CASE REPORT

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The effect of liraglutide on insulin allergy in a patient with glucocorticoid-induced diabetes and multiple sclerosis

Jiudan Zhang[1], Ye Chen[2], Jian Wang[3], Hong Xia[1] and Yang Zheng[1]

[1]*Department of Endocrinology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China*
[2]*Department of Internal Medicine, Nanjing Municipal Center for Prevention and Treatment of Occupational Disease, Nanjing, China*
[3]*Department of Endocrinology, Jinling Hospital, The Affiliated Hospital of Nanjing University, Nanjing, China*

ABSTRACT

Glucocorticoid use may trigger secondary diabetes or exacerbate hyperglycemia in patients with diabetes mellitus (DM). Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist used for the treatment of patients with type 2 diabetes. Few reports mention liraglutide as a treatment for steroid-induced DM (SIDM). Here, we report a patient with SIDM and multiple sclerosis, for whom switching to liraglutide combined with metformin therapy improved glucose levels and ameliorated the symptoms of insulin allergy. Liraglutide may be useful for treating SIDM with insulin allergy.

Keywords: liraglutide, insulin allergy, multiple sclerosis, steroid-induced diabetes mellitus

Abbreviations:
GLP-1: glucagon-like peptide
T2DM: type 2 diabetes
MS: multiple sclerosis

INTRODUCTION

Glucocorticoids are extensively used in almost every subspecialty of medicine.[1] Although widely prescribed glucocorticoids for their anti-inflammatory and immunosuppressive properties, they also have various common metabolic side effects including new-onset hyperglycemia in patients without a history of diabetes mellitus (DM), or severe uncontrolled hyperglycemia in patients with known DM.[2] The incidence of new-onset DM in patients treated with a glucocorticoid is 2–3 times in those without glucocorticoid treatment.[3] Usually, the blood glucose levels of non-diabetic patients normalize after discontinuing glucocorticoid use. However, some patients require close monitoring due to the risk of developing DM in the future.

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Corresponding Author: Yang Zheng, MD
Department of Orthopedics, The First Affiliated Hospital of Zhejiang Chinese Medical University, No.54, Youdian Road, Hangzhou 310000, Zhejiang, China.
Tel: +86 15158172770, E-mail: zhengyang1989.doctor@gmail.com

The traditional management of steroid-induced diabetes (SIDM) has been a combination of lifestyle measures and hypoglycemic drugs with insulin-sensitizing effects. Other oral hypoglycemic drugs or insulin can be considered as second-line treatment.[4] However, insulin allergy is an important adverse effect of insulin treatment in patients with DM, with a reported prevalence of approximately 2%.[5]

Glucagon-like peptide-1 (GLP-1) receptor analogs have recently been introduced worldwide as a therapeutic option to improve blood glucose control, and reduce body weight and hemoglobin A1c (HbA1c) in diabetic patients.[6,7] However, there are few reports regarding the use of liraglutide for treating SIDM that discuss alleviation of the symptoms of insulin allergy. We report a case in which switching to liraglutide therapy not only significantly improved blood glucose control, but also alleviated the symptoms of insulin allergy accompanied by severe hyperinsulinemia in a patient with SIDM. We also discuss the potential benefits of this therapy.

CASE PRESENTATION

Our patient was a 55-year-old man who had suffered from relapsing-remitting multiple sclerosis (MS) (Fig. 1) for 10 years, requiring methylprednisolone treatment, without a history of DM. After three rounds of high-dose intravenous methylprednisolone (500 mg/d), the patient was changed to oral methylprednisolone with a gradual dose reduction from 24 to 6 mg/day during a remission phase. He was also receiving methotrexate 7.5 mg/week, and Tripterygium wilfordii 60 mg/day as additional immunosuppression. His frequent bouts of hiccups improved immediately after receiving high-dose glucocorticoid therapy, while the numbness in his hands, particularly the left hand, continued. However, relief of the numbness was achieved after 3 months of methylprednisolone treatment combined with methotrexate and Tripterygium wilfordii.

Two years previously, the patient's fasting blood glucose level was 8.0 mmol/L, without a diet and exercise program. His fasting blood glucose level gradually increased to 13.0 mmol/L

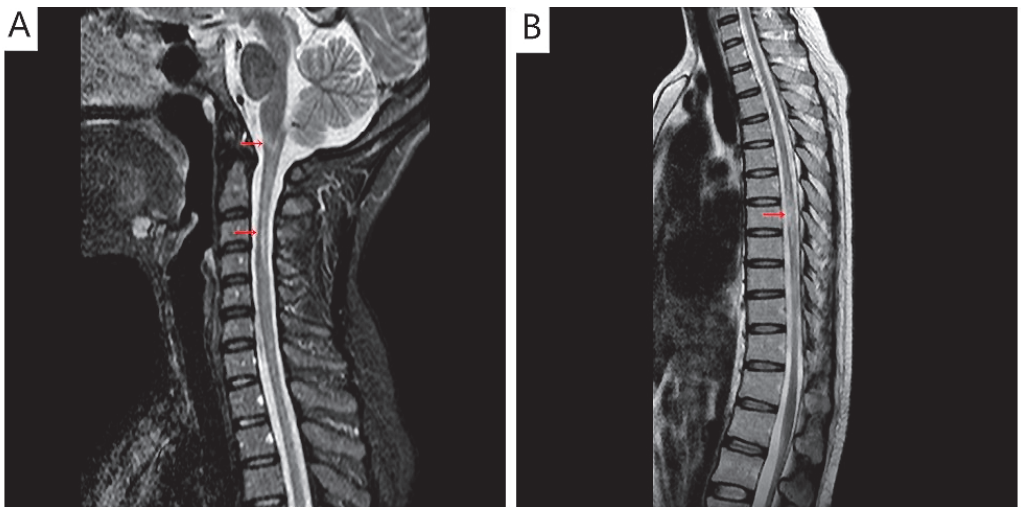

Fig. 1 Magnetic resonance imaging (MRI) of spinal cord
Fig. 1A: Patient demonstrates demyelination in C1 and C3 spinal cord.
Fig. 1B: Demyelination and marrow edema in T7 spinal cord.

Table 1 The result of Oral glucose tolerance test (OGTT)

Time (minutes)	PG (mmol/L)	C-P (ng/mL)	INS (μIU/mL)
0	10.68	4.6	117
30	14.79	11.7	144
60	17.44	14.9	>200
120	22.58	15.3	>200
180	16.86	11.5	186

C-P: C-peptide (0.3–3.7ng/mL)
PG: plasma glucose (3.89–6.11mmol/L)
INS: serum insulin concentrations (1.8–11.8μIU/mL)

(234 mg/dL), and his HbA1c level reached 12.4% 2 months prior to admission, when he was diagnosed with SIDM based on fasting blood glucose values ranging from 9.5 to 12.7 mmol/L (162–216 mg/dL), and postprandial blood glucose values ranging from 18.4 to 22.6 mmol/L (324–396 mg/dL).

He was admitted to our hospital due to his poor glycemic control, and to evaluate his residual insulin secretion ability. On admission, his physical examination was largely unremarkable except for a high body mass index (BMI) (height, 168 cm; body weight, 85 kg; BMI, 30.1 kg/m2; body temperature, 36.5 °C; blood pressure, 124/75 mmHg; pulse, 75 beats/minute, regular). Hyperinsulinemia and severe insulin resistance were revealed by the oral glucose tolerance test (Table 1).

The patient was prescribed diammonium glycyrrhizinate enteric-coated capsules as liver protection because of abnormal liver function tests (ALT 178 U/L, AST 198 U/L, γ-GTP 265 U/L). He was treated with 60 U/day insulin aspart, given before the three meals, and 26 U/day insulin glargine at bedtime, without adding metformin because of the liver enzyme abnormalities (Fig. 2). Unfortunately, he developed new-onset insulin allergy 3 days after insulin was initiated, when he started to develop wheals with redness and itching at the injection sites. Of note, these symptoms only occurred following the use of insulin aspart, and not after insulin glargine. Blood samples revealed hypereosinophilia, and a high total IgE level. His laboratory data at that time are shown in Table 2. A biopsy sample of the hardened part of the injection site revealed eosinophilic infiltration (Fig. 3). He was diagnosed with insulin allergy and was changed from insulin aspart plus glargine to insulin lispro plus glargine.

The patient was receiving a high total dose of insulin (> 90 U/day); however, his glycemic levels were still poorly controlled, with fasting and postprandial hyperglycemia levels of approximately 10 mmol/L (180 mg/dl) and 18 mmol/L (324 mg/dl) respectively; the high serum insulin level also persisted. After changing the insulin, he started to develop induration at the insulin injection sites, although there was no evidence of wheals or redness, and his hypereosinophilia persisted. After liver protection treatment for more than 1 week, once his serum hepatic enzyme concentrations were normal, we added metformin 1.5 g/day to decrease his total insulin requirements. One week later, because of his continuing unsatisfactory glucose control and symptoms of insulin allergy, he was started on liraglutide 0.6 mg/day by subcutaneous injection, in addition to the insulin glargine, insulin lispro, and oral metformin. After the therapeutic change, his fasting and postprandial hyperglycemia levels significantly decreased. One week later, his blood glucose level had returned to near normal (7.1 mmol/L). Based on these findings, we progressively reduced the dose of insulin lispro (60→54→46→30→18 U/day) and insulin glargine (26→20→16→10 U/day), and increased the dose of liraglutide (0.6→0.9→1.2 mg/day). During

this process, the patient experienced satiety without nausea and diarrhea, and the induration at the insulin injection sites diminished considerably. We decided to completely discontinue the insulin lispro after 2 months of liraglutide treatment. With this new regimen of liraglutide 1.2 mg/day in combination with oral metformin and 10 U/day insulin glargine, and with an HbA1c level of 8.6%, fasting blood glucose levels fluctuated within the range of 5.2–6.7 mmol/L. This was followed by improvements in his serum insulin and eosinophil levels. Meanwhile, he had no further allergic symptoms of wheals, redness, or itching at the insulin injection sites. In addition, his body weight decreased by 6.8 kg after 4 months of liraglutide treatment.

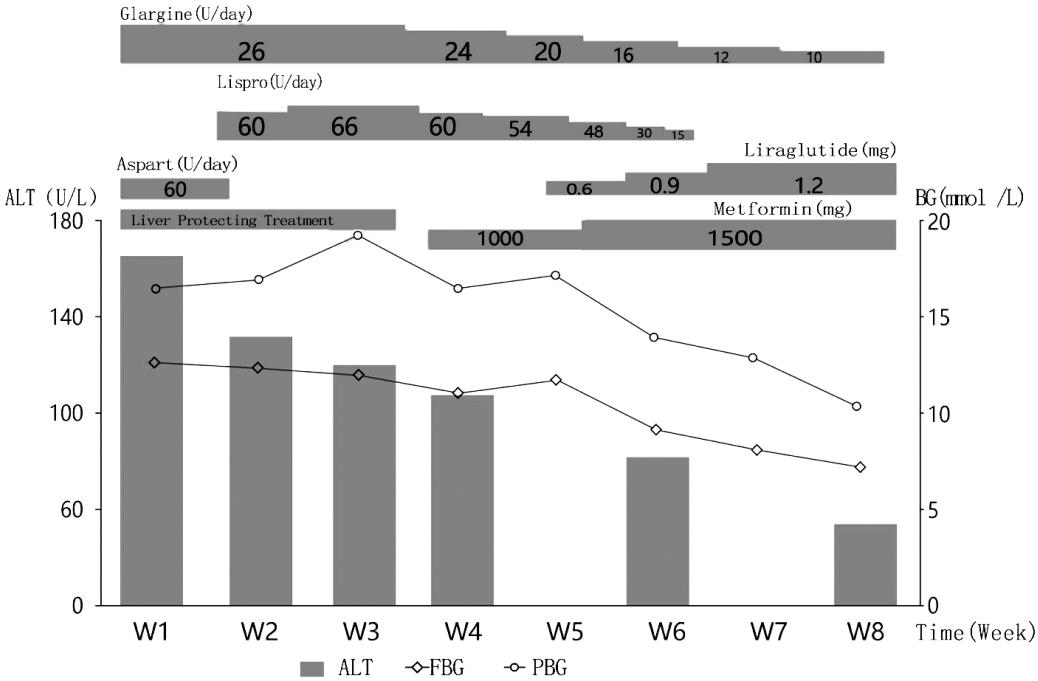

Fig. 2 A diagrammatic representation of FBG, PBG, ALT and treatment strategy after hospital admission
FBG: fasting blood glucose
PBG: postprandial blood glucose
ALT: alanine transaminase

Table 2 Laboratory data after developed insulin allergy

Parameter	Result (normal range)	Unit	Parameter	Result (normal range)	Unit
WBC	6.8 (3.5–9.5)	10^{-9}/L	ANA	Negative	
Neutrophil	62.4 (40.0–75.0)	%	Anti-SSA antibody	Negative	
Eosinophil	16.9((0.4–8.0)	%	Anti-SSB antibody	Negative	
Lymphocyte	15.7 (20.0–50.0)	%	Anti-ds-DNA antibody	Negative	IU/mL

Monocyte	4.6 (3.0–10.0)	%	RF	14.69 (0–40)	IU/mL
Basophil	0.4 (0.0–1.0)	%	IgE	864 (0–60)	IU/mL
Hb	151 (130–175)	g/L	IgG	10.32 (6.8–14.45)	g/L
PLT	130 (125–350)	10^{-9}/L	GADAb	Negative	
AST	128 (5–40)	U/L	IA-2Ab	Negative	
ALT	147 (10–42)	U/L	IAb	Negative	
γ-GTP	174 (11–50)	U/L	ZnT8Ab	Negative	
Ch-E	9745 (4500–13000)	U/L	TPOAb	127.8 (>5.61)	IU/mL
T-Bil	18.5 (3.4–20.5)	μmol/L	HbA1c	12.4	%
BUN	3.44 (2.9–8.2)	mmol/L	Glycoalbumin	4.63 (0.83–2.00)	mmol/L
Cre	64 (59–104)	μmol/L	TC	5.68 (3.10–5.18)	mmol/L
UA	448 (208–428)	μmol/L	TG	2.63 (0.40–1.80)	mmol/L
CK	172 (38–174)	U/L	HDL-c	2.17 (1.08–2.28)	mmol/L
AMY	45 (15–125)	U/L	LDL-c	3.43 (<3.10)	mmol/L
TP	54 (60–83)	g/L	FPG	10.98 (3.89–6.11)	mmol/L

ALT: alanine aminotransferase
AST: aspartate aminotransferase
AMY: amylase
BUN: blood urea nitrogen
Ch-E: cholinesterase
CK: creatine
Cre: creatinine
HDL-C: high density lipoprotein cholesterol
TC: total cholesterol
TG: triglyceride
FPG: fasting plasma glucose
γ-GTP: γ-glutamyl transpeptidase
T-Bil: total bilirubin
TP: total protein
UA: uric acid
HbA1c: glycated hemoglobin
WBC: white blood cells
PLT: platelets
Hb: hemoglobin
IgE: immunoglobulin E
IgG: immunoglobulin G
RF: rheumatoid factor
GAD: glutamic acid decarboxylase
ZnT8Ab: zinc transporter 8 autoantibody
IA-2Ab: insulinoma antigen 2 autoantibody
IAb: insulin autoantibodies
ANA: anti-nuclear antibody
Anti-ds-DNA: anti-double-stranded DNA
anti-SS-A: anti-Sjögren's syndrome A
anti-SS-B: anti-Sjögren's syndrome B

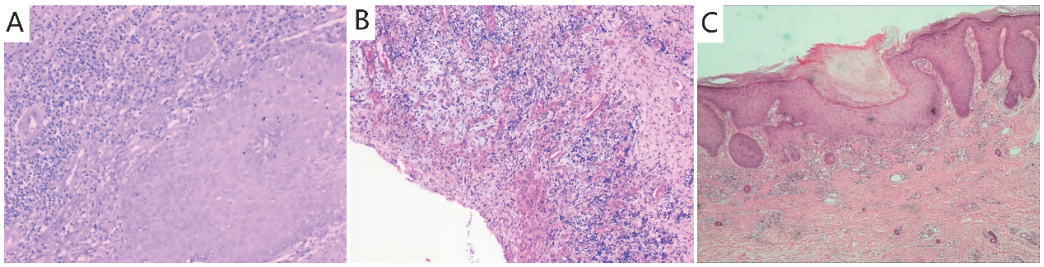

Fig. 3 Pathological results(Hematoxylin-eosin staining) of insulin injection site
The specimen obtained from the injection site of the patient. Hematoxylin-eosin staining showing predominant infiltration of eosinophils and the simultaneous infiltration of lymphocytic cells in the subcutaneous tissue. (A&B High-power micrograph 200×; C Low-power micrograph 40×)

DISCUSSION

Liraglutide treatment as a novel therapy to reduce the dose of insulin in patients with SIDM has been rarely documented. Only one case has been reported, in which liraglutide was used to alleviate the symptoms of insulin lispro allergy.[8] In our case, two important aspects should be mentioned. First, we describe a patient with SIDM who benefited greatly from liraglutide in combination with metformin and insulin therapy. Second, we provide a rare description of insulin allergy associated with hypereosinophilia in a patient with SIDM.

SIDM was recognized as a complication of glucocorticoid use in 1965.[9] Glucocorticoids are the drug group most often associated with the onset of hyperglycemia or DM.[2] Glucocorticoids also exacerbate hyperglycemia in patients with DM and unmask undiagnosed DM; moreover, they may precipitate the appearance of SIDM, which is an independent risk factor for other complications associated with the use of these drugs. Furthermore, although the blood glucose levels of non-diabetic patients should normalize after discontinuing glucocorticoid therapy, some patients require close monitoring due to the risk of developing DM in the future.[10]

Glucocorticoid-induced hyperglycemia is common in patients without a history of DM. According to a case-control analysis, the odds ratio for new-onset diabetes in patients treated with glucocorticoids is 1.36.[3] The predominant mechanisms responsible for hyperglycemia after administration of glucocorticoids may include increased gluconeogenesis, incremental hepatic glucose output, and insulin resistance. GLP-1 stimulates the β-cells to produce insulin, blocks glucagon secretion of pancreatic α-cells via somatostatin, and slows down gastric emptying. In addition, it improves peripheral glucose tolerance and suppresses appetite via its actions in the hypothalamus and amygdala, which reduces food intake, and promotes weight loss. Finally, it increases the β-cell mass and protects against glucolipotoxicity.[11-12] Interestingly, it also regulates bone physiology and improves systolic blood pressure.[13] The latest data show that liraglutide may be useful for weight management in adolescents with obesity.[14]

Insulin allergy is a recognized adverse effect of insulin treatment in diabetic patients. Ghazavi and Johnston reported a prevalence of allergic reactions to insulin products of approximately 2%.[5] In our patient, we believe that insulin aspart induced insulin allergy, based on the development of wheals, itching, and redness immediately after injections. Additionally, the patient showed an increase in eosinophils according to both local biopsy and systemic peripheral blood analysis, as well as a high level of serum IgE. This was consistent with the report by Nagai of immediate-type allergy to human insulin associated with marked eosinophilia in a patient with type 2 diabetes (T2DM).[15] Fortunately, the use of liraglutide in that patient allowed for a

reduction in the insulin dose and effectively alleviated the symptoms of insulin allergy. Based on this previous study, liraglutide might be a novel agent for the treatment of insulin allergy with hypereosinophilia in patients with T2DM.

Glycemic control remained globally unsatisfactory in our patient on corticosteroid treatment. He benefitted considerably and almost immediately from the addition of liraglutide, reflected in improved glycemic control and a reduction in the daily insulin dose. Liraglutide administration was also associated with a reduction of HbA1c level, from 12.4% to 8.6%. This improvement may be a result of suppressed ghrelin secretion due to the effects of liraglutide. Delayed gastric emptying, increased perception of satiety, reduced energy intake, and subsequently improved insulin sensitivity are possible contributing mechanisms.[16-17] Liraglutide may be a therapeutic option for SIDM treatment. Our patient was overweight, with high levels of fasting and postprandial C-peptide, which may have improved due to reduced insulin resistance and appetite suppression. Furthermore, long-term administration of glucocorticoids impairs lipid metabolism because of the stimulation of hepatic lipoprotein synthesis. In our patient, dyslipidemia, hypertension, hyperglycemia, and obesity all improved after treatment with liraglutide. By addressing these risk factors, the likelihood of cardiovascular disease could also be reduced.[18-19]

Incretin mimetics are used for the treatment of poorly controlled T2DM, particularly in obese patients. There are several reports describing the use of GLP-1 receptor agonists in patients with type 1 DM, maturity onset diabetes of the young (MODY), and C-peptide-negative diabetes, but few mention SIDM.[20-21] Ritzel et al reported that fasting hyperglycemia due to Cushing's disease can be normalized by intravenous GLP-1.[22] Furthermore, a dipeptidyl peptidase-4 (DPP-4) inhibitor improved glucose metabolism in a patient with SIDM.[23] Seetho et al reported that exenatide can improve hyperglycemia and weight loss in diabetic patients with Prader-Willi syndrome, but glycemic control worsened and their weight slightly increased over 1 year after commencing exenatide.[24]

Our study had certain limitations. Metformin was prescribed 1 week before the use of liraglutide, which was to improve insulin sensitivity. The effect of the blood glucose reduction may be attributed to the use of metformin and/or liraglutide. However, insulin aspart was switched to lispro after the allergy symptoms developed. Thus, a parallel control study is warranted. In a recent issue of Diabetes & Metabolism, Buysschaert et al reported a clinically significant improvement of psoriasis lesions in obese T2DM patients 1 year after initiating exenatide therapy.[25] However, glycemic control and psoriasis returned to pretreatment levels after cessation of exenatide treatment. MS is also an immune-mediated disorder, and we hope to see some positive effects of liraglutide treatment on our patient's MS disease at the next follow-up visit.

In conclusion, the beneficial effects of liraglutide on weight loss and appetite suppression suggest that it is a promising treatment for SIDM with insulin allergy. Further clinical research is needed to investigate this potential beneficial effect of GLP-1 receptor agonists in SIDM and other primary diseases.

DISCLOSURE

The authors have nothing to disclose.

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CONFLICT OF INTEREST

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