CASE REPORT

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

Sho Tanaka¹, Mikano Hishiki³, Junko Ogawara³, Erisa Sorimachi² and Mari Nakayama²

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

(Intern Med 56: 531-534, 2017)
(DOI: 10.2169/internalmedicine.56.7663)

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

¹Division of Nephrology, Hypertension and Endocrinology, Department of Medicine, Nihon University School of Medicine, Japan and ²Department of Diabetology and Endocrinology, Tokyo Metropolitan Hiroo Hospital, Japan

Received for publication April 30, 2016; Accepted for publication June 27, 2016
Correspondence to Dr. Sho Tanaka, tanakasho13@gmail.com
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°C, 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. There was no evidence of effusion around the 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 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 × 10^11 /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 lactate | 75.4 mmol/L (4-46) |
| Glycated hemoglobin | 6.9 % (4-6.2) |
| C-peptide       | 0.1 mg/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 O₂ 10L/min |
| pH 7.04 (7.350-7.450)                        |
| PaCO₂ 11.6 mmHg (35.0-45.0)                  |
| PaO₂ 322.3 mmHg (75.0-100.0)                 |
| HCO₃⁻ 3.1 mmol/L (20.0-26.0)                 |
| Base excess -25.5 mmol/L (3.1-3.1)            |

Intern Med 56: 531-534, 2017 DOI: 10.2169/internalmedicine.56.7663
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 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).

Acknowledgement

We thank Dr. Masayoshi Soma, Professor of Division of Nephrology, Hypertension and Endocrinology, Department of Medicine, Nihon University School of Medicine, for his help in providing clinical advice for this case.

References

1. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. Osaka IDDM Study Group. N Engl J Med 342: 301-307, 2000.
2. Imagawa A, Hanafusa T, Uchigata Y, et al. Fulminant type 1 diabetes: a nationwide survey in Japan. Diabetes Care 26: 2345-2352, 2003.
3. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women’s Health Initiative randomized trials. JAMA 310: 1353-1368, 2013.
4. Ferrara A, Karter AJ, Ackerson LM, et al. Hormone replacement therapy is associated with better glycemic control in women with type 2 diabetes: The Northern California Kaiser Permanente Diabetes Registry. Diabetes Care 24: 1144-1150, 2001.
5. Barata DS, Adan LF, Netto EM, Ramalho AC. The effect of the menstrual cycle on glucose control in women with type 1 diabetes evaluated using a continuous glucose monitoring system. Diabetes Care 36: e70, 2013.
6. Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. Cochrane Database Syst Rev 6: CD008613, 2013.
7. Scott AR, Dhindla P, Forsyth J, Mansell P. Effect of hormone replacement therapy on cardiovascular risk factors in postmenopausal women with diabetes. Diabetes Obes Metab 6: 16-22, 2004.
8. Bennal AS, Kerure SB. Glucose handling during menstrual cycle. Int J Reprod Contracept Obstet Gynecol 2: 284-287, 2013.
9. Cruzen CL, Baum ST, Colman RJ. Glucoregulatory function in adult rhesus macaques (Macaca mulatta) undergoing treatment with medroxyprogesterone acetate for endometriosis. J Am Assoc Lab Anim Sci 50: 921-925, 2011.
10. Bhattacharya S, Bank S, Hait S, K Sinha A. The control of hyperglycemia by estriol and progesterone in alloxan induced type 1 diabetes mellitus mice model through hepatic insulin synthesis. Int J Biomed Sci 10: 8-15, 2014.
11. Berenson AB, van den Berg P, Williams KJ, Rahman M. Effect of injectable and oral contraceptives on glucose and insulin levels. Obstet Gynecol 117: 41-47, 2011.
12. Sasaki S, Yasuda T, Kaneto H, Kuroda A, Fujita Y. Basal insulin requirements after progesterone treatment in a type 1 diabetic pregnant woman. Intern Med 52: 259-262, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).