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CLINICAL RESEARCH

Diabetes Remission and Insulin Secretion After Gastric Bypass in Patients with Body Mass Index <35 kg/m^2

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Abstract
Background Most morbidly obese patients who undergo gastric bypass experience rapid remission of type 2 diabetes mellitus (T2DM) but the response in non-morbidly obese patients is not clear. This trial prospectively assessed the effect of diabetes remission, glucose metabolism, and the serial changes of insulin secretion after gastric bypass in inadequately controlled T2DM patients with a BMI of 23–35 kg/m^2.
Methods A total of 62 consecutive patients with T2DM and a BMI of 23–35 kg/m^2 underwent gastric bypass. Data were prospectively collected before surgery and 1, 4, 12, 26, and 52 weeks and 2 years after surgery. Insulin secretion was measured by insulinogenic index and area under the curve (AUC) during a standard oral glucose tolerance test (OGTT). Remission of type 2 diabetes was defined as fasting glucose level <110 mg/dl and HbA1c <6.0% without any glycemic therapy.
Results Of the 62 patients, 24 were men and 38 were women (age 43.1±10.8 years). Their preoperative characteristics were as follows: BMI 30.1±3.3 kg/m^2, waist circumference 99.6±9.6 cm, C-peptide 3.1±1.4 ng/ml, and duration of T2DM 5.4±5.1 years. The mean BMI decreased postoperatively to 22.6±2.3 kg/m^2 in 1 year and 23.0±2.7 kg/m^2 in 2 years. The mean HbA1c decreased from 9.7±1.9% to 5.8±0.5% in 1 year and 5.9±0.5% in 2 years. Complete remission of T2DM was achieved in 57% in 1 year and 55% in 2 years after surgery. Before surgery, the OGTT test showed a blunted insulin secretion pattern with an insulinogenic index of 0.1±0.2 and AUC of 2,324±1,015 μIU min/ml. In 1 week after surgery, the insulinogenic index increased to 0.16 and AUC decreased to 1,366 μIU min/ml along with a rapid drop of insulin resistance. The insulinogenic index and AUC gradually increased to 0.27 and 3,220, respectively, 1 year after surgery and remained stable up to 2 years with a very low insulin resistance.
Conclusions Laparoscopic gastric bypass facilitates immediate improvement in the glucose metabolism of inadequately controlled non-severe obese T2DM patients, and the benefit is sustained up to 2 years after surgery. The benefit is regulated by the decrease in insulin resistance, increase in early insulin response, and total insulin secretion to glucose load.

Keywords Insulin secretion · Type 2 diabetes · Gastric bypass

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Introduction

Type 2 diabetes mellitus (T2DM) is now a global health concern [1]. It is estimated that more than 240 million people in the world suffer from T2DM and this number is

expected to rise to 360 million by the year 2025 [2]. More than 60% of the world's diabetic population comes from Asia where the incidence of T2DM is increasing more rapidly than in the rest of the world [3]. In Taiwan, the T2DM in adults increased by more than double from 4.6% to 9.3% in the past decade [4]. Unlike in the West, where the older population is the most affected, the burden of diabetes in Asian countries is disproportionately high in young to middle age adults [2]. For the early onset T2DM patients, the incidence rate of diabetic nephropathy is alarmingly high, especially in patients in whom the disease in not well controlled [5]. In Asia, 55% of cases newly diagnosed with end-stage renal disease are due to T2DM [2]. Controlling this chronic and deliberating disease is a very important health issue in Asia.

There is strong evidence that bariatric surgery can cure most of the morbidly obese patients with T2DM (BMI> 35 kg/m^2) [6–9]. Furthermore, the reduction of mortality by bariatric surgery, mostly gastric bypass, was mostly attributed to the reduction of diabetic-related death [10, 11]. This is why gastric bypass surgery has been recently proposed as a new treatment modality for obesity-related T2DM for patients with BMI<35 kg/m^2 [12–15]. However, the mechanism for diabetes remission after gastric bypass remained speculative [16]. Optimal outcomes for diabetes remission after metabolic surgery will occur if the mechanism is understood and the patients best suited to the surgery are selected and those who will predictably have a poor result are excluded [17]. To be able to make such decisions, we need a detailed follow-up study of a large number of cases with data of insulin secretion before and after surgery. This information is helpful for considering gastric bypass surgery as a metabolic surgery for type 2 diabetes treatments in the future. The aim of this study is to evaluate the results of diabetes remission after gastric bypass in non-severely obese subjects (BMI<35 kg/m^2), in whom diabetes is not well controlled, under medical treatment. We also continually assessed the insulin secretion to oral glucose tolerance test (OGTT) after surgery in order to elucidate the underlying mechanism associated with diabetes remission.

Methods

Eligibility

The study was conducted in the Department of Surgery of the Min-Sheng General Hospital, National Taiwan University. Prior approval for performance of the study was obtained from the ethics committee of the hospital. There was a total of 62 diabetic Asian subjects (24 men and 38 women; aged 43.1±10.8 years, mean). All patients referred for surgical treatment of T2DM were evaluated by a multidisciplinary and integrated medical unit consisting of a team of general physician, endocrinologist, psychiatrist, and dietician. A thorough assessment was performed on each patient's general condition and mental status, complications of diabetes, risk factors, and motivations for surgery.

The criteria for inclusion were patients aged 25 to 65 years who had a history of T2DM over 6 months, not well controlled (HbA1c ≥7.0%) and BMI below 35 but above 23 kg/m^2. The patients must have their C-peptide above 1 ng/ml and without irreversible major organ damage related to diabetes. All patients had to necessarily give written informed consent before undergoing surgery.

Study Protocol

Patients were studied for a day before surgery and again at 1, 4, 12, 26, and 52 weeks and yearly after surgery. OGTT with 75 g glucose (in a total volume of 300 ml) was administered in the morning after a 12-h overnight fast. A sample of blood was collected in 30, 60, and 120 min after oral glucose load. The blood sample was checked for blood glucose and insulin level.

Insulin resistance was measured by the Homeostatic Model Assessment (HOMA) index, calculated as plasma glucose (mmol/l)×insulin (UI/ml)/22.5 [18]. Insulin secretion during OGTT was measured by insulin total area AUC using the trapezoidal method. Early insulin secreting response to specific glycemic response was measured by " insulinogenic index" (Ii) [19]. The insulinogenic index was obtained by dividing plasma insulin enhancement above fasting value by the corresponding net increase of blood glucose (Δ insulin: Δ glucose) at 30 min during the OGTT test.

Surgical Technique

Two types of gastric bypass were performed in this series. One was standard Roux-en-Y gastric bypass with 80-cm bilio-pancreatic limb and 120-cm alimentary limb. Another type of gastric bypass was a simplified procedure known as "mini-gastric bypass" or " sleeved Billroth II gastric bypass". This procedure had been adopted in our center and previously described [20, 21]. To describe briefly, by a standard five-port laparoscopic technique, a long-sleeved gastric tube was created by the Endo-GIA stapler (Tyco, United States Surgical Corporation, Norwalk, CT, USA) approximately 2.0 cm wide along the lesser curvature from the antrum to the angle of His. A Billroth II type loop gastroenterostomy was created with the small bowel about 120 cm distal to the ligament of Trietz with the Endo-GIA stapler. No drain tube was left. All the trocar wounds were

closed by the mesh plug technique using a bio-absorbable hemostatic gauze (Cellulostat, Horng Tzer Medical Instruments, Ltd. Kaohsiung, Taiwan) [22].

Remission of Diabetes

Patients were followed up and their status assessed in 1, 4, 12, 26, and 52 weeks and 2 years postoperatively. According to the new ADA guideline, complete remission of T2DM was defined as fasting glucose levels less than 110 mg/dl in addition to HbA1c value less than 6.0% without the use of oral hypoglycemics or insulin [23]. Partial remission was defined as HbA1c <6.5% and improved as <7.0%. Routine laboratory tests and anthropometric measurements were also performed. Ideal body weight was calculated using BMI 23 as standard.

Statistical Analysis

All statistical analyses were performed using SPSS version 12.01 (SPSS Inc, Chicago, IL, USA), with baseline comparison made using Chi-square tests and two-sample *t* tests. Continuous variables were expressed as mean (standard deviation), with differences expressed as mean (95% CI). Binary logistic regression was used to examine the associates of diabetes remission. A two-sided *p* value of 0.05 was considered statistically significant.

Results

The characteristics of subjects are provided in Table 1. Their preoperative characteristics were as follows: BMI 30.1±3.3 kg/m^2, waist circumference 99.6±9.6 cm, C-peptide 3.1±1.4 ng/ml, and duration of T2DM 5.4±5.1 years. All the patients had oral medication, and insulin was used in 14 (23%) patients. All surgical procedures were performed laparoscopically, with a mean procedure time of 82 min (range 55–110) and mean hospital admission duration of 5 days (3–8 days). No major complication was experienced. Minor complication occurred in seven patients (11.3%).

Diabetes Remission and Weight Loss

Weight loss (kilogram) and percent of excess weight loss were 3.6 kg (22.9%), 7.2 kg (47.9%), 12.1 kg (78.2%), 15.7 kg (102.5%), 17.7 kg (108.0%), and 16.0 kg (103.8%) in 1, 4, 12, 26, and 52 weeks and 2 years separately. The mean BMI and HbA1c were 28.9 and 9.1, 26.7 and 7.2, 23.4 and 6.0, 23.8 and 5.7, 22.6 and 5.8, and 23.0 and 5.9 at 1, 4, 12, 26, and 52 weeks and 2 years after surgery, respectively. Around 90% of the patients had their HbA1c <7% in 26 weeks after surgery and up to 2 years (Table 2). Complete remission of type 2 diabetes was achieved in 0%, 11%, 37%, 53%, 57%, and 55% patients in 1, 4, 12, 26, and 52 weeks and 2 years after surgery, respectively. Figure 1 shows the weight reduction and decrease in HbA1c at different time periods. Both continued to decrease linearly after surgery and plateaued in 6 months.

Oral Glucose Tolerance Test and Insulin Secretion

The glucose metabolism represented by the AUC of OGTT improved immediately after surgery and is sustained up to 2 years (Table 1). Before the surgery, a typical post-prandial prolonged hyperglycemia diabetic OGTT pattern was observed (Fig. 2). After surgery, the AUC of OGTT and HOMA insulin resistance both dropped dramatically in the first week and persisted up to 2 years (Table 1). The

Table 1 Patient characteristics before and after the laparoscopic gastric bypass [mean (SD)]

	Before (n=62)	1 week (n=62) NON-MS	4 weeks (n=62)	12 weeks (n=45)	26 weeks (n=40)	52 weeks (n=30)	2 years (n−20)
BMI (kg/m^2)	30.1 (3.3)	28.9 (3.1)	26.7 (2.9)	23.4 (2.6)	23.8 (2.4)	22.6 (2.3)	23.0 (2.7)
Waist (cm)	99.6 (9.6)	97.8 (78.1)	91.6 (7.3)	85.1 (8.9)	80.4 (8.6)	79.1 (7.3)	79.3 (9.3)
EWL (%)		22.9 (30.2)	47.9 (36.1)	78.2 (41.2)	102.5 (71.3)	113 (37.3)	82.8 (28.8)
Glucose (mg/dl)	195.8 (75.8)	168.9 (52.0)	140.2 (41.6)	116.6 (25.9)	103.2 (19.2)	100.2 (19.4)	106.3 (18.8)
Insulin (μIU/ml)	8.4 (5.5)	4.6 (3.2)	4.5 (2.6)	5.0 (3.1)	5.2 (4.7)	4.6 (3.8)	2.8 (1.6)
HbA1c (%)	9.7 (1.9)	9.1 (1.1)	7.2 (1.2)	6.0 (0.8)	5.7 (0.6)	5.8 (0.5)	5.9 (0.5)
HOMA	9.2 (12.4)	3.1 (0.9)	1.7 (1.0)	1.4 (0.9)	1.4 (1.5)	1.2 (1.2)	0.73 (0.3)
Glucose (AUC)	41,709 (6,865)	28,617 (2,580)	26,591 (6,338)	24,181 (1,544)	22,610 (3,537)	22,532 (4,379)	23,270 (4,290)
Insulin (AUC)	2,324 (1,015)	1,366 (1,174)	1,827 (1,568)	2,295 (1,434)	3,486 (2,491)	3,220 (1,499)	3,322 (2,534)
Insulinogenic index (II)	0.1 (0.16)	0.16 (0.08)	0.19 (0.12)	0.20 (0.17)	0.17 (0.16)	0.27 (0.20)	0.20 (0.13)

EWL excess weight loss, *AUC* area under curve, *HOMA* HOMA index

Table 2 Diabetes remission after surgery

Time (no.)	1 month (62)	3 months (52)	6 months (45)	1 year (28)	2 years (20)
Improved, % (no.) [HbA1c <7%]	39 (24)	75 (39)	87 (39)	93 (26)	90 (18)
Partial remission, % (no.) [HbA1c <6.5%]	19 (12)	58 (30)	64 (29)	82 (23)	80 (16)
Complete remission, % (no.) [HbA1c <6.0%, glucose <110 mg/dl]	11 (7)	37 (19)	53 (24)	57 (28)	55 (11)

glucose curve in OGTT was rather stable from the first week after surgery and up to 2 years.

Before the surgery, a typical delayed insulin secretion diabetic OGTT pattern was observed (Fig. 2). The fasting plasma insulin was 8.4±5.5 μIU/ml and fasting plasma glucose was 195.8±75.8 mg/dl and progressively rose to a peak value of 18.8 μIU/ml and 386 mg/dl in 120 min in the OGTT test. After surgery, the fasting blood glucose and insulin level both dropped dramatically on the first week and persisted up to 2 years. In contrast to the stable glucose curve in OGTT from the first week after surgery, the delayed insulin secretion pattern in the OGTT gradually changed to an early secretion pattern over 2 years after the surgery (Fig. 2). A normal peak of early insulin secretion in 30 min can be observed 52 weeks after the surgery. The AUC of insulin during OGTT before surgery was 2,324±1,015 μIU min/ml and was 1,366±1,174, 1,827±1,568, 2,295±1,434, 3,486±2,491, 3,220±1,499, and 3,322±2,543 μIU min/ml in 1, 4, 12, 26, and 52 weeks and 2 years after surgery, respectively. The ratio of AUC (glucose)/AUC (insulin) before surgery was 17.2 and 8.1, 13.6, 10.5, 6.7, 7.0, and 6.9 at 1, 4, 12, 26, and 52 weeks and 2 years after surgery, respectively.

Insulinogenic Index and HOMA

The mean insulinogenic index (Δ insulin:Δ glucose in 30 min in OGTT) before surgery was 0.1 and was raised to 0.16 1 week after surgery; the insulinogenic index 4, 12, 26, and 52 weeks and 2 years after surgery was 0.19, 0.20, 0.17, 0.27, and 0.20, respectively (Table 1). Before surgery, the HOMA index was 9.2±12.4 which decreased immediately after surgery and was maintained during follow-up (Table 1). The HOMA index was 3.1±1.9, 1.7±1.0, 1.4±0.9, 1.4±1.5, 1.2±1.2, and 0.73±0.3 at 1, 4, 12, 26, and 52 weeks and 2 years after surgery.

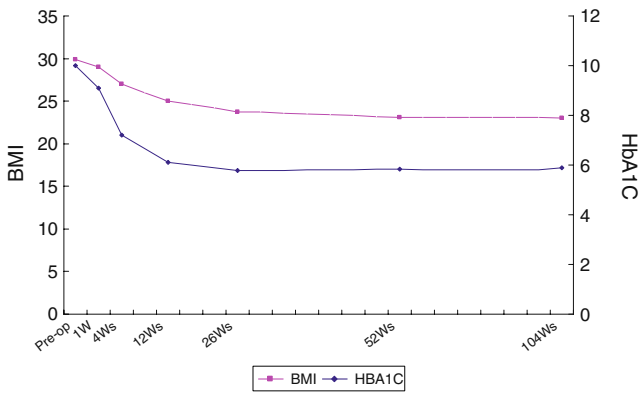

Fig. 1 Change in body mass index (BMI, kilogram per square meter) and HbA1c after gastric bypass

Discussion

This study confirmed the efficacy of gastric bypass in the treatment of non-severe obese (BMI<35) type 2 diabetes patients at longer follow-up [12–15]. Using the current laparoscopic gastric bypass surgery, we can achieve an improvement rate of 90% and a complete remission rate of 55% up to 2 years for those patients with poorly controlled diabetes. In addition, this study also provided a robust evidence of the underlying mechanism in diabetes remission after gastric bypass medicine. The glucose metabolism was found to dramatically improve immediately after surgery and sustained up to 2 years. About 90% of the patients had their HbA1c less than 7% in 26 weeks after gastric bypass surgery and up to 2 years. The mean HbA1c reduction 2 years after surgery was 3.8%. This is a great advancement in diabetes treatment. Considering the long-term survival benefit of gastric bypass surgery in obesity and diabetes treatment [10, 11], a freer usage of laparoscopic gastric bypass surgery in the treatment of non-severe obese (BMI<35) T2DM patients who are poorly controlled is expected under the current treatment [17].

In previous studies, an increase of insulin secretion was found immediately after gastric bypass or bilio-pancreatic bypass surgery [24–28]. However, in these studies, it is the increase of the early phase insulin response not the total insulin secretion. In the study of Pournaras et al., they measured insulin production by delta insulin [28]. Insulin production as measured by delta insulin between 0 and 15 min represents the early response of insulin secretion. Therefore, the insulin secretion is "improved" but not "increased" after gastric bypass. The mechanism for this improved early response of insulin secretion was attributed to the hindgut hormone, glucagon-like-peptide-1 (GLP-1), effect [24–28].

The most important finding of this study is that insulin secretion is actually decreased after gastric bypass although an early and dramatic effect of the glucose metabolism after

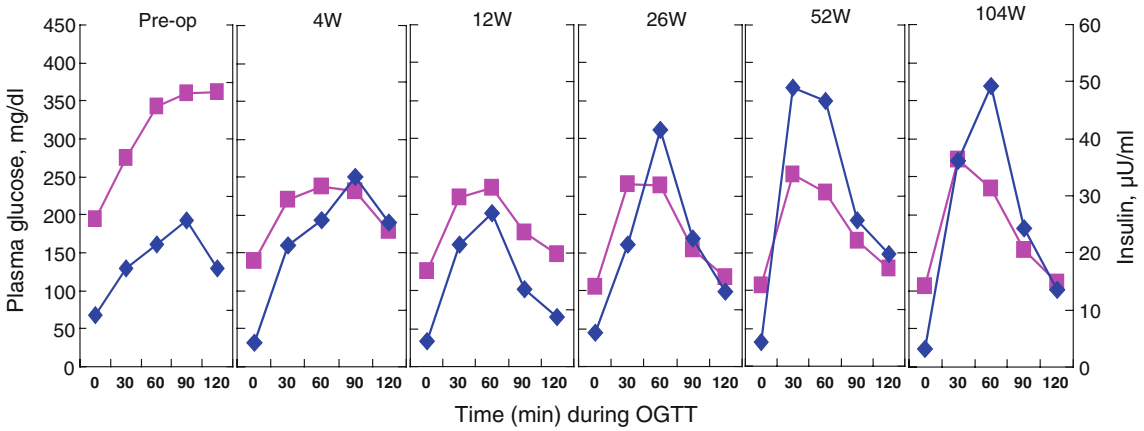

Fig. 2 Insulin secretion after oral glucose load (OGTT) before and after gastric bypass. Values for blood glucose and plasma insulin are plotted as mean ± standard error of the mean

gastric bypass reported in previous study was also confirmed in this study. In the present study, gastric bypass does not increase overall insulin secretion at early postoperative period until 6 months after surgery and was maintained up to 2 years. Although an increase in post-prandial plasma levels of GLP-1 early after gastric bypass surgery may improve the early response of insulin secretion, the incretin effect itself cannot explain the dramatic effect of glucose metabolism after gastric bypass because the total amount of insulin secretion was decreased. If the total amount of insulin secretion is decreased after gastric bypass, this dramatic effect of gastric bypass on the plasma glucose metabolism probably should be attributed to other mechanisms.

The most important mechanism for diabetes remission after gastric bypass could be due to the dramatic decrease of insulin resistance rather than the incretin effect immediately after surgery. This mechanism is very important for alleviating an already damaged insulinogenic mechanism after a prolonged excessive stimulation of beta cells. Similar to this study, we had also documented an immediate and persistent reduction in HOMA index in patients after bariatric surgery, including banding, bypass, or sleeve gastrectomy surgery [29, 30]. In the present study, we had documented a rapid and dramatic reduction of insulin resistance (HOMA index) and an increase of insulinogenic index (early insulin secretion) which corroborated with a recent study by Pournaras et al. [28]. In another long-term follow-up study, improvement of insulin resistance also played a crucial role in diabetes remission [31].

There are several possible mechanisms involved in the rapid decrease in insulin resistance after surgery. The first mechanism is due to the effect of decreased calorie intake after surgery. According to earlier studies, strict calorie restriction itself can bring normalization of plasma glucose and insulin levels before decreasing the body weight [32, 33]. Our studies also supported the starvation followed by weight reduction theory [16]. Another possible mechanism is the surgical effect itself. It was known that surgical stress may induce the secretion of catecholamine which can inhibit insulin secretion [34, 35].

Although a dramatic reduction in insulin resistance followed by a decrease in insulin secretion was found in the early 6 months, the total insulin secretion did increase 6 months after gastric bypass reflecting a recovering pancreas insulinogenic mechanism. A possible mechanism for the increase in insulin secretion is due to the increase in beta cell mass through "nesidioblastosis" [36]. With the finding of incretins, especially GLP-1, it has been postulated that chronic increase in the production of GLP-1 after gastric bypass surgery may result in an increase in beta cell mass [37]. Although the theory is difficult to be proven and the B-cell hyperplasia theory has been refuted by many researchers, a recent study does show that gut hypertrophy after gastric bypass is associated with increased GLP-2 [38]. In the present study, the total amount of insulin secretion increased again 6 months after gastric bypass and remained up to 2 years. We also investigated the gut hormone change 2 years after surgery and supported the theory by the findings of a robust increase in insulin secretion and elevated post-meal GLP-1 responses 2 years after gastric bypass surgery (data not shown). Therefore, the effect of long-term GLP-1 stimulation on B-cell mass requires further investigations. Other hindgut hormones may also play a role in weight reduction and diabetes remission, such as PYY [24–27].

The last intriguing possible mechanism is the bypass of the hormonally active foregut. Several reports supported the superior effect of gastric bypass over restricted procedures owing to a direct effect of bypass of the hormonally active foregut [26–28, 39]. Rubino and Marescaux supported the theory in an animal model [40, 41]. We investigated this theory by including a control group of sleeve gastrectomy. In a previous randomized study, gastric bypass with duodenum exclusion was found to have a significant higher diabetes remission rate than sleeve gastrectomy after a similar weight loss [42]. The mechanism was related to

reduction of insulin resistance. A recent randomized trial studying ileal transposition also supported the additional role of duodenum exclusion on diabetes treatment and reported a similar remission rate to the present study [43]. Many retrospective observation studies also supported the role of duodenum bypass on diabetes remission [44, 45]. Therefore, the effect of duodenum exclusion probably exists and might be related to a decrease in insulin resistance rather than an increase in insulin secretion.

The limitation of this study is the lack of preoperative gut hormone data. Without data on the accompanying change in the gut hormone, we cannot elucidate the underlying mechanisms for the remission of diabetes after gastric bypass surgery. However, this longitudinal study of insulin secretion after gastric bypass for T2DM treatment strongly supports further study in this metabolic surgery. Another limitation of this study is the lack of long-term follow-up. Although studies have illustrated the remission of T2DM after gastric bypass, some of the patients whose T2DM remission after surgery experienced a recurrence of their disease over time, especially in old patients with lower BMI and longer duration of the disease [46, 47]. We need data of long-term follow-up of 5 or 10 years in order to support surgery as a treatment option in non-morbidly obese diabetes patients. However, it is for sure that laparoscopic gastric bypass will play a role in diabetes treatment even some may recur later. If we can delay the appearance of a serious diabetic complication for 10 years, it means a lot for the patient and for the society. We may need to clarify the mechanism and predictor of diabetes remission in the future, so we can choose the most appropriate treatment and exclude those not appropriate. Further clinical studies with long-term follow-up are indicated to elucidate this issue.

In summary, laparoscopic gastric bypass is effective for remission of non-morbidly obese diabetic patients inadequately controlled by the current medical treatment. The glucose metabolism improved immediately after surgery. There was weight reduction and decrease of HbA1c plateau in 6 months. The mechanism in the early phase is relief of insulin resistance, and in the late phase, it is the relief of insulin resistance and augmentation of insulin secretion.

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