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CASE REPORT

Effects of Exenatide in a Morbidly Obese Patient with Type 2 Diabetes

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ABSTRACT

Introduction: The effect of exenatide in weight loss has been reported. Presented here is a case of a morbidly obese patient with type 2 diabetes using exenatide who dramatically lost her body weight in a year and experienced improved glycemic control.

Case report: Exenatide therapy was initiated for a 59-year-old morbidly obese Japanese woman with type 2 diabetes. To examine the effects of the exenatide treatment, continuous glucose monitoring was performed, and blood was drawn at 0, 30, 60, 120, and 180 min after breakfast to measure insulin, glucagon, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP) levels. After 1 year of exenatide therapy, the patient lost 37.5 kg, her glycemic control improved, and her insulin sensitivity recovered. The patient's levels of insulin, glucagon, active GLP-1, and total GIP also decreased after 1 year of exenatide treatment.

Conclusion: The exenatide treatment was effective for reducing body weight and improving glycemic control. After 1 year of exenatide treatment, decreased glucagon, active GLP-1, and total GIP levels were observed following a meal, suggesting that exenatide might affect these hormonal reactions.

Keywords: Exenatide; Glucagon; Glucose-dependent insulinotropic peptide; Glucagon-like peptide-1; Insulin sensitivity; Type 2 diabetes mellitus

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INTRODUCTION

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. The World Health Organization (WHO) estimates that at least 2.8 million adults die each year as a result of being overweight or obese and that 44% of the diabetes burden, 23% of the ischemic heart disease burden, and 7–41% of the burden associated with certain cancers are attributable to overweight and obesity [1].

Links between obesity and diabetes have been firmly established [2–4]. In obesity, visceral fat secretes adipocytokines such as tumor necrosis factor-α (TNF-α) [5] and resistin [6], resulting in insulin resistance, which then progresses to impaired insulin secretion. Weight reduction can attenuate the abnormal adipocytokine secretion and may improve insulin resistance and glucose metabolism [7]. Therefore, weight loss can be used as a therapeutic treatment for patients with obesity-induced diabetes; however, if the desired weight loss is not achievable, medication for diabetes management is necessary in addition to weight management.

Gut peptides, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted in a nutrient-dependent manner and stimulate glucose-dependent insulin secretion [8, 9]. Exenatide, a GLP-1 analog, is a new class of antidiabetic drug that potentiates glucose-dependent insulin secretion, lowers serum glucagon levels, slows gastric emptying, and may promote weight loss by increasing satiety [10–13]. The effect of exenatide in weight loss has been reported, with considerable variation in the amount of weight that is lost [14–23].

This case report presents a case of a morbidly obese patient with type 2 diabetes using exenatide who successfully lost 37.5 kg of body weight in a year and experienced improved glycemic control. To assess the efficacy of this drug, we also report hormonal changes in insulin, glucagon, GLP-1, and GIP levels before and after the exenatide treatment.

CASE REPORT

History of Obesity and Diabetes

A 59-year-old Japanese woman began experiencing weight gain at the age of 38 years due to overeating in response to mental stress. When she was 48 years old, she retired from work because of a disc herniation; as a result, she spent most of her time at home, decreased her physical activity, and gained additional weight. At the age of 49 years, her body weight reached 153 kg [height 156.2 cm, body mass index (BMI) 62.7 kg/m^2]. Hormonal examinations revealed that she was unlikely to have endocrinological diseases such as Cushing's disease or hypothyroidism. Her HbA1c level was 8.8% at this time, and she was admitted to the hospital for obesity and glucose management. After 15 weeks in hospital with a dietary intake of 1,200 kcal per day, her weight was successfully reduced to 131.2 kg (BMI 53.9 kg/m^2) and her HbA1c level also decreased to 6.5%. However, after discharge, she gradually regained weight to 163.0 kg (BMI 66.8 kg/m^2) and her HbA1c level increased to 9.3%. Thereafter, she repeatedly gained and lost weight and required ongoing weight management support. In 2010, at the age of 55 years and a weight of 144.1 kg (BMI 59.1 kg/m^2), she required a total dosage of 36 units of insulin by injection, and her glycemic control was poor (HbA1c 10.5%). However, as she gradually reduced her weight again to

121 kg (BMI 49.6 kg/m^2), her total dosage of insulin also decreased to 28 units. Finally, at a body weight of 114 kg (BMI 46.7 kg/m^2), she could maintain an HbA1c level of 6.6% without the use of medication, including insulin injections.

Previous weight management strategies included the use of the anti-obesity drug mazindol, a very low calorie diet (800 kcal/day), and counseling by a psychotherapist. Exercise therapy was restricted to the upper part of the body because of knee pain resulting from weight-induced osteoarthritis. While the aforementioned strategies were effective during a hospital admission, they did not result in long-term weight loss after discharge. Gastric surgery (e.g., sleeve gastrectomy) was also considered, but it was not performed due to her inability to cover the medical expense and the presence of renal dysfunction [eGFR, 21.8 mL/(min·1.73 m^2)].

Administration of Exenatide

Following the patient's weight reduction in March 2011 to 112.1 kg (BMI 45.9 kg/m^2), she regained her weight and more to reach 133.8 kg (BMI 54.8 kg/m^2) in August 2012, and her HbA1c level was 8.2%. Therefore, exenatide therapy was commenced with 5 μg injected twice a day within the 60 min before the morning and evening meals. The goals of this therapy were glycemic control and weight loss. In August 2013, following 1 year of exenatide therapy, her weight was 96.3 kg (BMI 39.5 kg/m^2).

Glucose metabolism was assessed at 3 occasions (March 2011, August 2012, and August 2013) with a continuous glucose monitoring system (CGMS) (CGMS®-GOLD™; Medtronic MiniMed, Northridge, CA, USA), and measurements of serum insulin and plasma glucagon were conducted using blood samples that were drawn at 5 time points (0, 30, 60, 120, and 180 min) after breakfast following a 14-h overnight fast.

In addition, to assess the changes in incretin markers before the exenatide treatment, baseline active GLP-1 and total GIP levels were also measured at the 5 time points after breakfast in August 2012. To assess the effect of the exenatide treatment over 1 year, a washout period (5 days without exenatide) was conducted prior to the assessment in August 2013, and active GLP-1 and total GIP levels were measured at the same 5 time points after breakfast. Blood samples for the determination of active GLP-1 and total GIP levels were collected into BD™ P800 tubes (Becton-Dickinson, Franklin Lakes, NJ, USA) containing spray-dried K_2EDTA anticoagulant and a proprietary cocktail of protease, esterase, and dipeptidyl peptidase 4 (DPP-4) inhibitors. The area under the curve (AUC) values for continuous glucose monitoring (CGM) measured glucose, insulin, glucagon, active GLP-1 and total GIP levels, after meal ingestion, were calculated using the trapezoidal rule.

For all occasions, total caloric intake was maintained at 1,600 kcal per day (breakfast 365–410 kcal). To assess the minimum amount of energy required by the patient, her resting metabolic rate (RMR) was measured using a FitMate metabolic system (Cosmed, Rome, Italy).

Finally, to evaluate the levels of insulin resistance and insulin secretion in this patient, the homeostasis model assessment of insulin resistance (HOMA-IR) and the homeostasis model assessment of β cell function (HOMA-β) were done [24, 25]. In addition, the quantitative insulin-sensitivity check index (QUICKI) was calculated using the standard formula: 1/[log (glucose) + log (insulin)] [26].

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from the patient for being included in the study.

RESULTS

During the periods of exenatide administration, the patient experienced mild gastrointestinal symptoms such as nausea and appetite loss; however, these adverse effects were not serious enough to cease the exenatide therapy. Changes in body weight, BMI, HbA1c levels, RMR, HOMA-IR, HOMA-β, and QUICKI at the 3 measurement points (March 2011, August 2012, and August 2013) are shown in Table 1. As weight was lost, the RMI and HOMA-IR reduced while QUICKI values increased. The value of HOMA-β decreased in August 2012 after the weight gain and did not change following the weight loss in August 2013.

Table 1 Anthropometric and glucose metabolism parameters at 3 time points

Parameter	2011 Mar	2012 Aug[a]	2013 Aug
Body weight (kg)	112.1	133.8	96.3
BMI (kg/m^2)	45.9	54.8	39.5
HbA1c (%)	6.0	8.2	5.1
RMR (kcal/day)	1,732	2,331	1,618
HOMA-IR	1.08	4.89	1.29
HOMA-β (%)	95.4	55.7	57.2
QUICKI	0.201	0.082	0.195

BMI body mass index, *RMR* resting metabolic rate, *HOMA-IR* homeostasis model assessment ratio, *HOMA-β* homeostasis model assessment β cell function, *QUICKI* quantitative insulin-sensitivity check index

[a] Exenatide treatment commenced (5 μg injected twice a day within the 60 min before the morning and evening meals) and continued until August 2013

Figure 1 shows the fluctuations in glucose levels measured by CGM. The average ± standard deviation (SD) of the CGM measurements for each of the three occasions (March 2011, August 2012, and August 2013) was 119.7 ± 7, 197 ± 16, and 117 ± 7 mg/dL, respectively, reflecting the attenuation of glucose fluctuations with weight loss.

Time-dependent changes in serum insulin, plasma glucagon, active GLP-1, and total GIP levels are shown in Fig. 2. The AUC values of these hormones up to 3 h after the meal ingestion are summarized in Table 2. Compared to August 2012, the insulin levels and insulin AUC values were lower at each measurement in March 2011 and August 2013 (Fig. 2a). Glucagon levels and glucagon AUC values at each measurement were lower in August 2013 compared to those in March 2011 and August 2012 (Fig. 2b). The active GLP-1 and total GIP levels decreased at all of the measurement points in August 2013 compared to those in August 2012 (Fig. 2c, d).

DISCUSSION

Although substantial lifestyle changes, such as an increase in physical activity and dietary modifications, are essential and effective for obesity management; low compliance results in a need for pharmacological or surgical intervention in some cases. For the patient in this report, dietary modifications, exercise, and a pharmacological intervention were not effective, and surgical intervention was not an option. However, the use of exenatide contributed to a 37.5 kg weight loss and improved glycemic control in the patient. This improvement in glycemic control was related to both the weight loss and exenatide therapy;

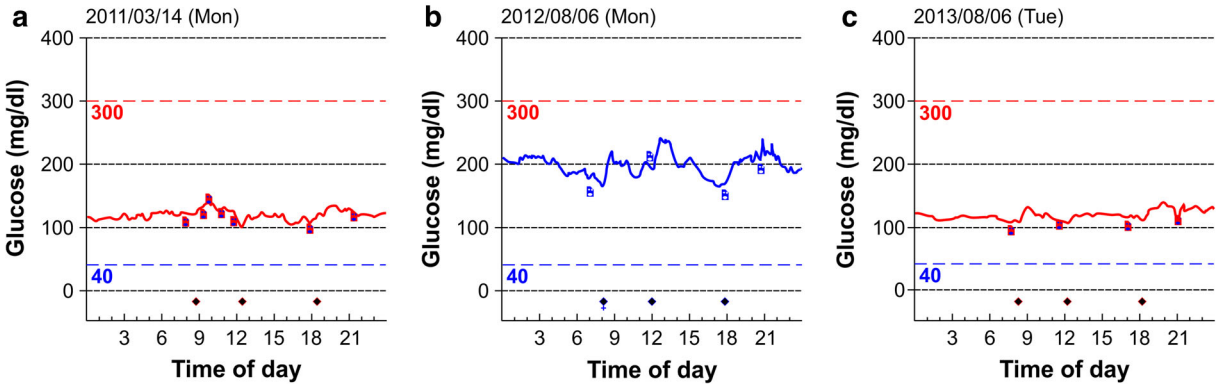

Fig. 1 The results of continuous glucose monitoring (CGM) in a morbidly obese female patient with type 2 diabetes in March 2011 (**a**), August 2012 (**b**), and August 2013 (**c**). Exenatide treatment commenced (5 μg injected twice a day within the 60 min before the morning and evening meals) in August 2012 and continued until August 2013. *Marks* on the *lines* indicate a calibration of the CGM system, and the *marks* at the *bottom* of the figures indicate the three meals

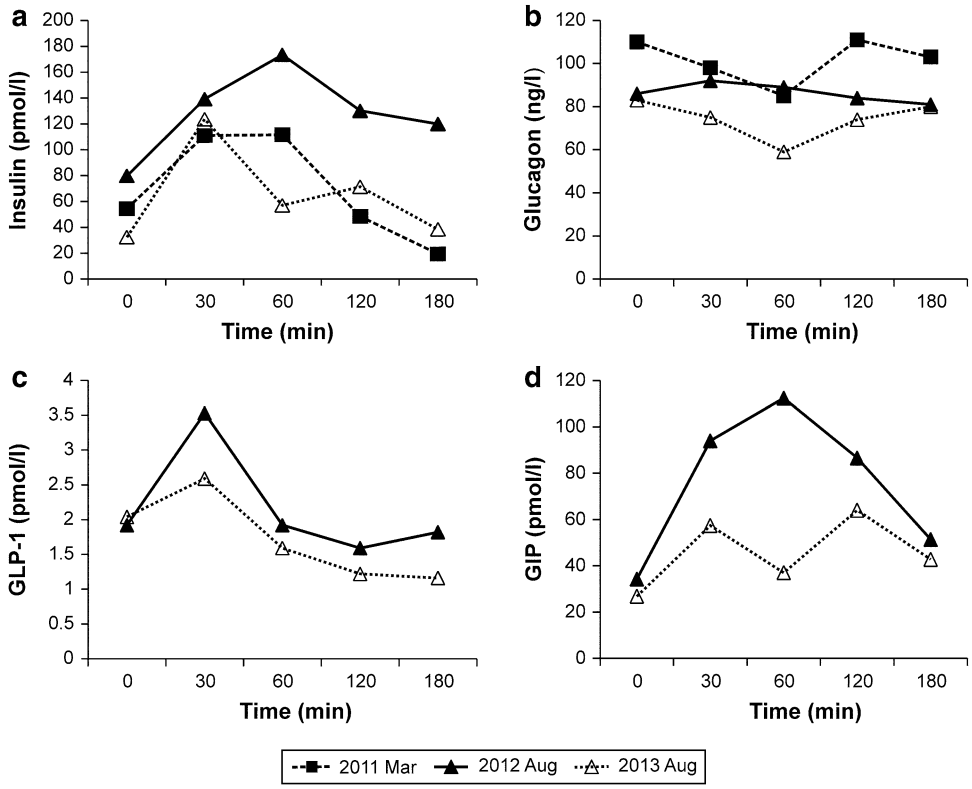

Fig. 2 Time course of insulin (**a**), glucagon (**b**), active glucagon-like peptide-1 (GLP-1) (**c**), and total glucose-dependent insulinotropic polypeptide (GIP) (**d**) levels before and after food intake in a morbidly obese female patient with type 2 diabetes. The *filled squares* indicate results in March 2011, the *filled triangles* indicate the results in August 2012, and the *clear triangles* indicate the results in August 2013. Exenatide treatment commenced (5 μg injected twice a day within the 60 min before the morning and evening meals) in August 2012 and continued until August 2013

Table 2 Area under the curve (AUC) values for the 3 h after breakfast

Parameter	2011 Mar	2012 Aug[a]	2013 Aug
Glucose (CGM) (10^3 × mg/dL·3 h)	23.4	34.9	21.4
Insulin (10^3 × pmol/L·3 h)	12.7	24.6	12.2
Glucagon (10^3 × ng/L·3 h)	18.2	15.5	13.0
GLP-1 (active) (10^2 × pmol/L·3 h)	N/A	3.7	2.9
GIP (total) (10^3 × pmol/L·3 h)	N/A	15.1	8.9

CGM continuous glucose monitoring, *GIP* glucose-dependent insulinotropic polypeptide, *GLP-1* glucagon-like peptide-1, *N/A* not available

[a] Exenatide treatment commenced (5 μg injected twice a day within the 60 min before the morning and evening meals) and continued until August 2013

however, the exenatide injections were ceased for the 5 days before the assessment in Aug 2013. Therefore, weight loss is likely to be the primary reason for the observed changes.

The fluctuations in the post-prandial insulin levels displayed in the patient were related to the changes in her weight; when her weight was higher (133.8 kg), the insulin levels increased, and when her weight was lower (112.1 and 96.3 kg), the insulin levels decreased. This relationship indicated that the level of insulin resistance decreased, and the hyperinsulinemia was ameliorated.

Glucagon levels decreased after 1 year of exenatide therapy, despite the decrease in glucose levels. Although GLP-1 is a powerful suppressor of glucagon secretion, a decrease in glucose levels should result in increased glucagon secretion. The balance of these phenomena may lead to a decrease in glucagon secretion. Secretion of GLP-1 is generally impaired in obesity [27] resulting in a reduction in the circulating GLP-1 levels in obese patients [10, 28, 29]. Moreover, the GLP-1 response to oral stimulation has been negatively correlated with BMI [27, 29], and weight loss is associated with an increased GLP-1 response to meal ingestion [28]. However, in this case report, the patient's GLP-1 levels were reduced at all of the post-prandial measurements following the exenatide treatment. This may be due to the decreased glucose levels because GLP-1 is secreted in a glucose-dependent manner. In addition, the effect of exenatide on gastric emptying or the inhibitory feedback for GLP-1 secretion may explain the reduction in GLP-1 levels [14, 30]. The post-prandial total GIP levels were also decreased in the patient following exenatide therapy. The potential reason for this is unclear, but it might be attributed to the reduction in glucose levels. Measurements of active GIP in future studies may provide more insight into this relationship.

Islet β cell failure in type 2 diabetes occurs when the islets are unable to sustain β cell compensation in the presence of insulin resistance. Weight loss often improves islet β cell function in association with reductions in insulin resistance [31, 32]. However, the islet β cell failure may be progressive and, therefore, not recoverable, particularly after hyperglycemia is established, which leads to poorly functioning, de-differentiated β cells, and a loss of β cell mass from apoptosis [33]. Preclinical studies provide strong evidence that exenatide plays an important role in the maintenance of β cell mass and function by increasing the expression of key β cell genes, stimulating islet cell proliferation and neogenesis, and inhibiting islet cell apoptosis [13]. However, human β cells appear to be much less responsive to proliferative agents such as GLP-1 compared to rodent β cells [34], and β cell replication is substantially diminished in older human subjects [35]. This may explain the changes observed in the HOMA-β values in the patient, which indicated that the ability to secrete insulin was not

recovered following exenatide treatment and concurrent weight loss.

Peptide $YY_{3–36}$ [36], leptin [37–40], resistin [6], and ghrelin [41] are the hormones that modulate appetite and affect food intake. The levels of these hormones were not measured; however, they may contribute to understanding the extreme weight loss by exenatide in the patient.

A previous study [42] demonstrated that 1 year of exenatide treatment significantly improved β cell function and decreased body weight in the presence of similar improvements in glycemic control, when compared with insulin glargine treatment. However, after cessation of the exenatide therapy, these beneficial effects were not sustained, suggesting that ongoing treatment is necessary for exenatide to be effective. Similarly, in the present study, the patient's appetite recovered after ceasing exenatide treatment, and she regained 3 kg within the following 2 months.

The treatment with another type of GLP-1 receptor agonist, liraglutide, led to weight loss in overweight or obese patients with or without type 2 diabetes [43–47]. In addition, the current phase 3, randomized, controlled trial demonstrates the efficacy of liraglutide 3.0 mg per day, combined with lifestyle modification, in facilitating the maintenance of clinically meaningful weight loss; thus, liraglutide holds promise as an anti-obesity drug [48]. Moreover, a once-weekly formulation of exenatide was developed recently, and patients treated with once-weekly exenatide showed better glycemic control with sustained overall weight loss than patients treated with insulin glargine [49, 50]. Therefore, these drugs can be an alternative option for patients such as the one described in this case report.

In conclusion, 1 year of exenatide treatment was effective for reducing body weight and improving glycemic control in a 59-year-old morbidly obese woman with type 2 diabetes. At the same time, her insulin sensitivity recovered but the ability to secrete insulin did not recover. After 1 year of exenatide treatment, decreased glucagon, active GLP-1, and total GIP levels were observed following a meal, suggesting that exenatide might affect these hormonal reactions.

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Conflict of interest. Miyako Kishimoto declares that she has no conflict of interest. Mitsuhiko Noda has received speaker honorarium from Drug Company Astrazeneca.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. Informed consent was obtained from the patient for being included in the study.

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