INTERNAL MEDICINE

□ CASE REPORT □

The Deterioration of the Glycemic Profile during Hormone Replacement Therapy in a Patient with Fulminant Type 1 Diabetes

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Abstract

Although most women with type 1 diabetes experience the normal transition to menopause, there is little information about the impact of hormone replacement therapy on their glycemic profiles. A 54-year-old postmenopausal woman with fulminant type 1 diabetes was admitted to our hospital due to diabetic ketoacidosis. She was treated with fluid replacement and a continuous insulin infusion. Thereafter, her glycemic profile was well maintained by daily multiple insulin injections. However, her glycemic profiles immediately deteriorated following the administration of progesterone in hormone replacement therapy. This transient deterioration implies that external progesterone can lead to the deterioration of glycemic profiles in postmenopausal women with type 1 diabetes.

Key words: diabetes mellitus, type 1, hormone replacement therapy, progesterone

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Introduction

Fulminant type 1 diabetes is a metabolic disease that is characterized by the rapidly progressive impairment of insulin secretion, which leads to diabetic ketoacidosis (1). While there is no sex-specific prevalence, women develop type 1 diabetes at a younger age (35.1±15.8 years) than men with or without an association with pregnancy or delivery (2). Thus, most women with fulminant type 1 diabetes experience a transition to menopause.

Hormone replacement therapy (HRT) is frequently administered to women with postmenopausal syndrome. The HRT regimens can be roughly classified into the 2 following types: estrogen only and estrogen plus progesterone. Although each regimen is associated with both risks and benefits, the estrogen plus progesterone regimen is preferably administered to women with an intact uterus to avoid estrogen-induced endometrial cancer (3). Furthermore, previous research has revealed that both HRT regimens improved the glycemic profiles of women with type 2 diabetes (4). In contrast, while glycemic fluctuations have been observed in parallel with the estrous cycles in women with type 1 diabetes (which would imply that HRT would alter the glycemic profile of such women (either positively or negatively), there is little detailed information on this matter (5-7).

We herein report a case of fulminant type 1 diabetes in a patient whose glycemic profile deteriorated during HRT using estradiol and medroxyprogesterone.

Case Report

A 54-year-old Japanese woman was admitted to hospital because of disturbance of consciousness, which followed 1 week of progressive appetite loss and nausea accompanied by vomiting. Her significant medical history included vasomotor symptoms associated with postmenopausal syndrome, which had been diagnosed when the patient was 50 years of age. She had been treated with an HRT regimen that consisted of estrogen plus medroxyprogesterone. With the exception of the patient's postmenopausal syndrome, her medical history, including the results of her previous check-ups

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Table 1. Laboratory Findings on Admission.

Hematological examination			
White blood cell	8,700	/μL	(3,500-9,500)
Hemoglobin	13.3	g/dL	(12.0-15.0)
Platelets	13.7×10^4	/μL	(14.0-38.0)
Total protein	7.2	g/dL	(6.3-8.5)
Urea nitrogen	97.9	mg/dL	(7.0-22.0)
Creatinine	4.1	mg/dL	(0.4-0.9)
Sodium	128	mEq/L	(136-146)
Potassium	6.2	mEq/L	(3.3-5.0)
Chloride	82	mEq/L	(95-110)
Total bilirubin	0.4	mg/dL	(0.3-1.0)
Aspartate aminotransferase	43	U/L	(8-37)
Alanine aminotransferase	62	U/L	(5-35)
Lactate dehydrogenase	168	U/L	(110-255)
Creatine kinase	2,242	U/L	(18-150)
Alkaline phosphatase	659	U/L	(120-385)
Amylase	4,221	U/L	(40-180)
Lipase	1,046	U/L	(17-57)
HDL cholesterol	53	mg/dL	(35-90)
LDL cholesterol	111	mg/dL	(70-139)
Triglyceride	73	mg/dL	(50-180)
C-reactive protein	2.7	mg/dL	(0.0-0.3)
Casual plasma lucose	75.4	mmol/L	(4-6)
Glycated emoglobin	6.9	%	(4.6-6.2)
C-peptide	0.1	ng/mL	(0.8-2.5)
Acetoacetic acid	5,440	μmol/L	(0-55)
3-Hydroxybutanoic acid	21,280	μmol/L	(0-85)
Urinary examination			
Protein	(±)		
Glucose	(4+)		
Ketone body	(2+)		
Occult blood	(2+)		
Atrial blood gas analysis under reservoir mask at O_2 10L/min			
pH	7.040		(7.350-7.450)
$PaCO_2$	11.6	mmHg	(35.0-45.0)
PaO_2	322.3	mmHg	(75.0-100.0)
HCO_3^-	3.1	mmol/L	(20.0-26.0)
Base excess	-25.5	mmol/L	(-3.0-3.0)

and her family and travel history, was unremarkable. She had never used tobacco and did not drink alcohol.

On physical examination, the patient's Glasgow Coma Scale (GCS) value was 13: E4 V3 M6, her body temperature was 34.3℃, her blood pressure was 82/46 mmHg, her pulse was regular at 104 beats/min, and her respiratory rate was 24 breaths/min. Body measurements could not be made on admission due to the patient's acute distress. After her recovery, her height (149.5 cm) and weight (39.3 kg) were measured. She had dry mucous membranes and decreased skin turgor. There was no sign of skin rash, lymph node swelling, thyroid enlargement, pathological rales/murmurs, remarkable abdominal findings, or pretibial edema.

The laboratory data on arrival revealed severe hyperglycemia and metabolic acidosis with ketone bodies. The patient's glycated hemoglobin level (6.9%) was still mild considering her plasma glucose value. Her serum levels of urea nitrogen, creatinine, transaminase, creatine kinase, amylase, and lipase were remarkably elevated. Her serum electrolyte levels were imbalanced. A urinalysis revealed proteinuria, glucosuria, ketonuria, and occult hematuria. Detailed data are shown in Table 1. Although computed tomography revealed mild pancreatomegaly, there was no evidence of effusion around the pancreas or abnormal findings in relation to the chest, liver, adrenal gland, kidney, spleen, uterus, or ovaries were evident.

The patient was diagnosed with diabetic ketoacidosis due to fulminant type 1 diabetes. She was simultaneously treated with fluid replacement and continuous insulin infusion to maintain her vital signs and her plasma glucose and electrolyte levels. On day 3, the patient's ketonuria, kidney function, electrolytes and vital signs had normalized. On day 4, the continuous infusion of insulin was withdrawn and daily multiple insulin injection therapy was administered with blood glucose monitoring. On day 5, the patient's liver function spontaneously normalized. The insulin dose was titrated and the mean preprandial blood glucose was maintained. On day 11, HRT was restarted; initially, only percutaneous estradiol gel (1 mg/day) was administered. Her glycemic profiles showed unremarkable changes during this period. On day 21, oral medroxyprogesterone (2.5 mg/day) was administered in addition to percutaneous estradiol gel. Subsequently, her glycemic profiles showed an immediate deterioration, despite a stable carbohydrate intake, suitable injection technique and a good physical condition. No factors that might have exacerbated the patient's glycemic control (such as fever, electrolytic imbalance, liver dysfunction, kidney dysfunction or heart failure) were observed. The mean preprandial blood glucose level was elevated to a maximum of 22.1 mmol/L on the day after the administration of medroxyprogesterone. HRT was discontinued, and her glycemic profile immediately improved. The average pre-prandial blood glucose level during administration of medroxyprogesterone was significantly higher than it was before ($p=0.0017$) and after ($p<0.001$) the administration (Table 2). The patient's glycemic profile from the day of admission until discharge are shown in Figure. The clinical course after this transient deterioration was uneventful. The patient was discharged on day 45.

The results of the serological findings and the patient's insulin secretory capacity, which were obtained subsequent to her recovery, are shown in Table 3. The patient was negative for autoantibodies and her insulin secretion were completely impaired. These findings were compatible with fulminant type 1 diabetes.

Discussion

Previous studies have revealed that HRT improves the glycemic profiles of women with type 2 diabetes (4). Conversely, the deterioration of the glycemic profile after the administration of medroxyprogesterone that was observed in the present case implied that the external application of progesterone can alter the glycemic profile of postmenopausal women with type 1 diabetes.

There are few reports on the impact of HRT on the glycemic profiles of women with type 1 diabetes. A meta-analysis pointed out that the previous randomized controlled trials were underpowered and concluded that there is little evidence about the impact of HRT on the glycemic profiles in

Table 2. Preprandial Blood Glucose around Medroxyprogesterone Administration.

	Preceding 5 days	During 5 days	Following 5 days
Average (±SD) mmol/L	10.8 (±3.1)	16.2 (±6.7)	9.5 (±3.4)

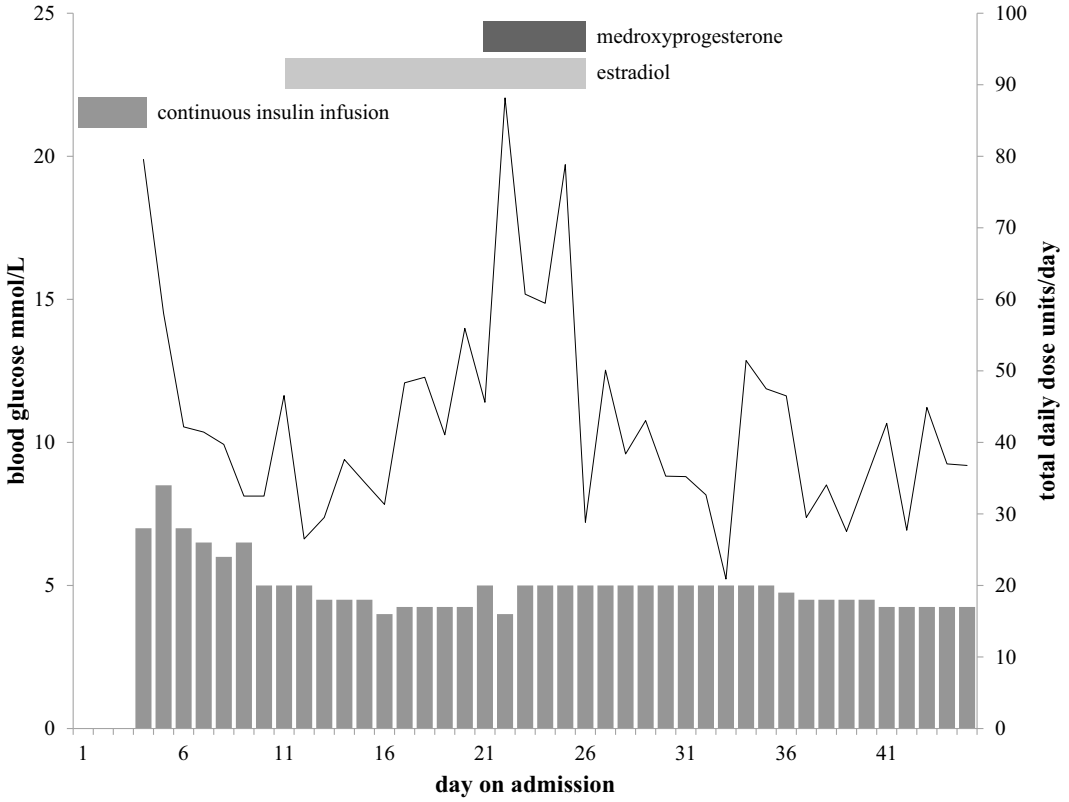

Figure. The clinical course of this case. The horizontal axis indicates the clinical time course. The solid line indicates the mean preprandial blood glucose values; the left vertical axis shows the units of glucose. The vertical gray bars indicate the total daily dose from multiple daily insulin injections; the left vertical axis shows the total daily dose units. The horizontal gray bars show continuous insulin infusion, estradiol, and medroxyprogesterone, respectively.

Table 3. Serological Findings and Insulin Secretory Capacity Subsequently Obtained after Patient's Recovery.

Serological examination			
Anti GAD antibody	1.8	U/mL	(0.0-1.4)
Anti IA2 antibody	<0.4	U/mL	(0.0-0.3)
Anti IAA antibody	0.7	%	(<0.3)
Anti TPO antibody	<5.0	U/mL	(<15.9)
Anti Tg antibody	<10	U/mL	(<27.9)
Insulin secretory capacity			
Fasting C-peptide	0.1	ng/mL	
Glucagon stimulated C-peptide	0.1	ng/mL	
Urine C-peptide	1.6	μg/day	(22.8-155.2)

women with type 1 diabetes (6). Moreover, our literature search revealed no detailed information about the impact of progesterone in HRT in women with type 1 diabetes.

Several investigators have reported a relationship between the glycemic profile and the estrous cycle. For instance, a mild upward trend in the postprandial plasma glucose values in the luteal phase was observed, even in young women without diabetes (8). Furthermore, the glycemic fluctuations that were observed in women with type 1 diabetes were more prominent; it was reported (and clinically experienced) that the glycemic profile deteriorated in the luteal phase and improved in the follicular phase (5). The cause of this fluctuation was presumed to be due to the increased level of progesterone in the luteal phase. Medroxyprogesterone worsened the insulin sensitivity of macaques. Furthermore, fundamental studies reported that the administration of estrogen and progesterone lowered and raised the plasma glucose levels, respectively, in an alloxan-induced type 1 diabetes mouse model (9, 10). Moreover in humans, the administration of medroxyprogesterone raised fasting glucose and insulin levels (11). Given this information, the glycemic profiles in type 1 diabetes seem to be fragile in the presence of sex steroid fluctuations and it was implied that HRT, especially medroxyprogesterone, can lead to a deterioration in the insulin sensitivity and thereby lead to a high glucose level.

Although there is a previously reported case of a pregnant

woman with type 1 diabetes whose glycemic profile deteriorated following an intramuscular injection of hydroxyprogesterone, the extent of her deterioration was milder than that which was observed in the present case (12). Certainly this patient's small build, her race, drug-specific effects, and the route of administration were candidate etiologies for this drastic glycemic fluctuation. However, it is very difficult to make a fair judgment due to the extreme scarcity of information about HRT in type 1 diabetes. The present study is associated with some limitations: we could not confirm whether the repeated oral administration of medroxyprogesterone would cause another episode of glucose deterioration. Because, the patient did not suffer from vasomotor symptoms, that is, hot flushes and night sweats despite the discontinuance of HRT, we did not approve the re-administration of medroxyprogesterone. Thus, there is a need for further studies about the impact of HRT, including progesterone, on large numbers of postmenopausal women with type 1 diabetes.

Opinions are divided among investigators as to whether women with type 1 diabetes have an earlier menopause than individuals without type 1 diabetes. However, if it is assumed that most patients with type 1 diabetes will experience a transition to menopause, an appropriate and safe HRT regimen should to be established. In summary, this case implies that the external administration of progesterone might deteriorate the glycemic profiles of postmenopausal women with type 1 diabetes and should alert physicians to the necessity of further investigation to establish a safe regimen of HRT for these women.

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

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