Switching from Insulin to Liraglutide Improved Glycemic Control and the Quality of Life Scores in a Case of Type 2 Diabetes and Active Crohn's Disease

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Abstract

A 44-year-old man with type 2 diabetes of five years' duration was admitted for the management of poor glycemic control despite the administration of insulin therapy. On admission, he received vigorous treatment for a 28-year history of Crohn's disease and a 14-year history of a psychiatric disorder. His glycosylated hemoglobin A1c (HbA1c) level was 11.3%, his fasting blood glucose level was 567 mg/dL and his C-peptide level was 1.0 ng/mL. His quality of life (QOL) was severely impaired as a result of frequent episodes of hyperglycemia and hypoglycemia. Treatment with liraglutide was commenced in place of insulin, which improved the patient's glycemic control to an HbA1c level of 5.5% and markedly increased his QOL score with no hypoglycemia.

Key words: Crohn's disease, glucagon-like peptide-1 analog, type 2 diabetes mellitus

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Introduction

Hypoglycemia is an occasional adverse effect in individuals with type 2 diabetes receiving hypoglycemic agents and is associated with a decreased health-related quality of life (QOL) (1). Glucagon-like peptides (GLP), which are derived from the gut, have increasingly been reported to play a role in the pathogenesis and treatment of various diseases, including GLP-1 in type 2 diabetes (2). GLP-1 is an incretin hormone that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner. Therefore, GLP-1 is less likely to produce hypoglycemia than exogenous insulin (3). Liraglutide, a GLP-1 analog, is an incretin-mimetic agent licensed for the treatment of type 2 diabetes. The efficacy and safety of incretin-based therapy, in which liraglutide is included, have been reported in patients with type 2 diabetes (2, 4). However, whether this therapy is also effective for treating type 2 diabetes complicated by inflammatory bowel disorders, such as Crohn's disease, is unclear. We herein report a case of type 2 diabetes in a patient who

improved his glycemic control following a change from insulin to liraglutide therapy under a psychiatric disorder and Crohn's disease associated with ongoing treatment with chemotherapy after resection of the small and large intestines.

Case Report

A 44-year-old man was admitted to our hospital for the management of inadequately treated type 2 diabetes of five years' duration. His clinical data were as follows: glycosylated hemoglobin A1c (HbA1c) = 11.3%, fasting blood glucose (FBG) = 567 mg/dL, C-peptide (CPR) = 1.0 ng/mL, C-reactive protein (CRP) = 7.0 mg/dL and body mass index (BMI) = 25.0 kg/m². The patient had a 28-year history of active Crohn's disease and was being treated with mesalamine and infliximab after having undergone resection of the terminal ileum and ascending sigmoid colon. He also had a 14-year history of obsessive-compulsive disorder and was being treated with a number of psychopharmaceuticals, including risperidone, levomepromazine maleate, promethazine methylenedisalicylate, flunitrazepam and diazepam. Al-

Figure 1. Daily profile of the plasma glucose levels and serum CPR levels before and after breakfast under insulin therapy and GLP-1 analog therapy.

though the patient had maintained his mental stability, he had a history of a suicidal act in the past.

Due to the patient's Crohn's disease and psychiatric disorder, dietary and lifestyle modification was suboptimal for adequately controlling his diabetes. He was started on basal bolus insulin therapy, including an injection of a long-acting insulin analogue once a day in addition to the injection of a rapidly acting insulin analogue three times a day. However, his glycemic control did not improve (the FBG level remained at approximately 175-235 mg/dL) despite increasing the insulin dose to 44 U per day. His Crohn's disease made food intake unstable, which caused episodes of both hyperglycemia and hypoglycemia. Insulin therapy appeared to have a limited effect due to the unstable glycemic excursions and unpredictable risk for suicide raised by the psychiatric disorder.

We proposed treatment with liraglutide instead of insulin, and the patient was started on therapy comprising the subcutaneous injection of 0.3 mg of liraglutide once daily before breakfast. The dose was increased to 0.6 mg at week 1 then to 0.9 mg at week 2, without any gastrointestinal symptoms, such as nausea or vomiting. A marked improvement in daily blood glucose readings was observed, with the FBG decreasing to 94-120 mg/dL and a postprandial glucose level of 116-179 mg/dL. The patient's insulin secretory capacity remarkably improved, as assessed according to the serum CPR level stimulated by a meal, as well as the C-peptide index (CPI: fasting CPR $\times$ 100/FBG). His insulin secretory capacity increased from a CPR level of 0.3 ng/mL (blood glucose: 181 mg/dL) at fasting to a CPR level of 2.3 ng/mL (blood glucose: 292 mg/dL) after breakfast observed before the insulin-to-liraglutide switch and a CPR level of 1.8 ng/mL (blood glucose 120 mg/dL) to 4.8 ng/mL (blood glucose: 179 mg/dL) after the switch. The CPI also increased from 0.055 before to 1.50 after the insulin-to-liraglutide

switch (Fig. 1). Thereafter, glycemic control was maintained with no marked hyperglycemic or hypoglycemic excursions. The patient reported feeling much better and was able to sleep without fear and willingly join social activity groups. His HbA1c level improved to 7.6% one month later and subsequently to 5.7% four months later. Ten months after the commencement of liraglutide therapy, the HbA1c level decreased to 5.5% (a 5.8% reduction following the switch to liraglutide) without any gain or loss in body weight. The fasting CPR level further increased to 3.0 ng/mL at a FBG value of 107 mg/dL (CPI: 2.80). The infliximab therapy was continued during this treatment process. Although the patient's Crohn's disease status continued to be unstable, no bloody bowel discharge was observed, and his hemoglobin concentration remained stable.

The change in QOL following the insulin-to-liraglutide switch was evaluated using the Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire. The DTR-QOL is a 29-item questionnaire that can be used to assess the influence of diabetes treatment on a patient's QOL with good reliability and validity (5). The DTR-QOL can be applied regardless of the treatment method, which enables the clinician to detect differences in the QOL between before and after switching the treatment regimen. The DTR-QOL consists of four categories: "burden on social activities and daily activities" (13 items), "anxiety and dissatisfaction with treatment" (8 items), "hypoglycemia" (4 items) and "satisfaction with treatment" (4 items). The patient's QOL scores for all four factors improved, and his total QOL score significantly increased from 20.7% to 88.5% ($p < 0.001$) (Fig. 2).

Discussion

Crohn's disease is a chronic, idiopathic, nonspecific inflammatory disease of the gastrointestinal tract (6). Our pa-

Figure 2. Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire scores for insulin therapy vs. GLP-1 analog therapy. Factor 1: “burden on social activities,” Factor 2: “anxiety and dissatisfaction with treatment,” Factor 3: “hypoglycemia,” Factor 4: “satisfaction with treatment.” The scores for all four factors and the total score significantly improved after GLP-1 analog therapy. ** $p < 0.0001$, * $p < 0.05$

tient had active Crohn’s disease for 28 years and a psychiatric disease for 14 years and developed diabetes five years prior to admission. His dietary intake was unstable due to gastrointestinal symptoms of Crohn’s disease and as a consequence of bowel resection. He suffered from episodes of hyperglycemia and hypoglycemia despite the administration of insulin therapy; for this reason, we changed the therapy from insulin injections four times daily to liraglutide injections once daily. After the change in therapy, the patient’s HbA1c level decreased to the range of good glycemic control without hypoglycemia or adverse effects. Changing insulin to incretin-mimetic therapy not only achieved glycemic control, but also greatly improved the patient’s QOL.

When patients with type 2 diabetes experience repeated episodes of hyper- or hypoglycemia, a patient-centered approach is required for successful management (7), paying the utmost attention to the individual’s condition, so that a balance between the insulin dose and nutritional intake is achieved. Because hypoglycemia caused by insulin therapy remarkably decreases the QOL (8), preventing hypoglycemia is as important as controlling hyperglycemia in type 2 diabetics. GLP-1 is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion in a glucose-dependent manner, and treatment with GLP-1 analogs may decrease both hyperglycemic and hypoglycemic episodes (3).

As of yet, the prevalence of diabetes in patients with Crohn’s disease remains unknown, and there are little data examining the interactions between comorbid diabetes and Crohn’s disease in their natural progression, given the pro-inflammatory nature of both conditions (9). The application of corticosteroid therapy to treat Crohn’s disease is likely to induce or aggravate diabetes, although our patient was not

on diabetogenic therapeutics. The enhanced secretion of GLP-1 has been reported in patients with Crohn’s disease (10). However, the relationship between the enteropancreatic axis and insulin secretion in these patients remains unclear. In this case, resection of the terminal ileum and ascending sigmoid colon may have resulted in a decreased GLP-1 level. Therefore, the liraglutide treatment may have effectively compensated for a GLP-1 deficiency. Although the patient’s GLP-1 concentration was not measured, his capacity for insulin secretion and insulin sensitivity robustly improved following the administration of liraglutide therapy; the patient exhibited a lower level of CPR secretion and a much lower CPI than the estimated predictive values for better glycemic control after the insulin-to-liraglutide switch (11, 12), and the serum CPR and CPI values subsequently markedly improved. Although preservation of the beta cell function is usually required for effective treatment with liraglutide, there may well be certain highly responsive patients, similar to the present patient, with a short duration of diabetes and a low CPI. Insulin treatment in patients with type 2 diabetes reduces the level of CPR secretion due to the reduction in blood glucose rather than the supply of exogenous insulin (13, 14). This was not the case with our patient, as he displayed a lower CPR level and higher blood glucose level under insulin treatment, both of which improved with liraglutide therapy. The metabolic improvement observed in this case may be solely due to the improved glycemic control, although the GLP-1-mimetic effects of liraglutide stimulating insulin secretion may also have played a role.

To our knowledge, this is the first case report demonstrating the successful use of liraglutide in a type 2 diabetic patient with active Crohn’s disease. The patient tolerated the

therapy well, with no adverse effects for 10 months, and sustained an impressive improvement in glycemic control without hypoglycemia or body weight changes. Most importantly, the patient's QOL dramatically improved, despite the presence of two chronic diseases as well as a psychiatric disorder. This case indicates that the administration of an incretin-mimetic agent is very useful for improving both biomedical and mental conditions, i.e., fluctuating glycemia and a reduced QOL, as observed in this patient with type 2 diabetes and difficult to control concurrent diseases.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

Informed consent was obtained from the patient to allow the authors to publish this case report. The HbA1c values were expressed in accordance with the National Glycohemoglobin Standardization Program as recommended by the Japanese Diabetes Society (15).

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