

Raltegravir-associated Diabetic Ketoacidosis in a Patient with HIV Infection: A Case Report

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Antiretroviral drugs, especially protease inhibitors (PI), are known to induce disorders of lipid and glucose metabolism. However, there are only a few reports of these side effects in patients treated with integrase strand transfer inhibitors (INSTI). We encountered the case of a 46-year-old man who had been treated for type 2 diabetes with diet and exercise. He contracted immunodeficiency virus (HIV) infection two years earlier and received highly active antiretroviral therapy (HAART). Three months before the current admission, HAART was switched from a non-nucleic acid reverse transcriptase inhibitor (NNRTI) to an INSTI (raltegravir: 800 mg/day). He developed diabetic ketoacidosis and was admitted for treatment. The state of health prior to admission was not well documented but he showed no clinical signs of acute infection. Accordingly, diabetic ketoacidosis was considered to be associated with INSTI. Diabetic ketoacidosis was treated appropriately and blood glucose level was controlled with medications before discharge from the hospital. Although the present case does not provide direct evidence for raltegravir-induced diabetic ketoacidosis, we caution physicians about the potential of such side effect associated with the use of INSTI.

Key words: human immunodeficiency virus, integrase strand transfer inhibitor, Hyperglycemia

INTRODUCTION

One of the side effects of antiretroviral drugs is the induction of disorders of lipid and glucose metabolism [1]. In particular, protease inhibitors are known to be associated with disorders of glucose metabolism [2, 3]. However, there are only a few reports of disorders of glucose metabolism induced by the use of integrase strand transfer inhibitors (INSTI), although the package inserts provided by the manufacturers warn of the potential of development of diabetes [4-7]. We encountered a patient with type 2 diabetes mellitus (T2DM) and human immunodeficiency virus (HIV) infection who had been treated with highly active antiretroviral therapy (HAART). The patient developed diabetic ketoacidosis after switching HAART to INSTI. While the dietary habits of this patient immediately before admission were unknown, the patient had no signs of acute or chronic infection; hence we believe that INSTI could have been responsible for the development of diabetic ketoacidosis. Although the cause of hyperglycemia in this patient is controversial, we report the case for the sake of discussion about the potential of INSTI-induced disorders of glucose metabolism.

CASE REPORT

Patient: a 46-year-old man

Main complaint: Thirst, malaise, weight loss

Medical history: Hepatitis B: 39 years of age, hypertension, diabetes, hyperuricemia, and hyperlipidemia: 40 years of age

Infection with *Toxoplasma gondii*: 43 years of age
HIV infection and AIDS-related lymphoma: 44 years of age

Family history: Father, T2DM (diet therapy)

Current medical history: Six years ago, the patient was diagnosed with T2DM but treated with diet and exercise regimen. HIV infection was diagnosed after the development of *T. gondii* infection 2.5 years before the current admission. HAART was initiated. Repeated measurements showed stable values of glycated hemoglobin (HbA1c) levels at approximately 5%. However, blood glucose control deteriorated gradually about 1 year before current admission mainly due to irregular diet habit. Subsequently, HAART was switched from a non-nucleic acid reverse transcriptase inhibitor (NNRTI) to an INSTI (raltegravir: 800 mg/day) at 3 months before admission due to poor control of hyperlipidemia and T2DM, which was considered to be a side effect of the NNRTI. Two months before the current admission, the HbA1c level was elevated at 9.9%, and the patient was thus prescribed metformin orally (250 mg/day) and was instructed to reduce carbohydrates intake, including sweetened soft drinks.

Malaise and thirst were observed by the patient 8 days before admission. He complained also of loss of appetite 7 days before admission followed by complete loss of interest in food. He reported loss of 10 kg weight within 2 weeks. He also reported spending most of his time in bed due to malaise, but finally decided to visit our hospital as an outpatient.

Table Laboratory findings

Blood gas analysis		Peripheral blood	
pH	7.218	WBC	$6.9 \times 10^3 / \mu\text{l}$
pCO ₂	12.3 torr	RBC	$6.22 \times 10^6 / \mu\text{l}$
pO ₂	119 torr	Hb	19.6 g/dl
HCO ₃ ⁻	4.8 mmol	Ht	56.1%
Lac	13 mmol	PLT	$19.2 \times 10^4 / \mu\text{l}$
Blood Chemistry		Urinalysis	
TP	8.5 g/dl	Na	126 mEq/L
Alb	4.4 g/dl	K	5.1 mEq/L
CK	26 U/l	Cl	96 mEq/L
AST	15 U/l	T.Bil	0.5 mg/dl
ALT	13 U/l	TSH	0.887 $\mu\text{U/ml}$
LDH	140 U/l	FT3	2.67 pg/ml
γ -GTP	32 U/l	FT4	1.77 ng/dl
Cr	1.32 mg/dl	GAD Ab	< 0.3 U/ml
UA	14.5 mg/dl	HIV-RNA	< 20 copy/ml
BUN	34 mg/dl	CD4	174/ μl
eGFR	48 mg/dl	CD4/CD8	0.27
Glu	545 mg/dl		
HbA1c	18.4%	Protein	1+
TG	372 mg/dl	Glucose	4+
TC	234 mg/dl	Ketone	3+
LDL-Cho	127 mg/dl		

Illness at visit: Height: 170 cm; weight: 75 kg (85 kg, 2 weeks ago; maximum weight: 99 kg, 4 years ago), body mass index (BMI) 25.9 kg/m²; body temperature: 36.9°C; pulse rate: 113 beats/min; arterial blood pressure: 110/70 mmHg; anemia/jaundice; but no lymphadenopathy in the cervical lymph nodes. Lung fields; clear; heart sound: dull. Abdomen: flat/soft; with decreased bowel sound. Physical examination also showed severe dehydration, hyperventilation, but lack of swelling of the limbs, skin rash and decreased turgor.

Laboratory findings at visit: The laboratory findings measured at admission are summarized in Table. Arterial blood gases showed metabolic acidosis. Blood glucose level was 545 mg/dL, and HbA1c was 18.4%. Urine ketone test was positive. In addition, serum creatinine, uric acid, and urea nitrogen levels were elevated, together with hypertriglyceridemia, hyponatremia, and hyperkalemia. Leukocyte count was normal. Based on these findings, he was diagnosed with diabetic ketoacidosis. Tests for HIV infection showed low CD4⁺ T-lymphocyte count (174/ μL), and RNA level of < 20 copies/mL. Chest X-ray image showed no abnormal findings. Based on the poor clinical condition, the patient was admitted to the hospital for further management.

Clinical course after hospitalization (Fig. 1): Oral administration of the antiretroviral drug was continued, while insulin therapy and treatment for hyponatremic dehydration were initiated. Continuous insulin infusion (50 units in 50 mL of normal saline) was started at 3 mL/h. Hyperkalemia rapidly improved after insulin therapy. Marked clinical improvement was noted at day 2 of admission, with resolution of acidosis and hyponatremia. On the same day, intensive insulin therapy was supported by dietary restriction with 1,200 kcal/d diabetic meals. The volume of continuous insulin

infusion was gradually decreased and terminated on day 3 of admission. Urine CPR measured on day 6 of admission was 58.9 $\mu\text{g/day}$, indicating active endogenous insulin secretion. Insulin was gradually increased to a maximum of 36 units/day but reduced following a fall in blood glucose level. Finally, blood glucose was controlled at 100–140 mg/dL under treatment with insulin (24 units/d). The patient was discharged from the hospital 16 days after admission.

DISCUSSION

We encountered the case of a patient who developed diabetic ketoacidosis with deterioration of glucose control after switching HAART therapy to INSTI. Several studies reported that certain protease inhibitors, nucleic acid reverse transcriptase inhibitors (NRTI), and NNRTIs can cause disorders of glucose metabolism [8–10]. For this reason, caution is advised after initiation of HAART treatment for HIV infection to prevent any deterioration in blood glucose control [11, 12].

Raltegravir, an INSTI, was introduced in Japan in 2008 for the treatment of HIV infection, and is reported to be clinically efficacious, with only a few subjective side effects and minimal effects on glucose/lipid metabolism [13]. NNRTIs and PIs are inducers or inhibitors of the activity of cytochrome P450 (CPY450) and substrates of CPY450; hence, these drugs interact with many other drugs that are metabolized through the CPY450 system [14]. On the other hand, INSTI has less drug interaction problems because it is metabolized through glucuronidation [13]. In our patient, HAART was switched from NNRTI to raltegravir due to worsening of hyperlipidemia and poor control of blood glucose level (Fig. 2). We also show the speed of exacerbation of diabetes before and after INSTI (Fig. 2). It shows that HbA1c level progress from 6.0% to 6.7% about for 8 months before INSTI. On the other hand, it exacerbated from 7.1% to 18.4% in just only 3 months after INSTI. Therefore, it can be said that the

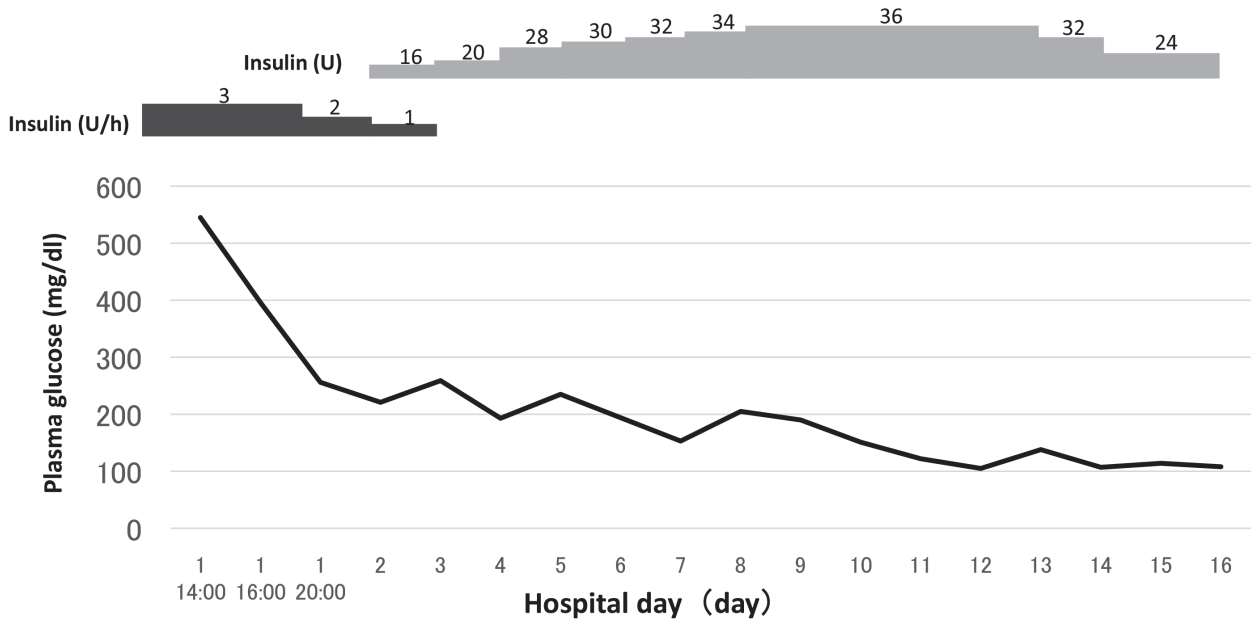


Fig. 1 Clinical course after admission to the hospital.

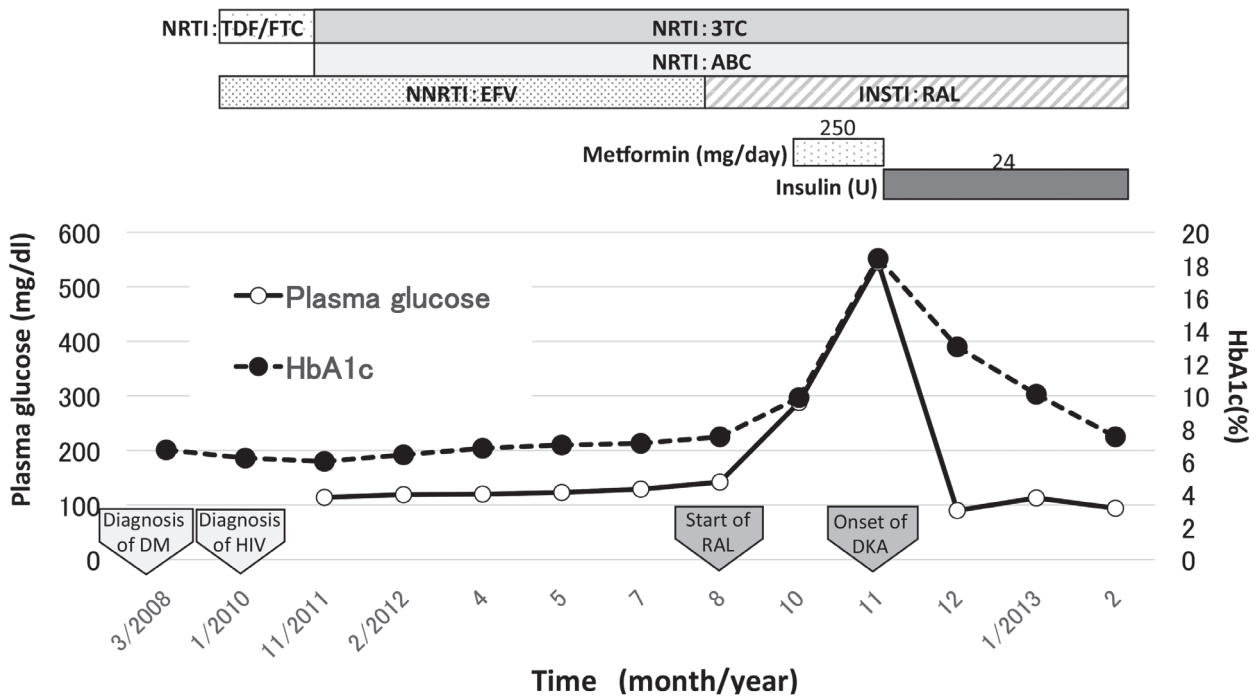


Fig. 2 Medications used for HIV and the clinical course of diabetes mellitus. TDF/FTC: emtricitabine, tenofovir disoproxil fumarate, EFV: efavirenz, 3TC: lamivudine, ABC: abacavir sulfate, RAL: raltegravir, DKA: diabetic ketoacidosis, DM: diabetes mellitus.

speed of exacerbation of diabetes is faster after INSTI. It is known that homeostasis model assessment of insulin resistance (HOMA-IR) is a surrogate marker of insulin resistance. However unfortunately fasting blood insulin level wasn't measured before and after INSTI, we can't calculate HOMA-IR. Therefore it is not clear whether insulin resistance exacerbated before and after INSTI. Interestingly, HIV-RNA level had been maintained below 20 copies/mL and favorably controlled since treatment for HIV was started in 2010.

The patient showed no clinical signs or symptoms suggestive of an infection at admission and thyroid

hormone levels were normal. Furthermore, Cushing's syndrome was ruled out based on the physical and laboratory findings. While it is possible that the calorie intake increased before the development of diabetic ketoacidosis, the patient did not have a large intake of sweetened soft drinks during that period. Then patient admitted to skipping one or two doses of antiretroviral drugs during the outpatient treatment; however, it was not clear whether this also included metformin. Dietary intake and poor drug compliance were not suspected as the causes of diabetic ketoacidosis. Rather, since diabetes is described in the package insert of

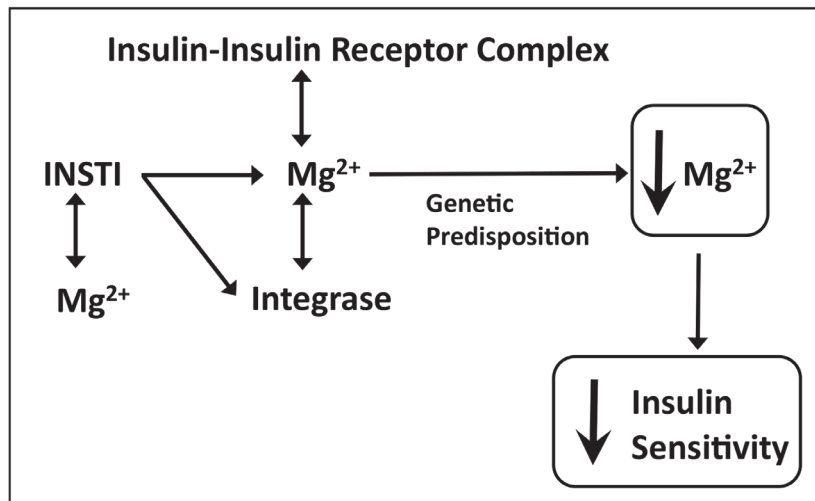


Fig. 3 Schematic diagram of the proposed mechanism of reduced insulin sensitivity, leading to diabetic ketoacidosis.

raltegravir as a possible side effect, it is suspected that raltegravir induced a large increase in blood glucose level.

Fong *et al.* [7] reported that administration of INSTI resulted in a rise in blood glucose level and HbA1c, and that blood glucose control improved after discontinuation of INSTI [7]. HIV is integrated into the host DNA by integrase, an enzyme that requires magnesium ion [7]. INSTI inhibits the integration of HIV into the host DNA by chelating magnesium ion. However, since magnesium ion also serves as a coenzyme in insulin action, chelating magnesium ion by INSTI may lead to disorders of glucose metabolism [7] (Fig. 3). In particular, magnesium ion can trigger autophosphorylation of insulin after binding to the insulin receptor. Thus, INSTI-induced decrease in magnesium ion level may lead to an increase in insulin resistance.

Immune abnormalities and chronic inflammation due to HIV infection itself may worsen insulin resistance [11, 15]. The production of proinflammatory cytokines and TNF- α is enhanced in patients with HIV infection [15–17]. Proinflammatory cytokines inhibit the production of adiponectin by adipocytes, while TNF- α diminishes the expression of glucose transporter type 4 (GLUT4) in skeletal muscles and adipose tissue; both are considered to cause of insulin resistance. Kuller *et al.* [17] reported that patients with HIV infection were at a higher risk of development of T2DM than non-infected individuals.

Based on the above background, the following are possible causes of abnormal glucose control that resulted in the development of diabetic ketoacidosis in our patient: (1) INSTI impaired glucose metabolism, (2) NRTI and NNRTI impaired glucose metabolism, and/or (3) HIV infection itself worsened insulin resistance. Raltegravir, an INSTI, is a relatively new drug with reportedly fewer side effects, though it has already been reported to induce disorders of glucose metabolism [7].

The problem in this case was that INSTI use continued without considering the possibility that it could potentially lead to disorders of glucose metabolism. If this possibility had been fully considered, close attention could have been paid to diet, daily life style, and blood sampling interval. We report this case to caution

physicians about the importance of monitoring glucose metabolism and any sign of glucose intolerance in patients treated with INSTI. For the purpose of information sharing, we encourage other researchers to report cases of patients treated with INSTI who develop glucose intolerance.

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