Early improvement in type 2 diabetes mellitus post Roux-en-Y gastric bypass in Asian patients

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ABSTRACT

Introduction: Obesity is a growing problem worldwide that is closely related to type 2 diabetes mellitus (T2DM). The Roux-en-Y gastric bypass (RYGBP), a restrictive and malabsorptive bariatric procedure, shows mounting evidence of inducing improvement of T2DM. Few studies, especially those examining the early changes in diabetic parameters, have been done in the Asian population.

Methods: All morbidly obese patients with T2DM undergoing RYGBP at our institution from August 2008 to January 2010 were prospectively studied. Six patients had RYGBP, and one had a laparoscopic sleeve gastrectomy with a duodeno-jejunal bypass. Data collected included pre- and postoperative 75 g oral glucose tolerance test, daily postoperative fasting plasma glucose, and haemoglobin A1c (HbA1c) pre-operation and at two, four and 12 weeks post operation.

Results: After 12 weeks, the mean drop in HbA1c was 2.29 +/− 1.39 percent. The change in HbA1c at four (p is 0.039) and 12 (p is 0.005) weeks showed significant improvements. A significant decrease in diabetic medication usage was observed, with four (57 percent) patients not requiring medications within four weeks. Remission of DM was achieved in two (28.6 percent) patients within 12 weeks. Weight loss by various parameters was significant from two weeks onwards.

Conclusion: The cure rate of 28.6 percent and an improvement rate of 100 percent of T2DM in morbidly obese Asian patients within 12 weeks post operation are promising. Many patients discontinued their diabetic medications in the immediate postoperative period, even before significant weight loss had occurred, indicating that RYGBP has an effect on hormonal mechanisms that influence glucose homeostasis in the body.

Keywords: Asian, haemoglobin A1c, morbid obesity, Roux-en-Y gastric bypass, type 2 diabetes mellitus

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INTRODUCTION

Obesity is a growing problem worldwide. It is associated with many comorbidities such as hypertension, obstructive sleep apnoea and type 2 diabetes mellitus (T2DM). Obesity-related T2DM is often referred to as "diabesity". The worldwide prevalence of obesity is currently estimated to be 15%–20%,[1] and is expected to grow exponentially, especially in Asian countries. This trend is no different in Singapore.[2]

Bariatric surgery has long been proven to be effective in weight reduction in the morbidly obese, as well as in maintaining long-term weight reduction. With this weight reduction, obesity-related comorbidities, including T2DM, tend to improve or resolve completely. Roux-en-Y gastric bypass (RYGBP) has been shown to induce remission of T2DM in more than 80% of subjects.[3] This DM resolution in RYGBP often happens before significant weight reduction has been recorded, and in some cases, in the immediate postoperative period. Bypass of the foregut in RYGBP has been suggested as the reason. This phenomenon is also well recorded in the case of biliary-pancreatic diversion (BPD), which also involves a foregut bypass.

Such findings have been well reported in the western literature, but studies on Asian population are still sparse. Given the differences in several genetic and non-genetic pathogenic factors for T2DM between Asians and Westerners,[4] the effect of RYGBP in Asian diabetics may be different. We report our initial experience with a unique Singapore racial mix of T2DM resolution after foregut bypass was carried out for morbid obesity, with a focus on early postoperative improvements.

METHODS

All morbidly obese patients with T2DM undergoing RYGBP at our institution from August 2008 to January 2010 were prospectively studied. Six patients had

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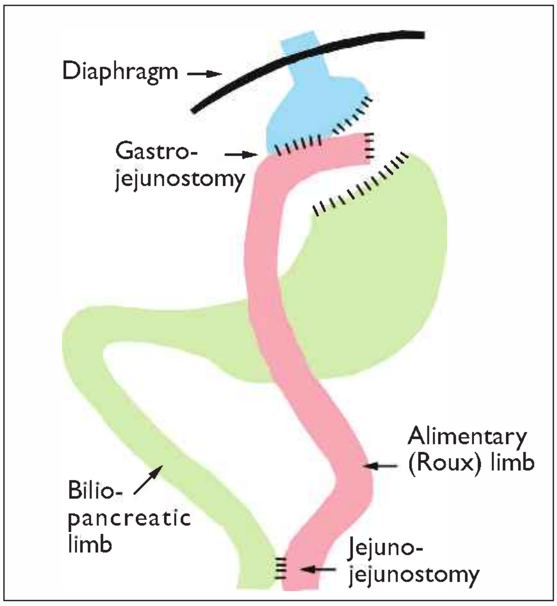

Fig. 1 Diagram shows the Roux-en-Y gastric bypass.

Table I. Preoperative demographic characteristics of the patients (n = 7).

Characteristic	Value
Age (yrs)	35.0 ± 11.1
Gender	
Male	5 (71.4)
Female	2 (28.6)
Ethnicity	
Chinese	1 (14.3)
Malay	4 (57.2)
Others	2 (28.6)
Weight (kg)	117.6 ± 34.2
BMI (kg/m^2)	43.0 ± 11.4
Duration of DM (yrs)	5.1 ± 3.0
HbA1c (%)	9.2 ± 2.2

Data is presented as mean ± standard deviation, or number of patients (%).
BMI: body mass index; DM: diabetes mellitus; Hb: haemoglobin

RYGBP and one had a laparoscopic sleeve gastrectomy with a duodenojejunal (DJ) bypass. All the patients met the Singapore Ministry of Health (MOH) Clinical Practice Guidelines for Obesity criteria for bariatric surgery.[5] This study was approved by the National Healthcare Group Institutional Review Board.

The metabolic profiles of these seven patients were evaluated according to a structured protocol. This includes a preoperative 75 g oral glucose tolerance test (OGTT), daily postoperative fasting plasma glucose (taking into consideration the concomitant use of insulin), postoperative OGTT either before discharge or at the follow-up visit, haemoglobin A1c (HbA1c) pre-operation and at two, four and 12 weeks post operation (or at the discretion of the endocrinologist managing the patient).

After a thorough history, physical examination and metabolic workup, all patients referred for consideration of bariatric surgery underwent a structured weight reduction program for four months under the supervision of a team of professionals, including nutritionists, physiotherapists and endocrinologists. They were offered surgery when the weight reduction after four months was deemed unsatisfactory despite the patients having demonstrated that they were committed to follow the strict dietary and lifestyle changes required for the bariatric procedure to be successful.

All patients were given a choice of three bariatric procedures, namely laparoscopic adjustable gastric band, sleeve gastrectomy and RYGBP. A sleep study and an upper gastrointestinal endoscopy were performed prior to the surgery. Triple therapy for *Helicobactor pylori* was given, if indicated. Those with significant obstructive sleep apnoea (OSA) were given pre- and postoperative continuous positive airway pressure (CPAP). Patients with a body mass index (BMI) > 50 were put on a very low-calorie diet for two weeks.

Patients were admitted on the day of the operation. Deep vein thrombosis prophylaxis consisted of subcutaneous low-molecular-weight heparin, perioperative graduated compression stockings and intraoperative calf pneumatic compression devices. Under general anaesthesia, the patient was positioned in the Lloyd-Davies and reverse Trendelenburg position with the standard five ports inserted, including the Nathanson liver retractor for liver retraction. The jejunum was divided 50–100 cm from the DJ flexure, with the proximal part forming the biliopancreatic (BP) limb. The alimentary limb was then measured to the desired length of 100–150 cm, and anastomosed to the BP limb with a linear stapling device to form the jejuno-jejunostomy (Fig. 1).

The length of BP limb and alimentary limb was dependent on the preoperative BMI, with a longer limb for patients with a higher BMI. In the case of DJ bypass patients, the respective BP and alimentary limbs were 30 cm and 50 cm, respectively. A 30-ml proximal gastric pouch was formed via linear stapler, and the gastric fundus was separated with the rest of the stomach and completely bypassed. The Roux limb was advanced in an antecolic fashion to create the gastro-jejunostomy using either a stapling device or by intra-corporeal suture. All mesenteric defects were closed with intracorporeal suturing. An oesophagogastroduodenoscopy as well as a leak test was performed at the end of the procedure.

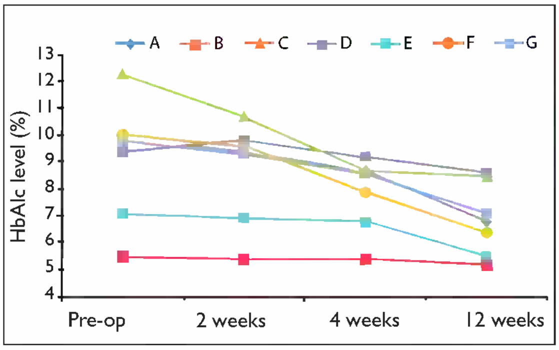

Fig. 2 Graph shows the drop in haemoglobin A1c values over time in each patient.

Table II. Results and percentage change of mean HbA1c at each follow-up interval from the preoperative HbA1c.

Time of testing	HbA1c (%)	change in HbA1c (%)	p-value
Preoperative	9.2 ± 2.2	-	-
2 weeks	8.7 ± 2.0	− 5.4	0.113
4 weeks	7.9 ± 1.3	− 14.1	0.039
12 weeks	6.9 ± 1.3	− 25.0	0.005

Data is presented as mean ± standard deviation, unless otherwise stated.
HbA1c: haemoglobin A1c

A Blake drain was placed at the left subdiaphragmatic space. Local anaesthesia was used generously for the incision wounds.

Post procedure, the patients were nursed in the high-dependency ward or intensive care unit for the first 24 hours, depending on their preoperative comorbidities and risk factors. Patients with severe OSA were put on bilevel positive airway pressure or CPAP ventilatory support. After a satisfactory Ultravist swallow performed the following day, oral fluids were started. The patients were reviewed by a dietician, and a fluid diet for the first two weeks was recommended and subsequently, a soft diet, as tolerated. An endocrinologist saw the patients prior to discharge and adjusted their medications, if necessary. Patients were discharged on postoperative Day 2 or 3 after the removal of the abdominal drain, and were followed up two weeks later.

Preoperatively, the data collected from all seven patients included their demographics, height and weight as well as diabetic status and control. All the patients were followed up by the bariatric surgical team and the diabetic centre at our institution. All the diabetic medications, including the dosages, were recorded. Postoperatively, the patients were followed up at two, four and 12 weeks. During these visits to our clinic, their weight was recorded, the HbA1c level obtained and the diabetic medication status noted. Most of these patients also had a 75 g OGTT performed before and after surgery, either before discharge or at the first follow-up visit. Both pre- and post-surgery weights were measured using the Tanita weight management clinic scales. (Tanita Corporation of America Inc, Arlington Heights, IL, USA). Weight loss was expressed in terms of change in the BMI or the percentage of excess weight loss (%EWL), which was calculated based on an ideal upper limit of normal (BMI of 23).

For the purpose of our study, HbA1c levels were taken as the biochemical marker for diabetic control. According to the Singapore MOH Clinical Practice Guidelines for Diabetes, an ideal HbA1c level indicates those within the normal range (4.5%–6.4%), while an optimal level would be one that approaches the normal range (6.5%–7.0%). Suboptimal levels range from 7.1% to 8.0% while unacceptable levels are those > 8.0%.[6] As a practical measure, the medication status of a diabetic patient not only provides an accurate indicator of disease severity and status, but it also has an impact on the everyday life of the patient in terms of the cost and side-effect of the medications. Therefore, the number of agents, dose and frequency was recorded at each follow-up in order to give an indication of clinical improvement or deterioration. This included all oral hypoglycaemic agents as well as insulin. Our patients' preoperative diabetic management came from a variety of sources. Their postoperative management was conducted by our institutional diabetologists, who selected and titrated each agent according to the patient's symptoms and clinical parameters, such as the daily 7-point blood glucose levels.

Using HbA1c and diabetic medication status, a patient's DM was considered to be in remission if no diabetic medications were required and a normal HbA1c was achieved. A reduction in diabetic medication or a significant reduction in HbA1c (> 1%) was taken as an improvement of DM. If there was no reduction in the medication or HbA1c levels, the patient's diabetic status was considered to be unchanged, while any increase was deemed as a deterioration of DM. The timeline at which the HbA1c normalised and the medications were reduced or taken off was also considered. All parametric values were analysed with a paired, two-tailed student *t*-test. A p-value < 0.05 was considered to be statistically significant. All analyses were performed with the Microsoft Excel 2000 programme (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The preoperative demographics and other details of the seven patients included in this study are presented

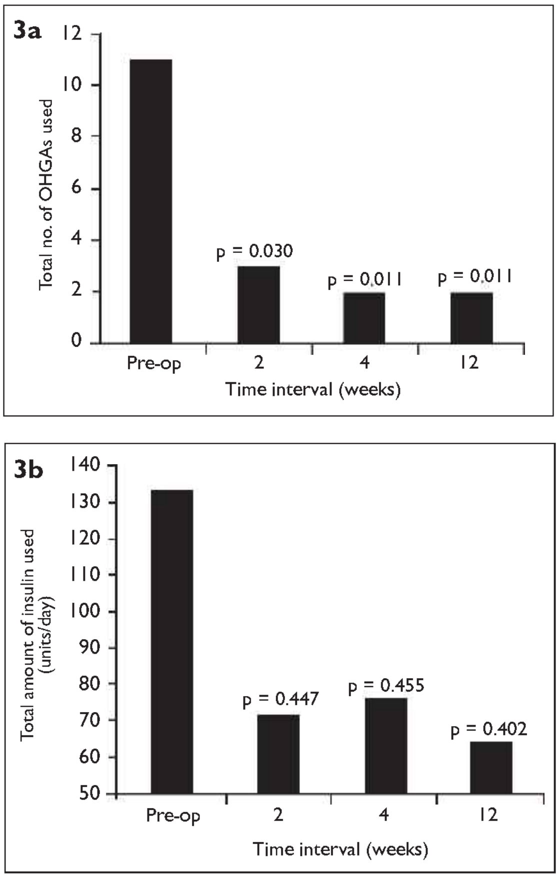

Fig. 3 Bar charts show (a) the usage of oral hypoglycaemic agents over time and (b) the usage of insulin over time.

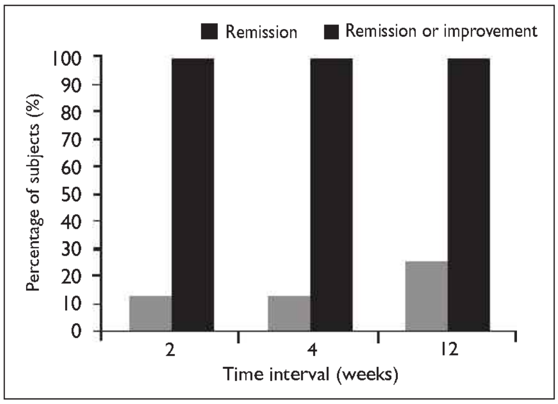

Fig. 4 Bar chart shows the percentage of patients achieving remission or improvement in diabetic status over time.

Table III. Mean excess weight loss at each follow-up interval.

Time interval	EWL (%)	p-value
Preoperative	0	-
2 weeks	19.2 ± 15.2	0.015
4 weeks	28.4 ± 12.5	< 0.001
12 weeks	45.1 ± 27.3	0.005

Data is presented as mean ± standard deviation, unless otherwise stated.
EWL: excess weight loss

in Table I. All the patients underwent successful operations with no intraoperative complications and the mean operating time was 249 ± 57 minutes. One patient developed intra-abdominal sepsis secondary to a delayed jejunal perforation that required an exploratory laparotomy, but was subsequently discharged well.

The HbA1c values of each patient at every visit were plotted on a graph. Values for all but one patient showed a downward trend over the entire time period (Fig. 2). However, Patient D showed an increase in HbA1c at two weeks, although this was slight and the subsequent follow-ups reverted to a downward trend. Noticeably, the steepest lines were those with higher preoperative HbA1c levels, indicating that the greatest changes occurred in those with poorer initial control. Also, the percentage change in mean HbA1c levels at each follow-up with regard to the mean HbA1c pre-surgery showed significant improvements in HbA1c levels at four and 12 weeks (Table II). The mean drop in HbA1c after 12 weeks was 2.29% ± 1.39%.

Preoperatively, all patients required at least one oral hypoglycaemic agent (OHGA). The total number of agents used was 11 (1.6 agents per patient). This number decreased to three (0.43 agents per patient) at two weeks post surgery, with three (43.8%) patients no longer requiring any form of medication. Post surgery, most of the patients had their medications discontinued before discharge from the hospital. At four weeks post surgery, only two agents (0.29 agents per patient) were in use, with four (57%) patients requiring no medication (Fig. 3a).

With regard to insulin usage, two patients were initially on a regime of either rapid-acting and intermediate-acting insulins or pre-mixed insulins. Their combined daily dose of insulin decreased from 134 to 72 units (– 46.3%) over two weeks, and from 134 to 64 units (– 52.2%) over 12 weeks (Fig. 3b). The two patients who were initially on insulin continued to be on it throughout the follow-up, but their medications now consisted primarily of low doses of long-acting insulins.

Remission of DM, as defined previously, was achieved in one (14.3%) patient by the end of two weeks (Fig. 4). Another patient (28.6%) also achieved remission at the end of the 12-week follow-up. In addition, all the subjects in the study achieved improvement in their diabetic status, with no unchanged or deteriorated statuses. Furthermore, all of them achieved improvement by the first follow-up at two weeks, and continued to show further improvement, as evidenced by the downward trend in both HbA1c levels and medication status. Thus, with a longer follow-up period, the percentage of subjects achieving remission was expected to increase.

Weight loss by all parameters was significant. Mean %EWL was 19.2% ± 15.2% after two weeks, 28.4% ± 12.5% after four weeks and 45.1% ± 27.3% after 12 weeks (Table III). The BMI of all the patients showed a drop at two weeks, with all maintaining a steady downward trend (Fig. 5). The mean drop in BMI was significant after just two weeks (Table IV), with a continued drop in the mean BMI over the 12-week follow-up.

DISCUSSION

T2DM associated with obesity resolves or improves after weight reduction. This phenomenon is well reported. Indeed, starvation on its own improves T2DM, as reported by the Rockefeller Institute in New York as far back as the early 1900s. Depending on the type of bariatric procedure, up to 80% resolution of T2DM has been reported. Unlike purely restrictive operations like the adjustable gastric band, surgery that bypasses the foregut appears to be more effective in this respect. Buchwald et al reported a higher resolution rate of 98% and 84% for BPD and RYGB, respectively, and a lower rate of 48% for gastric banding.[3] Our own gastric banding data confirmed the improvement in DM status after surgery.[7] More interestingly, improvement often occurs very soon after the bypass, even before significant weight loss has occurred.[8,9]

The current perception is that RYGBP causes an improvement in a diabetic patient's status through a variety of mechanisms. First and foremost, RYGBP enforces severe calorie restriction through both mechanical restriction and the up-regulation of satiety signals such as anorexigen peptide YY.[10] Ghrelin is secreted primarily by the stomach and proximal small intestine, and acts on the hypothalamus to regulate appetite. Observational studies have shown that ghrelin levels fall after RYGBP,[11] resulting in appetite reduction. The decrease in caloric intake is by itself able to result in the improvement of T2DM.[12]

Other hormonal mechanisms may also play a part in the improvement of T2DM prior to weight loss. There is restoration of a near-normal, post-prandial insulin response soon after RYGBP,[13] which is associated with a rise in Glucagon-like Peptide-1 (GLP-1) levels.[14] GLP-1 is a potent insulin secretagogue that is secreted by the distal ileum in response to ingested nutrients. Glucose-dependent insulinotropic polypeptide (GIP) is also manufactured and released in the duodenum and proximal jejunum in response to glucose and fat intake, stimulating an increase in insulin synthesis and secretion.[15] In T2DM, there is a chronic "GIP-resistant state", where defects in the signaling pathway result in decreased or inappropriate secretion of insulin despite the elevated levels of GIP.[16] It has been proposed that the bypass of the foregut in RYGBP restores normal GIP sensitivity and normalises the GIP levels.[8] Another hormone that is involved is leptin, which is known to inhibit glucose-stimulated insulin secretion, indicating its role in insulin resistance.[17] Hickey et al demonstrated a decrease in leptin levels despite a constant BMI in a group of morbidly obese patients who underwent RYGBP, matched by BMI to a control group of morbidly obese patients who did not undergo surgery.[9]

There are thus two different theories: the hindgut theory by Cummings et al[11] and the foregut theory by Rubino.[18] In the foregut hypothesis, exclusion of the foregut from the food stream causes a decrease in insulin resistance through the secretin pathway, thus improving the DM status. The hindgut theory proposes that the rapid transit of nutrients to the hindgut improves glucose metabolism, probably through GLP-1. The two theories are not mutually exclusive.

Given that such mechanisms come into play so early after RYGBP, it is reasonable to expect results in terms of improvement in T2DM early as well. Although weight loss appears to be statistically significant at two weeks, diabetic medications taken by patients tend to be reduced drastically even before discharge, when their postoperative weight has yet to be taken. This is confirmed by Pories et al, who reported a significant improvement in glycaemic control after only one week, before any significant weight loss was noted.[19] HbA1c is an accurate reflection of a patient's long-term diabetic status, as it is not affected by the wide variation of blood glucose levels throughout the day. Furthermore, HbA1c is closely related to the complications of DM. Elevated levels are also associated with retinopathy, neuropathy and nephropathy. For every one percentage point increase, the risk of microvascular complications increases by 37%,[20] and the relative risk of cardiovascular disease, stroke and peripheral arterial disease increases to 1.18, 1.17 and 1.28, respectively.[21] At a mean decrease of 2.3 percentage points in HbA1c over 12 weeks in our patients, we can expect a lower rate of complications from their DM in the long run.

We also noted a significant decrease in the amount of OHGAs used, with four (57%) patients requiring no medication after four weeks. The patients who continued to require medications tended to have a longer duration of DM and required high doses of insulin preoperatively.

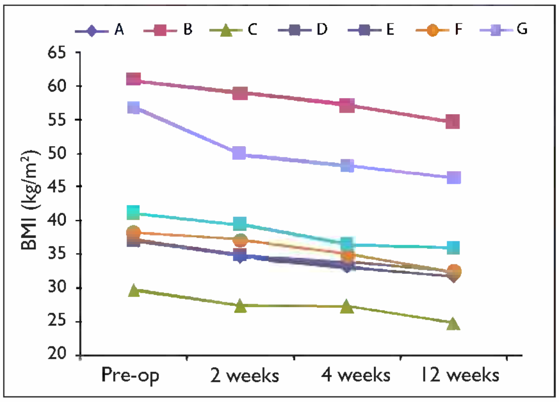

Fig. 5 Graph shows the change in body mass index over time in each patient.

Table IV. Mean body mass index and percentage change at each follow-up interval.

Time interval	BMI (kg/m²)	change in BMI (%)	p-value
Preoperative	43.0 ± 11.4	-	-
2 weeks	40.4 ± 10.7	− 6.0	0.010
4 weeks	38.8 ± 10.3	− 9.8	0.001
12 weeks	36.9 ± 10.2	− 14.2	< 0.001

Data is presented as mean ± standard deviation, unless otherwise stated.
BMI: body mass index

Sugerman et al reported a decrease in OHGA usage (from 35% to 9% of patients) and insulin usage (from 39% to 20% of patients) after RYGBP.[22] Also, MacDonald et al showed that after a six-year follow-up period, RYGBP was able to decrease diabetic medication requirements in a group of morbidly obese patients with T2DM from 31% to 8.6% ($p < 0.001$), while diabetic medication requirements increased from 56.4% to 87.5% ($p < 0.003$) in a group of control patients that only had conventional medical treatment.[23] The decrease in medication requirement and the attendant potential side effects, including hypoglycaemia, gastrointestinal symptoms and weight gain, have an impact on the patient's quality of life, not to mention the cost involved.

Our early results regarding T2DM remission correlate with other reports in the literature. In the Swedish Obese Subjects study, subjects that underwent bariatric surgery had much lower incidence rates of DM after ten years, as compared to medically treated controls.[24] Schauer et al reported that 83% out of the 240 patients with either T2DM or impaired fasting glucose had normalised fasting plasma glucose and HbA1c after undergoing RYGBP.[25] We expect our long-term results to be similar.

Asians have been reported to have a higher risk of metabolic diseases at a lower BMI than Westerners given the higher central and visceral obesity in Asians at the same BMI.[26] Therefore, the T2DM burden in Asia is disproportionally higher. A Taiwan study reported that after bariatric surgery, the HbA1c of T2DM and impaired fasting glucose patients decreased rapidly over the first three months and then stabilised, with a mean decrease of 2.2% ± 1.9% over one year.[27] Our study's follow-up period over these crucial three months showed similar results in HbA1c improvement (2.28% ± 1.39%). The literature suggests several predictors of T2DM resolution after bariatric surgery, including a longer duration of T2DM, a greater need for medications (insulin usage), and the magnitude of weight loss (EWL).[25,28] Our results showed the same trends; our patients who did not require insulin preoperatively achieved resolution of DM within the first 12 weeks, whereas those on insulin preoperatively were less likely to do so despite some improvement in their diabetic status.

There is no argument against bariatric surgery as an option for the morbidly obese with T2DM. The current best medical treatment includes calorie restriction and medical treatment with drugs to achieve an optimal HbA1c level. With that, one can expect modest weight loss ranging from 3–5 kg or 2–3 BMI units, and this is often not sustained beyond one year.[25] In the community setting, HbA1c levels in T2DM patients hover between 8.5% to 9% above the optimal level.[29] Furthermore, intense medical treatment carries a 2%–4% yearly incidence of severe hypoglycaemia, which can be fatal.[29] Therefore, surgery has been proven to be superior to medical treatment in terms of maintaining weight loss and altering the natural course of T2DM, which has been considered medically incurable.[24,30] Despite the obvious risks of surgery, the risks of morbid obesity as well as all its associated comorbidities make surgery a viable option in those who are eligible.

Bariatric surgery is more effective the shorter the duration of T2DM, and before the complications of T2DM have set in. Sugerman et al also found that a young age was a positive predictor for T2DM resolution.[22] A younger age and the lack of complications of T2DM enable these patients to better withstand the stresses of anaesthesia and surgery, thus giving them a better chance of a successful surgery. Early surgery also preempts irreversible pancreatic B-cell deterioration, giving a higher chance of DM resolution after surgery.[30]

In conclusion, our study has shown positive early effects of RYGBP on morbidly obese T2DM Asian patients before significant weight loss occurred. However, the hormonal mechanism responsible is still not fully understood. As our results correlated with larger studies with a longer follow-up period, the case for early RYGBP for the morbidly obese with T2DM is further substantiated.

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