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Case Report

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Improved Glycemic Control due to Reduction in Glucagon Levels by the Administration of Once-Weekly Dulaglutide in a Non-Obese Patient With Type 2 Diabetes

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Abstract

Treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) is a cornerstone for the management of obesity and type 2 diabetes. GLP-1RAs improve the glycemic control by suppressing glucagon secretion and stimulating insulin secretion in patients with type 2 diabetes. Here, we report the case of a patient with type 2 diabetes with postprandial hyperglucagonemia who was successfully treated by the administration of once-weekly dulaglutide. A 67-year-old, non-obese woman was admitted to our hospital for preoperative glycemic control. Her glycemic control significantly improved after the administration of dulaglutide. Both fasting and postprandial plasma glucagon levels were effectively suppressed by dulaglutide, which ameliorated hyperglycemia. Thus, to achieve an optimal glycemic control, clinicians should consider suppressing glucagon secretion in addition to improving insulin secretion and sensitivity.

Keywords: Type 2 diabetes; Glucagon-like peptide-1 receptor agonist; Glucagon

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been used for a decade and are recognized as cornerstones for the management of obesity and type 2 diabetes. A systematic review and meta-analysis have shown that a once-weekly treatment with dulaglutide reduced the hemoglobin A1c (HbA1c) level by 1.21% compared with that reduced by placebo [1]. Recently, a beneficial cardiovascular effect of GLP-1RAs has also become clear; cardiovascular and all-cause mortality was relatively decreased by approximately 10% in patients who underwent GLP-1RA treatment [2]. Mann et al [3] have shown that liraglutide, which is a once-daily GLP-1RA, can prevent the progression of diabetic kidney disease and may also improve non-alcoholic fatty liver disease [4]. An adequate weight loss by the administration of GLP-1RAs may also lead to these beneficial effects. Generally, treatment with GLP-1RAs causes a weight loss of 3 kg in overweight or obese patients with or without type 2 diabetes [5]. However, the efficacy and safety of GLP-1RAs were equivalent in Asian patients with type 2 diabetes, regardless of their weight [6]. Thus, GLP-1RAs can be used for normal weight and obese patients with type 2 diabetes. Moreover, GLP-1 suppresses the glucagon secretion, which is supposed to be a major determinant of the glucose-lowering effect of GLP-1 action [7]. Here, we report the case of a patient with type 2 diabetes with postprandial hyperglucagonemia who was successfully treated with once-weekly dulaglutide.

Case Report

A 67-year-old woman was admitted to our hospital for pre-

Table 1. Characteristics of the Patient

Age (years)	67
Height (cm)	156.2
Weight (kg)	50
BMI (kg/m^2)	20.5
WC (cm)	82.5
Duration of diabetes (years)	15
AST (U/L)	55
ALT (U/L)	60
BUN (mg/dL)	7.3
Cre (mg/dL)	0.48
eGFR (ml/min/1.73 m^2)	95.7
Plasma glucose (mg/dL)	206
HbA1c (%)	11.1
GA (%)	29.6
U-ACR (mg/gCre)	0

BMI: body mass index; WC: waist circumference; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cre: creatinine; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; GA: glycoalbumin; U-ACR: urinary albumin creatinine ratio.

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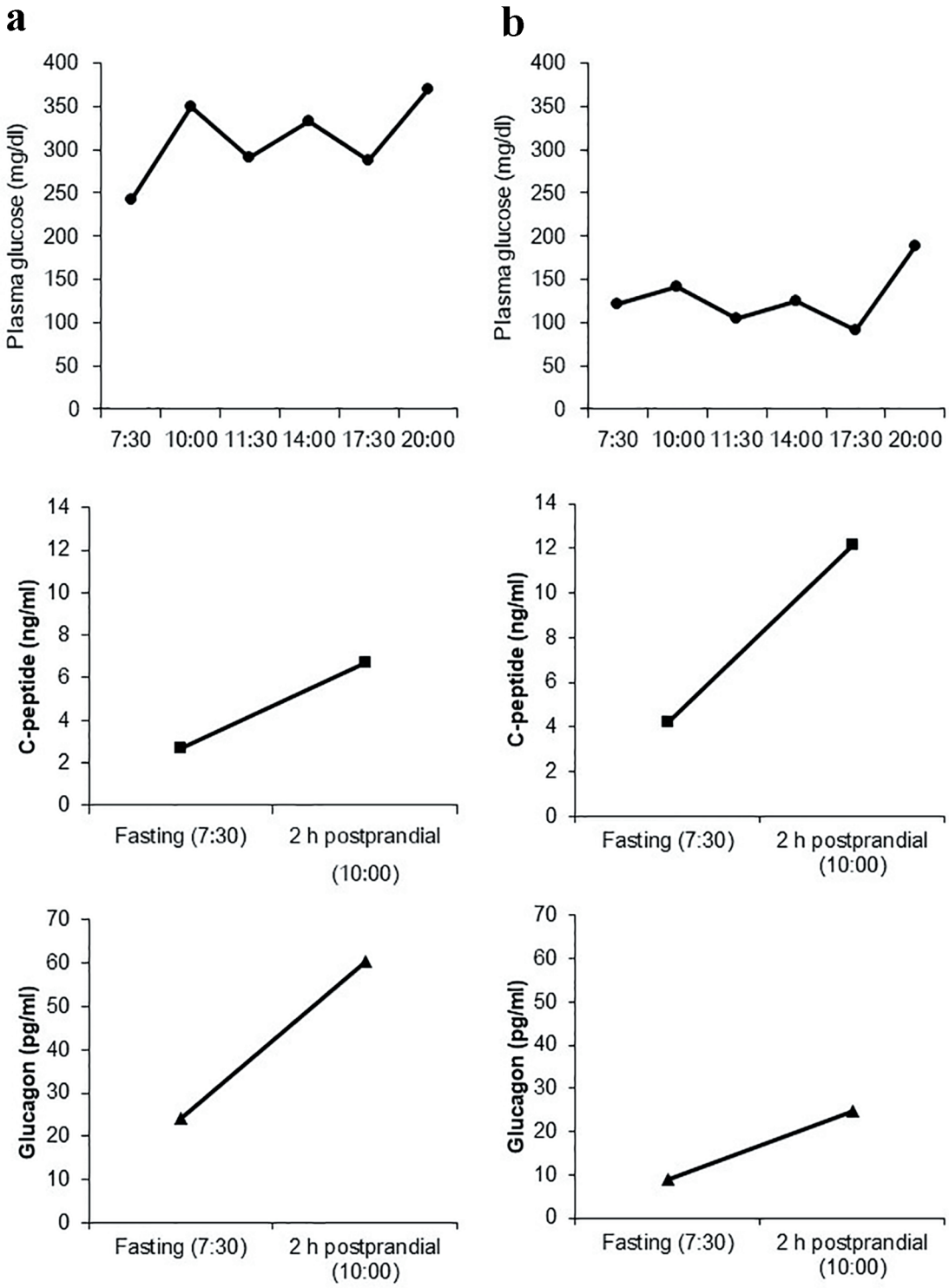

Figure 1. Daily plasma glucose profile as well as fasting and 2-h postprandial levels of C-peptide and glucagon before the administration of once-weekly dulaglutide (a) and after switching from vildagliptin to dulaglutide (b).

operative glycemic control. Her height, weight, and waist circumference were 156.2 cm, 50 kg, and 82.5 cm, respectively. Her anthropometric, demographic, and biochemical data are shown in Table 1. She was diagnosed with type 2 diabetes 15 years ago and was treated with 500 mg of metformin and 100 mg of vildagliptin. She also suffered from depression, and her dietary intake was unstable. On admission, her plasma glucose and HbA1c levels were 206 mg/dL and 11.1%, respectively.

Diet therapy (1,600 kcal/day) was started, which did not ameliorate her glycemic control. We added 500 mg of metformin 5 days after admission; however, blood glucose levels remained at 200 - 300 mg/dL. Her plasma glucose, serum C-peptide (E-test TOSOH II; Tosoh, Tokyo, Japan), and plasma glucagon (Glucagon ELISA; Cosmic, Tokyo, Japan) levels were measured before and 2 h after breakfast to investigate the α- and β-cell functions. Her endogenous insulin secretion was good, and postprandial glucagon secretion was elevated (Fig. 1a). We administered a once-weekly dulaglutide injection 8 days after admission, which ameliorated her glycemic control. She initially presented with nausea, which gradually disappeared. Her plasma glucose levels were 150 mg/dL (fasting), 238 mg/dL (2 h after breakfast), 215 mg/dL (before lunch), 156 mg/dL (2 h after lunch), 117 mg/dL (before dinner), and 269 mg/dL (2 h after dinner). We added 0.75 mg of repaglinide to improve the postprandial hyperglycemia. Before discharge, her plasma glucose levels had improved and were 122 mg/dL (fasting), 141 mg/dL (2 h after breakfast), 104 mg/dL (before lunch), 124 mg/dL (2 h after lunch), 91 mg/dL (before dinner), and 189 mg/dL (2 h after dinner). We also remeasured her serum C-peptide and plasma glucagon levels before discharge (Fig. 1b) and found that both fasting and postprandial plasma glucagon levels were significantly decreased. The difference in plasma glucagon levels between fasting and 2-h postprandial state (ΔGlucagon) was significantly decreased from 36.2 to 15.7 pg/mL by the administration of dulaglutide, and that in serum C-peptide levels between fasting and 2-h postprandial state (ΔCPR) was increased from 4.05 to 7.95 ng/mL. However, the ratio of glucagon to C-peptide was significantly decreased from 9.1×10^3 to 2.13×10^3 (fasting) and from 9×10^3 to 2.03×10^3 (2-h postprandial), thereby suggesting that the suppression of glucagon secretion due to dulaglutide mainly contributed to the improved glycemic control.

Discussion

This case report shows that dulaglutide can effectively ameliorate glycemic control by reducing plasma glucagon levels in a non-obese patient with type 2 diabetes. We used a highly specific electrochemiluminescent sandwich immunoassay to measure plasma glucagon levels, which provided an accurate method for quantifying glucagon when compared with a previous radioimmunoassay [8]; thus, the results are highly reliable. Glucagon plays an important role in maintaining glucose homeostasis; however, it is abnormally secreted in patients with type 2 diabetes [9]. Clinicians have focused on insulin secretion and resistance/sensitivity during the treatment for type 2 diabetes; however, glucagon levels and variability should also be considered to achieve an optimal glycemic control. Hare et al [10] have reported that insulin secretion and glucagon suppression equally contribute to the glucose-lowering effect of GLP-1. Glucagon is a promising target for the treatment of type 2 diabetes. GLP-1RAs suppress glucagon secretion and promote insulin secretion and glucose uptake in muscles [11]. Considering this mechanism of action, although GLP-1RAs are usually used for obese patients with type 2 diabetes, these may also be effective for glycemic control in normal weight patients if no adverse effects occur. However, various unknown endocrine factors may also mediate glucose homeostasis. Recent studies have also suggested that GLP-2 plays a role in glucose metabolism and energy homeostasis [12, 13]. To elucidate the underlying mechanism, further research is required.

Competing Interests

The authors declare that they have no competing interests.

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