

CASE REPORT

Possible Type 1 Diabetes Reverted to Non-Insulin-Requiring Stage with Liraglutide: A Case Report

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ABSTRACT

Context Some studies have indicated that Glucagon-like peptide-1 analogs efficiently improve glycemic control in type 1 diabetes without hypoglycemia, but it is difficult to confirm long time efficacy in clinical cases. **Case report** A sixty-five-year-old woman experienced hyperglycemic symptoms, decreased body weight, and had anti-glutamate decarboxylase antibody in October 2010 (hemoglobin A1c; 12.6%, anti-glutamate decarboxylase antibody; 2563.4 U/mL). She was initially treated with multiple insulin injections and oral medication, namely insulin glulisine, insulin glargine, metformin, and miglitol, and her glycemic control gradually improved. In August 2012, we started combination therapy with liraglutide and insulin injections. The patient reported occasional mild hypoglycemic symptoms, but her overall glycemic control was well-maintained so we gradually decreased the insulin dose and finally discontinued it completely. The patient's glycemic control was well-maintained for over one year after discontinuation of the insulin injection. We also performed continuous glucose monitoring that showed almost the same level in her daily life both for the insulin and liraglutide combination injection therapy and the liraglutide mono-injection therapy. No adverse effect occurred. Her hypoglycemic symptoms disappeared entirely and the serum C-peptide response to 1 mg glucagon stimulated tests was maintained even after the insulin injection was discontinued. **Conclusions** We describe herein a patient with possible type 1 diabetes who was successfully treated with liraglutide and retained relatively residual β -cell function. As some studies have suggested, the efficacy of liraglutide for type 1 diabetes may be explained by preserving β -cell function and inhibiting islet inflammation.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) analogs have been developed as a therapeutic agent for type 2 diabetes. They have also been tried in the treatment of type 1 diabetes and some studies have reported improvement of glycemic control with a combination therapy of a GLP-1 analog and insulin injection [1]. However, there have been few clinical reports on the improvement of insulin secretion or being able to discontinue insulin therapy.

We recently treated a patient with possible type 1 diabetes who was successfully treated with liraglutide,

one of the long acting GLP-1 analogs, and finally insulin injections were discontinued for more than 15 months with a good glycemic control after the discontinuation. This case report provides detailed information regarding the patient's condition and daily and long-term glucose profile including data using continuous glucose monitoring (CGM), in addition to information on residual insulin secretion assessed by 1 mg glucagon stimulated tests in the course of liraglutide therapy before and after the discontinuation of insulin. Written informed consent was obtained from the patient.

CASE REPORT

A Sixty-five-year-old woman lost nearly 5 kg body weight from May 2010, developed leg cramps and became very thirsty. She visited her home doctor in July 2010, and hyperglycemia was discovered (plasma glucose; 646 mg/dL, hemoglobin A1c [HbA1c]; 12.6% [reference range 4.6-6.2%], anti-glutamate decarboxylase antibody [GAD-Ab]; 10900.0 U/mL) together with ketosis as a urinary quantitative analysis. Insulin therapy was started and the patient came to our hospital because she wanted to investigate her disease

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Abbreviations CGM continuous glucose monitoring; GA glycated albumin; GAD-Ab anti-glutamate decarboxylase antibody; GLP-1 Glucagon-like peptide-1; HbA1c hemoglobin A1c

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and its treatment more precisely in October 2010. Our first examination showed that her endogenous insulin secretion had decreased (C-peptide, 24-h Urine; 38.7 $\mu\text{g/day}$ [reference range: 22.8-155.0], the incremental difference between serum C-peptide levels before and 6 minutes after 1mg glucagon stimulated test; 0.2 ng/mL [reference range: > 2.0 ng/mL]). She had normal liver and renal function, thyroid level, and tumor markers. Her body weight was 44.6 kg and she was 158 cm high (body mass index, 17.9). Furthermore, her GAD-Ab titer was extremely high (2563.4 U/mL, [reference range: 0.0-1.4]). Therefore, we diagnosed the patient as having possible type 1 diabetes. She had no relevant past medical history nor delivering excessively large fetuses. She didn't have familial history of diabetes, diabetic complications, and viral infection before the onset.

At discharge, we prescribed insulin glulisine (5 units before breakfast, 4 units before lunch, and 4 units before dinner), insulin glargine (5 units before lunch), metformin (250 mg before every each meal), and miglitol (75 mg before every each meal).

The patient's clinical course is shown in **Figure 1**. The HbA1c maintained below 6.0% and she sometimes had mild hypoglycemia. August 2012, we stopped the miglitol

and administrated liraglutide. After that, her glycemic control was consistently very well-maintained, so we carefully decreased the insulin dose. Insulin glulisine was discontinued in April 2013 and insulin glargine was discontinued in November 2013. Liraglutide 0.9 mg per day, which has been approved as the maximum dose in Japan, and metformin 750 mg/day were continued without any gastrointestinal side effect (**Figure 1**).

We constantly assessed the results of 1 mg glucagon stimulation tests throughout the course. These tests were conducted between 3 and 4 hours after breakfast and insulin injection in an outpatient setting, because it was a long distance from her home to our hospital and the patient was afraid to skip breakfast and did not want to inject insulin before leaving home. The tests showed that endogenous insulin secretion was maintained.

We also conducted CGM before and after discontinuing the insulin injection (insulin and liraglutide combination injection therapy vs. liraglutide mono-injection therapy). The glycemic levels and fluctuations maintained well within the ideal boundaries (**Figure 2**).

The HbA1c levels have been kept under good control and the patient experienced no hyper- and hypoglycemic

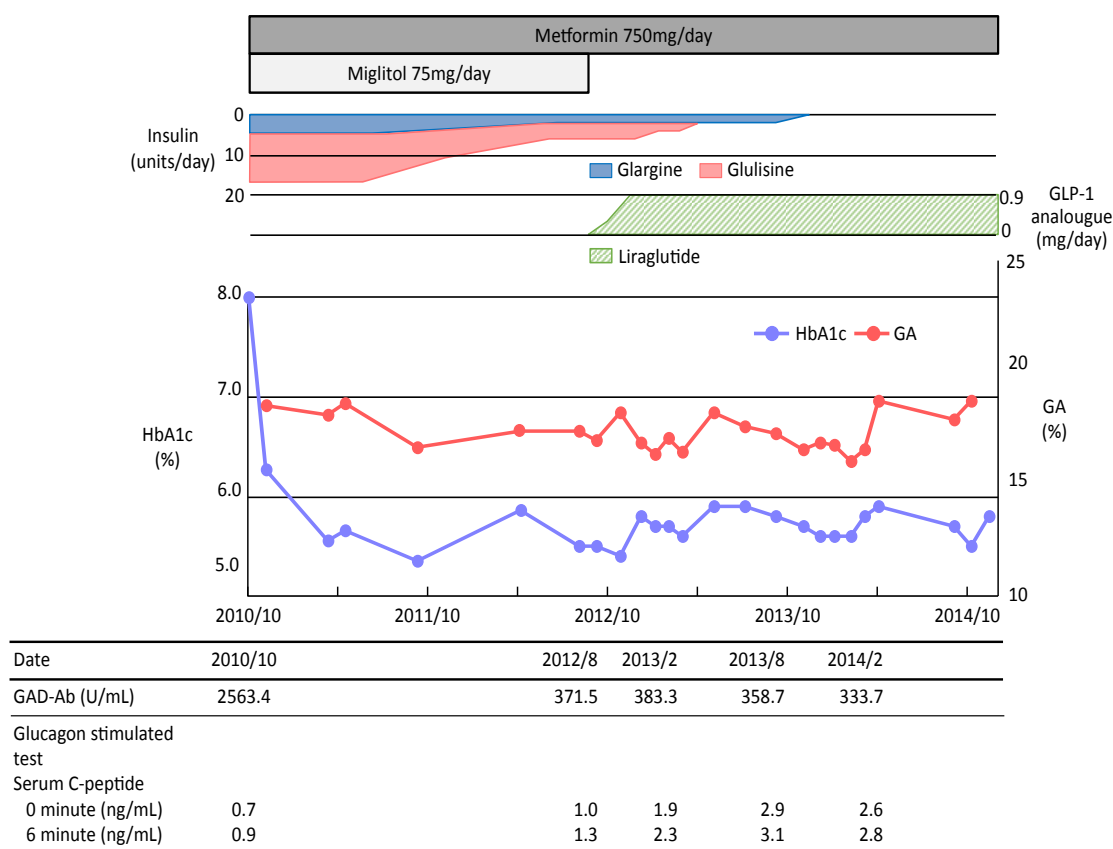


Figure 1. The clinical course of the patient.

The top and second bars of the graph indicate the prescription of oral hypoglycemic agents; the dark gray rectangle indicates metformin and the light gray rectangle indicates miglitol. Trapezoid graphs indicate insulin dose and liraglutide dose; the blue trapezoid indicates insulin glargine dose, the red trapezoid indicates insulin glulisine dose, and the green trapezoid indicates liraglutide dose. Two line graphs indicate glycemic controls; the blue line indicates HbA1c change and the red line indicates glycated albumin (GA) change.

GAD-Ab and serum C-peptide levels following the 1 mg glucagon stimulated test are shown.

The reference range of GAD-Ab is 0.0-1.4 U/mL. The reference range of incremental serum C-peptide level ("delta", the difference between serum C-peptide levels before and 6 minutes after 1mg glucagon stimulated test) is > 2.0 ng/mL, and that of serum C-peptide level at 6 minutes after 1 mg glucagon stimulated test is > 4.0 ng/mL.

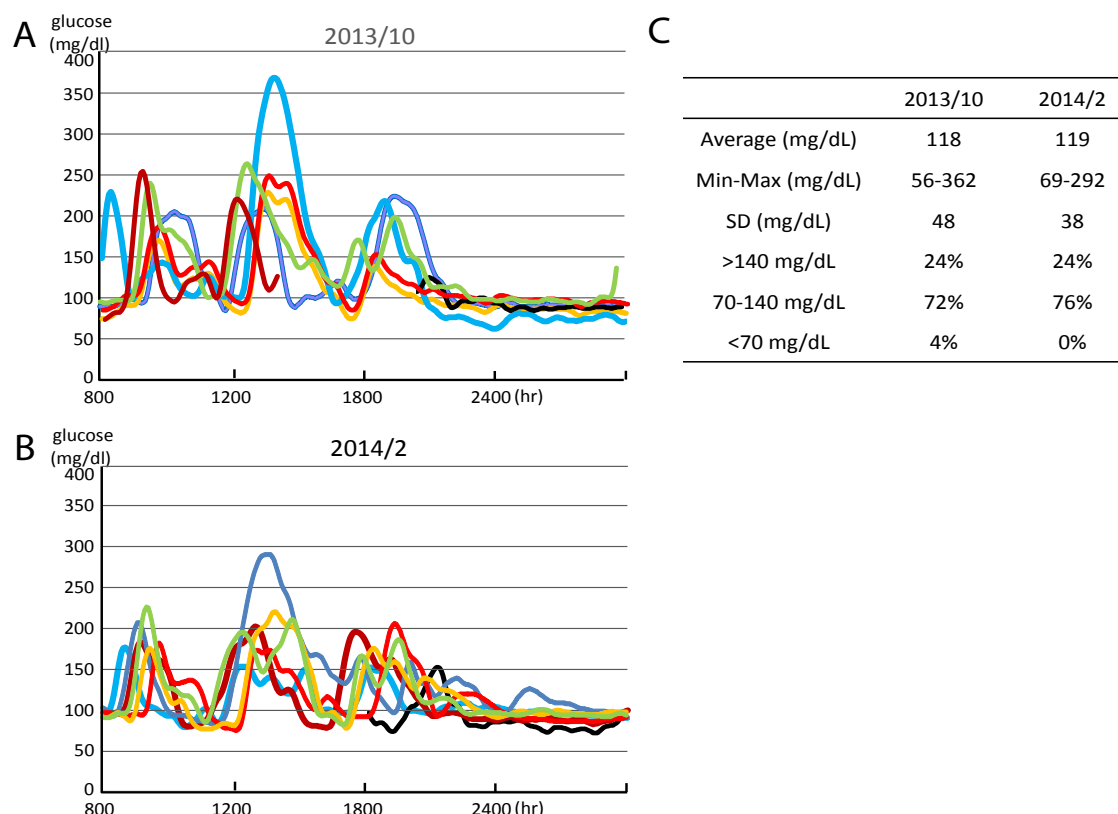


Figure 2. Continuous glucose monitoring at the inpatient and outpatient period

(a.) Continuous glucose monitoring with insulin glargine and liraglutide combination injection therapy in her daily outpatient life (October 2013). Each color line indicates the following days (Black line; October 10, Blue line; October 11, Orange line; October 12, Red line; October 13, Green line; October 14, Light Blue line; October 15, Deep Red line; October 16). **(b.)** Continuous glucose monitoring with liraglutide mono-injection therapy in her daily outpatient life (February 2014). Each color line indicates the following days (Black line; February 12, Blue line; February 13, Orange line; February 14, Red line; February 15, Green line; February 16, Light Blue line; February 17, Deep Red line; February 18). **(c.)** The average, Minimum and Maximum (Min-Max), and Standard deviation (SD) of the glucose levels (October 10-16th, 2013 and February 12-18th, 2014).

symptoms at all with the liraglutide mono-injection therapy. Although her body weight increased up to 49.3 kg with insulin therapy, it decreased gradually and was maintained at 45 kg after initiation of the liraglutide therapy.

DISCUSSION

We diagnosed this patient as having type 1 diabetes because she had extreme hyperglycemia, ketosis, high GAD-Ab titer and decrease of the endogenous insulin secretion at the onset. However, her endogenous insulin secretion levels have been maintained for at least three and a half years after the onset of diabetes, possibly helped by GLP-1 therapy in the latter of the course.

GLP-1 is one of the incretin hormones, which has a wide variety of actions such as potentiation of glucose-stimulated insulin secretion, reduction of appetite, delay of gastric emptying and effects on glycemic control. They are also indicated to have favorable effects on β -cells: replication of β -cell within the islets, reduction in apoptotic rates of existing β -cells, and β -cell neogenesis from ductal cell precursors [1].

Some studies have reported the efficacy of a relatively long term use of liraglutide for type 1 diabetes. Kielgast *et al.* [2] reported that insulin dose and HbA1c decreased in type 1 diabetes treated with the addition of liraglutide to the insulin therapy for 4 weeks and a few C-peptide

positive patients completely discontinued insulin therapy with liraglutide. Varanasi *et al.* [3] also reported that combination therapy of liraglutide and intensive insulin therapy for 24 weeks improved HbA1c, and reduced the insulin dose and body weight. In both studies, endogenous insulin secretion did not change between before and during liraglutide therapy. Furthermore, Dejgaard *et al.* [4] have reportedly planned to investigate the efficacy and safety of liraglutide added to insulin therapy in overweight patients with type 1 diabetes using a randomized, double-blinded, placebo-controlled study. In our case, the insulin dose was also reduced with the addition of liraglutide and ideal HbA1c levels were maintained for over one year after discontinuation of insulin therapy. In the course of treatment, CGM demonstrated maintenance of the same glycemic levels both at fasting and postprandially during her daily life. The serum C-peptide levels were also well-maintained. A decrease in the patient's body weight was also achieved with liraglutide.

In other studies, exenatide, one of the short-acting GLP-1 analogs, was also reported as having similar favorable effect for type 1 diabetes. Paisley *et al.* [5] reported a case of a 66-year-old woman who exhibited a type 1 phenotype for 18 years after the diagnosis of type 2 diabetes. She was treated with exenatide in addition to insulin therapy and that improved her glycemic control with reduction of hyperglycemia and frequent

hypoglycemia, and also resulted in a lower body weight and decreased insulin dose. However, her C-peptide level remained undetectable.

These reports indicate that GLP-1 analogs can efficiently utilized for the treatment of type 1 diabetes with particular regard to glycemic control, *i.e.*, reduction of glycemic excursion without hypoglycemia, independently of residual endogenous insulin secretion. We also have successfully treated a patient accomplishing almost ideal glucose control levels over a long time of period by using liraglutide, and the important differences of our case from the previous reports lie in that the insulin secretion levels were rather increased during insulin-free period and that the duration of that period was longer. Furthermore, we infer that this case was not in the honeymoon period (partial remission of type 1 diabetes), because this typically occurs by one year after the onset of hyperglycemia even in childhood [6].

In our case, after discontinuation of insulin therapy, she reported reduction in mild hypoglycemic symptoms that had often taken place when her glucose level had been down to around 50-70 mg/dl at which levels she had felt the symptoms with the combination therapy of insulin and liraglutide; although she never experienced severe hypoglycemic symptoms in the entire course of treatment.

There are many basic studies that reported the effect of GLP-1 analogs on β -cell proliferation and preservation with decreasing islet inflammation [1]. Our patient was treated with liraglutide from a relatively early time after the onset of possible type 1 diabetes. This might have exerted a preserving effect on her β -cell function that might have constantly and naturally decreased.

Finally, although our patient is currently not showing depleted endogenous insulin, we should be careful to ensure that her insulin secretion level is maintained so as to avoid hyperglycemia and complications associated with chronic hyperglycemia in the long run.

A few additional points should be taken into consideration. First, the clinical course might be attributable to the early improvement in the blood glucose level in response to the multiple insulin injections, changes in her immune condition, and/or the natural disease course. Second, the evaluation of β -cell function using glucagon-stimulated tests might have been affected by the discontinuation of the insulin therapy. Nevertheless, this case report has a significant implication in that the GLP-1 analog was capable of maintaining glycemic control without the occurrence of either hyperglycemia or hypoglycemia in a patient with type 1 diabetes who was not receiving insulin therapy.

We reported herein a patient with possible type 1 diabetes who was treated with liraglutide and succeeded in

achieving good glycemic control over a long time without insulin injection. Her residual β -cell function was relatively retained. In this sense, we consider that this case's disease reverted to non-insulin-requiring stage of type 1 diabetes. Although our results suggest the potential of GLP-1 analog therapy for the treatment of type 1 diabetes, more long-term observation is needed in a larger patient population to confirm our results.

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NIS treated the patient and wrote the paper. DT treated the patient, joined the discussion and was involved in drafting the manuscript. MN treated the patient, participated in the design of the report, supervised the work, and joined the discussion. All authors have read and approved the final manuscript.

Declaration of Conflicting of Interests

Noriko Ihana-Sugiyama, and Daisuke Takarabe declare that they have no conflict of interest. Mitsuhiro Noda received grants from Mochida Pharmaceutical CO. LTD., Astra Zeneca K.K., Sanwa Kagaku Kenkyusho Co. Ltd., Takeda Pharmaceutical Co. Ltd., Kowa Pharmaceutical Co. Ltd., Kyowa Hakko Kirin Co. Ltd., Daiichi Sankyo company, and Mitsubishi-Tanabe Pharma Corp. as well as lecture fees from Sanofi K.K., Mitsubishi-Tanabe Pharma Corp., Daiichi Sankyo company, Eli Lilly Japan K.K., MSD K.K., Novo Nordisk Pharma Ltd., Kissei Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Astellas Pharma Inc., Kowa Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Meiji Seika Pharma Co. Ltd., Kyowa Hakko Kirin Co. Ltd., and AbbVie Inc.

Research Ethics

Ethics approval was obtained from the institutional review board of the National Center for Global Health and Medicine in Tokyo, Japan. (No. 1746)

Patients Consent

Informed consent was obtained from the patients for being included in the report.

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