REVIEW ARTICLE

Role of Bariatric Surgery for Reducing Glycated Hemoglobin (HbA1c) in Type 2 Diabetes Mellitus Compared to Current Medicaments Therapy

Firas Farisi Alkaff[1], Ricardo Adrian Nugraha[1], Michael Jonatan[1],Sulistiawati[2]

[1]Faculty of Medicine, Universitas Airlangga – Dr Soetomo General Hospital
[2]Department of Public Health, Faculty of Medicine, Universitas Airlangga – Dr Soetomo General Hospital

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) Corresponding author:
firasfarisialkaff@gmail.com

ABSTRACT

Background: Type II is the most common type of Diabetes Mellitus, and one of the most common non-communicable diseases globally. In Indonesia, diabetes contributes to 6% of total deaths. Current medicaments therapy available can only control the disease, not to cure it. Recently, there has been new treatment that has been recommended into standard care for type II Diabetes Mellitus. It was in September 2015 at the second Diabetes Surgery Summit that the introduction of bariatric surgery has been put into standard care for type II Diabetes Mellitus.
Objective: To draw a comparison of the effectiveness between bariatric surgery and current medicaments therapy in reducing HbA1c to achieve remission.
Methods: Literature study was conducted to identify relevant literature showing comparison study between bariatric surgery and medicaments therapy, and comparison study between types of bariatric surgery. 16 Studies are included in this article from 230 studies found.
Results: HbA1c remission in bariatric surgery is significantly higher than medicaments therapy in all studies, ranging from 66.7% vs 0% to 57.1% vs 9.5% during 6-24 months after therapy. Between all types of bariatric surgery, most of the studies shows that Roux-en-Y Gastric Bypass achieves HbA1c remission higher than other types of surgery.
Conclusion: Bariatric surgery is better than current medicaments therapy in achieving HbA1c remission.

Introduction

There are two types of Diabetes Mellitus, type I and type II. Type II is the most common type of Diabetes Mellitus and it is one of the most common metabolic diseases in adult age, and one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries (1). In Indonesia, diabetes contributes to 6% of total deaths (2). Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. Diabetes is certain to be one of the most challenging health problems in the 21st century(3). Type II diabetes can only be controlled, it cannot be cured. Currently there are 5 stage of therapy that is recommended now to control this metabolic disease; the first one is the education therapy, the second one is lifestyle changing, the third one is exercise, the fourth one is medicaments therapy, and the last one is pancreatic transplant (4). However, the latest study about

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current status of organ transplant in Asian Countries on 2004 shows that there are no data available about pancreatic transplant in Indonesia during 2000-2001 period (5). It leaves Indonesian people to medicaments therapy as their final option for treating diabetes. Medicaments in diabetes is using 2 kinds of drugs, the oral drug and the insulin injection. If patients enter this stage of therapy, it means that the patients will need to consume the drugs for the rest of their life's, or until they got a pancreatic transplant.

Now, there has been new treatment that has been recommended into standard care for type II Diabetes Mellitus. It was in September 2015 at the second Diabetes Surgery Summit that the introduction of bariatric surgery has been put into standard care for type II Diabetes Mellitus (6). At first, bariatric surgery was used to treat patient with obesity that cannot be treated with other therapy. But most of the obese people also have diabetes mellitus as a co- morbid. WHO stated that 1 in 10 diabetes patients is obese (2). The first article that report about the effectiveness of bariatric surgery as a therapy for adult-onset diabetes mellitus was published in 1995. It stated that no other therapy has produced such durable and complete control of Diabetes Mellitus(7). After the article was published, there comes a lot more study about the bariatric surgery as a therapy for Type II Diabetes Mellitus. Recently in 2016, metabolic surgery was included in the diabetes treatment algorithm (8). In the next few years, we believe that Indonesia will also put bariatric surgery as one of the treatment for type II Diabetes Mellitus. This literature review will show the effectiveness of bariatric surgery compare to current therapy in reducing HbA1c to achieve remission, to compare each types of bariatric surgery in achieving HbA1c remission, and to understand the complication of each types of the surgery.

Methods

Literature study was conducted on PubMed to identify relevant literature showing comparison study between bariatric surgery and conventional therapy, comparison study between types of bariatric surgery, and adverse effect of bariatric surgery. Keyword "bariatric surgery vs medical therapy", "bariatric surgery diabetes", "Roux-en-Y gastric bypass vs sleeve gastrostomy" were used. Inclusion criteria in this study were availability of full text, English language, follow up study using retrospective cohort or randomize control study method, and diabetes remission as primary or secondary study. Exclusion criteria were animal subjects. 16 Studies were included in this article from 230 studies found.

Discussion

Indication of Bariatric Surgery for Obesity in General

There are numbers of guidelines exist on the use of bariatric surgery for the treatment of obesity in general. According to American Society for Metabolic and Bariatric Surgery, the qualification for Bariatric Surgery are a). BMI ≥40 or more than 100 pounds overweight, or b). BMI ≥35 and at least two obesity-related co-morbidities such as type II diabetes (T2DM), hypertension, sleep apnea and other respiratory disorders, non-alcoholic fatty liver disease, osteoarthritis, lipid abnormalities, gastrointestinal disorders, or heart disease, or c). Inability to achieve a healthy weight loss sustained for periods of time with prior weight loss efforts (9). This guideline is similar to NIH guidelines back in 1991 (10). The Asian-Pacific Bariatric Surgery Group recommends bariatric surgery for obese Asians with a BMI ≥32 with co-morbidities or BMI ≥ 37 without co-morbidities (11). In 2011, IFSO-APC published a guideline for Asian regarding bariatric surgery during consensus summit. It stated that bariatric surgery should be considered for the treatment of obesity for acceptable Asian candidates with BMI greater than 35 regardless of the existence of co-morbidities, and bariatric surgery should be considered for the treatment of T2DM or metabolic syndrome for patient who are inadequately controlled by lifestyle alternation or medical treatment with BMI ≥30 (12).

3.2 Indication of Bariatric Surgery for T2DM

Until last year, there was no guidelines exist for the bariatric surgery for T2DM even though there are already a lot of study about the effect of Bariatric Surgery for T2DM since 1995. ADA is the first to publish this guideline, using the recommendation from the Diabetes Surgery Summit 2015 (6). (Figure 1)

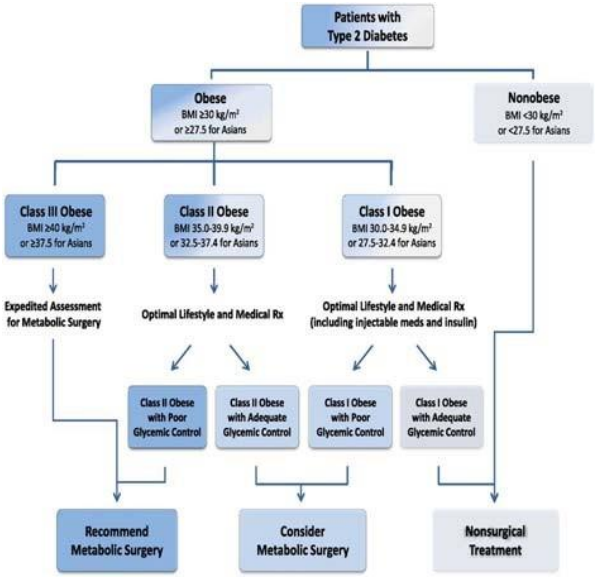

Figure 1: Algorithm for the treatment of T2DM, as recommended by Diabetes Surgery Summit (8)

Type of Bariatric Surgery

According to American Society for Metabolic and Bariatric Surgery, the most common bariatric surgery procedures were gastric bypass, sleeve gastrostomy, adjustable gastric band, and biblio pancreatic diversion with duodenal switch. Of course, each surgery has its own advantages and disadvantages (9).

Gastric Bypass

Gastric Bypass procedure is also called Roux-en-Y Gastric Bypass, is considered the "gold standard" of weight loss surgery. Some advantage of this surgery is significant long term weight loss, restrict the amount of food that can be consumed, lead to condition that increase energy expenditure, and produce favorable change in gut hormones that reduce appetite and enhance safety. The disadvantages of this surgery are the complexity of the operation, vitamin and mineral deficiency, longer hospital stay, and need dietary recommendation.

Sleeve Gastrostomy

This surgery is a laparoscopic surgery. The advantages of this surgery are; it will restrict the amount of the food the stomach can hold, it will induce rapid and significant weight loss similar to RYBG, it require no foreign object, no bypass or rerouting of the food stream, short hospital stay, cause favorable change in gut hormone that suppress hunger, reduce appetite, and improve satiety. Some disadvantages of this surgery are irreversible procedure, early complication rate, has potential for long-term vitamin deficiency.

Gastric Band

The advantages of this surgery are it can reduce the amount of the food the stomach can hold, induced excess weight loss, involves no cutting or rerouting, shortest hospital stay, reversible and adjustable, lowest rate of mortality and complication, and has the lower risk for vitamin and mineral deficiency. Some disadvantages of this surgery are, it gives less early weight loss than other surgery, require foreign device to remain in the body, highest rate of re-operation, can result in dilatation of the esophagus, and can have a mechanical problem with the band.

Bibliopancreatic Diversion with Duodenal Switch Gastric Bypass

This procedure can give the greatest weight loss than other procedures, patient can eat near "normal" meal, and it cause favorable change in gut hormones to reduce appetite and improve satiety. Some disadvantages of this procedure are that it has highest complication rates, highest mortality risk, longer hospital stay, and has a greatest potential to cause protein vitamin and mineral deficiencies.(Picture 2)

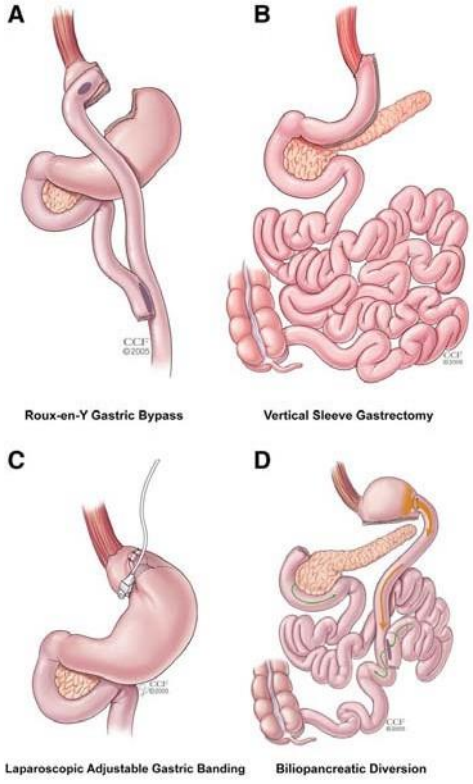

Figure 2: Diagrams of the four bariatric / metabolic operations currently in common clinical use (8)

Efficacy of Bariatric Surgery

"Who would have thought it? An operative proves to be the most effective therapy for adult-onset diabetes mellitus", an interesting article title published in Annals of Surgery 1995. This is the first published article ever about the efficacy of bariatric surgery on remission of diabetes mellitus. Pories, et al conducted an observational study for 14 years on 608 obese patients that underwent gastric bypass.(7) Before surgery, 146 patients had non-insulin-dependent diabetes mellitus (NIDDM) and another 152 patients had impaired glucose tolerance (IGT). After 14 years of bariatric surgery, 121 out of 146 patients (82.9%) who presented with NIDDM maintained normal values of blood glucose and glycosylated haemoglobin. And for the IGT, 150 of 152 patients (98.7%) reverted to euglycemia. Additionally, bariatric surgery also reduces the number of hypertension patients from 58.1% (353/608) to 14%. Even though this observational study put T2DM as a secondary outcome, but since then several Randomized Cntrolled Trial (RCT) and Retrospective Cohort Study (RCS) has been conducted and shows significant remission in diabetes not only as a secondary outcome but also as a primary outcome.

Remission of Diabetes: Retrospective Cohort Study

Arteburn et al reported a follow up study for 24 months of obese subjects with diabetes remission as primary outcome. Remission criteria in this study defined as the co-occurrence of: a) diabetes medication discontinuation for □ 90 days after last prescription end date and b) control of T2DM (fasting glucose <126 and/or HbA1c <7% occurring ≥ 90 days after last prescription end date). The remission of surgery group was higher than non-surgical group (73.7% vs. 6.9%; p<0.05). Moreover, surgery group were significantly less likely to experience T2DM relapse (HR = 0.19; 95% CI: 0.15 to 0.23).(13) The eighteen months follow up study with diabetes remission as secondary outcome with obese subject conducted by Heo et al also found that surgery group had higher remission (57.1% vs. 9.5%; p < 0.001). This study use ADA criteria as the remission criteria (no use of medication, fasting blood glucose level □ 126 mg/dl, or HbA1C concentration ≥ 6.5%). Additionally, hypertension and dyslipidemia also resolved much frequently in surgery group (all p < 0.001).(14)

Remission of Diabetes: Randomized Controlled Trial

Courcoulas et al conducted a comparative study of bariatric surgery vs. lifestyle intervention in obese patient with 12, 24, and 36 months follow up. The data used was 12 months follow up, since bariatric surgery group also get lifestyle intervention after 12 months follow up. At 1-year follow up, T2DM remission (ADA Criteria) only achieved by surgery group (34% vs. 0%, P< 0.05%). For the secondary outcomes of this study (lipid levels, blood pressure, body composition), surgery group also had a significant decrease compare to lifestyle group (All P < 0.001).(15) Another comparative study of RYBG and conventional therapy with 1, 2-year follow up conducted by Ikramuddin et al found that only RYBG group could achieve remission (ADA criteria) (66.67% vs. 0%; p < 0.0001). Interestingly, at 1-years follow up, both groups showed no remission. RYBG group also shows significant decrease in BMI, weight loss, weight circumference, blood pressure, and all serum lipids except LDL (all p < 0.05). (16)

Parikh et al has conducted comparative study of bariatric surgery with intensive medical weight management. Interestingly, other than diabetes remission as the primary outcome, this study also measures the HOMA-IR for the primary outcome. And for the secondary outcome, this study also measures sRAGE other than HbA1C and weight, which have never been done in any other study. After 6 months follow up they found that surgery group is the only group that achieve diabetes remission (65% vs. 0%; p < 0.0001), and had improved HOMA-IR (-4.6 vs. +1.6; p = 0.0004). For the secondary outcome, the surgery group had lower HbA1C (6.2 vs. 7.8; p=0.002), lost more weight (7.0 BMI vs. 1.0 BMI; p<0.0001), and higher baseline sRAGE (r=-0.641; p=0.046), which was associated with better weight loss outcomes. In this study, there was no significant difference in lipid panels or blood pressure measurements, unlike the other studies.(17)

One year follow up study to determine the long-term effect of RYBG compared with an intensive diabetes medical weight and management program for type 2 diabetes by Haperin et al shows that 58% of RYBG group has achieve remission (ADA criteria) while only 16% remission have been reached by medical therapy group (p=0.03).(18) The odds of resolution of hyperglycemia were 6.9 times greater in the RBYG group at 1 year. All RYBG group also achieve 10% weight loss before 3 months, while only 37% of the medical therapy group achieve it. Waist circumference, blood pressure, and all lipid panels except LDL resolved much more frequently in RBYG group (all p < 0.05). Another comparative study by Courcoulas et al compared bariatric surgery (RYBG and LAGB) with LWLI, found 58.69% in surgery and 0% in LWLI had diabetes remission (ADA Criteria) at the end of 1 year (p = 0.0005). Significant reduction in BMI, weight, and waist circumference in surgery group also shown in this study (all p < 0.0001).(19) Ikramuddin et al in 12 months follow up of multicenter international two-arm unblended RCT study compare RYBG with intensive medical management, using HbA1c < 7.0%, LDL-C < 100mg/dl, and SBP <130mmHg as main outcome

measurement. At the end of the study, RYBG group achieves primary outcome more than medical management group (49% vs. 19%; OR = 4.8, 95% CI: 1.9 to 11.6). The RYBG group also had significantly better result for the secondary outcome of glycemia, HDL, cholesterol, triglyceride, and diastolic blood pressure. (20)

Kashyap et al did 24 months follow up with glycemic control as secondary outcome found that 35.13% patients in surgery group had HbA1c 6.0% and only 5.9% patient in intensive medical therapy group had reach the same HbA1c level. Body weight, BMI, total body fat, and HDL level in surgery group are also shows significant change compared to non-surgery group (all $p < 0.0001$).(21) One year follow up study by Cummings et al compared the RYBG with ILMI with diabetes remission as primary outcome found that the remission was significantly higher in RYBG group (60% vs. 5.9%; $p = 0.002$). Weight loss comparison was also shown a significant difference (25.8±14.5% vs. 6.4±5.8%; $p< 0.001$). In this study, all baseline characteristics between two groups were equivalent, except that RYBG group which had longer diabetes duration. (22)

Remission of Diabetes: Comparison between RYGB, SG, and GB

Lee et al compared RYGB, SG, and GB in the 18 months follow up using multicenter retrospective comparative cohort study for obese patients. The measure outcomes of this study were weight loss and resolution of comorbidity (diabetes, hypertension, and dyslipidemia). In term of weight loss, the three procedures showed similar result at 18 months (69.2% in RYGB, 52.1% in SG, and 61.0% in GB; p value not significant). And for the remission of diabetes was more frequent in patients who underwent RYGB (65.9%, 30.2%, and 40% of patients; $p < 0.05\%$). For the other comorbidities, the remission also more frequent in patients who underwent RYGB (all $p < 0.05\%$). However, another comparative study between RYGB, SG, and GB with 6- months follow up conducted by Parikh et al (17) found that SG can reach post- operative diabetes remission more often than the others (33%, 91%, 33%; $p = 0.025$). Other measurement that have been compared in this study are HOMA-IR, fasting glucose, and glucose after OGTT requiring T2DM meds. In HOMA-IR, the change between those 3 procedures was not significant. For the fasting glucose, the change was the best in SG operation (36.7%, 45.9%, 16.1%; $p = 0.093$). And for the OGTT, GB operation shows highest change than the others (33%, 0%, 67%, $p = 0.016$). (23)

Remission of Diabetes: Comparison between RYGB and SG

Park et al have conducted a comparative study in an obese patient to compare the mid-term outcomes (36 months) between these two surgeries, and to see the resolution of comorbidities as well. Apparently, there were no significant different between these two techniques for the resolution of comorbidities (diabetes, hypertension, and dyslipidemia; all $p > 0.05$). However, for the body weight and BMI parameter, RYGB was significantly superior compare to SG (all $p < 0.05$). And for the %TWL and %EWL, even though RYGB is seemed to be superior as well, there was no significant correlation (all $p > 0.05$).(24) Another 36-months follow up study by Yang et al compared the long-term effect of these two most favorite bariatric surgeries. In this study, the primary outcome was glycemic control as an indicator for diabetes remission. It appeared that diabetes remission was achieved more in RYGB group (92.6% vs. 89.3%). However, the difference was not significant between these two surgeries ($p = 0.10$). For the other outcomes (%EWL, %TWL, change in weight, and change in BMI and waist circumference) all show that RYGB was superior to SG (all $p< 0.05$). (25)

Huang et al have conducted a comparative study in bariatric surgery for old age with obesity using Asia Pacific Guidelines. 39 out of 44 patients in RYGB group have diabetes, while in SG group were 12 out of 24. After 1-year follow up, they found that more from RYGB group has already achieved diabetes remission compare to SG group (69.2% vs. 33%; $p = 0.001$), while others measured outcome showed no significant difference between two groups (all $p > 0.05$).(26) Another study about the effect of bariatric surgery in obese patients have been conducted by Peterli et al with weight loss as the primary end points and remission rate of the associated comorbidities as the secondary end points. They found that there was a significant weight loss at 1 year in both groups, but there was no significant difference between these groups. For the secondary end points, there was no difference between RYGB and SG in remission of T2DM (67.90% vs. 57.70%; $p > 0.05$). (27)

Kashyap et al in their comparative study which use HbA1c <6.0% as the remission criteria have found that either in 12-months and 24-months follow up there was no difference between RYGB and SG (44.44% vs. 26.32%, 33.3% vs. 10.5%; all $p>0.05$). For the other measured outcome, the differences between these 2 groups were only significant in body weight and BMI (all $p <0.001$). (21) Another comparative study in China with T2DM obese young patients as subjects (age < 65 years old) with 2 years follow up done by Tang, et al used T2DM remission (ADA criteria) as primary outcome. They found that there were no differences between these 2 groups in achieve remission (57.9% vs. 76.5%; $p < 0.08$). For the other outcome, the differences between these two groups are only in HDL and LDL cholesterol level. (28)

3.13 Remission of Diabetes: Comparison between RYGB and GB

Only 2 studies were found that really draw comparison between RYGB and GB, and both studies have been done by Courcoulas et al in their first study, they used ADA criteria to determine the T2DM remission with 12-months follow up.(19) They found that there was no difference between these two groups (50% vs. 27.3%; $p = 0.1146$). The differences were found in BMI, weight, and waist circumference only (all $p < 0.05$). In their second study, they also used ADA criteria to determine the T2DM remission with 12, 24, 36 months follow up after surgery. However, after 12 months follow up, both surgery groups had additional intervention lifestyle therapy, which can disrupt the long-term effect of the surgery itself. After 12-months follow up, 50% of RYGB groups achieve T2DM remission, while only 29% of LABG group achieves it. After 36-months follow up, the RYGB group remission have declined to 40%, while the LABG group still 29% ($p = 0.0876$) (15). In this study, there was no difference in lipid levels between these two groups. However, they found that the blood pressure measurement either systolic or diastolic shows difference (all $p < 0.05$).

3.14 Early and Late Post-Operative Complication Following Bariatric Surgery

Every intervention procedure has a chance to cause complication, whether it is early or late complications. Heo, et al in their comparative study of 3 different bariatric surgeries (RYGB, GB, and SG) reported an adverse event in 51 out of 261 subject (19.5%) with total 61 complications. Complication occurred within 30 days after bariatric surgery in 26 patients, while after 30 days it occurs in 32 patients. Wound complication was most frequent complication that occurred within 30 days, while port/band revision/removal related complications were most frequent. Total complication rate was higher in GB than other two procedures.(14) Courcoulas et al has also reported an adverse event in their comparative study of 2 different bariatric surgeries (RYGB and GB) with non- surgery. Serious adverse event occurs after 30 days of operation, 1 from RYGB and 3 from GB patients. Other adverse events and complication within 30 days of operation have been reported in 14 out of 41 patients. In general, GB procedures cause complication more often than RYGB.(15)

Lee et al in their comparative study of 3 different types of bariatric surgeries reported complication within 30 days occurs in 26 out of 261 patients (9.9%), while complication later than 30 days occurs in 32 patients (12.3%). The most frequent complication within 30 days was surgical site infection, followed by pneumonia/atelectasis. Occurrence of port leak/revision and band erosion/removal was the most frequent complication after 30 days of operation. There was also 1 death case reported from RYGB group due to aspiration pneumonia, while other group reported no death case. In total, either early complication or late complication, GB patients have more complication than the others but not statistically significant.(23)

Comparative study between 2 types of bariatric surgery (RYGB and SG) conducted by Huang et al reported an early and late complication in both groups. In total there are 10 morbidities out of 51 patients, 6 within 30 days, 4 after 30 days. In RYGB group, 6 morbidities within 30 days, 3 morbidities after 30 days, and 1 death case have been reported. In SG group, there is only 1 morbidities, occurs after 30 days of surgery.(26)

Body Mechanism after the Surgery

There is no debate as to whether bariatric surgery is much more likely to achieve long-term weight loss when applied prospectively to groups of people than is dietary advice. That is an enormously important clinical consideration. However, this should not be confused with the mechanism of how reversal of type 2 diabetes comes about.

The major mechanism of the decrease in plasma glucose after bariatric surgery is acute negative calorie balance. Acute negative calorie produced same effect on blood glucose that was produced by gastric bypass itself. 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(29). Additionally, it has been discovered that surgery also plays role in gut hormone independently from caloric restriction. There are some theories for this mechanism, which are hindgut theory, midgut theory, and foregut theory.

Hindgut Theory

The hindgut or incretin theory suggests that increased glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) release, because of rapid nutrient delivery to the distal small intestine, are responsible for improved glucose metabolism, leading to hyperglycemia reversal (30, 31)

Foregut Theory

The foregut theory concentrates on the role of exclusion of nutrients from the duodenum and jejunum. It is supposed that nutrients in the proximal small bowel may stimulate release of unidentified anti- incretin factor, which may be responsible for decreased incretin secretion. Operations that bypass the duodenum and jejunum may restore balance between anti-incretin and incretin secretion and improve glucose control (32).

Midgut Theory

It is suggested that derivation of food into the distal small intestine after gastric bypass activates gluconeogenic enzymes and increases glucose concentrations in the portal vein, which is sensed and transmitted to the brain by vagal afferents. This results in

increased suppression of hepatic glucose production by insulin and improves glucose homeostasis (33).

Conclusion

Bariatric surgery, the latest therapy for T2DM that has been put into recommendation by ADA since it was first discovered beneficial effects back in 1995, showed that it can gives not only more significant and but also faster in achieving T2DM remission compare to current therapy such as lifestyle intervention, oral drugs, and insulin injection. Moreover, its benefit was not limited only to the remission of T2DM only, but also in lipid profile and blood pressure. Until now, there are 4 registered bariatric surgery procedures in ADA, which are RYGB, GB, SG, and BPD. The most famous procedure is RYGB procedure, while the least popular procedure is BPD procedure. No comparison study was found due to the limitation of study available that compare all of the registered types of bariatric surgeries, hence further research is still needed to determine which procedure is the best option for patients with T2DM. For the post-operative complication, it appeared that SG procedure gave more complications compared to RYGB. However, since only limited study about the adverse effect of bariatric surgery for T2DM therapy available, further short and long-term research is needed.

Conflict of Interest

The author stated there is no conflict of interest

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