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【 CASE REPORT 】

Sleeve Gastrectomy Induced Remission of Slowly Progressive Type 1 Diabetes in a Morbidly Obese Japanese Patient

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Abstract:
The effects of bariatric/metabolic surgery on glycemic control in obese type 1 diabetic patients are controversial. We herein report a case of a morbidly obese 35-year-old woman who completely recovered from slowly progressive type 1 diabetes (SPIDDM) following laparoscopic sleeve gastrectomy. Preoperatively, her body mass index (BMI) was 49.8 kg/m^2 and hemoglobin A1c was 5.7% with intensive insulin therapy. Six months after bariatric/metabolic surgery, her BMI decreased to 33.2 kg/m^2 and her glycemic control was normal despite the discontinuation of all diabetic medicine. This case demonstrates the usefulness of bariatric/metabolic surgery for achieving glycemic control in morbidly obese patients with SPIDDM in Japan.

Key words: type 1 diabetes, morbid obesity, bariatric surgery

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Introduction

The prevalence of obesity and type 2 diabetes (T2D) continues to increase worldwide (1). The clinical manifestations of obesity and T2D are closely associated with each other. It is difficult to achieve good glycemic control in morbidly obese diabetic patients with conventional medical therapies due to severe insulin resistance. Bariatric surgery was recently proven to be effective not only for reducing body weight, but also improving metabolic diseases, particularly T2D (2). The metabolic benefits of this surgery are also observed prior to significant body weight loss and their magnitude is markedly greater than may be explained by the loss of body weight alone; thus, the concept of metabolic surgery has emerged. Patients with type 1 diabetes (T1D) are often lean individuals. However, the prevalence of obesity has increased faster in patients with T1D than in the general population, and approximately 60% of adults with T1D in the USA are overweight or obese (3). This increase in obesity with T1D may be attributed to the greater prevalence of intensive insulin therapy with increasing doses of insulin to maintain good glycemic control. Previous studies have demonstrated the comprehensive effects of bariatric surgery on type 1 diabetic patients worldwide. Three recent meta-analyses revealed that bariatric surgery is useful for decreasing the body weights of and insulin doses required by obese type 1 diabetic patients; however, its ability to improve glycemic control has not yet been demonstrated (4-6).

To the best of our knowledge, only one study in Japan has described the effects of bariatric surgery on obese type 1 diabetic patients (7). We herein report that laparoscopic sleeve gastrectomy resulted in the complete remission of slowly progressive type 1 diabetes/slowly progressive insulin-dependent diabetes mellitus (SPIDDM) in a morbidly obese patient using high-dose insulin along with a GLP-1 receptor agonist and several oral hypoglycemic agents.

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Table 1. Laboratory Data on Admission.

[Biochemistry]		[Blood cell count]	
AST	15 IU/L	WBC	6,100 /μL
ALT	14 IU/L	RBC	475×10⁴ /μL
γGTP	10 IU/L	Hb	12.4 g/dL
T-BIL	0.6 mg/dL	Ht	39.4 %
ALP	132 IU/L	MCV	82.9 fL
LDH	208 IU/L	MCH	26.1 pg
CPK	71 IU/L	MCHC	31.5 %
UN	8.2 mg/dL	Plt	34.9×10⁴ μL
UA	4.3 mg/dL	[Urinary data]	
Cr	0.44 mg/dL	pH	7.5
TP	7 g/dL	SG	1.013
Alb	4.2 g/dL	Pro	±
AMY	49 IU/L	OB	–
Na	140 mEq/L	Uro	–
K	4 mEq/L	[Thyroid function]	
Cl	102 mEq/L	TSH	2.63 μIU/mL
Ca	9.1 mEq/L	FT4	1.3 ng/dL
CRP	0.75 mg/dL	[Adrenal function]	
TG	65 mg/dL	ACTH	10.1 pg/mL
HDL-Cho	47 mg/dL	COR	7.89 μg/dL
LDL-Cho	96 mg/dL	[Gonadal function]	
[Glucose metabolism]		LH	2.68 mIU/mL
FBS	86 mg/dL	FSH	5.60 mIU/mL
HbA1c	5.7 %	PRL	10.9 ng/mL
Anti-GAD Ab	623 U/mL	E2	34 pg/mL

AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ glutamyl transpeptidase, T-BIL: total bilirubin, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CPK: creatine phosphorus kinase, UN: urea nitrogen, Cr: creatinine, TP: total protein, Alb: albumin, AMY: amylase, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, CRP: C-reactive protein, TG: triacylglycerol, HDL-Cho: high-density lipoprotein cholesterol, LDL-Cho: low-density lipoprotein cholesterol, FBS: fasting blood sugar, HbA1c: hemoglobin A1c, Anti-GAD Ab: anti-glutamic acid decarboxylase antibody, WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, Plt: platelets, SG: specific gravity, Pro: protein, OB: occult blood, Uro: urobilinogen, TSH: thyroid-stimulating hormone, FT4: free thyroxine 4, ACTH: adrenocorticotropic hormone, COR: cortisol, LH: luteinizing hormone, FSH: follicle-stimulating hormone PRL: prolactin, E2: estradiol

Case Report

The patient was a 35-year-old woman who was diagnosed with diabetes at 17 years of age and who was being treated with oral hypoglycemic agents. Insulin treatment was introduced when her diabetes was proven to be SPIDDM at 25 year of age. She had been obese from childhood. Regarding her family history, both of her parents had T2D and her grandmother and younger sister were obese. At 20 years of age, her height and weight were 152 cm and 90 kg, respectively, and her body mass index (BMI) was 39.0 kg/m^2. Her body weight continued to increase and, at 35 years of age, reached 120.8 kg with a BMI of 52.3 kg/m^2. Since medical therapy was judged to be ineffective for the treatment of her morbid obesity, she was introduced to the Department of Bariatric Surgery in our hospital. Her diabetes was being treated with metformin (2,250 mg, daily), pioglitazone (15 mg, daily), miglitol (150 mg, daily) and dulaglutide (0.75 mg, weekly) along with insulin (62 units, daily). Her hemoglobin A1c (HbA1c) level was 6.8%. On admission for a more detailed examination to decide whether bariatric/metabolic surgery was indicated, her HbA1c level had improved to 5.7% and her daily insulin dose was decreased to 35 units due to subsequent strict lifestyle modifications (Table 1). Her antibody titer against glutamic acid decarboxylase (GAD) was elevated (623 U/mL). The plasma C-peptide immunoreactivity (CPR) response to the administration of glucagon, a good marker for assessing residual insulin secretion, was 1.21 ng/mL, suggesting that the endogenous insulin secretory capacity of β cells had not been abolished (8) (Table 2). We considered body weight loss induced by bariatric/metabolic surgery to be helpful for reducing her insulin requirements, diminishing the secretory burden on β cells, and prolonging the viability of β cells. We therefore decided to perform bariatric/metabolic surgery even though her glycemic control was good due to combination therapy. Based on her low ABCD score (4 out of 10 points), which predicts a poor postoperative improvement in diabetes (9), sleeve gastrectomy with duodenojejunal bypass was more suitable than simple gastrectomy alone because of its stronger effects regarding the postoperative improvement of glucose metabolism (10, 11). Although it currently remains unclear whether the postprandial blood glucose levels are increased more rapidly and to a greater extent by sleeve gastrectomy with duodenojejunal bypass than by sleeve gastrectomy alone, we selected sleeve gastrectomy to avoid possible postprandial hyperglycemia due to the rapid and direct influx of gastric contents into the jejunum and incomplete postprandial insulin secretion when the patient's T1D progresses in the future. Within days of surgery, her blood glucose level stabilized, in spite of the cessation of all medications, except for 5 units of insulin glargine daily. Although insulin was discontinued at two months after surgery, at 6 months after surgery her HbA1c level was 5.8% (Table 2). At that point, her body weight had decreased to 76.1 kg and the percentage of

Table 2. Alterations in Glycemic Metabolism.

Variables	Preoperative value	Postoperative value
FBG (mg/dL)	86	85
HbA1c (%)	5.7	5.8
F-CPR (ng/mL)	1.1	0.89
CPI	1.28	1.05
CPR response to glucagon (ng/mL)	1.21	2.34

CPI is [fasting-CPR (ng/mL)/fasting blood glucose (mg/dL)] ×100. The CPR response to glucagon means an increase in the plasma concentration of glucagon 6 min after the intravenous administration of 1 mg glucagon. FBG: fasting blood glucose, HbA1c: hemoglobin A1c, F-CPR: fasting C-peptide immunoreactivity, CPI: C-peptide immunoreactivity index

Table 3. Alterations in Anthropometric Data.

Variables	Preoperative value	Postoperative value
Ht (cm)	151.3	151.3
BW (kg)	111.4	76.1
BMI (kg/m^2)	49.8	33.2
%EWL (%)	–	66.6
Abdominal fat area (cm^2)	968	233
Subcutaneous fat area (cm^2)	609	162
Visceral fat area (cm^2)	359	71
Fat mass (kg)	59.0	24.9
Muscle mass (kg)	49.8	48.1
Protein mass (kg)	10.4	9.9
Body fat percentage (%)	53.0	32.7

%EWL is [preoperative body weight (kg)-postoperative body weight (kg)/preoperative body weight (kg)-body weight at BMI 25 (kg)] ×100. The abdominal fat area was calculated using an abdominal CT image. Fat mass, muscle mass, protein mass, and body fat percentage were measured by InBody 270. Ht: height, BW: body weight, BMI: body mass index, %EWL: percentage of excess weight loss

excess weight loss (%EWL), an excellent marker for evaluating body weight loss after bariatric surgery, was 66.6%, indicating satisfactory body weight loss (Table 3). After surgery, her abdominal fat area markedly decreased from 968 cm^2 to 233 cm^2; and visceral fat area decreased from 359 to 71 cm^2 (Table 3). In addition, her muscle mass loss remained at 1.7 kg, whereas her fat mass loss had reached 34.1 kg (Table 3). These results suggest that ideal body weight loss was achieved in this case. Regarding endogenous insulin secretion, the plasma CPR response to glucagon increased from 1.21 to 2.34 ng/mL (Table 2), suggesting an improvement in her endogenous insulin secretory function. No severe adverse events were observed.

Discussion

We herein report a case in which sleeve gastrectomy markedly reduced the body weight of a morbidly obese patient with SPIDDM, leading to the discontinuation of all diabetic medicines at 6 months after surgery, despite the use of a large volume of insulin before surgery. These results indicate that sleeve gastrectomy is potentially a very useful therapy for obese type 1 diabetic patients in whom the function of endogenous insulin secretion remains.

Although bariatric surgery has been proven to be effective for improving T2D with obesity (2, 12), the utility and effectiveness of this surgery for T1D remain controversial. A recent systematic review and meta-analysis showed that obese patients with T1D achieved marked reductions in body weight as well as improved glycemic control, as reflected by a decreased insulin requirement and improvement in HbA1c after bariatric surgery (4, 5). Furthermore, bariatric surgery has been reported to improve blood pressure, lipid metabolism, sleep apnea syndrome, and albuminemia in patients with T1D (13). In contrast, another recently published meta-analysis found no significant improvement in glycemic control in obese type 1 diabetic patients (6). This discrepancy may be attributed to the wide diversity of pathogeneses in T1D. Our patient had SPIDDM, or latent autoimmune diabetes in adults (LADA), which is characterized by adult-onset diabetes, obesity, the features of metabolic disorders, circulating islet autoantibodies (most commonly GAD), and, initially, the lack of a requirement for insulin treatment (14). In this type of diabetes, it is important to remove the overload on β cells for an excessive insulin demand in order to prevent early β cell failure. The secretory burden on β cells elicited by insulin resistance associated with obesity triggers ER stress in β cells and their subsequent apoptosis if the burden is prolonged (15). Insulin intervention to preserve the β cell function was previously reported to be more effective for preventing progression to an insulin-dependent state in the treatment of SPIDDM than sulfonylurea therapy, which burdens the β cell function (16). Furthermore, obesity-induced insulin resistance is assumed to increase β cell stress and intensify autoimmune responses in these cells in genetically predisposed patients (17). Enlarged adipose tissue secretes proinflammatory cytokines, including TNFα, IFNγ, and IL-1β, into the circulation (18). They play a prominent role in the pathophysiology of T1D (19, 20), indicating that these proinflammatory cytokines impair β cells and cause a loss of β cell mass (21, 22). Thus, the reduced fat mass elicited by bariatric/metabolic surgery-particularly in SPIDDM-is important for maintaining the β cell function. In the present study, a marked increase in the insulin secretion of the patient's β cells was observed after surgery.

In the present case, glycemic control was maintained despite the discontinuation of all diabetic medicine. This may be closely associated with the maintenance of the preoperative endogenous insulin secretory capacity in β cells. Thus, bariatric/metabolic surgery may be very useful for not only achieving weight reduction, but also for improving in glycemic control-particularly in obese patients with SPIDDM in which endogenous insulin secretion has not been abolished. A recent study reported that bariatric surgery was effective for achieving weight loss and glycemic control in 5 morbidly obese Japanese patients with SPIDDM (7); the anti-GAD Ab titers of the 5 patients were all weakly positive (range, 3.5-6.5 U/mL), whereas the titer of the patient in the present case was very high. Thus, the anti-GAD antibody titer does not appear to be associated with the effects of bariatric/metabolic surgery on weight loss or improved glycemic control.

One limitation of the present study was the short observation period. The patient needs to be followed up over a longer period. In addition, it will be interesting to investigate the effects of bariatric/metabolic surgery on obese type 1 diabetes patients in whom endogenous insulin secretion is abolished. The number of obese type 1 diabetes patients is expected to increase in Japan in the future. Thus, the present case will be helpful when considering treatment options for

obese patients with T1D.

The authors state that they have no Conflict of Interest (COI).

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