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Case Report

# Excellent Blood Glucose Levels for 5 Years with Well Maintained Insulin Secretion by the Treatment Comprising a Once-Weekly Injection of Dulaglutide: GLP- 1RA Alone in a Patient with Type 2 Diabetes Mellitus

**Seiho Nagafuchi, MD, PhD[1,2*#]; Keiichiro Mine, PhD[2#]; Taizo Shiratsuchi, BA[1]; Erika Shibayama, RN[1]; Azusa Mitsueda, RN[1]; Hirokazu Takahashi, MD, PhD[3]; Keizo Anzai, MD, PhD[2]**

[1]Department of Internal Medicine, Fukuoka Heartnet Hospital, Fukuoka, 819-0002, Japan

[2]Division of Metabolism and Endocrinology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, 849-8501, Japan

[3]Liver Center, Faculty of Medicine, Saga University Hospital, Saga University, Saga 849-8501, Japan

***Corresponding author: Seiho Nagafuchi**
Department of Internal Medicine, Fukuoka Heartnet Hospital, Fukuoka, 819-0002, Japan.
Email: su2733@cc.saga-u.ac.jp

[#]These authors contributed equally to the manuscript.

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## Abstract

As a result of worsening of diabetes mellitus control to 9.1% hemoglobin A1c, a 61-year-old male Japanese patient began treatment with once-weekly subcutaneous injection of 0.75mg dulaglutide (a glucagon-like peptide-1 receptor agonist) alone. As a result, he demonstrated excellent diabetes mellitus control at an approximate 6.0% to 6.7% hemoglobin A1c level with this treatment alone for 5 years. The insulin secretion activity was well maintained as assessed by the HOMA-β score from 2.7 to 10.2. Interestingly, slight increase of insulin resistance, as assessed by the HOMA-IR was observed from 0.7 to 1.1. Taken together, the mild increase of insulin secretion may have been a positive reaction to keep good control of diabetes mellitus in response to slightly increased insulin resistance. Thus, a long-lasting favorable effect of treatment with dulaglutide alone, not only for diabetes mellitus control, but also for keeping insulin secretion, was demonstrated by this patient.

**Keywords:** β-cell; Dulaglutide; Glucagon-like peptide-1 receptor agonist (GLP-1RA); Insulin resistance; Type 2 diabetes mellitus

## Introduction

A recent IDF report indicated that the number of patients with diabetes mellitus globally is now approximately 800 million, which will increase by 8 million annually [1]. Almost all patients are expected to have type 2 diabetes mellitus, and an appropriate prevention program and effective and safe treatment regimens are essential. Fortunately, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1RA) stimulate insulin secretion in response to diet-induced hyperglycemia, without the risk of hypoglycemia, which is in contrast to sulfonylureas (SUs) and/or insulin [2-4].

GLP-1 RA has been also reported to be useful not only to control diabetes, but also to reduce the risks of cardiovascular diseases, obesity and renal disorders [4]. The mechanisms of GLP-1RA-stimulated insulin release in pancreatic β-cells are displayed in Figure 1. Briefly, GLP-1RA stimulates pancreatic β-cells to increase the production and release of insulin through increasing Cyclic Adenosine Monophosphate (cAMP) production and calcium ($Ca^{2+}$) elevation, followed by protein kinase A activation, leading to upregulation of proinsulin gene transcription and subsequent insulin secretion [3].

The SU group of drugs stimulate β-cells to secrete insulin, irrespective of the blood glucose concentration; thus, the risk of hypoglycemia is high. In addition, the accumulation of β-cell damage following long-term SU drug use frequently leads to the requirement for insulin treatment. By contrast, GLP-1RA drugs are believed to stimulate insulin secretion without damaging β-cells [2-4]. However, the long-term effects of GLP-1RA treatment on β-cell function and insulin secretion requires further investigation [4,5].




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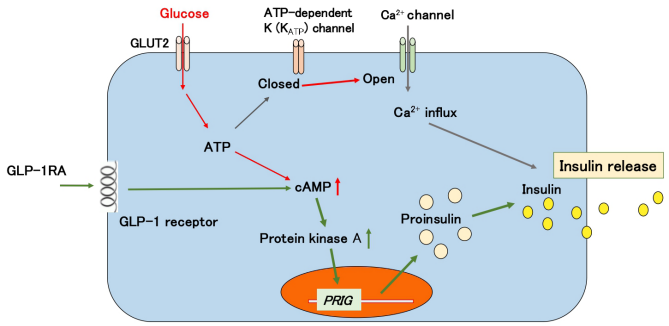


**Figure 1:** The mechanisms of GLP-1RA-stimulated insulin release in pancreatic β-cells.
*ATP: adenosine triphosphate; GLUT2, glucose transporter 2; K, potassium; *PRIG*: promoter region of insulin gene.

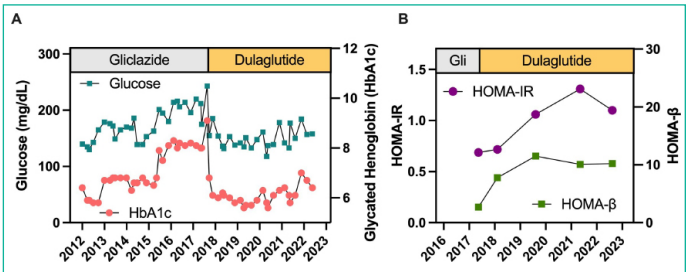


**Figure 2:** Clinical time course of the patient.
A: Profile of fasting blood glucose and hemoglobin A1c (HbA1c).
B: Profile levels of homeostasis model assessment of β cell function (HOMA-β) and insulin resistance (HOMA-IR).
Gliclazide (Gli): 40mg/day; Dulaglutide: 0.75mg subcutaneous injection/week

## Case Report

We report a patient who achieved a significant long-term effect with GLP-1RA treatment alone. A 42-year-old man (height: 163cm; weight: 55.0kg; body mass index: 20.7kg/m$^2$) was diagnosed with type 2 diabetes mellitus in 1998. Until 2016, his diabetes mellitus was well controlled by diet, exercise, and daily 40mg oral gliclazide: SU treatment. From 2016 to 2017, his diabetes mellitus control worsened (>8.0% hemoglobin A1c (HbA1c) (Figure 2A) without any sign of improvement, suggesting that the gliclazide treatment had lost its effectiveness. The patient did not have obesity or anti-glutamic acid decarboxylase antibody [6]. During worsening, he did not experience flu-like syndrome, and he was negative for the virus-induced diabetes susceptibility gene, *Tyrosine kinase 2* promoter *variant* [7,8], suggesting that autoimmunity or viral infection did not contribute to the deterioration in his condition. In July 2017, dulaglutide injection therapy was suggested. However, because his brother who also had type 2 diabetes mellitus and had received multiple daily insulin injections for 10 years, suddenly died in the bathroom of an unknown cause, he first refused the therapy. Three months later, his diabetes mellitus control deteriorated to a HbA1c level of 9.1%. His insulin secretion activity decreased, as assessed by a fasting C-peptide concentration of 0.8ng/ml, an insulin concentration of 1.4μU/ml, and a homeostatic model assessment of β-cell function (HOMA-β) [9] score of 2.7. Fortunately, he understood the difference between daily insulin therapy and once-weekly subcutaneous injection of 0.75mg dulaglutide. Since he did not like to be given drugs, he accepted dulaglutide alone treatment. This treatment enabled him to obtain excellent control of diabetes mellitus with a 6.0%–6.7% HbA1c level for 5 years (Figure 2A). Throughout the observation period, he had kept body weight around 55.5kg and good exercise every day. His clinical data regarding liver, kidney, electrolyte, and uric acid all showed normal without hyperlipidemia. In addition, he had no diabetic retinopathy nor microalbuminuria. His insulin secretion was well maintained, and the fasting insulin concentration moderately increased to 2.8μU/ml, with a HOMA-β score of 10.2 (Figure 2B), which was consistent with the mild elevation in the fasting C-peptide concentration from 0.8 to 1.1ng/ml. Interestingly, slight increase of insulin resistance, as assessed by the HOMA-IR [10], was observed from 0.7 to 1.1 (Figure 2B). Taken together, the mild increase of insulin secretion may have been a positive reaction to keep good control of diabetes mellitus in response to slightly increased insulin resistance.

Thus, a long-lasting favorable effect with dulaglutide treatment alone on diabetes mellitus control and insulin secretion was evident in this case. Because aging is an important factor associated with impaired β-cell function and increased insulin resistance [11], the mild increase in insulin secretion in this patient may play a role against the worsening of insulin resistance.

## Discussion

We report that dulaglutide, a GLP-1RA, provided excellent control of blood glucose concentration for 5 years in a 66-year-old Japanese man with type 2 diabetes mellitus, with well maintained insulin secretion. Although the long-term favorable effect of GLP- 1RA treatment has been reported, the significant improvement was not maintained for more than 12 months [5]. Actually, its effectiveness reduced year on year over a 72-month observation period [5]. By contrast, as shown in the present case study, dulaglutide: GLP-1RA therapy alone provided excellent blood glucose control for 5 years without losing its effectiveness. In a previous study, all patients received combinations of other anti-diabetic drugs. Most importantly, 45.9% of the patients received SUs [5], suggesting that long-term SU drug combination therapy may reduce the long-term effectiveness of GLP-1RA.

Control of diabetes mellitus is influenced by many factors, including body weight, age, sex, duration, exercise, race [11,12], and combinations of other anti-diabetic drugs.

Because the patient rejected being prescribed other drugs, he had been taking only dulaglutide, which was not combined with other drugs. Although the contribution of these factors remains to be clarified, this case demonstrated the effectiveness of long- term dulaglutide treatment alone, not only for the control of diabetes mellitus, but also for maintaining good insulin secretion in a patient with type 2 diabetes mellitus. Thus, dulaglutide treatment alone is a good choice for the treatment of type 2 diabetes mellitus. This case report not only promotes the use of GLP-1RA alone therapy for the treatment of diabetes mellitus, but it also enhances clinical research to assess the significance of GLP-1RA application and to find combined appropriate anti-diabetes drug(s) not to reduce the long-term effectiveness of GLP-1RA for the treatment of type 2 diabetes mellitus.

## Author Statements

### Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fukuoka Heartnet Hospital.

### Informed Consent Statement

Written informed consent was obtained from the patient to publish this paper.

**Data Availability Statement**

All of the data described in this case report are available freely.

**Conflict of Interest**

SN, KM, TS, ES, and AM have no conflicts of interest. HT received grants from Astellas Pharma Inc. and AbbVie Inc. KA received grants from Sumitomo Pharma, Mitsubishi Tanabe Pharma, and Novo Nordisk Pharma.

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**Contribution of Each Author**

SN took clinical care of the patient, collected the clinical data, and wrote the report. KM assessed the laboratory data, performed genetic analysis of the *TYK2* gene, drew the figure, and co-wrote the report.

TS contributed to patient care and clinical data collection. ES took clinical care of the patient.

AM took clinical care of the patient.

HT contributed to the analysis of the clinical data.

KA contributed to the analysis of the clinical data and co-wrote the manuscript.

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