□ CASE REPORT □

A Morbid Obese Japanese Woman with a Body Mass Index of 83.2 kg/m²: Before and after Sleeve Gastrectomy

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Abstract

A 34-year-old Japanese woman presented at our institution weighing 182.7 kg, 148.2 cm tall, and with a body mass index of 83.2 kg/m². She had been overweight since childhood, but no abnormality was found to explain her obesity. Treatments, including mazindol, bofu-tsusho-san, dietary restriction, and BioEnterics Intra-gastric Balloon, did not result in improvement of her obesity. Finally, we performed sleeve gastrectomy, and she has maintained her weight within 130-140 kg without rebounding for 2 and a half years. We followed the clinical changes before and after the operation. This case provides potentially interesting information regarding operative treatment for morbid obesity in Japanese.

Key words: morbid obesity, Japanese, obesity surgery, sleeve gastrectomy

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Introduction

Obesity prevalence rates are dramatically increasing worldwide, leading to greater cardiovascular disease and all-cause mortality (1). In Japan, treatment for obesity mainly depends on non-invasive procedures such as dietary restriction, exercise therapy, and oral administration of drugs. For morbidly obese patients, though surgery has been reported to be effective for long-term treatment option (2-6), it is not covered by the national insurance in Japan, and the treatment option is limited.

Laparoscopic sleeve gastrectomy belongs to the purely restrictive operations (7) which has been initially performed as part of a staged surgical approach for high-risk morbidly obese patients to reduce morbidity and mortality (8-10), and has recently been thought to have the potential as a single weight loss operation (11). The major effect is thought to exerted by reducing the level of ghrelin through the resec-

tion of the fundus (12, 13). Here, we present of a case of a morbidly obese Japanese woman who underwent a sleeve gastrectomy.

Case Report

A 34-year-old Japanese woman, weighing 182.7 kg, 148.2 cm tall, was born at 2,900 g. She had been overweight since childhood. By the age of 13 years, her height stopped increasing at 150 cm, and she weighed 63 kg. Her weight was 88 kg at the age of 15, and kept increasing to 105 kg by age 18. She was hospitalized for medical evaluation several times, but no medical abnormality was found to explain her obesity. Nothing remarkable was seen on her abdominal CT imaging, and there was suppression in the 1 mg dexamethasone test. At the age of 29, continuous positive airway pressure was started for her obstructive sleep apnea. Treatment including mazindol, bofu-tsusho-san (an Oriental herbal medicine), and dietary restriction during hospitalization were

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Table 1. Clinical Laboratory Data

Urinalysis		Blood Chemistry	
glucose	(-)	TP	6.8 g/dL
protein	(1+)	Alb	3.6 g/dL
ketone	(-)	T-Bil	1.2 mg/dL
CCR	55.3 mL/min	AST	21 IU/L
microalbumin	104 mg/day	ALT	30 IU/L
Hematological analysis		LDH	295 IU/L
WBC	4,200 / μ L	γ -GTP	15 IU/L
RBC	649 $\times 10^4$ / μ L	BUN	8.4 mg/dL
Hb	16.1 g/dL	Cr	0.53 mg/dL
Hct	55.9 %	Na	137 mEq/L
Plt	15.3 $\times 10^4$ / μ L	K	3.9 mEq/L
PT	10.7 sec	Cl	97 mEq/L
APTT	30.2 sec	CRP	1.01 mg/dL
Fib	335 mg/dL	T-Cho	146 mg/dL
Arterial Blood Gas Analysis on Room Air		TG	129 mg/dL
pH	7.368	HDL-Cho	53 mg/dL
pO ₂	55.5 mmHg	Endocrine	
pCO ₂	47.2 mmHg	TSH	2.55 μ IU/mL
HCO ₃ ⁻	27.4 mmHg	free T4	1.04 ng/mL
B.E.	1.7 mmol/L	BNP	12.9 pg/mL

Alb, albumin; ALT, alanine aminotransferase; APTT, active prothrombin time; AST, aspartate aminotransferase; B.E., base excess; BNP, brain natriuretic protein; CCR, creatinine clearance; CK, creatine phosphokinase; Cr, creatinine; CRP, C reactive protein; Fib, fibrinogen; γ GTP, γ glutamyltranspeptidase; Hb, hemoglobin; HDL-Cho, high density lipoprotein cholesterol; Ht, hematocrit; LDH, lactate dehydrogenase; Plt, Platelet; PT, prothrombin time; RBC, Red blood cell; Tbil, total bilirubin; T-Cho, total cholesterol; TG, triglyceride; TP, total protein; TSH, thyroid stimulating hormone; WBC, White blood cell.

not effective. Her weight kept increasing to 190-200 kg, and the self-reported maximum weight was 200 kg (BMI 91.1 kg/m²), and 198.8 kg (BMI 90.5 kg/m²) in outpatient visit by the age of 32. She finally reached her present weight, consuming approximately 5,000 calories per day.

Apart from oral medications for control of mild hypertension, there was no other past medical history. Her father and younger sister were obese (BMI 39.0 and 35.5 kg/m², respectively). The present patient's menarche began when she was 11 years of age, and her menses came regularly until she was 20 years old, whereafter they became irregular, finally occurring only once every few months.

The physical examination revealed a height of 148.2 cm and a body weight of 182.7 kg, giving a body mass index (BMI) of 83.2 kg/m², corresponding to class III obesity (14). Further findings were as follows: waist circumference, 160 cm; a blood pressure, 132/88 mmHg; and pulse rate, 64/min. Contact dermatitis was observed in her lower abdominal skin because of the extent of her fat, though no other significant abnormalities were observed.

Laboratory findings are described in Table 1. Albuminuria and elevated serum levels of C reactive protein (CRP) were seen. Blood-gas values, measured in arterial blood drawn with the patient reclining in bed while breathing room air, were pO₂ 55.5 mmHg, pCO₂ 47.2 mmHg, pH 7.368, and base excess 1.7 mmol/L. At 29 years of age, the results of her blood-gas values were pO₂ 71 mmHg, pCO₂ 43 mmHg, pH 7.39, base excess 0.9 mmol/L, and her respiratory insufficiency was thought to have been exacerbated over time be-

cause of her obesity. Following a six-minute walk, her SpO₂ measured by a pulse oximeter showed a decrease from 96% to 64%. The results of the pulmonary function tests were vital capacity 80.5%, forced expiratory volume in one second 98.6%, and diffusing capacity for carbon monoxide 68.6%.

She had been hospitalized several times for weight reduction and had been surveyed for obesity. At 23 years of age, she received a 1 mg overnight dexamethasone suppression test, and her plasma cortisol level was suppressed at <1.8 μ g/dL. There were no particular abnormalities in her abdominal CT. There was no episode of hypoglycemia. Since her dietary intake was approximately up to 5,000 kcal/day, her obesity was thought to come from hyperphagia, but she did not fully meet the ICD-10 criteria. Furthermore, during her hospitalization, since Melanocortin 4 receptor (MC4R) deficiency is reported to be related to obesity (15), we sequenced the coding region of the MC4R gene from genomic DNA isolated from whole-blood samples, but no gene mutation was observed.

After hospitalization, we started exercise therapy mainly using her upper extremities because of her knee pain, and a diet menu of consisting 1,600 kcal/day, which was the least calorie intake which she considered possible to continue. She had received mazindol, boku-tsusho-san (16), and dietary restriction within hospitalization in her past, but her weight consistently rebounded back to 180-200 kg. We tried metformin up to 1,500 mg/day and fluvoxamine up to 300 mg/day respectively, but these regimens were discontinued since no appetite regulation was observed. For her respira-

Table 2. Changes before and after the Operation

Days from surgery	Day -449	Day -1	Day 9	Day 77	Day 107	Day 310
Weight (kg)	182.7	154		137.7	137.2	136.7
BMI (kg/m ²)	83.2	70.1		62.7	62.5	62.2
Waist circumference (cm)	160	161		144.5	144.8	128
Active Ghrelin (fmol/mL)	7*	4	< 3	< 3	< 3	4
Des-acyl Ghrelin (fmol/mL)	42*	58	20	23	23	21
GIP (pg/mL)		29		19.1		
GLP-1 (pmol/L)		< 2.0**		< 2.0**		2.5***
				< 2.0***		
PAI-1 (ng/mL)		64	74	23	19	27
Leptin (ng/mL)	57.6*	33.5	24.1	25.9	25.3	29.7
Total adiponectin (μg/mL)	8.9*	6.1	6.3	7.1	5.6	5.4
High molecular adiponectin (μg/mL)	2.0*	2.4	2.6	2.9	2.5	2.5
TSH (μIU/mL)		2.6			2	
free T3 (pg/mL)		3.1			3.2	
free T4 (ng/dL)		1.2			1.3	
GH (ng/mL)		0.21	0.22	0.1	0.41	0.8
IGF-1 (ng/mL)		162.7	98.7	132.7	141	183.8
ACTH (pg/mL)		69.9	27.3	35.4	38.9	30.8
Cortisol (μg/dL)		15	8	6.4	8.4	12
LH (mIU/mL)		5.2	4.6	6	1.5	7.6
FSH (mIU/mL)		4.3	5.1	8.2	2.4	8.3
DHEA-S (ng/mL)		2,770	2,918	2,206	2,246	2,243
Estradiol (pg/mL)		64.8	89.8	46	90.6	36.1
Progesterone (ng/mL)		< 0.1	< 0.1	< 0.1	3.2	< 0.1
Testosterone (ng/dL)		108.1	83.3	83.5	77.5	102.6
Prolactin (ng/mL)		21.7	28.8	14.6	18.9	12.9
Transferrin (mg/dL)	271.4	209.7	168.4	193.2	179.8	221.8
Retinol binding protein (mg/dL)	2.0	2.2	1.1	2.3	2.2	2.8
Transthyretin (mg/dL)	13.7	16.6	6.6	17.4	17.4	22.3
HbA1c (%)	6.1	5.9		5.6	5.7	5.7
Insulin (μU/mL)		9.3	8.5	11.2	6.6	13
C peptide (ng/mL)		3.1	3.7	2.8	2.2	
Fasting plasma glucose (mg/dL)		91	87	87	83	89
HOMA-R		2.09	1.83	2.41	1.35	2.86

ACTH, adrenocorticotrophic hormone; BMI, body mass index; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin like growing factor-1; GIP, Gastric inhibitory peptide; GLP-1, Glucagon like peptide 1; HOMA-R, homeostasis model assessment ratio; LH, luteinizing hormone; PAI-1, plasminogen activator inhibitor-1; TSH, thyroid stimulating hormone.

*399 days before the operation.

**The data are for reference purpose only, since the blood samples were incubated with EDTA-2Na, and no DPP-4 inhibitor was loaded.

***Samples were incubated with DPP-4 inhibitor.

tory insufficiency, since she had mask intolerance during continuous positive airway pressure, we started biphasic positive airway pressure (17).

BioEnterics Intragastric Balloon was tried with the expectation of preoperative weight reduction. It was not, however, effective, and her weight stayed at 190-200 kg. Because surgical treatment was thought necessary to treat her obesity, she underwent dietary restriction for 750-800 kcal/day as an inpatient, and her weight was reduced to 154 kg for the operation.

Finally, we conducted a laparoscopic sleeve gastrectomy. The changes in weight, waist circumference, HbA1c, active ghrelin levels, des-acyl ghrelin levels, gastric inhibitory peptide (GIP) levels, glucagon-like peptide-1 (GLP-1) levels,

plasminogen activator inhibitor-1 (PAI-1) levels, leptin, total adiponectin, high molecular adiponectin, transferrin, retinol binding protein, and transthyretin are shown in Table 2. The blood samples were collected under fasting conditions. The value for HbA1c (%) is estimated as an NGSP equivalent value (%) calculated by the formula $HbA1c\ (%) = HbA1c\ (JDS)\ (%) + 0.4\ %$, considering the relational expression of $HbA1c\ (JDS)\ (%)$ measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) (18). Her bodyweight was decreased to 137 kg, waist circumference from 161 cm to 144.5 cm, and she has maintained her weight within the 130-140 kg range without rebounding for 2 and a half years. We also assessed hunger, satiety, fullness and food consumption by visual analogue

Table 3. The Results of 75 g Oral Glucose Tolerance Tests

Year of age		0 min.*	30 min.	60 min.	120 min.	HOMA-R	Insulinogenic index	Weight (kg)
19	PG	88	170	150	121	5.2	3.0	116
	IRI	24	270	220	120			
23	PG	85	171	176	103	4.4	1.6	145
	IRI	21	160	210	64			
24	PG	81	150	163	118	3.6	1.3	135
	IRI	18	110	87	60			
27	PG	86	151	173	123	1.9	1.1	178
	IRI	9.3	81	95.2	59.7			
33	PG	91	130	136	102	2.4	0.92	182
	IRI	10.5	47.1	26.4	25.4			
34**	PG	89	169	146	83	2.9	1.5	137
	IRI	13.0	130.1	68.7	12.8			

HOMA-R, homeostasis model assessment ratio; IRI, insulin ($\mu\text{U/mL}$); PG, Plasma glucose (mg/dL).

*min., minutes after 75 g oral glucose tolerance test.

**310 days after surgery.

scores (VAS) (19), 10 cm length with words at each end, expressing the most positive or most negative rating. Before and after the operation, the rating of VAS changed as follows: hunger; 9.9 cm to 8.2 cm, satiety; 2.3 cm to 9.9 cm, fullness; 9.8 cm to 7.3 cm, and food consumption; 9.8 cm to 1.8 cm. Though a secondary operation such as laparoscopic Roux en Y gastric bypass or biliopancreatic diversion with duodenal switch had been planned after weight reduction, she did not wish to take further treatment because she was satisfied with the improvement of her quality of life together with the reduction of the knee pain and shortness of breath.

Active ghrelin was at a low level before the operation, which was maintained after the surgery. Des-acyl ghrelin decreased after the operation. The GIP level decreased after the operation. The GLP-1 level before the operation is given for reference only, since we could not load a DPP-4 inhibitor into the blood sample. The GLP-1 level increased from day 77 to day 310 after the operation. Total PAI-1 and leptin levels declined after the operation. Total adiponectin and high molecular adiponectin did not markedly change before and after the operation. After the operation, an increase in transferrin, transthyretin, and retinol-binding protein was observed. In the 75 g oral glucose tolerance tests, from 1994 to 2008, though she was not diagnosed as having diabetes, the insulinogenic index showed a decrease. At 8 months postoperatively, an increase in the insulinogenic index was observed (Table 3).

Discussion

In this case of a morbidly obese Japanese woman, treatment with mazindol, bofu-tsusho-san, dietary restriction, metformin, and fluvoxamine or insertion of a BioEnterics Intragastric Balloon were all ineffective, and her weight remained at 190-200 kg. After sleeve gastrectomy, she has maintained her weight within the 130-140 kg range. Although our patient is still overweight, her weight gain has stopped, and no rebound has been seen in the 2 and a half

years after the operation. Mazindol and bofu-tsusho-san (16) are available in Japan for obesity treatment under the national insurance system, but they were not effective. Neither orlistat nor sibutramine are covered by the Japanese insurance system. At the time before the operation, metformin was the only antidiabetic agent available which was expected to have effect on weight reduction. The evidence for metformin in obesity is insufficient (20), and few studies have reported the effect of metformin on obesity (21, 22). In the present case, neither metformin nor fluvoxamine were affective to alter her appetite. As it has been previously reported (2-6), for morbidly obese patients, surgery seems to be the only treatment with a long-term effect. Albuminuria was observed, and has been reported that obesity with visceral fat is related to renal function (23). In the present case, we could not measure the visceral fat volume since the CT scan was unable to cover the full abdominal area. Though the elevation of CRP may have been the result of the dermatitis observed in her lower abdomen, it has also been reported that CRP is related to low adiponectin and high PAI-1 (24), and there may be some association.

Ghrelin is likely to be present in gastric endocrine cells, and it has been reported that a gastric bypass is associated with markedly suppressed ghrelin levels, possibly contributing to the weight-reducing effect (25, 26). Two major forms of ghrelin, ghrelin and des-acyl ghrelin exist (27), and the nutritional state is determined by plasma ghrelin (28). In the present case, des-acyl ghrelin levels decreased in the fasting phase after sleeve gastrectomy, and active ghrelin maintained the same low levels before and after the surgery. Though the acylated form of ghrelin has been reported to have an effect, close to 90% of the total ghrelin is des-acyl ghrelin, and recently des-acyl ghrelin has been reported to function in dietary regulation (29, 30). The meaning of the reduction in des-acyl ghrelin levels still remains controversial, though this may be one of the reasons our patient is maintaining her weight without rebounding.

GIP and GLP-1, a hormone synthesized by the intestinal mucosa in response to food and rapidly inactivated by serine

protease dipeptidyl-peptidase (31), has been reported to increase after bariatric surgery (11, 32, 33). In the present case, though the GLP-1 level measured before the operation is for reference only, the GLP-1 level showed a small elevation, and the GIP levels decreased. We only measured GIP and GLP-1 in fasting states, and this may be the reason for these changes.

PAI-1, which is thought to be synthesized and released from the liver, endothelial cells, and fat cells (34), is reported to be positively associated with obesity and insulin resistance, and could be reduced with weight loss (35, 36). In the present case, the decline of PAI-1 level may come from the reduction of fat cells due to weight reduction and improvement of insulin resistance.

Leptin is a fat cell derived circulating factor which regulates nutrient intake and metabolism (37-39), and has a positive relation with BMI (40). In the present case, the level of leptin may be relatively low for the BMI, and showed a decline after the operation. The decrease in leptin after the operation was thought to due to reduction of the excretion from the adipocytes. It has been reported that hypoadiponectinemia is associated with insulin resistance (41), though in the present case, adiponectin levels were within the normal range (42), and did not remarkably change after the operation compared with before. This may be one of the factors that she is maintaining her normal glycemia and lipid profiles despite her continued obesity. Though an increase in TSH levels has been reported in the morbidly obese (43), the levels of TSH, fT3 and fT4 in the present case were in normal range and did not change postoperatively.

Growth hormone (GH) secretion is influenced by body composition, and in patients with obesity, GH production peaks are few and suppressed (43-45). Also, it has been reported that GH is stimulated by ghrelin (46, 47). In obesity, insulin-like growth factor-1 (IGF-1) levels are normal or in the upper levels, and this is thought to be a product of over nutrition and high insulinemia. Low GH levels are thought to come from IGF-1 feedback. In the present case, the GH and IGF-1 levels were normal for her age, and the GH level showed a rise after the operation. The reduction of body weight may be the reason behind the GH elevation.

It has been reported that hyperprolactinemia is associated with obesity, and that the prolactin level decreases after bariatric surgery (48). In the present case, though the prolactin level before the operation was within the normal range, it showed a decrease after the operation. It has also been reported that spontaneous adrenocorticotrophic hormone (ACTH) secretion is enhanced in menopausal women with obesity, whereas cortisol production is within the normal range (49), and that an amplified ACTH drive is accompanied by decreased secretory regularity and diminished forward coupling of ACTH and cortisol (50). In the present case, the ACTH level decreased after the operation, the cortisol level did not show any constant change, and the decrease in ACTH may have come from weight reduction after

the operation.

In obesity, the conversion of androgen to estrogen is accelerated in the adipose tissues, the reduction of sex hormone binding globulin is observed, and in women, estrogen and androgen levels are elevated (51). In this case, levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEA-S), estradiol, and progesterone were within the normal range, and the testosterone level increased. In the present case, the increase in the testosterone level may have been the reason for the menstrual irregularity.

Increases in transferrin, transthyretin, retinol-binding protein were observed. The cause of these nutritional deficiencies in overweight and obese individuals is not completely known, but in the large part is likely due to a higher intake of higher-calorie processed foods associated with poor nutritional quality, particularly in highly developed countries in which there is an abundance of relatively cheap, high-calorie, but nutrient-poor food (52).

HbA1c levels did not change after the operation compared with the preoperative levels. Insulin, C peptide, and HOMA-R showed no consistent changes comparing levels before and after the operation. Importantly, in the 75 g oral glucose tolerance tests, the insulinogenic index kept decreasing until the sleeve gastrectomy, and showed a rise after the operation. It has been reported that in diabetic patients, restoration of insulin secretion, improvement of insulin sensitivity and HOMA-R are observed after a sleeve gastrectomy (32, 53), and it has also been reported that ghrelin may regulate islet function (54). In the present patient, though insulin resistance was observed, she had not been diagnosed as having diabetes, probably because of excess insulin secretion, and the changes reported in preceding studies were not apparently observed.

The present case provides important issues in obesity surgery for the morbidly obese in Japan. For morbidly obese patients, complications within obesity are progressive, and physicians should not miss the opportunity to inform patients of the surgical treatment options.

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

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