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**Metabolic surgery: A paradigm shift in type 2 diabetes management**

Pappachan JM *et al.* Metabolic surgery in type 2 diabetes management

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**Abstract**

Obesity and type 2 diabetes mellitus (T2DM) became major public health issues globally over the past few decades. Despite dietary interventions, lifestyle modifications and the availability of several pharmaceutical agents, management of T2DM with obesity is a major challenge to clinicians. Metabolic surgery is emerging as a promising treatment option for the management of T2DM in the obese population in recent years. Several observational studies and a few randomised controlled trials have shown clear benefits of various bariatric procedures in obese individuals in terms of improvement or remission of T2DM and multiple other health benefits such as improvement of hypertension, obstructive sleep apnoea, osteoarthritis and non-alcoholic fatty liver disease. Uncertainties about the long-term implications of metabolic surgery such as relapse of T2DM after initial remission, nutritional and psychosocial complications and the optimal body mass index for different ethnic groups exist. The article discusses the major paradigm shift in recent years in the management of T2DM after the introduction of metabolic surgery.

**Key words:** Metabolic surgery; Bariatric procedures; Type 2 diabetes mellitus; Body mass index; Diabetes remission

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**Core tip:** Metabolic surgery or bariatric surgery has revolutionised the 21st century management of type 2 diabetes mellitus (T2DM) in obese patients. Marked reduction of body weight following the bariatric procedures results in improvement or remission of T2DM in a significant number of patients along with improvement of other diseases associated with obesity such as hypertension, obstructive sleep apnoea, osteoarthritis and non-alcoholic fatty liver disease. Uncertainty exists about the long-term outcomes in terms of diabetes relapse, nutritional and psychosocial complications. However, the marked benefits of metabolic surgery outweigh the risks related to the procedure that has resulted in a major paradigm shift in the management of obese population with T2DM in recent years which is the topic of discussion of this paper.

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**METABOLIC SURGERY: A PARADIGM SHIFT IN TYPE 2 DIABETES MANAGEMENT**

Obesity has become a global pandemic in recent years that affects more than 600 million adults worldwide[1]. World Health Organization (WHO) estimated that 39% of adults aged 18 years and over were overweight [Body Mass Index (BMI) ≥ 25 kg/m2; more than 1.8 billion persons], and 13% were obese (BMI ≥ 30 kg/m2) in the year 2014. A majority of these individuals reside in the developed countries although obesity and overweight are major public health issues even in developing nations. The National Health and Nutrition Examination Survey (NHANES) 2011-2012 regarding population prevalence in obesity revealed that 34.9% of the adults were obese and 33.6% were overweight in the United States[2]. Although data on the prevalence of obesity is scant from most other countries, comparable figures probably exist in many developed countries.

Obesity is a major risk factor for type 2 diabetes mellitus (T2DM). By 2014 diabetes affected 387 million people worldwide and 4.9 million deaths in 2014 alone were directly related to diabetes[3]. The global diabetes disease burden is mainly from T2DM and a majority of these cases are related to obesity. Despite diet and lifestyle interventions and the availability of pharmaceutical agents with weight losing properties the long-term management of obesity with these measures are disappointing. Different gastric bypass procedures collectively termed as bariatric surgery/metabolic surgery have emerged as very promising methods to treat obesity in the past 3 decades that can improve and potentially cure diabetes and many other diseases related to obesity. Through this paper we discuss the major paradigm shift in the management of T2DM in recent years after the introduction of metabolic surgery. We also discuss the long-term health benefits, adverse complications and emerging research questions related to metabolic surgery.

**TYPES AND EFFICACY OF DIFFERENT BARIATRIC PROCEDURES**

Although there are a multitude of bariatric procedures developed over the past 50 years the common techniques used in present day clinical practice are adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and bilio-pancreatic diversion (BPD). The different surgical procedures are depicted in the Figure 1.

AGB and SG are predominantly restrictive procedures whereas RYGB and BPD are mainly mal-absorptive procedures that reduce effective area of nutrient absorption in the intestinal mucosa. Food passes through the alimentary limb in RYGB and BPD with gastrointestinal secretions in the bilio-pancreatic limb mixing with the nutrients where both limbs form the common channel.

In various randomised controlled trials (RCTs), the reported mean percentage (%) excess body weight loss (with 95%CI in parenthesis) achieved at one year after AGB, SG and RYGB were 33.39 (22.57-44.21), 69.70 (41.09-98.32) and 72.32 (64.60-80.04) respectively[4]. The % excess weight loss (%EWL) reported with BPD was 76.89 ± 1.53 that is significantly higher than RYGB (67.17 ± 1.43; *P* = 0.0004)[5]. AGB procedures are losing popularity in the recent years because of inferior efficacy and the necessity for repeated surgery in a higher proportion of cases years after the initial surgery[6]. Although BPD is associated with a significantly higher %EWL and T2DM remission compared to other bariatric procedures the post-operative complication rates are higher[7] making this a less preferred operation.

**BARIATRIC SURGERY IN T2DM**

The major RCTs reporting the effects of metabolic surgery on T2DM are summarised in Table 1. The total number of patients in these RCTs is relatively small for a common condition like T2DM and the duration of follow-up is limited to 12-24 mo. However there are cohort studies and non-randomized trials reporting benefits of metabolic surgery from different regions of the world. There are also several systematic reviews and meta-analyses reporting the beneficial effects of metabolic surgery and individual bariatric procedures on T2DM published recently[12-15].

In a meta-analysis of weight loss and remission of T2DM evaluated in RCTs and observational studies of bariatric surgery vs. conventional medical therapy over a 17 month period the mean excess weight loss (EWL) for the bariatric surgery and the conventional treatment groups were 75.3% and 11.3% respectively; the corresponding T2DM remission rates were 63.5% and 15.6%[12]. The limitation of the meta-analysis was that many short-term observational studies were included and surgery was not always compared directly to more vigorous medical weight loss interventions. There was lack of standardization in the definition of diabetes remission and it was unclear how specific bariatric procedures were chosen or what criteria were used for performing bariatric surgery.

A comparison of the mean changes in body mass index (BMI) and haemoglobin A1c (HbA1c) achieved with individual procedures[12] are shown in the Table 2.

A few long-term cohort studies give us insight on the beneficial effects of metabolic surgery on T2DM[16]. For example, the Swedish Obese Subjects (SOS) study, started in 1987 is a prospective case-control study with 2010 obese subjects who underwent bariatric procedures (predominantly vertical banded gastrostomy which is considered to be less effective and no longer undertaken)[16,17]. A 72% remission of T2DM after two years and 36% durable remission after 10 years were observed in obese subjects in the SOS study[16,18]. Compared to control the risk of developing T2DM was reduced by 96%, 84%, and 78% after 2, 10, and 15 years in obese subjects without T2DM at baseline[19].

Utah obesity study retrospectively compared 7925 obese subjects who underwent RYGB with the same number of age, sex and weight matched controls and after an average follow up period of 7.1 years, found a 40% reduction in all cause mortality, 49% reduction of mortality from cardiovascular diseases and 92% reduction of death related to T2DM[20]. The Longitudinal Assessment of Bariatric Surgery (LABS-2) study is an ongoing multi-center cohort study that showed T2DM remission in 67% and 28% of those who underwent RYGB and AGB respectively after 3 years of follow up[21].

**MECHANISMS OF DIABETES IMPROVEMENT/ REMISSION FOLLOWING METABOLIC SURGERY**

*Reduction in calorie intake*

Typically, patients are put on a calorie-restricted diet after bariatric procedures. The average caloric intake ranges from 400-800 kcal/d in the first month[22]. Calorie restriction has a significant impact on hyperglycemia with reduction of blood glucose levels. In fact, in a recent case-control study[23], post-bariatric diet implemented before metabolic surgery resulted in more profound glucose reduction in T2DM patients than in the post-surgical period, indicating the role of calorie restriction in glycemic control after bariatric procedures. Very low calorie diet alone resulted in improvement of insulin sensitivity and β-cell function in obese T2DM cases (comparable to those who had bariatric surgery) in the short-term[24]. Generally, a calorie-restricted diet should be maintained in patients following metabolic surgery on a long-term basis.

*Alterations in gut hormones*

The acceleration of gastrointestinal transit time after bariatric procedures results in augmented secretion of gut hormones such as glucagon-like peptide-1 (GLP-1), Glucose-dependent insulinotropic peptide (GIP) peptide-YY (PYY) and oxyntomodulin (OXM) that alter energy and glucose metabolism[25]. The anorexient and weight losing properties of GLP-1 is well established in experimental and clinical models. Several studies showed significant elevation of GLP-1 levels during oral glucose challenge and with meals after bariatric procedures such as SG[26], RYGB[27] and BPD[28]. Elevated GLP-1 levels following metabolic surgery was also shown to reverse the obesity-induced endothelial dysfunction conferring cardiovascular protection in the obese[29].

Increased PYY levels following bariatric procedures result in weight loss in obese subjects. PYY administration resulted in a 30% reduction in the calorific value of a meal consumed 2 h after PYY infusion and a 33% reduction in food consumption over 24 h period in human beings[30]. Similarly, OXM administration has been shown to reduce appetite, amount of food ingested and body weight[31]. Ghrelin (a gut-derived peptide hormone that stimulates hunger) level was found to be low after RYGB, whereas the level was high in diet-induced weight loss, indicating the impact of suppression of hunger signals in subjects following bariatric surgery[32]. Hypergastrinemia following SG has been recently reported in rat models of T2DM, although its impact on metabolic pathways and body weight changes have been unclear[33]. The alteration in these gastrointestinal hormonal factors together contributes to significant improvement in T2DM and the body weight of the individual.

*Pancreatic β-cell function*

Improvement in insulin sensitivity and pancreatic β-cell function are important factors that contribute to improvement/remission of T2DM in obese subjects. Increase in secretion of incretin hormones (GLP-1 and GIP) and proliferation of the β-cell mass have been demonstrated following bariatric procedures in human beings and experimental animals[34]. Although these factors clearly contribute to T2DM control, there may be other mechanisms which are not yet clear.

*Hepatic and peripheral insulin sensitivity*

Significant improvement of hepatic insulin sensitivity is observed within few days of bariatric procedures much earlier than the significant weight loss occurs[25,35]. Reduction of energy intake from the post-bariatric diet may contribute significantly to the improvement in hepatic insulin sensitivity. Although peripheral insulin sensitivity is not altered in the immediate post-operative period, delayed improvement is observed in patients[25,35]. Reduced hepatic fat content and body weight loss account for the sustained improvements in hepatic and peripheral insulin sensitivity during long-term follow up of patients who had metabolic surgery[25].

*Role of bile acids*

Bariatric procedures were shown to increase the plasma levels of bile acids that improved glucose and lipid metabolism[25,36]. However, the exact mechanisms by which bile acids improve glycemic control and body weight remain elusive.

*Gut microbiata*

Major changes in the gut microbiota have been demonstrated following bariatric procedures in animal models and human beings[37]. Increase in numbers of some of these intestinal microbial flora, and the related changes in the gut biochemical environment, may affect glucose and lipid metabolism that contribute to weight loss and diabetes improvement[25,37]. More research is necessary on the role of gut flora in glucose and fat metabolism following bariatric procedures.

*Body weight loss and diabetes remission*

The major mechanism by which improvement and/or remission of T2DM occurs in obese subjects following metabolic surgery is the significant weight loss after the procedure. Analysis of participants in the Look AHEAD (Action For Health in Diabetes) study clearly showed a progressive increase in odds ratios for HbA1c reduction with higher proportions of weight loss[38]. The odds ratios for % weight reduction (in parenthesis) were: 1.80 (≥ 2 to < 5), 3.52 (≥ 5 to < 10), 5.44 (≥ 10 to < 15) and 10.02 (≥ 15%) respectively for HbA1c reduction of 0.05% in the study subjects. Substantial loss of body weight post-bariatric surgery therefore would explain the remarkable improvements in glycemic control and even remission of T2DM in the majority of patients.

Overall, a multitude of physiological, behavioural and anatomical alterations following the bariatric procedure result in significant improvements in metabolic and glycemic parameters that may even result in potential cure of T2DM in a good number of patients after the metabolic surgery.

**COST BENEFITS AND OTHER HEALTH-RELATED OUTCOMES**

Data from the National Bariatric Surgery Registry (NBSR) of the United Kingdom that included 18283 cases from 2010 to 2013 clearly showed compelling evidence of the cost effectiveness of bariatric surgery as a treatment option for severely obese T2DM patients[39]. NBSR data showed that 61% of patients with obstructive sleep apnoea could come off their treatment after surgery 65% of patients with T2DM could stop their diabetic medications. A recent systematic review and meta-analysis revealed important cardioprotective effects of metabolic surgery in terms of regression of left ventricular hypertrophy, improvement of diastolic function and reduction of left atrial size[40]. Improvement of hypertension, hypercholesterolemia, gastro-esophageal reflux disease, and arthritis are some of the other reported major beneficial effects of bariatric surgery[41].

**IMMEDIATE AND LONG-TERM COMPLICATIONS**

The main complications in the immediate post-operative period are pulmonary complications, vomiting, wound infections, bleeding and anastomotic leak[16,17]. In a recent systematic review and meta-analysis the peri-operative and post-operative mortality rates were 0.08% and 0.31% respectively in RCTs and 0.22% and 0.35% respectively in observational studies (OBS)[4]. The overall complication rates were 17% in RCTs and 10% in OBS, and the reoperation rates were 7% and 6% respectively.

The most common long-term complications were iron deficiency anaemia in up to 15% of cases and re-operations in up to 8%[14,16]. Psychological issues are emerging as an important complication on follow up of the cases, and alcohol overconsumption and substance misuse are increasingly being reported in patients on long-term follow up[16,42]. For unknown reasons, the suicidal rates were found to be higher in patients who underwent bariatric surgery[16,20]. Nutritional deficiencies including deficiencies of calcium, vitamin D, iron, zinc, and copper, are common after bariatric surgery[16,43]. Periodic checking for deficiencies and nutritional supplements are indicated in patients.

Massive weight loss after the surgery may result in abnormal body contour because of extensive skin folds that may affect the psychological well being of many patients. Body contouring surgery improves this problem and may help improvement of physical and mental well being in these patients although financial cost may become an issue in many healthcare systems[44]. Post-prandial hypoglycaemia is a common problem in many patients after metabolic surgery. Rapid transit of contents from stomach with smaller capacity could be a reason in many cases that can be treated with small frequent meals and complex carbohydrates. However, severe hypoglycaemic episodes caused by hyperinsulinemia from pancreatic islet cell hyperplasia (nesidioblastosis) can sometimes be crippling necessitating pancreas resection, reversal of gastric bypass and restriction of gastric pouch in extreme cases[45].

Diabetic microvascular complications such as retinopathy, neuropathy and nephropathy can sometimes get worse if there is rapid (abrupt) improvement of longstanding severe dysglycemia in patients with poorly controlled diabetes. A similar situation could be expected following metabolic surgery with acute improvement in glycaemic control. There is some evidence of worsening of pre-existing diabetic retinopathy in a proportion of cases following bariatric procedures, although improvement of the disease is also noted in some others[46,47]. Therefore, counselling about this potential complication before surgery and close monitoring after the procedure are advisable. Though the data is insufficient, there is some evidence for improvement of diabetic neuropathy[48] and nephropathy[49] after bariatric surgery. There are no reports of worsening of these conditions after improvement of T2DM following bariatric procedures.

Pregnancies after bariatric surgery were found to be associated with significantly lower risk of gestational diabetes [odds ratio (OR): 0.25; 95%CI: 0.13–0.47], large-for-gestational-age infants (OR: 0.33; 95%CI: 0.24-0.44) and shorter gestation (mean difference: – 4.5 d; 95%CI: –2.9 to –6 d; *P* < 0.001)[50].However, there were significantly higher risk of small-for gestational-age infants (OR: 2.20; 95%CI: 1.64 to 2.95; *P* < 0.001). The risk of stillbirth or neonatal death post-bariatric pregnancies appeared to be higher [1.7% *vs* 0.7% (OR: 2.39; 95%CI: 0.98 to 5.85; *P* = 0.06)] although this risk did not reach statistical significance.

**APPROPRIATE PATIENT CATEGORY FOR METABOLIC SURGERY**

There is no clear and uniform consensus from different international bodies about the minimum BMI cut off for consideration of the bariatric procedure in obese individuals. The National Institute for Health and Clinical Care Excellence (NICE) of the United Kingdom recently recommended bariatric surgery for people with a BMI of > 40 kg/m2 and > 35 kg/m2 in the presence of co-morbidities such as T2DM or hypertension[51]. For people of Asian family origin a lower BMI threshold should be considered. NICE also recommends expedited assessment for Bariatric surgery to people with BMI of 30-34.9 kg/m2 who have recent onset T2DM. This is based on the evidence that earlier intervention can improve the chances of remission following bariatric surgery[39].

The Canadian Diabetes Association Clinical Practice Guidelines (2013) recommend bariatric surgery for people with class III obesity (BMI ≥ 40.0 kg/m2) or class II obesity (BMI = 35.0 to 39.9 kg/m2) in the presence of co-morbidities, with an inability to maintain weight loss following adequate trial of health behaviour intervention[52].

The American Association of Clinical Endocrinologists, the Obesity Society and the American Society for Metabolic and Bariatric Surgery (2013) recommend metabolic surgery in obese individuals with a BMI of ≥ 40 kg/m2 without coexisting medical problems and surgical risk[53]. For patients with BMI ≥ 35 kg/m2, surgery may be offered if one or more severe obesity-related co-morbidities exist including T2D, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (a combination of OSA and OHS), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), pseudotumor cerebri, gastroesophageal reflux disease (GERD), asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life. Patients with BMI of 30–34.9 kg/m2 and T2DM or metabolic syndrome may also be offered a bariatric procedure, although evidence for this recommendation is inadequate with the unavailability of long-term data[53].

With robust clinical and epidemiological data emerging from all continents of the world, a global consensus on the appropriate patient categories that get definite benefits from metabolic surgery is expected to emerge in the near future.

**AREAS OF UNCERTAINTY**

Although there is accumulated experience from different regions of the world on the excellent outcomes of bariatric procedures, there is not enough data from resource poor nations of Asia, Arabian Peninsula, Africa and South America to generalise the recommendations of metabolic surgery, even though obesity epidemic is becoming a public health issue in these regions. Moreover, the BMI cut off for obesity in Asians is different from that of the western populations. For example BMI of ≥ 25 kg/m2 isconsidered as obesity in India[54] and ≥ 27 kg/m2 in Taiwan[55] Diabesity (diabetes caused by overweight or obesity) is different for populations of Asian and Afro-Caribbean ethnic background owing to the difference in abdominal adiposity in these groups compared to other races, making generalisation of BMI cut offs metabolic surgery inappropriate.

For a common condition like diabetes there are only a handful of RCT’s of short duration comparing bariatric surgery to medical therapy which ranged from standard care to intensive medical intervention. There are a few prospective studies available on long term outcomes of bariatric surgery. However, T2DM being a lifelong multisystem disease with almost all organs of the body involved, more data based on lifelong follow up of cases is necessary to understand the true impact of bariatric procedures. This requires maintenance of nationwide bariatric registries globally along the lines of NBSR in the UK which can provide valuable information.

Though there are some studies on the impact of bariatric surgery on the psychosocial, nutritional and mineral metabolic status of patients, long-term data on these areas are still inadequate. Similarly the optimal management of post-bariatric nesidioblastosis that emerged as a challenging clinical problem is not yet clear.

Different multicentre on-going prospective clinical trials would be expected to answer these unresolved questions.

**CONCLUSION**

Metabolic surgery is emerging as a major paradigm shift in the 21st century management of T2DM, and has revolutionised the care of diabesity. Massive weight loss with remission of T2DM in a significant proportion of cases along with improvement of most other obesity-related ailments makes the treatment a very attractive option for clinicians and patients. A recent analysis of the NBSR data clearly showed its cost effectiveness. Appropriate patient selection and long-term follow up of cases are necessary to optimise the outcomes and reduce the complications.

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**Figure 1 The diagrammatic representation of different bariatric surgical procedures.** A: Adjustable gastric band; B: Sleeve gastrectomy; C: Roux-en-Y gastric bypass; D: Bilio-pancreatic diversion. Figure reproduced with permission from John Wiley and Sons. *Obesity* (Silver Spring) 2013 Mar; 21 Suppl 1: S1-27.

**Table 1 Major randomised controlled trials reporting effects of metabolic surgical procedure on type 2 diabetes mellitus**

|  |  |  |  |
| --- | --- | --- | --- |
| **RCT**  | **Study details** | **Outcome** | **Diabetes remission** |
| Dixon *et al*[8], 2008 | Un-blinded RCT. *N* = 60Obese patients with recent onset T2DM Conventional therapy *vs* LAGB Follow-up: 2 yr  | Weight loss –1.7% ± 5.2% in conventional group and –20.7% ± 8.6% in the surgical group | 73% in surgical group 13% in conventional group (Remission of T2DM defined as FBS < 7.0 mmol/L and HbA1c < 6.2%) |
| Mingrone *et al*[7], 2012 | Single centre non-blinded RCT. *N* = 60. Severely obese patients. T2DM of at least 5 yr duration and HbA1c > 7.0%. Conventional medical therapy *vs* RYGB or BPD Follow-up: 2 yr  | Weight loss −4.7% ± 6.3% with medical therapy, −33.3% ± 7.8% with RYGB and −33.8% ± 10.1% with BPD  | 75% in RYGB group; 95% in BPD group. None in the conventional group (Remission defined as FBS < 5.6 mmol/L and HbA1c < 6.5%) |
| Schauer *et al*[9], 2012 | Single centre non-blinded RCT in obese uncontrolled T2DM. *N* = 150 Intensive medical therapy *vs* RYGB or SG Follow-up: 12 mo  | Weight loss –5.4 ± 8.0 kg in medical therapy group, -29.4 ± 9.0 kg in RYGB group and – 25.1 ± 8.5 kg in SG group | 12% medical therapy group 42% in RYGB group 37% SG group (Remission/primary outcome defined as HbA1c of 6% or less) |
| Ikramuddin *et al*[10], 2013 | Un-blinded RCT in obese T2DM with HbA1c over 8% with average duration of 9 yr. *N* = 120. Intensive medical therapy *vs* RYGB Follow-up: 12 mo  | Difference in weight loss between surgical and medical group – 17.1 ± 5.6 kg. % weight change in medical *vs* Surgical group – 7.9 ± 2 *vs* – 26 ± 2 | 75% RYGB group 32% in medical group (Remission defined as HbA1c < 7%) |
| Liang *et al*[11], 2013 | RCT in obese T2DM. *N* = 108. RYGB compared with standard care with or without Exenatide therapy Follow-up: 12 mo  | Reduction in BMI (kg/m2) in standard *vs* Exenatide *vs* RYGB: –0.56 ± 1.66 *vs* –3.44 ± 1.21 *vs* –5.97 ± 0.91  | 90% in RYGB group None in patients receiving standard care with or without Exenatide (Remission defined as HbA1c < 6.5%)  |

RCTs: Randomised controlled trials; T2DM: Type 2 diabetes mellitus; N: Number of subjects; LAGB: Laparoscopic gastric banding; FBS: Fasting blood sugar; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; BPD: Bilio-pancreatic diversion.

**Table 2 The mean changes in body mass index and haemoglobin A1c achieved with different gastric bypass procedures**

|  |  |  |
| --- | --- | --- |
| **Bariatric procedure**  | **Body mass index (kg/ m2)** | **HbA1c (%)** |
| Pre-surgery  | Post-surgery | Mean reduction (95%CI) | Pre-surgery  | Post-surgery |  Mean reduction (95%CI) |
| **AGB** | 37 | 29.5  | 7.5 (5.9-9.1) | 7.8 | 6.0 | 1.8 (1.3– 2.3) |
| **SG** | 41.3  | 28.3 | 13.0 (10.1-15.9) | 7.9 | 6.0 | 1.9 (1.0– 2.8) |
| **RYGB** | 34.6 | 25.8 | 8.8 (5.2- 12.4) | 8.2 | 6.1 | 2.1 (1.3– 2.9) |
| **BPD** | 50.5 | 34.6 | 15.9 (11.8- 20.0) | 8.0 | 5.2 | 2.8 (2.1- 3.5) |

AGB: Adjustable gastric banding; SG: Sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; BPD: Bilio-pancreatic diversion; HbA1c: Haemoglobin A1c.