Evaluation of the Effects of Exenatide Administration in Patients with Type 2 Diabetes with Worsened Glycemic Control Caused by Glucocorticoid Therapy

Koji Matsuo, Takuo Nambu, Yuki Matsuda, Yugo Kanai, Shin Yonemitsu, Seiji Muro and Shogo Oki

Abstract

Glucocorticoid-induced hyperglycemia is common in patients with or without known diabetes mellitus. Exenatide, a glucagon-like peptide-1 receptor agonist, improves glycemic control without causing weight gain or hypoglycemia and is currently widely used in patients with type 2 diabetes mellitus. We herein report four cases of patients with type 2 diabetes with worsened glycemic control due to glucocorticoids who were successfully treated with exenatide administration.

Key words: diabetes mellitus, glucocorticoids, incretin

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Introduction

Glucocorticoids (GCs) are widely prescribed to treat autoimmune and malignant diseases due to their anti-inflammatory and immunosuppressive effects (1). However, in addition to their desired effects, GCs are known to be associated with several adverse effects (2). Of these, GC-induced hyperglycemia is common in patients with or without known diabetes mellitus, as GCs cause increases in plasma glucagon concentrations, impaired glucose uptake and decreased insulin secretion (3-7). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, improves glycemic control through various mechanisms such as promoting glucose-dependent insulin secretion, decreasing glucagon secretion, slowing gastric emptying and suppressing food intake. In addition, it is currently widely used in patients with type 2 diabetes mellitus (8). Moreover, the administration of a GLP-1 receptor agonist reportedly decreased the blood glucose levels in a patient with diabetes mellitus caused by Cushing’s disease (9). Exenatide has been reported to improve GC-induced hyperglycemia in healthy individuals as well (10); however, no reports have been published regarding the effectiveness of exenatide in patients with GC-induced diabetes mellitus. We herein present four cases of patients with type 2 diabetes whose glycemic control worsened due to GC therapy and who were successfully treated with exenatide administration.

Subjects and methods

Four patients with type 2 diabetes whose glycemic control was worsened by GC therapy were admitted to Osaka Red Cross Hospital (Osaka, Japan) and treated with exenatide (5 μg twice/day). The glycated hemoglobin (HbA1c) levels were defined according to National Glycohemoglobin Standardization Program (NGSP) standards. In Cases 1 and 2, the continuous blood glucose levels were recorded by the Continuous Glucose Monitoring System (CGMS) (CGMS Gold; Medtronic MiniMed, Northridge, CA, USA). The 24-hour glycemic variations, mean amplitudes of glycemic excursions (MAGE) and M-values were calculated as previously reported (11).

Ethics

Informed consent was obtained from all patients. This study was approved by the relevant ethics committee and was conducted in accordance with the Declaration of Helsinki.
hyperglycemia after lunch. In order to control the afternoon meal, once/day). Thereafter, CGMS showed marked postprandial hyperglycemia (>180 mg/dL) observed during 37.0% of the total monitoring time (Fig. 1A). Subsequently, liraglutide was substituted by exenatide (5 μg twice/day before breakfast and dinner starting on day 5, along with the continuation of metformin therapy (250 mg twice/day) and the addition of glitazide (20 mg once/day). Thereafter, CGMS showed marked postprandial hyperglycemia after lunch. In order to control the afternoon meal, the exenatide injections were modified from 5 μg twice/day before breakfast and dinner to 5 μg twice/day before breakfast and lunch starting on day 9. This modification suppressed the blood glucose spikes that occurred after lunch and improved the patient’s glycemic control. In addition, her mean blood glucose levels, M-values and MAGE also decreased (Table 2). Eventually, her blood glucose levels before each meal decreased to <150 mg/dL (Fig. 2A), and she was discharged from the hospital on day 13. Four months after initiating exenatide therapy, the patient’s HbA1c levels and body weight decreased along with her systolic blood pressure and low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels (Fig. 3).

Case 2

Our second case involved a 73-year-old man with a 4-year history of type 2 diabetes mellitus. He was on glimepiride and metformin therapy for two years until he was diagnosed with myasthenia gravis. GC therapy for myasthenia gravis induced poor glycemic control and multiple daily insulin injections were subsequently introduced into his drug regimen. One year after the initiation of insulin treatment, his weight increased from 57 kg to 60 kg. His HbA1c levels also gradually increased from 6.5% to 8.3%, and he was admitted to our hospital for re-evaluation of his diabetes status. On admission, his BMI was 22.2 kg/m² and his daily oral drug regimen included the following drugs: 7 mg of prednisolone (once/day after breakfast), 50 mg of losartan, 5 mg of amiodipine, 30 mg of lansoprazole and 500 mg of metformin. His insulin regimen included biphasic insulin aspart 70/30 at a dose of 10 units before breakfast and dinner and 14 units before lunch (i.e., 34 units/day). His clinical characteristics are listed in Table 1. Diet therapy (1,440 kcal/day) and an incremental increase in his insulin dose (38 units/day) lowered his blood glucose level to <130 mg/dL before each meal. He wanted to reduce the frequency of insulin injections; therefore, biphasic insulin aspart 70/30 was substituted with exenatide (5 μg twice/day) before breakfast and dinner starting on day 5, along with the continuation of metformin therapy (250 mg twice/day) and the addition of glitazide (40 mg once/day). However, CGMS indicated marked postprandial hyperglycemia after lunch (Fig. 1B); therefore, the exenatide injections were modified from 5 μg twice/day before breakfast and dinner to 5 μg twice/day before breakfast and lunch starting on day 8. Subsequently, this modification suppressed the large blood glucose spikes that occurred after lunch and improved the patient’s glycemic control. In addition, his mean blood glucose level, M-value and MAGE also decreased, as listed in Table 2. Eventually, his blood glucose level before each meal decreased to <130 mg/dL (Fig. 2B), and he was discharged from the hospital on day 14. Four months after the initiation of exenatide, the patient’s HbA1c level and body weight decreased along with his systolic blood pressure and LDL-C level (Fig. 3).

**Table 1. Characteristics of Present Four Cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (year)</th>
<th>BMI (kg/m²)</th>
<th>DM duration (year)</th>
<th>Fasting blood glucose (mg/dL)</th>
<th>HbA1c (%)</th>
<th>Gly-A (%)</th>
<th>Fasting CPR (ng/mL)</th>
<th>Delta CPR (ng/mL)</th>
<th>Urine CPR (mg/day)</th>
<th>Antihypertensive agents</th>
<th>Lipid-lowering agents</th>
<th>Diabetic retinopathy</th>
<th>Diabetic neuropathy</th>
<th>Urine albumin (mg/day)</th>
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<td>31.8</td>
<td>15</td>
<td>133</td>
<td>7.7</td>
<td>16.1</td>
<td>5.2</td>
<td>8.2</td>
<td>216</td>
<td>Yes</td>
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<td>No</td>
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<tr>
<td>Case 2</td>
<td>M</td>
<td>73</td>
<td>22.2</td>
<td>4</td>
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<td>8.3</td>
<td>24.4</td>
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<td>0.6</td>
<td>21</td>
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<td>No</td>
<td>No</td>
<td>12.1</td>
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<tr>
<td>Case 3</td>
<td>M</td>
<td>43</td>
<td>25.3</td>
<td>1</td>
<td>228</td>
<td>15.4</td>
<td>45.8</td>
<td>1.4</td>
<td>0.2</td>
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<td>No</td>
<td>No</td>
<td>53</td>
<td></td>
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<tr>
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<td>M</td>
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<td>28.0</td>
<td>20</td>
<td>203</td>
<td>8.7</td>
<td>22.3</td>
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<td>No</td>
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</tbody>
</table>


**Case Reports**

**Case 1**

Our first case involved a 63-year-old woman with a 15-year history of type 2 diabetes mellitus. She was on voglibose therapy (0.2 mg three times/day) until she received a diagnosis of rheumatoid arthritis two years previously. GC therapy for rheumatoid arthritis induced poor glycemic control, and subsequent multiple daily doses of insulin were introduced into the patient’s drug regimen to control her blood glucose levels. One year after the initiation of insulin treatment, her weight increased from 70 kg to 86 kg. Her insulin treatment was switched to liraglutide to avoid additional weight gain. One year after the initiation of liraglutide therapy, her weight decreased from 86 kg to 79 kg; however, her HbA1c level gradually increased from 6.5% to 7.7%. She was subsequently admitted to our hospital for re-evaluation of her diabetes status. On admission, her body mass index (BMI) was 31.8 kg/m² and her daily drug regimen included the following drugs: 7 mg of prednisolone (once/day after breakfast), 0.9 mg of liraglutide, 500 mg of metformin, 20 mg of glitazide, 20 mg of fluvasatin, 80 mg of valsartan, 4 mg of benidipine and 1 mg of indapamide. Her clinical characteristics are listed in Table 1. Initially, in addition to receiving diet therapy (1,840 kcal/day), she continued to take liraglutide at a dose of 0.9 mg; however, CGMS readings indicated poor glycemic control with hyperglycemic periods (>180 mg/dL) observed during 37.0% of the total monitoring time (Fig. 1A). Subsequently, liraglutide was substituted by exenatide (5 μg twice/day before breakfast and dinner) on day 6 along with oral hypoglycemic agents (metformin: 250 mg twice/day and glitazide: 20 mg once/day). Thereafter, CGMS showed marked postprandial hyperglycemia after lunch. In order to control the afternoon meal, the exenatide injections were modified from 5 μg twice/day before breakfast and dinner to 5 μg twice/day before breakfast and lunch starting on day 9. This modification suppressed the blood glucose spikes that occurred after lunch and improved the patient’s glycemic control. In addition, her mean blood glucose levels, M-values and MAGE also decreased (Table 2). Eventually, her blood glucose levels before each meal decreased to <150 mg/dL (Fig. 2A), and she was discharged from the hospital on day 13. Four months after initiating exenatide therapy, the patient’s HbA1c levels and body weight decreased along with her systolic blood pressure and LDL-C level (Fig. 3).
Our third case involved a 43-year-old man with a 1-year history of type 2 diabetes mellitus. His diabetes was well controlled with diet and exercise therapy until he was diagnosed with amyopathic dermatomyositis. GC therapy for amyopathic dermatomyositis induced poor glycemic control. His HbA1c level dramatically increased to 15.4% over the next six months, and he was admitted to our hospital for treatment of hyperglycemia. On admission, he weighed 80 kg with a BMI of 25.3 kg/m². His daily drug regimen included the following drugs: 10 mg of prednisolone (once/day after breakfast), 100 mg of allopurinol and 10 mg of rabeprazole sodium. His clinical characteristics are listed in Table 1. In addition to diet therapy (1,840 kcal/day), biphasic insulin aspart 70/30 at a dose of 16 units before breakfast, 22 units before lunch and 12 units before dinner (i.e., 50 units/day) was introduced to control his blood glucose levels. On day 10, the patient’s blood glucose levels were <120 mg/dL before each meal. He wanted to reduce the frequency of insulin injections; therefore, biphasic insulin aspart 70/30 was replaced with exenatide (5 μg twice/day) before breakfast and lunch on day 13, along with the addition of gliclazide (20 mg once/day). Eventually, his blood glucose level before each meal decreased to <130 mg/dL (Fig. 2C), and he was discharged from the hospital on day 16. Four months after the initiation of exenatide therapy, his HbA1c levels and body weight decreased dramatically to 5.9% and 64.5 kg, respectively; in addition, his TG levels decreased (Fig. 3).
**Case 4**

Our fourth case involved an 82-year-old man with a 20-year history of type 2 diabetes mellitus. His diabetes was well controlled with multiple daily insulin injections until he was diagnosed with rheumatoid arthritis three years previously. After the initiation of insulin therapy, his weight increased from 70 kg to 76 kg. GC therapy for rheumatoid arthritis induced poor glycemic control, and the patient’s HbA1c levels gradually increased from 7.5% to 8.7% over the preceding two years with repeated hypoglycemic attacks. He was admitted to our hospital for a re-evaluation of his diabetes status. On admission, he weighed 78 kg with a BMI of 28.0 kg/m². His daily oral drug regimen included the following drugs: 2 mg of prednisolone (twice/day, after breakfast and dinner), 10 mg of rabeprazole sodium, 100 mg of aspirin, 2 mg of pitavastatin calcium, 20 mg of cilnidipine, 12 mg of candesartan cilexetil and 1,000 mg of salazosulfapyridine. His insulin regimen included biphasic insulin aspart 70/30 at a dose of 24 units before breakfast, 14 units before lunch and 18 units before dinner (i.e., 56 units/day). His clinical characteristics are listed in Table 1. The addition of diet therapy (1,840 kcal/day) lowered his blood glucose levels before each meal decreasing to <150 mg/dL (Fig. 2D), and he was discharged from the hospital on day 13. Four months after the initiation of exenatide therapy, his HbA1c levels and body weight decreased dramatically to 6.9% and 68 kg, respectively; in addition, his LDL-C and TG levels reduced (Fig. 3).

**Discussion**

GCs are widely prescribed to treat autoimmune and malignant diseases due to their anti-inflammatory and immunosuppressive effects (1). In addition to their desired effects, GCs are known to cause several adverse effects such as gastric ulcers, hypertension, dyslipidemia and osteoporosis (2). Among these, GC-induced hyperglycemia is common in patients with or without known diabetes mellitus. Hyperglycemia is observed in 56% of patients treated with GCs who do not have a previous history of diabetes mellitus, and the odds ratio for new-onset diabetes mellitus in patients treated with GCs ranges from approximately 1.5 to 2.5 (1, 10).

GCs regulate glucose metabolism through their effects on muscles, adipocytes, the liver, the pancreas, etc. They inhibit insulin-stimulated glucose transport in muscles by impairing perfusion of insulin-sensitive glucose transporter (GLUT4) to the cell surface (4, 5). They promote gluconeogenesis by facilitating the expressions of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver (12), increasing plasma glucagon concentrations (3) and impairing.

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**Figure 2.** The four-point blood glucose profiles (before each meal and at bedtime) of the reported patients. The dotted lines indicate the mean blood glucose levels three days before the administration of exenatide (A: liraglutide: 0.9 mg, B: biphasic insulin aspart 70/30 at 38 units/day, C: biphasic insulin aspart 70/30 at 50 units/day, D: biphasic insulin aspart 70/30 at 56 units/day). The solid lines indicate the mean blood glucose levels after three days of administration of exenatide. M: morning, L: lunch, D: dinner, B: bedtime. The bars represent the mean ± SEM.
leads to increases in visceral adipose tissue exposure stimulates adipogenesis via phosphorylation of cyclic AMP response element-binding proteins in vitro (13). This leads to increases in visceral adipose tissue in vivo (14). Cumulatively, GCs impair glucose metabolism through the foregoing mechanisms. The treatment strategy for GC-induced diabetes mellitus is similar to that for type 2 diabetes mellitus. In addition to exercise and diet therapy, oral hypoglycemic agents are often prescribed for mild hyperglycemia; however, insulin injections are required to achieve acceptable glycemic control. In the treatment of GC-induced diabetes mellitus, although hyperglycemia is improved, weight gain is a common problem, especially in patients requiring insulin therapy. While insulin interacts with satiation signals and regulates meal size (15), it also decreases the rate of lipolysis in adipose tissue and accumulates adipocytes through inhibitory effects on hormone-sensitive lipase activity (16). In addition, defensive increases in caloric intake are caused by fear of episodes of hypoglycemia (17). As a result, excessive weight gain in patients receiving insulin therapy is often observed in routine care, as was demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS) (18). Weight gain increases insulin resistance, thus resulting in the need for higher insulin doses, thereby inducing weight gain in a vicious circle. Weight gain also induces insulin secretion by decreasing the glucose transporter (GLUT2) expression along with stimulating the transcription of serum- and GC-inducible kinase 1 (6, 7). Chronic GC exposure stimulates adipogenesis via phosphorylation of cyclic AMP and worsens hypertension and dyslipidemia and exerts adverse effects on these cardiovascular diseases (19).

Incretin-related drugs, a new class of anti-diabetic medications, are divided into two categories: GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. These drugs suppress glucagon secretion, confer β-cell protective effects and do not cause body weight gain (20). The aforementioned effects have not been observed with conventional drugs; therefore, incretin-related drugs are expected to provide an entirely new treatment option for patients with diabetes mellitus. Impairment of the incretin effect is reportedly one of the causes of GC-induced hyperglycemia (21, 22), and several studies have recently reported the efficacy of GLP-1 receptor agonists in treating GC-induced glucose intolerance. In one study, intravenous administration of a GLP-1 receptor agonist decreased the plasma glucose levels by stimulating insulin secretion and suppressing glucagon secretion in a patient with diabetes mellitus caused by Cushing’s disease (9). Continuous intravenous infusion of exenatide significantly improves GC-induced hyperglycemia in healthy individuals in association with restoration of initial insulin secretion and decreased glucagon concentrations (10). In addition, subcutaneous exenatide administration has been reported to lower the blood glucose levels in GC-induced glucose intolerant mice, resulting in decreased insulin resistance (23). Considering the above-mentioned mechanisms, we suggest the following reasons for the su-

Figure 3. Changes in body weight and metabolic parameters in the reported cases before and after the administration of exenatide. Pre: before the administration of exenatide, Post: four months after the initiation of exenatide therapy. HbA1c: glycated hemoglobin, sBP: systolic blood pressure, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride...
cessful use of exenatide in the four cases presented in this report: (i) restoration of the endogenous incretin effect; (ii) restoration of initial insulin secretion; and (iii) decreases in glucagon concentrations. In addition to improved glycemic control, exenatide treatment is associated with reduced hypoglycemia. It also promotes weight loss by reducing appetite by suppressing the elimination of gastric contents or acting on the central nervous system (8, 24). In these reported cases, before exenatide administration, the prescription of insulin for glycemic control improved the blood glucose levels per se; however, weight gain was observed in three cases (Cases 1, 2 and 4). In addition, one patient frequently experienced hypoglycemia (Case 4). Such disadvantages of insulin may be overcome by switching to exenatide, enabling satisfactory treatment of patients with diabetes. In addition to improving the blood glucose levels in patients with type 2 diabetes mellitus, exenatide has been reported to decrease the incidence of MAGE (an indicator of daily glycemic fluctuations) compared with sulfonylureas (25). Fluctuating blood glucose levels can have greater deleterious effects on endothelial function and oxidative stress when compared with consistently high blood glucose levels, resulting in macrovascular disease progression (26). In two of the reported cases (Cases 1 and 2), exenatide administered before breakfast and lunch lowered the incidence of MAGE as well as the M-values, which may inhibit the progression of macrovascular diseases.

The pharmacodynamics of GCs are characterized by significant elevations in the blood glucose levels in the afternoon and evening when oral prednisolone is given in the morning (27). The half-life of exenatide is 3.5 to 4 hours, and the drug is usually administered before breakfast and dinner as per the information regarding its prescription (28). In the present three cases (Cases 1-3), oral prednisolone was prescribed once/day after breakfast. We initially administered exenatide before breakfast and dinner; however, we detected postprandial hyperglycemia after lunch. Then, we modified the exenatide injections to occur before breakfast and lunch in order to suppress large glucose spikes after lunch. Likewise, the efficacy and safety of exenatide administered before the two largest meals in the day—lunch and dinner—were reported in 377 Latin American patients with type 2 diabetes mellitus (29). On the other hand, oral prednisolone is sometimes given in the morning and evening; therefore, it is possible that the blood glucose levels might rise before bedtime or the next morning. In fact, in Case 4, oral prednisolone was prescribed twice/day after breakfast and dinner. We decided to administer exenatide injections in the morning and evening, which resulted in good glycemic control. These results suggest that it may be necessary to adjust the timing of exenatide administration based on the blood glucose profile of each individual patient.

The improvements in the HbA1c levels and the body weight reduction observed in Case 3, which involved a young patient with a shorter diabetic history, were noteworthy. We recently reported that another GLP-1 analogue, liraglutide, is more effective in earlier stages of diabetes (30). Similarly, sitagliptin, the first oral DPP-4 inhibitor, is more effective in patients with a shorter duration of diabetes (31). Likewise, in patients whose glycemic control is worsened by GC therapy, it is plausible to consider that earlier intervention with exenatide is more effective as well as other incretin-related drugs.

There are some limitations to this report. First, the metabolic parameters dramatically improved in the reported cases (Fig. 3). However, these results were based on data collected four months after discharge from our hospital; therefore, hospitalization may have influenced the effects of exenatide treatment. Furthermore, in some patients in whom the HbA1c levels initially decreased, relapse was reported after six months of DPP-4 inhibitor therapy (32). Further studies are essential in order to observe the long-term effects of exenatide over a longer period of time, such as a year. Second, exenatide should not be considered a substitute for insulin, and a patient’s insulin-dependent status should be determined to gauge whether exenatide treatment is appropriate before administration (33). We recently reported that a switch from insulin to liraglutide may be associated with higher C-peptide immunoreactivity (CPR) levels (30). However, in the present report, most patients (Cases 2-4) were successfully treated, even those with low CPR levels. Although no definitive explanation can be provided for this, we speculate that the insulin used to avoid glucose toxicity lowered the CPR levels in these cases. Third, the reported downregulation of the GLP-1 receptor expression due to hyperglycemia indicates the ineffectiveness of exenatide under glucotoxic conditions (34). In the reported cases, we carefully administered exenatide after confirming that the blood glucose levels were lowered to approximately <150 mg/dL before each meal. Under glucotoxic conditions, physicians should avoid administering exenatide; it should be used only after lowered blood glucose levels have been confirmed. Furthermore, we administered exenatide to patients with known diabetes mellitus whose glycemic control was worsened by GC therapy. The effects of exenatide in patients with new-onset diabetes developing after the administration of GC therapy have not been confirmed. However, exenatide has been reported to improve GC-induced hyperglycemia in healthy individuals (10). Therefore, although an increased number of patient studies are needed to confirm this, exenatide is expected to be effective in patients with new-onset diabetes developing after the administration of GC therapy.

In conclusion, we herein report four cases of patients with type 2 diabetes whose glycemic control was worsened by GC therapy who were successfully treated with exenatide administration on a modified injection schedule. Exenatide administration not only improved the patients’ blood glucose levels, but also decreased their weight, which thus led to improvements in hypertension and dyslipidemia. Our findings therefore indicate that exenatide may be a suitable option for the treatment of GC-induced diabetes mellitus.
The authors state that they have no Conflict of Interest (COI).

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References

30. Nambu T, Matsuda Y, Matsuo K, et al. Lisiraglutide administration in type 2 diabetic patients who either received no previous treatment or were treated with an oral hypoglycemic agent showed greater efficacy than that in patients switching from insulin. J Diabetes Invest 2012(in press).