

Bariatric surgery and diabetes remission: Who would have thought it?

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and obesity are increasingly common and major global health problems. The Edmonton obesity staging system clearly pointed towards increased mortality proportionate to the severity of obesity. Obesity itself triggers insulin resistance and thereby poses the risk of T2DM. Both obesity and T2DM have been associated with higher morbidity and mortality and this calls for institution of effective therapies to deal with the rising trend of complications arising out of this dual menace. Although lifestyle changes form the cornerstone of therapy for both the ailments, sustained results from this modalities is far from satisfactory. While Look AHEAD (action for HEAalth in diabetes) study showed significant weight loss, reduction in glycated hemoglobin and higher remission rate of T2DM at 1st year following intensive lifestyle measures; recurrence and relapse rate bounced back in half of subjects at 4 years, thereby indicating that weight loss and glycemic control is difficult to maintain in the long term with lifestyle interventions. Same recurrence phenomenon was also observed with pharmacotherapy with rimonabant, sibutramine and orlistat. Bariatric surgery has been seen to associate with substantial and sustained weight loss in morbidly obese patients. Interestingly, bariatric surgeries also induce higher rates of short and long-term diabetes remission. Although the exact mechanism behinds this diabetes remission are not well understood; improved insulin action, beta-cell function and complex interplay of hormones in the entero-insular axis appears to play a major role. This article reviews the effectiveness of bariatric procedures on remission or improvement in diabetes and put a perspective on its implicated mechanisms.

Key words: Bariatric surgery, diabetes remission, incretin, Type 2 diabetes

INTRODUCTION

The Edmonton obesity staging system proposed by Sharma, *et al.* suggested an increase in mortality proportionate to the severity of obesity.^[1] Both Type 2 diabetes mellitus (T2DM) and obesity are increasingly common global health problems and future forecasts also point to a gloomy picture with 439 million people being predicted to have diabetes by 2030.^[2] Dietary changes, lifestyle modification (LSM) form the cornerstone of therapy for both the ailments.

Pharmacotherapy for obesity is another approach if LSM alone is inadequate.

Look AHEAD (action for HEAalth in diabetes) study clearly hinted that intensive LSM result in significant weight loss and reduced glycated hemoglobin (HbA1c) levels, although primary objective of reduction in cardiovascular (CV) events were not achieved. At 1-year, intensive LSM interventions resulted in higher remission of T2DM than routine lifestyle advices. However, the average weight loss in the intensive lifestyle intervention group decreased from 8.6% at 1st year–4.7% at 4th year and the rate of patients achieving T2DM remission also markedly reduced from 12% at 1st year–7% at 4th year,

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indicating that weight loss and glycemic control is difficult to maintain in the long term even with the intensive LSM.^[3] Meta-analysis of studies involving pharmacotherapy for obesity also finds significant failure of several anti-obesity agents such as rimonabant, sibutramine, and orlistat after initial improvement for 1st year.^[4] With this modest weight loss and recurrence following LSM and pharmacotherapy, bariatric surgery is increasingly acquiring prominent role in the management of obesity.

Substantial data now suggest that bariatric surgery could be the most effective therapy for obesity that also provide significantly higher rates of resolution or improvement of T2DM. Bariatric surgeries lead to substantial and sustained weight loss for most patients, with the magnitude varying according to the procedure performed. The Swedish Obesity Subjects (SOS) study, a long-term, prospective, controlled trial, demonstrated sustained mean weight loss of 18% by 20 years in contrast to the matched controls on usual medical care who had no significant weight change over this same. Additionally, bariatric surgery is associated with improvements or remission of diabetes in up to 80%, and reduction in incidental diabetes by 73%, apart from the improvement in hypertension and dyslipidemia. Furthermore, bariatric surgery was associated with reduced incidence of myocardial infarction (29%), stroke (34%), cancer in women (42%), and overall mortality (30–40%).^[5] However, many consider bariatric surgery as a draconian last-resort step for obesity and diabetes management, in part due to surgical risks as well as uncertainty about long-term efficacy.

Principally, bariatric surgeries can be of three types-A. Restrictive procedure-adjustable gastric band (AGB), sleeve gastrectomy (SG), B. malabsorptive procedure-duodeno jejunal bypass and C. mixed procedure-biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD-DS), and Roux-en-Y gastric bypass (RYGB). Restrictive procedures resulted in delayed glycemic control related majorly to weight loss however the malabsorptive procedures lead to remission of T2DM very early within days to few weeks after surgery and much before significant weight loss has occurred.^[6] RYGB is currently the gold standard technique.^[7] Recently, some studies have also highlighted the usage of ileal interposition (II) as a novel mode for remission in diabetes.^[8]

Moreover, a nonsurgical duodenal-jejunal bypass liner (DJBL), delivered and retrieved endoscopically, has been developed to mimic RYGB-related proximal small intestinal exclusion. The DJBL is a 60 cm long impermeable liner, anchored proximally at duodenal bulb and works as a barrier for bile as well as enzymes to get

mixed with food in foregut. However, unlike RYGB, the anatomy of the stomach and small intestine is not affected enabling mechanistic studies focusing exclusively on the role of the proximal intestine in T2DM. Some studies have demonstrated a significantly improved of glycemic control with DJBL; however, it is recommended to be removed at 6–12 months.^[9]

With this advancement, bariatric surgery has recently been proposed in nonobese diabetic patient denominated as “metabolic surgery,” primarily aimed to treat T2DM and metabolic abnormalities. In spite of the move to describe the procedure as “metabolic surgery,” there is no widespread adoption of this procedure for diabetes, although barriers are slowly being overcome. This could perhaps be due to two major reasons. (a) Imperfect understanding of how weight loss surgery works most clinician would be reluctant to prescribe a treatment when we do not understand how it works, even if it is effective and (b) the unpredictability of the outcomes of surgery - A trial to assess effectiveness can be widely acceptable for drugs, but the same cannot be said for surgery as it is risky, invasive, irreversible, and often the last resort.

The current article reviews the effectiveness of bariatric procedures on diabetes remission or improvement and put a perspective on its implicated mechanisms.

REVIEW METHODS

The PubMed/Medline search was conducted to identify relevant literature showing the effects of bariatric surgical procedures on diabetes improvement or remission and its implicating mechanism. In view of the exhaustive scope of the review, all randomized controlled clinical trials (RCTs) and large observational studies were chosen with a particular focus to those published in English language since 2000–2014.

Indication of bariatric surgery

In 1998, National Institute of Health guidelines recommended bariatric surgery in morbidly obese (body mass index [BMI] ≥ 40 kg/m²) or patients with BMI ≥ 35 kg/m² with co-morbidities such as diabetes and hypertension.^[10] Following the success of bariatric surgery several other guidelines have emerged since then and some of these recent recommendations are compiled in Table 1.

Efficacy of bariatric surgery on remission of diabetes in patient with body mass index > 35 kg/m²

Who would have thought it? An operation proves to be the most effective therapy for adult onset diabetes mellitus, quoted a paper published in 1995 in *Annals of*

Table 1: Indication of bariatric surgery

Guidelines	Year	Indication
NIH	1991	Patients with BMI ≥ 40 kg/m ² or patients with a serious co-morbidities and BMI ≥ 35 kg/m ²
Asia-pacific	2005	Patients with BMI > 37 kg/m ² Patients with BMI > 32 kg/m ² with T2DM or ≥ 2 co-morbidities
IFSO-APC	2011	Patients with BMI > 35 kg/m ² Patients with BMI > 30 kg/m ² with T2DM or metabolic syndrome
IDF	2011	Asian patients with BMI 27.5-32.5 kg/m ² and T2DM not controlled by medical treatment in presence of CV risk factor

NIH: National Institute of Health, IFSO-APC: International Federation for the Surgery of Obesity and Metabolic Disorders Asia Pacific, IDF: International Diabetes Federation, BMI: Body mass index, T2DM: Type 2 diabetes

Surgery. Pories *et al.* conducted a prospective observational study (1980-1995) on severely obese patients ($n = 608$) with T2DM ($n = 165$) or impaired glucose tolerance (IGT) ($n = 165$) subjects subjected to RYGB. After a long 14 years of follow-up (mean 7.6 years), 83% of the diabetic subjects were off their anti-diabetic drugs, while normoglycemia achieved in 99% of patients with IGT. Additionally, a significant improvement in dyslipidemia, hypertension, osteoarthritis, and obstructive sleep apnea were also observed in this subjects.^[11] Since then, several observational as well as RCT finds significant improvement or remission in diabetes not only as a secondary outcome but also as a primary outcome.

Improvement or remission of diabetes as a secondary outcome: Observational studies

The 10 years long follow-up data from SOS study which involved severely obese subjects (mean BMI 41 kg/m²) who underwent either bariatric surgery or conventionally treated, found a higher rate of recovery from diabetes, hypertension and hypertriglyceridemia, apart from showing a significantly higher sustained and long term weight loss in the surgical arms. Remission rate of diabetes who underwent bariatric surgery compared to well-matched control at 2 and 10 years were eight versus 1% and 24 versus 7% respectively although hypercholesterolemia was same in both the arms.^[12] Hofso *et al.* reported a 1-year follow-up study of morbidly obese subjects (mean BMI 45.1 kg/m²) treated with RYGB or intensive lifestyle intervention, found a significantly higher remission rate of diabetes (70% vs. 33%, $P = 0.027$) and hypertension (49% vs. 23%, $P = 0.016$) in RYGB group. Furthermore, RYGB arm had significantly higher reduction in the prevalence of metabolic syndrome, albuminuria and electrocardiographic left ventricular hypertrophy.^[13] Adams *et al.* also found diabetes, dyslipidemia and hypertension resolved much more frequently in RYGB group (all $P < 0.001$) at 2 years of follow-up. Additionally, other quantitative outcome of BMI, blood pressure (BP), lipids, resting metabolic rate,

sleep apnea, and health-related quality of life also improved significantly in the RYGB group ($P < 0.001$) at 2 years.^[14] An Asian (Korean) 18 months follow-up study finds, 57% recovery from diabetes following bariatric surgery. Recovery from dyslipidemia (84%), hypertension (47%) was significantly higher in surgical group compared to LSM group where 10%, 24%, and 20% of subjects recovered from diabetes, dyslipidemia, and hypertension, respectively.^[15]

Interestingly, a 1-year follow-up study by Martins *et al.* found no differences in co-morbidities resolution (total or low density lipoprotein (LDL) cholesterol, triglycerides (TG) or glucose) between bariatric versus LSM group in spite of significant weight loss ($P < 0.0001$) in the surgical arms although there was higher resolution of hypertension and little rise in high density lipoprotein in the surgical arm.^[16]

Improvement or remission of diabetes as a primary outcome: Observational studies

Several observational studies have been conducted primarily in diabetic subjects and directly compared improvement or resolution of diabetes after bariatric surgery to anti-diabetic therapies. Leonetti *et al.*, after 18 months of follow-up found 80% of patients had diabetes resolution following laparoscopic SG compared to medical arm where all patients continued or increased their hypoglycemic therapy. Obstructive sleep apnea syndrome also reduced by 5 times and there was significant reduction of hypertension as well as anti-lipid medication in surgical arm in contrast to the increase in medications and no change in obstructive sleep apnea in the medical arm.^[17] Dorman *et al.* in a 1-year follow-up study compared the efficacy of medical management and two bariatric surgical methods (DS and LAGB) to RYGB for the treatment of T2DM. Results suggested that the DS was superior to RYGB, while RYGB was superior to LAGB and medical therapy, in improving diabetes although similar weight loss observed between DS and RYGB at the end of 1-year.^[18] Leslie *et al.* in a 2 years follow-up study compared RYGB to routine medical management (RMM) and found RYGB group having increased (10.5–38.2%, $P < 0.001$) achievement of the American Diabetes Association (ADA) goals (composite of HbA1c $< 7.0\%$, LDL < 100 mg/dL, and systolic blood pressure [SBP] < 130 mmHg) compared to the RMM group (13.9–17.4%, $P = 0.47$). RYGB group also had significant decrease in medication use.^[19]

A 10 years long follow-up data also evaluated the long-term effects of bariatric surgery (BPD) on diabetic micro-vascular outcome (micro- and macro-albuminuria, glomerular filtration rate [GFR]) as a primary objective and analyzed macro-vascular outcomes, Type 2 diabetes

remission, hyperlipidemia as a secondary objective. All BPD subjects recovered from micro-albuminuria; in contrast, it progressed to macroalbuminuria in conventional arm. GFR and probable risk of coronary artery disease significantly decreased in surgical arm compared to conventional arm ($P < 0.001$) owing to reduction in major risk factors such as BP and hyperlipidemia. Moreover, remission from Type 2 diabetes occurred in all patients within 1-year of surgery.^[20]

Table 2 summarizes the results from the observational studies.

Improvement or remission of diabetes as a primary outcome: Randomized controlled trial

Several RCT investigated the outcome of bariatric surgery in diabetic subjects and directly compared it to the intensive medical management (IMM). Dixon *et al.* in 2 years follow-up from a nonblinded RCT compared the effect of AGB to medical therapy on remission of Type 2 diabetes (fasting glucose level <126 mg/dL and HbA1c $<6.2\%$ without medication) as the main objective, in patient with <5 years of diabetes duration. Seventy-three percentage with AGB had remission of Type 2 diabetes compared to 13% in medical therapy group. Relative risk of remission for the surgical group was 5.5 (95% confidence interval [CI] 2.2–14.0), and it was proportionally related to the weight loss ($P < 0.001$) as well as with the lower baseline HbA1c levels ($P < 0.001$).^[21]

Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study a 1-year nonblinded RCT, compared the efficacy of intensive medical therapy (IMT) alone to medical therapy plus RYGB

or SG, on glycemic endpoints (achieving HbA1c $<6.0\%$). Results found 42, 37 and 12% of patient achieved the target HbA1c of $<6.0\%$ in RYGB ($P = 0.002$), SG ($P = 0.008$) and IMT, respectively. While the IMT alone group had higher HbA1c of 7.5% in spite of a larger use of drugs, only 28% of the SG group required anti-diabetic drugs therapy and none required drugs in RYGB group. Furthermore, the requirements of drugs to lower glucose, lipid, and BP levels were significantly decreased after both surgical procedures, while it was increased in IMT alone group. Interestingly, remission rate were comparatively lower (42% by RYGB and 37% by SG) in this study as it was done in mainly advanced diabetics.^[22]

Another nonblinded RCT conducted by Mingrone *et al.*, comparing RYGB and BPD with medical therapy, found 95% in BPD, 75% in RYGB and 0% in medical therapy had diabetes remission (fasting plasma glucose [FPG] <100 mg/dl and HbA1c $<6.5\%$ without medication) at the end of 2 years ($P < 0.001$ for both comparison). All patients in both surgical groups discontinued oral hypoglycemic drugs and insulin therapy within 15 days after surgical intervention. Interestingly, age, sex, baseline BMI, duration of diabetes, and weight changes were not significant predictors of diabetes remission at 2 years.^[23]

A 12-month follow-up of Diabetes Surgery Study, a nonblinded RCT conducted by Ikramuddin *et al.* also compared RYGB to IMM on achieving composite goal of HbA1c $<7.0\%$, LDL <100 mg/dL, and SBP <130 mm Hg. While the 49% in RYGB and 19% in IMM group achieved the composite end point (odds ratio [OR] 4.8; 95% CI, 1.9–11.7), RYGB group also needed 3 times

Table 2: Observational studies showing diabetes remission after bariatric surgery

Author, year	Country	n	Study type	Follow-up (month)	Bariatric surgery	T2DM remission rate (%)		P
						Bariatric	Conventional	
Sjostrom <i>et al.</i> , 2004	Sweden	3505	nRCT	24;120	LAGB-19% VBG-68% RYGB-13%	72	21	<0.001
Hofsø <i>et al.</i> , 2010	Norway	146	nRCT	12	RYGB	79	0	<0.005
Adams <i>et al.</i> , 2010	USA	816	nRCT	24	RYGB	78.7	2.6	<0.001
Serrot <i>et al.</i> , 2011	USA	34	Retrospective	12	RYGB	64.7	0	<0.001
Martins <i>et al.</i> , 2011	Norway	179	Prospective	12	RYGB	67	36.8	0.17
Iaconelli <i>et al.</i> , 2011	Italy	50	Prospective	12–120	BPD	100	45	<0.001
Scopinaro <i>et al.</i> , 2011	Italy	68	Prospective	12	BPD	83	0	<0.001
Leonetti <i>et al.</i> , 2012	Italy	60	Prospective	3; 6; 12; 18	LSG	80	0	<0.001
Heo <i>et al.</i> , 2012	Korea	485	Retrospective	18	RYGB-28% LAGB-27.6% LSG-44.4%	57.1	9.5	<0.001
Dorman <i>et al.</i> , 2012	USA	58	Retrospective	12	RYGB-60.1% LAGB-20.9% DS-18.8%	65	3.4	<0.001
Leslie <i>et al.</i> , 2012	USA	267	Prospective	24	RYGB	38.2	17.4	<0.001

nRCT: Nonrandomized controlled trial, T2DM: Type 2 diabetes mellitus, RYGB: Roux-en-Y gastric bypass, LSG: Laparoscopic sleeve gastrectomy, LAGB: Laparoscopic adjustable gastric banding, BPD: Biliopancreatic diversion, DS: Duodenal switch, VBG: Vertical banded gastroplasty

fewer medications compared to IMM. This achievement of composite end-point was primarily attributable to weight loss, although more people experienced nutritional deficiency in RYGB group.^[24]

Furthermore, a recent 3 years follow-up data from STAMPEDE study finds T2DM remission rates of 38, 24 and 5% who received RYGB, SG and IMT respectively. Nevertheless, STAMPEDE also reported a glycemic relapse (defined as a patient who had a HbA1c \leq 6% at 1-year but did not maintain at 3 years) of 5, 24, and 80% for RYGB, SG and IMT respectively. In conclusion, STAMPEDE 3 years follow-up trial finds that HbA1c \leq 6% was achieved in only 38% of RYGB, 24% of SG and in 5% of the patients on IMT.^[25]

Table 3 summarizes the outcomes of bariatric surgery in RCT.

Improvement or remission of diabetes: Meta-analysis

There are few systematic review and meta-analysis in literature which comprehensively analyzed outcomes of bariatric surgery. A review by Tice *et al.* comparing RYGB with LAGB finds diabetes resolution in 78% after RYGB and 50% after LAGB.^[26] A meta-analysis by Buchwald *et al.* also echoed same finding and suggested an average of 78% achieved complete resolution without any anti-diabetic medications. Furthermore, 87% had either diabetes improved or resolved and required only fewer anti-diabetic medications following bariatric surgery and diabetes resolution were greatest for patients undergoing BPD/DS, followed by RYGB, and least for LAGB.^[27] Another meta-analysis by Buchwald and Oien involving 1,846 diabetic patients finds diabetes resolution in 99, 84, 72 and 48% patients after BPD/BPD-DS, RYGB, gastroplasty and gastric banding respectively.^[28] A recent meta-analysis by Chang *et al.* reported an overall diabetes remission of around 90% after bypass surgeries (pooled data of RYGB and BPD) and 70% after gastric banding.^[29]

Most recent meta-analysis of 16 studies ($n = 6131$) by Ribaric *et al.* demonstrated, 63.5% diabetes remission after

bariatric surgery compared to 15.6% after conventional therapy ($P < 0.001$).^[30]

Figure 1 demonstrates the efficacy of bariatric surgery in diabetes remission in observational studies and RCT.^[30]

Remission of diabetes following bariatric surgery using recent criteria of remission

It should be noted that definition of diabetes remission varied amongst these studies mentioned above and enough controversy exist regarding T2DM remission rates following bariatric surgery due to the heterogeneity in its definition. Hence, in an attempt to develop standardized definitions that can be used consistently in clinical studies, consensus groups from ADA in 2009 and International Diabetes Federation (IDF) in 2011, proposed certain criteria to define remission and cure in diabetes [Table 4].^[31,32]

There are several observational studies which analyzed diabetes remission following bariatric surgeries using recent ADA or IDF criteria. The diabetes remission rate varied from 24% to 53% in these retrospective studies.^[33-39] Pournaras *et al.* in a retrospective review of 209 T2DM patients who underwent gastric bypass, SG or gastric banding, analyzed diabetes remission rate by 2009 ADA remission criteria (HbA1c $<$ 6%, FPG $<$ 100 mg/dl in

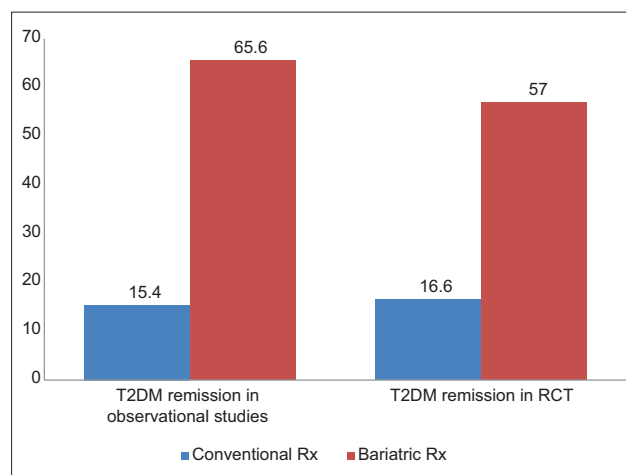


Figure 1: Type 2 diabetes mellitus remission rate (%) following bariatric surgery

Table 3: Randomized controlled trial showing diabetes remission after bariatric surgery

Author, year	Country	n	Study type	Follow-up	Bariatric surgery	T2DM remission rate (%)		P
						Bariatric	Conventional	
O'Brien <i>et al.</i> , 2006	Australia	80	RCT	24	LAGB	93	46.7	<0.01
Dixon <i>et al.</i> , 2008	Australia	60	RCT	24	LAGB	73	13	<0.001
Mingrone <i>et al.</i> , 2012	Italy	60	RCT	24	RYGB-50%	85	0	<0.001
Schauer <i>et al.</i> , 2012	USA	150	RCT	12	BPD-50%	39.4	12	<0.005
Ikramuddin <i>et al.</i> , 2013	USA	120	RCT	12	RYGB	49	19	<0.001

T2DM: Type 2 diabetes mellitus, RCT: Randomized controlled trial, RYGB: Roux-en-Y gastric bypass, LSG: Laparoscopic sleeve gastrectomy, LAGB: Laparoscopic adjustable gastric banding, BPD: Biliopancreatic diversion

Table 4: ADA and IDF criteria of diabetes remission

Guidelines, year	Terminology	Criteria
ADA, 2009	Complete remission	HbA1c <42 mmol/mol (6.0%) Fasting glucose <5.6 mmol/l (100 mg/dl) At least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures (ADA criteria of complete remission >5 years is defined as "cure" of diabetes)
	Partial remission	HbA1c <48 mmol/mol (6.5%) Fasting glucose 5.6-6.9 mmol/l (100-125 mg/dl) At least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures
IDF, 2011	Optimization of metabolic state	HbA1c ≤42 mmol/mol (6.0%) No hypoglycemia Total cholesterol <4.0 mmol/l LDL-C <2.0 mmol/l Triglycerides <2.2 mmol/l Blood pressure <135/85 mmHg >15% weight loss With reduced medication from the preoperated state or without other medications (where medications are continued, reduced doses from pre-surgery with minimal side effects would be expected)
	Substantial improvement of metabolic state	Lowering of HbA1c by >20% LDL-C <2.3 mmol/l Blood pressure <135/85 mmHg With reduced medication from the preoperated state

ADA: American diabetes association, IDF: International diabetes association, BMI: Body mass index, LDL-C: Low density lipoprotein cholesterol, HbA1c: Glycated hemoglobin

absence of pharmacologic treatment for 1-year). At a median follow-up of 23 months, study found 41, 26, and 7% had diabetes remission after gastric bypass, SG and gastric banding, respectively ($P < 0.001$ between groups). Interestingly, the remission rate for gastric bypass was significantly (17%) lower with the ADA criteria compared to previously used (40.6 vs. 57.5%; $P = 0.003$).^[33]

In another study evaluating metabolic control in T2DM patients ($n = 125$) after bariatric surgery found, 36% had diabetes remission ($P < 0.001$) by ADA criteria while 50% were "nonremitters" (defined as HbA1c <7%, LDL-cholesterol <100 mg/dL, TG <150 mg/dL, and HDL-cholesterol >40 in male or >50 mg/dL in female) after a 1-year of follow-up. However, 92% of nonremitters had HbA1c of <7% thereby suggesting a significant improvement in overall diabetes control.^[34] In another retrospective study of 141 T2DM patient, 52.5% had diabetes remission at 1-year of follow-up. Excess weight loss were directly correlated with diabetes remission ($P = 0.037$) while duration of diabetes, prior insulin use, age, and female sex were inversely associated with remission ($P = 0.004$).^[35]

A 18 months follow-up data of T2DM patient ($n = 110$) who underwent bariatric surgery found, 50% had complete and 12.7% had partial remission (HbA1c 6–6.4%, FBS 100–125 mg/dl without anti-diabetics for 1-year) while applying 2009 ADA consensus criteria.^[36] A 6 years long median follow-up studies in T2DM patient ($n = 217$) who underwent bariatric surgery had 24% complete remission while 26% had partial remission. Additionally, 34% had more than 1% HbA1c reduction thereby suggesting that 84% had

improvement in diabetes after bariatric surgery. Curiously, 19% had recurrence after initial diabetes remission. Shorter duration of diabetes and higher long-term excess weight loss predicted the long-term remission.^[37]

A study by Miras *et al.* conducted on 396 morbidly obese T2DM patients who underwent bariatric surgery found 14% had diabetes remission by IDF and 38% by the ADA criteria at 1-year which decreased to 8 and 9% respectively at the end of 2 years, thereby suggesting somewhat a lower remission rate.^[38] Another 3 years follow-up data to determine the effectiveness of RYGB in T2DM remission in patients with BMI below 35 kg/m² ($n = 100$) finds 53.2, 9.6, 25.5, and 11.7% achieved complete remission, partial remission, improvement, and no improvement, respectively. Multivariate analysis suggested that remission of diabetes seen with only noninsulin use (OR = 15.1, 95% CI 2.8–81.2; $P = 0.002$).^[39]

Table 5 summarizes the diabetes remission in retrospective studies using ADA criteria.

Improvement and remission of diabetes following duodenal-jejunal bypass liner

Regarding DJBL, although it looks to be a promising nonsurgical tool for glycemic improvement of T2DM in short term [Table 6], safety data is still scarce.^[9,40-42] A recent meta-analysis involving 10 trials ($n = 342$) did not recommend DJBL for routine use, owing to very little evidence. Majority of trials with DJBL were short term, compared with sham procedure and not directly with optimal pharmacological treatment. While a sham

Table 5: Retrospective studies that have assessed diabetes remission rates according to ADA criteria

Author, year	Procedure	Follow up	Number	Remission rates (%)	
				Complete	Partial
Pouranas <i>et al.</i> , 2012	RYGB, VSG, BPD	23 months	209	34	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	1-year	125	36	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	1-year	141	53	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	18 months	110	50	13
Brethauer <i>et al.</i> , 2013	RYGB, VSG, BPD	5-6 years	217	24	26
Miras <i>et al.</i> , 2014	RYGB, LGB, VSG, BPD - DS	1-2 years	90	38	52
Boza <i>et al.</i> , 2014	RYGB	3 years	94	53	10

RYGB: Roux-en-Y gastric bypass, VSG: Vertical sleeve gastrectomy, LGB: Laparoscopic gastric band, BPD: Bilio-pancreatic diversion, BPD-DS: Biliopancreatic diversion with duodenal switch, Not reported/retrievable, ADA: American diabetes association

Table 6: DJBL and glycemic response in type 2 diabetes

Author, year	n	Study type	BMI (kg/m ²)	Weight loss (kg)	HbA1c reduction
Rodriguez <i>et al.</i> , 2009	18	Pilot	38.9 (mean)	NR	-2.4% at 6 month
De Moura <i>et al.</i> , 2012	22	Open prospective	40-60	NR	-2.1% at 1-year
De Jonge <i>et al.</i> , 2013	17	Open prospective	30-50	-12.7	-1.4% at 6 month
Koehestanie <i>et al.</i> , 2014	77	RCT	30-50	-10.6 at 6 month -6.8 at 1-year	-1.3% at 6 month -1.0% at 1-year

n: Number of patients, RCT: Randomized controlled trial, BMI: Body mass index, NR: Not reported/retrievable, Kg: Kilogram, DJBL: Duodenal-jejunal bypass liner, HbA1c: Glycated hemoglobin

procedure ensures the validity of the study, it is not yet known whether the DJBL would have produced any net benefit compared to optimal standard care. Also, the majority of these studies investigated a prototype rather than the commercialized product; hence, the benefit-risk relation remains unknown until date. Although high grade obese patients benefitted with DJBL in short-term excess weight loss, other patient-relevant endpoints, including glycemic control is either not available or ambiguous.^[43]

Taken together, all these data points to an impressive outcome of diabetes remission following bariatric surgery keeping in mind the associated several inherent limitations of observational studies.

Bariatric surgery in Type 2 diabetes mellitus patients with body mass index < 35 kg/m²

A RCT by O'Brien *et al.* conducted in 80 adults with mild to moderate obesity (BMI 30–35 kg/m²) assigned to either intensive medical treatment or LAGB, found considerable (93%) reduction in the prevalence of metabolic syndrome in surgical arm ($P < 0.002$), apart from significantly higher effective weight reduction ($P < 0.001$) and improvement in quality of life at the end of 2 years.^[44]

Improvement or remission of diabetes: Observational studies

Several observation studies have also been conducted in patients with BMI <35 kg/m². A large 1-year prospective observational study ($n = 820$) compared the effect of laparoscopic mini gastric bypass in person with BMI >35 to BMI <35 kg/m² in T2DM/impaired fasting glucose patient ($n = 201$). Ninety-two and 77% achieved successful

goal of diabetes remission (HbA1c <7.0%, LDL <100 mg/dl, and TG < 150 mg/dl) in BMI >35 and BMI <35 respectively ($P = 0.05$), thereby suggesting an overall success of diabetes control in 87%. Slightly lower response of DM resolution in BMI <35 was suggested to be attributable to the significantly higher age, female predominance, and lower C-peptide level.^[45]

Another study ($n = 60$) evaluated the results of II into the proximal jejunum with SG (II-SG) to II with diverted SG (II-DSG) for treating metabolic syndrome in patients with T2DM with BMI <35. At the mean follow-up of 7.4 months; 87, 82, 90 and 91% had adequate sugar, TG, HDL and BP control, respectively. Moreover, II-DSG was more effective procedure in improving metabolic syndrome.^[46] An Indian study group also evaluated the outcome of II-SG ($n = 43$, mean of BMI 33 kg/m²) and II-DSG ($n = 17$, mean BMI of 29 kg/m²) on diabetes remission in T2DM patient in two different study. Diabetes remission rate (HbA1c <6.5% without medication) were 47% after II-SG and 71% after II-DSG. Additionally, there was significant improvement in hypertension and dyslipidemia in both of this study.^[47,48]

Study by Serrot *et al.* conducted in BMI <35 suggested that at 1-year the RYGB group had a significant decrease in anti-diabetic medication use compared to nonsurgical group ($P < 0.001$). However, SBP and LDL did not significantly change in either group as surgical group ceased the use of antihypertensive and antihyperlipidemia drugs.^[49] Scopinaro *et al.* also found 83% had HbA1c $\leq 7\%$ without anti-diabetic medication, 1-year after BPD. Additionally,

acute insulin response to intravenous glucose significantly increased in surgical arm suggesting improvement of insulin sensitivity and beta cell function. Moreover, diabetes remission correlated positively with BMI.^[50]

Another multicentric Asian study ($n = 200$) evaluated the effect of different bariatric surgical procedure (RYGB, SG, LAGB) on diabetes remission (defined as FPG <110 mg/dl and HbA1c $<6.0\%$ at 1-year without anti-diabetic medication) in T2DM ($n = 87$) with BMI <35 kg/m² found 72.4% had diabetes remission. Interestingly, diabetes duration of <5 years had a better remission rate compared to diabetes of >5 years (90.3% vs. 57.1%; $P = 0.006$) and BMI >30 kg/m² had a better diabetes remission rate compared to BMI <30 kg/m² (78.7% vs. 62.5%; $P = 0.027$). RYGB group lost more weight and had a higher diabetes remission rate compared to other procedures. Overall, duration of diabetes and type of surgery predict the diabetes remission in multivariate analysis.^[51] A long 6 years prospective observational study ($n = 66$) evaluating the diabetes remission (HbA1c $<6.5\%$ without diabetes medication) following RYGB in T2DM with BMI 30–35 kg/m², found 88% diabetes remission rate. This improvement correlated with the weight independent anti-diabetes mechanisms of RYGB. Additionally, improvement in hypertension and dyslipidemia yielded overall 50–84% reductions in predicted 10-year CV risk.^[52]

Another 1-year well matched controlled study ($n = 30$) assessed diabetes remission (HbA1c $<6.5\%$ and normal oral glucose tolerance test) and investigated insulin sensitivity and β -cell function by euglycemic clamp, following BPD in nonobese TDM patients. Although 40% had diabetes remission, glycemia improved in all patients. Insulin resistance resolved quickly at 2 months and were similar in remitters and nonremitters thereby indicating a weight independent effect of diabetes remission while insulin-mediated suppression of endogenous glucose production remained impaired.^[53]

Improvement or remission of diabetes: Meta-analysis

An integrated reviews conducted by Fried *et al.* from 16 studies ($n = 343$) finds 85.3% patients having diabetes remission (FPG <105.2 mg/dl and HbA1c $<6\%$ without anti-diabetic medications). Diabetes resolution were greatest following malabsorptive/restrictive procedures and in mildly obese (BMI 30.0–35.0) compared to overweight (BMI 25.0–25.9).^[54] A meta-analysis of 13 trials ($n = 357$) conducted by Li *et al.*, a 6 months–18 years of follow-up, found 80.0% achieved adequate glycemic control (HbA1c $<7\%$ without anti-diabetic medication). Additionally, significant improvement in hypertension, TG and HDL also observed.^[55] Another review of 29

studies ($n = 675$) conducted by Reis *et al.*, found overall 84% had diabetes resolution (A1c $<7\%$ without anti-diabetes medication) following bariatric surgery in patients with BMI <35 kg/m². While T2DM remission (A1c $<6\%$ without anti-diabetes medication), control, and improvement were seen in 55.4, 28.5, and 14.3%, respectively; 2% had similar or worse glycemic control after the surgery. Interestingly, mini gastric bypass (72.22%) and RYGB (70.43%) had higher remission rate.^[56]

To sum up, meta-analysis conducted to assess the metabolic effect of bariatric surgery in T2DM patient with BMI <35 kg/m² found, 55–85% patients could achieve HbA1c <6 –7% without anti-diabetic medications during mean follow-up ranging from 6 months to 18 years [Table 7].^[54–56]

Mechanism of glucose control following bariatric surgery

There seems to be no debate currently with the available data, as to whether bariatric surgery would more likely to achieve long-term sustained weight compared to intensive life style or pharmacotherapy. However, this should not be confused with the mechanism of how reversal of Type 2 diabetes happens.

The hindgut hypothesis by Cummings *et al.*, suggests that insulinotropic gut hormones including glucagon like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY), are produced when nutrients arrive at distal intestine, leading to hyperglycemia reversal.^[57] The foregut hypothesis by Rubino *et al.* suggests that upon exposure to food, duodenum produces gastric inhibitory polypeptide (GIP), which is diabetogenic hence when duodenum and the proximal jejunum is not exposed to food after RYGB, these anti-incretin factors are not released.^[58] In T2DM patients, GIP functions mainly as a glucagonotropic agent and weakly insulinotropic.

The major mechanism of the decrease in plasma glucose after bariatric surgery is acute negative calorie balance. The father of bariatric surgery, Walter Pories pointed out decades ago that acute negative calorie produced same effect on blood glucose that was produced by gastric bypass itself.^[59] Induction of sudden negative calorie balance by any means would normalize plasma glucose levels within days, and this appears to be the predominant mechanism underlying the early metabolic changes after bariatric surgery. Additionally, surgically induced direct delivery of nutrients to GLP-1 producing distal jejunum will increase GLP-1 substantially and this complex interplay of hormones in the entero-insular axis appears to play another major role in enhancing the insulin response and thereby improving diabetes. Figure 2 depicts the mechanisms operating at different point of time.

Table 7: Meta-analysis: Diabetes remission following bariatric surgery in patients with BMI <35 kg/m²

Study, year	Number of patients (study included)	Remission rate	Remission criteria
Fried <i>et al.</i> , 2010	343 (16 studies)	85%	HbA1c <6% at 0.5-1.5 year
Li <i>et al.</i> , 2012	357 (13 studies)	80%	HbA1c <7% at 0.5 year and HbA1c <6% at 18 th year
Reis <i>et al.</i> , 2012	1209 (29 studies)	55%, (RYGB -70%, MGB -72%)	HbA1c <6% at 1-year (1.7% had similar or worse glycemic control)

RYGB: Roux-en-Y gastric bypass, MGB: Mini gastric bypass, HbA1c: Glycated hemoglobin

Following factors have been implicated behind diabetes improvement or remission.

Improvement in hepatic and peripheral insulin sensitivity

There was an early and marked improvement in hepatic insulin sensitivity, 1-week after RYGB, which persisted for up to 1-year. This dramatic improvement in hepatic insulin sensitivity was observed even before any significant weight reduction has occurred. However, the peripheral insulin sensitivity at skeletal muscle and adipose tissue were unchanged during the early postoperative period which only improved gradually thereafter.^[60] It is believed that calorie restriction in early postoperative period would decrease intrahepatic fat content and might be playing a crucial role in improving early hepatic insulin sensitivity while improvement in peripheral insulin sensitivity is only observed after substantial weight loss following RYGB. Although, there are many mechanisms for improved insulin sensitivity after RYGB, weight loss induced improvement in insulin sensitivity is of utmost importance.^[61]

Role of ghrelin

Ghrelin is an orexigenic hormone produced maximally in the gastric fundus. Des acyl ghrelin is activated to acyl ghrelin in the stomach through ghrelin O-acyltransferase enzyme (GOAT). Ghrelin exerts its orexigenic action through specific modulation of sirtuin1/P53 and activated protein kinase pathways to increase the agouti-related protein and neuropeptide Y expression in the hypothalamic arcuate nucleus. Ghrelin stimulates hypothalamic expression of mammalian target of rapamycin signaling pathway (mTOR). The mTOR pathways and ghrelin/GOAT axis interact reciprocally.^[62,63] Additionally, Acyl ghrelin stimulates glucagon secretion and decreases adiponectin levels leading to insulin resistance. Proximal gastric resection, as in SG and RYGB leads to decreased ghrelin production. Lack of food exposure in stomach and duodenum following gastric bypass may result in a

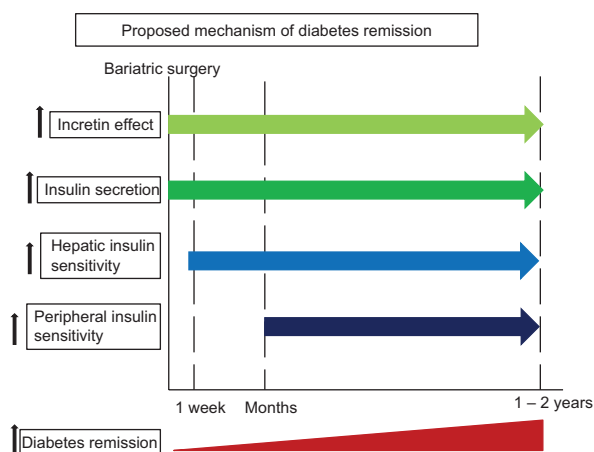


Figure 2: Mechanism operating at different times in improving diabetes following bariatric surgery

continuous signal to inhibit ghrelin, favoring weight loss after surgery. Vagal nerve damage during RYGB may also decrease ghrelin. The ghrelin level remains high after LAGB which leave the gastric fundus and the vagal nerve intact. Zhang *et al.*, hypothesized that ghrelin hormone could be involved in efficacy of SG equivalent to RYGB in T2DM remission. SG may inhibit GOAT activity. Reduced food intake after SG results in peripheral negative energy balance, leading to inhibition of mTOR activity.^[64]

Role of incretin

It appears that endogenous native GLP-1 following bariatric surgery increases by approximately 20-folds.^[65] This GLP1 increment is significantly higher and sustained compared to exogenous GLP-1 agonist injection or dipeptidyl peptidase (DPP)-4 inhibitors therapy. Several explanations have been hypothesized for the limited efficacy of subcutaneous GLP-1 agonist compared to intravenous GLP-1 infusion.^[66-68] Although both GLP-1 and GIP is potent insulinotropic agent, GLP-1 defect plays a major role while GIP remains a weak insulinotropic agent in T2DM. Additionally, GIP is a glucagonotropic agent and therefore the reduction in GIP following bypass variety of bariatric surgery could be responsible for improvement in diabetes as proposed by Rubino. Typically malabsorptive bariatric procedures result in rapid increment in postprandial GLP-1 secretion while no increase noticed after restrictive bariatric procedure alone. In contrast reduction in postprandial GIP levels observed 2 weeks after jejunioleal bypass or RYGB or BPD, however GIP may be elevated after SG.^[69]

Role of cholecystokin

Duodenum and Jejunum after getting exposed to lipids and proteins produce cholecystokin (CCK) from I cells which has two main receptors-CCK1R and CCK2R.

CCK1R is responsible for reduction of food intake, while CCK2R regulates glucose homeostasis. *In vitro*, CCK stimulates glucagon release and increases pancreatic β cell proliferation. Mumphrey *et al.*, demonstrated increase in numbers of I cells in the Roux and common limbs (not the biliopancreatic limb) following RYGB in rat model. This contributes to the higher circulating levels of CCK, which potentially leads to suppression of food intake and stimulation of insulin secretion.^[70] Postprandial CCK response was significantly increased 2 weeks after RYGB and SG.^[71]

Role of enteroglucagon

The enteroglucagon peptide is expressed primarily in the distal intestinal L cells. It refers to the intestinal GLPs, glicentin and oxyntomodulin (OXM). Glicentin acts as a double agonist for the GLP-1 receptor with a very low affinity (50 times weaker than that of GLP-1). It stimulates the secretion of insulin and inhibits glucagon and gastric acid secretion; and regulates intestinal motility.^[72] It reduces appetite by acting directly on the hypothalamic centers to reduce appetite. OXM increases insulin secretion and inhibits pancreatic β cell apoptosis and is inactivated rapidly by DPP-4. Rubino *et al.* found an increase of OXM after 1-month of RYGB ($n = 20$), but not on following diet ($n = 10$) induced equivalent weight loss and increase in OXM was significantly correlated with an increase in GLP-1 and PYY.^[73]

Role of peptide tyrosine tyrosine

PYY (1–36) is released by the intestinal L cells of ileum, colon, and rectum in response to lipids and carbohydrates. PYY inhibits gastrointestinal motility, exocrine pancreas and gastric secretions. It also reduces lipolysis, therefore increases insulin sensitivity by decreasing the concentration of circulating fatty acids. DPP-4 enzyme cleaves the N terminal of PYY's orexigenic form (1–36) and produces its anorectic form (3–36).^[74] High plasma concentrations of DPP-4 enzyme after bariatric surgery resulted in increases of PYY (3–36). The truncate form PYY (3–36) is induce satiety via the Y2 receptor in the hypothalamus. After malabsorptive surgeries, there is postprandial increase in PYY in the earliest postsurgical period even before weight loss occurs.^[75,76]

Altered bile acid metabolism

Bile acids have been implicated in the glucose homeostasis. Mechanistically, two nuclear receptors, farnesoid X receptor (FXR) and TGR5, are believed to mediate the genomic and nongenomic effects of bile acids, respectively. Bile acid activation by FXR, reduces the expression of gluconeogenic genes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. Furthermore,

FXR also modulate hepatic glucose production and may have a partial regulatory role in peripheral insulin sensitivity. Additionally, bile acids may induce secretion of GLP-1 through the activation of GPCR that is TGR5. These all mechanism implicated in improving glucose mediated via bile acid following bariatric surgery. Plasma levels of bile acids have been found to be increased both after RYGB or SG.^[77-79]

Changes in gut microbiota

Alterations in the composition and capacity of gut microbiota have been seen to potentially contribute obesity and insulin resistance leading to systemic inflammation as well as to nonalcoholic fatty liver disease development.^[80] In obese humans a shift toward more firmicutes and reduced bacteroidetes (the two major bacteria phyla of gut microbiota) observed. The microbe *Faecalibacterium prausnitzii*, less abundant in diabetics and obese persons is inversely related to inflammatory markers. A substantial change in gut microbiota happens following bariatric surgery.^[81] A rapid increase in the proportion of *Gammaproteobacteria* (*Escherichia*), *Verrucomicrobia* (*Akkermansia*) and useful microbe *F. prausnitzii*, in the gut has been observed following RYGB.^[82] It is believed that the alteration in the production of short-chain fatty acids by these gut microbiota might be playing some role in weight reduction following RYGB. Interestingly, transfer of gut microbiota from mice subjected to RYGB, to nonoperated germ-free mice, resulted in significant weight loss and decreased fat mass. Intriguingly, experimental study of human fecal transplant from a lean donor to metabolically unhealthy people resulted in increased population of butyrate-producing gut microbiota and improved insulin sensitivity.^[83]

In summary, it appears that change in gut microbiomes may be playing a crucial role in metabolic changes following bariatric surgery. Table 8 provides the summary of hormonal changes during different bariatric surgical procedure.

Predictive factors for Type 2 diabetes mellitus remission after bariatric surgery

Wang *et al.* in a recent meta-analysis of 15 studies ($n = 1,753$) found following characteristics of patient who had poor diabetes remission following bariatric surgery. Older age, long duration of diabetes, current insulin use, and poor glycemic control were associated with negative predictors of diabetes remission. While gender and preoperative BMI had no significant association for both Asian and nonAsian, Asian T2DM patients showed better remission rate and correlated well with the lower severity of T2DM.^[84] Other observational studies also echoed the same predictive

factor. However, Kim *et al.* finds weight loss (BMI reduction ratio) following bariatric surgery holds a direct correlation to remission not the type of surgery and this could be another predictor for the success of metabolic surgery in T2DM.^[85]

Christopher *et al.*, proposed a diabetes remission (DiaRem) score for prediction of remission in diabetes following RYGB using four different parameters including age, HbA1c, treatment with insulin, and usage of other diabetes drugs.^[86] An Indian study group by Ugale *et al.*, also used seven different parameters like age, BMI, duration of T2DM, micro and macovascular complications, preoperative insulin usage, stimulated C-peptide level to predict remission following IL.^[87] Both score system proposed that higher the score, lesser is the chances of diabetes remission following bariatric surgery [Table 9].

Bariatric surgery associated complications

As with any surgical intervention, bariatric surgery is also associated with some complications. While the risk of early mortality ranges from 0.1% to 2.0% depending on the surgical procedure, The Longitudinal Assessment of Bariatric Surgery (LABS) consortium reported 0.3% mortality rate with RYGB at postoperative day 30.^[88] The most dreaded complications include postoperative sepsis, bleeding, anastomotic leaks, venous thromboembolism and rarely fatal pulmonary embolism. Male gender, age older than 65 years, reduced cardiorespiratory fitness levels associated with increased mortality apart from surgeon's experience. Long-term changes in the gastrointestinal tract anatomy will also likely cause deficiencies in Vitamin B12, folate and iron. Calcium, Vitamin D and trace element

deficiencies could also occur months to years after the procedure.^[89] However, these issues can be overcome with proper supplementation. Recurrent postprandial hypoglycemia which is ascribed as dumping syndrome (an extreme metabolic reaction to surgery) is another common problem although Swedish bariatric surgery registry finds the absolute risk of recurrent hypoglycemia to be fairly small.^[90]

Taken together, modern bariatric surgical procedure has an acceptable risk/benefit profile, especially with careful patient selection and care from experienced multidisciplinary team.

CONCLUSIONS

Current evidence highlights the importance of understanding the intestine as a metabolically active organ that may be utilized in the future to improve health. Novel bariatric procedures offer a unique opportunity to understand the pathophysiology of T2DM. Moreover, these procedures also provide additional exploration to identify the potential pharmacologic targets for effective treatments or may be a potential cure. Bariatric surgery leads to changes in gastrointestinal anatomy resulting in effective treatment of obesity and associated co-morbidities. The early remission of T2DM after RYGB is a direct consequence of gastrointestinal anatomy restructuring and

Table 8: Hormonal change during bariatric surgery

	SG	AGB	RYGB	BPD	BPD-DS
Ghrelin	Decreased	No change Increased	Decreased Increased	No change Increased	Decreased
GLP-1	No change Increased	No change	Increased No change	Increased No change	Increased
GIP	Not known Increased	No change	Decreased No change	Decreased	Not known
PYY	Increased No change Decreased	No change	Increased No change	Increased	Increased
CCK	Increased No change	Not known	Increased No change	Not known	Not known
OXM	Not known	Not known	Increased No change	Not known	Not known
Leptin	Decreased	Decreased	Decreased	Not known	Not known
Bile acid	Increased	Not known	Increased	Not known	Not known

OXM: Oxyntomodulin, CCK: Cholecystokinin; PYY: Peptide tyrosine tyrosine, GIP: Gastric inhibitory polypeptide, GLP-1: Glucagon like peptide-1, SG: Sleeve Gastrectomy, AGB: Adjustable gastric banding, RYGB: Roux-en-Y gastric bypass, BPD: Bilio-pancreatic diversion, BPD-DS: Biliopancreatic diversion with duodenal switch

Table 9: Prediction score for diabetes remission

	Diabetes remission score (Christopher <i>et al.</i>), 2014		Diabetes remission score (Ugale <i>et al.</i>), 2014	
	Parameters	Score	Parameters	Score
Age (year)	<40	0	30-60	1
	40-49	1	<30 or >60	2
	50-59	2		
	≥60	3		
HbA1c (%)	<6.5	0		
	6.6-6.9	2		
	7.0-8.9	4		
	≥9.0	6		
BMI (kg/m ²)			≥27	1
			<27	2
Duration of diabetes (year)			<10	1
			≥10	2
Preoperative insulin use	No	0	No	1
	Yes	10	Yes	2
Other diabetes drug	Metformin only	0		
	Sulfonyurea or drugs other than metformin	3		
Stimulated C-peptide (ng/mL)			≥4	1
			<4	2
Microvascular complications			No	1
			Yes	2
Macrovascular complications			No	1
			Yes	2
Total score	22		14	

HbA1c: Glycated hemoglobin, BMI: Body mass index

not exclusively a result of decreased food intake and/or weight loss. Until now there is no consistent hypothesis to explain improvement in glycemic control after surgery, however, the hindgut hypothesis has been suggested as a potent mechanism of T2DM remission. Increase in GLP-1 and PYY levels after malabsorptive surgeries like RYGB could also play a bigger role.

It is also important to recognize that long-term follow-up is required in considering the usefulness of bariatric surgery, before assigning these modalities having extraordinary therapeutic effect primarily because of the potential for weight regain or relapse of diabetes. It should also be realized that a certain percentage of patients will suffer from relapse of their diabetes as diabetes is a lifelong disease.

However, despite the favorable results of bariatric-metabolic surgery and acceptable risk: Benefit profile, many uncertainties also remain. Which bariatric surgical procedure would be most appropriate? Can it be used safely in all T2DM patients? What would be the impact on long-term micro and macro-vascular outcome? Safety, cost-effectiveness and mechanisms of metabolic improvement or remission need further exploration. Elaboration of causes of remission in diabetes, especially in nonobese subjects, exploration of other intestinal factors helping in metabolic improvement, applicability of bariatric surgery for remission in nonobese T2DM subjects, preoperative predictability of chances of success and data analysis for any long term surgical or nutritional complications are another important area which needs to be evaluated. Only further research and larger RCT can enlighten more about the role of bariatric-metabolic surgery for remission of the T2DM. Finally, there is also an urgent need to formulate bariatric surgery referral guidelines for the Indian physicians/endocrinologists.

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Conflicts of interest

There are no conflicts of interest.

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