique

Anti-colic anti-gastric LRYGB was performed for all patients using the six-port technique. The length of the biliopancreatic limb was 50 cm from the ligament of Treitz and that of the alimentary limb was 250 cm. A jejuno-jejunostomy was done using the triple-staple technique. The mesenteric defect was closed with a non-absorbable continuous suture. A 25–30 cm³ vertical gastric pouch was created, and a gastrojejunostomy was performed using a 25-mm circular stapler. Under water gastroscopy was performed intra-operatively in all cases.

Post-operative Course

A water-soluble oral contrast study was done for all patients on postoperative day 1, after which, they were started on clear liquids for 2 days. They were kept on full liquids until day 15 followed by soft diet until day 30. Normal diabetic diet albeit in restricted quantities was started after 1 month of surgery. LMWH was continued for 7 days post-operatively. Follow-up visits were scheduled at 7 days, 1 month, 3 months, 6 months, 1 year, and once every year thereafter. Anti-diabetic, statins, and anti-hypertensive medications were reduced as per the opinion of the endocrinologist. Lifelong nutritional supplementation for iron, calcium, and vitamin B_{12} was advised to all patients.



Table 1 Details of anti-diabetic treatment

| Type of treatment | Number of patients | Details |
|---------------------------------|--------------------|--|
| Diet and lifestyle modification | 6 | |
| OHA | 64 | 1 to 4 OHA |
| OHA+insulin | 31 | 12 to 130 U of insulin (mean 52.6±33.9 units)+1 to 4 OHA |
| Only insulin | 5 | |

OHA oral hypoglycemic agents

Statistical Analysis

Descriptive Analysis Continuous variables were summarized by using summary statistics (number of observations, mean, and standard deviation) and categorical values by using frequencies and percentages.

Tests of Significance In this study, changes in efficacy variables like weight, BMI, and waist/hip ratio were estimated by using Student's t test from baseline to each follow-up with Bonferroni corrections. Secondary variable was also estimated by Student's t test. Chi-square test was used to associate the relation between age in years, duration of T2DM, pre-op BMI, insulin use, and fasting C-peptide levels with remission of T2DM. All P values are two-sided, and all the statistical tests have been interpreted at 5 % level of significance level.

Results

All procedures were completed laparoscopically. The mean operating time was 55 ± 20 min. Mean blood loss was 45 ± 30 cm³. There were no intraoperative complications, and all patients were discharged on postoperative day 1.

Excess Weight Loss

As shown in Fig. 1, mean %EWL was 58.2 ± 18.2 % after 1 year, 64.9 ± 19.8 % after 2 years, 63.7 ± 19.2 % after 3 years, 61.7 ± 20.3 % after 4 years, and 61.4 ± 20.3 % after 5 years. Table 2 shows the mean weight and BMI over 5 years.

Weight Regain

Patients (57.7 %) showed a mean weight regain of 3.9 ± 3.1 kg at the end of 3 years. At 4 years, 60.7 % patients experienced a mean weight regain of 7.7 ± 6.1 kg, and at the end of 5 years, a mean weight regain of 8.6 ± 6.2 kg was seen in 63.6 % of the patients.

Resolution of Co-morbidities

At 5 years, mean HbA1c dropped significantly from 8.7 ± 2.1 to 6.2 ± 01.3 %. Mean total cholesterol levels showed a decline of 3.5 % at 5 years which was not statistically significant. Mean triglycerides showed a decline of 31 % from the time of surgery, and serum HDL showed a rise of 18.4 % at 5 years from pre-operation levels which were statistically significant. Mean LDL levels showed a decline of 6.8 % over 5 years, but this difference was not statistically significant. Mean systolic and diastolic blood pressures also showed a significant fall over 5 years. Table 2 depicts the biochemical parameters over 5 years.

Complications

Two patients had minor complications in the form of wound infections in the left subcostal port site. It was treated with daily dressings. There were no major complications. There were no mortalities.

Predictors of Resolution of Type 2 Diabetes

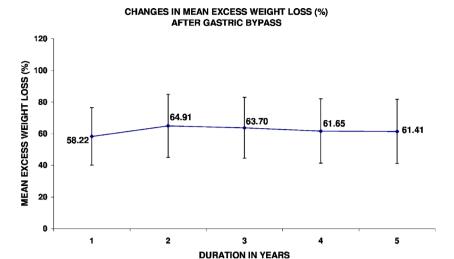
Age of the patient, pre-operative BMI, fasting C-peptide levels, duration of T2DM, and pre-op use of insulin were evaluated as prognostic markers for remission of T2DM after surgery. A statistically significant higher rate of remission of T2DM was seen in patients with C-peptide levels \geq 3, duration of T2DM \leq 5 years, BMI \geq 40 kg/m², and in patients who were not on insulin pre-operatively. In this study, the age of the patient did not show any statistical significance with relation to resolution of T2DM; only those who were more than 60 years of age at the time of surgery showed a statistically significant poor rate of remission. Table 3 depicts the resolution rates with the five parameters evaluated in this study.

Discussion

There is ample evidence in literature to suggest that all kinds of bariatric procedures lead to an improvement in the diabetic status in obese individuals [1, 8, 9]. It is also known that



Fig. 1 EWL% from 1 to 5 years after LRYGB in Indian patients



*Follow up rate: 1st year- 100%, 2nd year-94.3%, 3rd year- 84.9%, 4th year- 84.9%, 5th year- 84.9%

malabsorptive procedures like biliopancreatic diversion and duodenal switch lead to better results in terms of diabetes remission as compared to purely restrictive surgeries like gastric banding [1]. However, very little work has been done to study and establish the predictors of diabetes remission in those patients undergoing surgery [16, 18, 19].

In this study, we have prospectively studied the long-term effect of LRYGB on 106 moderate to severely obese patients with T2DM over 5 years. In addition to the evaluation of standard outcomes such as %EWL, weight regain, remission of co-morbidities, and complication rates, we have also studied predictors of T2DM resolution in these patients such as age, BMI, duration of diabetes, fasting C-peptide levels, and pre-op use of insulin.

One of the aims of this study was to evaluate long-term outcomes after LRYGB in the Indian obese diabetic population. In this study, mean %EWL was 58.2 ± 18.2 % after 1 year, 64.9 ± 19.9 % after 2 years, 63.7 ± 19.2 % after 3 years, 61.7 ± 20.3 % after 4 years, and 61.4 ± 20.3 % after 5 years. These

results are comparable to long-term results observed by other investigators. In a meta-analysis published by Buchwald et al. in 2004, mean EWL% after LRYGB was reported as 68.2 % (61.5 to 74.2 %) [2]. In 2003, Phil Schauer et al. and Sugerman et al. reported 5-year EWL% results after LRYGB in diabetic patients as 60 % and 66 % respectively [9, 10].

At 5 years, a mean weight regain of 8.6±6.2 kg was seen in 63.6 % of the patients in this study. Similar weight regain has been demonstrated by other investigators in long-term results [2, 9]. In spite of weight regain in our study, mean HbA1c levels were maintained at 06.2±01.3 % at 5 years and remergence of T2DM was not observed in any of these patients. Di Giorgi et al. have reported a re-emergence of T2DM in 24 % of the patients towards the end of 3 years after LRYGB. In their study, patients with greater weight loss failure rates, weight regain of up to 37.7 %, and those with higher postoperative glucose levels tended to experience recurrence of T2DM [11]. Last year, a retrospective study by Ramos et al. also reported a 21 % recurrence rate after

Table 2 Mean weight, BMI, waist circumference, and biochemical parameters in Indian patients over 5 years

| Parameter | Pre-op | 1 year | 2 years | 3 years | 4 years | 5 years |
|-----------------------------------|-------------------|------------------|------------------|-----------------|------------------|------------------|
| No. of patients at each follow-up | N=106 | N=106 | N=100 | N=90 | N=90 | N=90 |
| Mean weight (Kg) | 121.6 ± 22.7 | 88.6 ± 17.5 | 84.4 ± 16.4 | 84.9 ± 16.9 | 86.3 ± 17.6 | 86.4 ± 17.7 |
| Mean BMI (kg/m ²) | 45.9 ± 07.9 | 33.6 ± 06.1 | 32 ± 06.1 | 32.3 ± 05.9 | 32.7 ± 06.4 | 32.8 ± 06.4 |
| Mean WC (cm) | 133.1 ± 15.9 | 105.1 ± 24.6 | 104.6 ± 24.7 | 105.2 ± 25 | 105.6 ± 24.9 | 105.5 ± 25.1 |
| Mean HbA1c (%) | 8.7 ± 02.1 | 05.9 ± 01.6 | 06.2 ± 01.2 | 06.1 ± 01.3 | 06.2 ± 01.3 | 06.2 ± 01.3 |
| Mean total chol (mg/dl) | 174.9 ± 39.9 | 161.5 ± 41.4 | 167.2 ± 29.1 | 170 ± 28.9 | 166.1 ± 38.2 | 168.9 ± 34.8 |
| Mean Tg (mg/dl) | 181.4 ± 63.3 | 117.5 ± 44.8 | 111.5±35.2 | 115.9 ± 0.5 | 123.9 ± 69.4 | 125.1 ± 68.7 |
| Mean HDL (mg/dl) | 38.6 ± 06.6 | 41.8 ± 10.6 | 43.1 ± 07.3 | 46.2 ± 09.9 | 45.3 ± 10.4 | 45.7 ± 10.1 |
| Mean LDL (mg/dl) | $10.4.7 \pm 34.9$ | 094.3 ± 33.6 | 099.9 ± 23.3 | 100.8 ± 3.8 | 095.7 ± 26.3 | 097.6±24.1 |

BMI Body Mass Index, WC waist circumference, Chol cholesterol, Tg triglycerides HbA1c, glycosylated hemoglobin, HDL high density lipoprotein, LDL low density lipoprotein



Table 3 Predictors of resolution of type 2 diabetes mellitus (T2DM) in Indian patients

| Parameter evaluated | % T2DM remission | p value |
|--|------------------|---------|
| Fasting C-peptide levels | | |
| 1 to 3 | 60.9 | 0.05 |
| 3 to 6 | 85 | |
| More than 6 | 90 | |
| Duration of T2DM in years | | |
| <5 | 100 | < 0.05 |
| 5 to 10 | 66.7 | |
| 10 to 15 | 70.5 | |
| More than 15 | 76.9 | |
| Pre-operative BMI in Kg/m ² | | |
| 35 to 40 | 73.7 | < 0.05 |
| More than 40 | 91 | |
| Age of the patient in years | | |
| 20 to 30 | 100 | >0.05 |
| 30 to 40 | 100 | |
| 40 to 50 | 80.6 | |
| 50 to 60 | 81.3 | |
| More than 60 | 66.7 | |
| Insulin use | | |
| Diet and lifestyle modification | 84.6 | >0.05 |
| Oral hypoglycemic agents alone | 90.9 | >0.05 |
| Oral hypoglycemic agents+insulin | 64.5 | |
| Insulin alone | 60 | |

BMI body mass index

LRYGB at the end of 5 years [12]. Patients with longer duration of T2DM were more likely to experience remergence in their study.

In terms of remission of T2DM, mean HbA1c dropped significantly from 8.7 ± 2.1 to 6.2 ± 01.3 % after 5 years. Mean triglycerides showed a statistically significant decline of 31 % and serum HDL showed a rise of 18.4 %; however, mean LDL levels showed a decline of only 6.8 % over 5 years which was not statistically significant. Mean systolic and diastolic blood pressures also showed a significant fall over 5 years. These results were comparable to other studies with long-term results after LRYGB [8, 10]. Lifestyle modification and medical management remain the mainstay in the treatment of T2DM; however, they are not as successful in the long term, and diabetes control has been challenging and unsatisfactory with just medical treatment. In the last few years, three randomized controlled trials have yielded level 1 evidence and proved that control of T2DM in obese diabetics is far superior with patients who have undergone LRYGB as compared to those receiving medical management alone [13–15].

The aims of this study were to evaluate the efficacy and remission rates of T2DM with LRYGB over 5 years and to evaluate the factors that determine success after surgery to help clinicians decide which patient has the best chances to have success with surgery. In the past, various researchers have studied factors that affect the outcome of diabetes remission after bariatric surgery [9, 16]. Age, duration of T2DM, insulin usage, BMI, C-peptide levels, ethnicity, fasting plasma glucose levels, HbA1c, presence of co-morbidities, and type of surgery have all been analyzed as predictors in earlier studies.

In this study, we evaluated the significance of age, fasting C-peptide levels, duration of T2DM, BMI, and pre-op insulin use as predictors of diabetes remission after LRYGB. Patients with fasting C-peptide levels ≥3, duration of T2DM ≤5 years, BMI≥40 kg/m², and those who were not on insulin pre-operatively experienced the best results in terms of remission of diabetes. Although the results reflected a trend that younger patients achieved better remission of T2DM, age of the patient did not emerge as a statistically significant factor for success in this study except for those above 60 years who fared the worst.

Fasting C-peptide levels were used as a surrogate marker for assessing the function of beta cells of the pancreas in this study. As shown in a previous study done by us on lower BMI patients, fasting C-peptide levels are a good predictor of glycemic response after surgery in overweight to class 1 obese patients as well [17]. In this study, patients with fasting Cpeptide levels ≥3 achieved remission rates up to 85 % and those with levels ≥6 up to 90 %. Patients with levels between 1 and 3 had a relatively poorer remission rate of 60.9 %. The relevance of C-peptide levels has also been studied in the Chinese population with similar results. In a study published in 2012, W J Lee et al. investigated the clinical significance of C-peptide in diabetic patients for bariatric surgery. They observed that patients with levels greater than 6 experienced up to 90 % remission of T2DM [18]. In 2013, Dixon et al. also demonstrated that Taiwanese patients with higher C-peptide levels experienced better responses after LRYGB.

The case for an early surgical intervention has been argued before, and patients with shorter duration of diabetes (<5 years) are most likely to experience best remission rates [9, 10]. In our study, patients with T2DM less than 5 years duration experienced 100 % remission. Patients with longer duration of diabetes (5 to 15 years or more) experienced 65 to 75 % resolution with no statistical difference between groups of patients with duration of T2DM from 5 to 10 years, 10 to 15 years, or more than 15 years, hence drawing the new cutoff for assured success at 5 years. Similar findings were observed by us in the lower BMI diabetics as well. In the lower BMI (30 to 35 kg/m²) group, also patients with duration of diabetes less than 5 years had the best results, thus strengthening the case for early intervention with surgery for best results [17]. Similar findings have been reported by Dixon et al. in the Taiwanese population where longer duration of T2DM reduced the response to surgery [19].



While a lot of work is being done on low BMI diabetics. most studies have shown that initial weight and BMI do play a significant role in surgical outcomes for T2DM. In this study, patients with BMI ≥40 kg/m² experienced up to 91 % remission of T2DM. Our low BMI study demonstrated that though there was a 96.2 % improvement in the overall metabolic status, the complete remission of T2DM at 5 years was only 57 %. Patients with higher weight had more weight loss and have experienced greater remission of T2DM even in the low BMI group [17]. The remission rates of T2DM after LRYGB cannot be explained by weight loss alone, but weight loss does play a pivotal role and is a significant factor that contributes to the beneficial effects of LRYGB on T2DM remission. Weight loss is said to decrease insulin resistance and improve insulin sensitivity by four to fivefold and goes a long way in the maintenance of the state of remission [20]. Dixon et al. also substantiated that initial weight of the patient and post-surgery weight loss can help to predict the T2DM remission in these

Pre-operative use of insulin also emerged as a significant factor affecting remission of T2DM in this study. Patients who were on diet and lifestyle modification or on oral hypoglycemic agents alone showed 84 to 90.0 % remission. In patients who were on insulin pre-operatively, the remission rates were only 60 %.

Although all bariatric/metabolic procedures have shown a significant effect on remission of T2DM over the years, there is still considerable ambiguity over patient and procedure selection. With the rise of the diabetes epidemic and an increase in the number of bariatric/metabolic surgeries being performed for the treatment of obese diabetics, there is an unquestionable need for predictors of success after surgery that can help clinicians to select those patients who are most likely to benefit from the surgical approach to treat T2DM.

The limitations of this study are that we have studied the outcomes with only a single procedure, i.e., the LRYGB. A randomized controlled trial across various types of bariatric procedures in different ethnicities would be an ideal platform to assess the efficacy of these predictors.

Conclusion

LRYGB is a safe and efficacious surgical option for the Indian obese diabetic patients and has demonstrated sustained weight loss along with prolonged remission of T2DM over 5 years. A small amount of weight regain did not lead to a re-emergence of T2DM in these patients. Fasting C-peptide levels ≥3, BMI ≥40 kg/m², duration of diabetes ≤5 years, and those who were not on insulin pre-operatively were the best prognostic markers of good remission rates after surgery. Younger patients showed better responses, but age did not emerge as a statistically significant prognostic marker in this study except

in those ≥60 years who fared poorly. Prior assessment of predictors of T2DM remission can be helpful tools for selecting the right patients and prioritizing them for surgery.

Conflict of interest The authors have no potential conflicts of interest of a financial or any other nature related to the topic of the manuscript.

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