Two Cases of Thyrotoxicosis and Euglycemic Diabetic Ketoacidosis Under Sodium-glucose Transport Protein 2 Inhibitor Treatment

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Abstract:
Thyrotoxicosis and sodium-glucose transport protein 2 inhibitors (SGLT2is) are associated with the induction of euglycemic diabetic ketoacidosis (euDKA). We herein report two cases of euDKA in patients with diabetes mellitus wherein both thyrotoxicosis and SGLT2i treatment were the underlying causes. One patient developed thyrotoxicosis during the course of type 2 diabetes mellitus, whereas the other patient was suspected of developing slowly progressive insulin-dependent diabetes mellitus during the course of Graves’ disease. Although such cases are rare, there is some concern that similar cases may occur because of the increased frequency of SGLT2i use in recent years.

Key words: thyrotoxicosis, thyroid storm, Graves’ disease, euglycemic diabetic ketoacidosis, SGLT2 inhibitor

Introduction
Sodium-glucose transport protein 2 inhibitors (SGLT2is) are oral antidiabetic agents that decrease blood glucose levels by increasing urinary glucose excretion. Some SGLT2i drugs protect against the development of heart failure and the progression of chronic kidney disease (1-3). Therefore, some SGLT2i have become a treatment option for patients with chronic heart failure or chronic kidney disease, with or without comorbid diabetes, and the number of patients using them is expected to increase. In addition, SGLT2is increase fat catabolism, which can have a weight-reducing effect; however, their use also increases the accumulation of ketone bodies, which can cause euglycemic diabetic ketoacidosis (euDKA).

Excess thyroid hormones are also known to cause DKA by increasing fat catabolism and ketone body production. Thyroid dysfunction complications are not rare in patients with diabetes (4). According to a previous report, 2.0% of patients with diabetes had hyperthyroidism (5), while the calculated annual incidence of hyper- and hypothyroidism in the general population is reported to be 0.5% in women and <0.1% in men (6). If diabetic patients receiving SGLT2is develop thyrotoxicosis, euDKA may be more likely to develop due to the presence of both mechanisms.

Recently, we treated two patients with diabetes mellitus complicated by thyrotoxicosis who developed euDKA after SGLT2i treatment. To our knowledge, there have been no previous reports of euDKA induced by either mechanism, except for Case 1, which was originally reported in a Japanese article (7).

In these two contrasting cases, one patient diagnosed with type 2 diabetes mellitus developed thyrotoxicosis, while the other was suspected of developing slowly progressive insulin-dependent diabetes mellitus during the course of Graves’ disease. These two cases highlight the potential relationship between hyperthyroidism and diabetes and suggest that caution should be exercised when using SGLT2is.
**Case Reports**

**Table 1. Laboratory Findings on Admission of Case 1.**

| Parameter | Value | Unit   | Parameter | Value | Unit   |
|-----------|-------|--------|-----------|-------|--------|
| ALB       | 4.3 g/dL |       | Arterial blood gas analysis* |       |        |
| AST       | 62 U/L  |       | pH        | 7.035 |        |
| ALT       | 116 U/L |       | PaCO₂     | 15.4 mmHg |       |
| ALP       | 154 U/L |       | PaO₂      | 139 mmHg |       |
| LDH       | 175 U/L |       | HCO₃⁻     | 3.9 mmol/L |       |
| T-Bil     | 0.36 mg/dL |       | AG        | 29.1 mEq/L |       |
| AMY       | 43 U/L  |       | Lac       | 4.8 mmol/L |       |
| CK        | 77 U/L  |       |           |        |        |
| UA        | 14 mg/dL |       |           |        |        |
| Posm      | 313 mOsm/kg | Protein | (2+) |       |
| BUN       | 24.7 mg/dL |       | Glucose   | (4+) |       |
| Cre       | 0.60 mg/dL |       | Ketone    | (3+) |       |
| Na        | 138 mg/dL |       |           |        |        |
| K         | 5.1 mg/dL |       |           |        |        |
| Cl        | 105 mEq/L |       | PG        | 259 mg/dL |       |
| Ca        | 8.6 mg/dL |       | HbA1c     | 7.8 % |       |
| IP        | 6.1 mg/dL |       | AcAc      | 3,730 μmol/L |       |
| CRP       | 0.04 mg/dL |       | β-OHBA    | 9,720 μmol/L |       |
| BNP       | 443.5 pg/mL |       | ACTH      | 120.3 pg/mL |       |
| WBC count | 23,200 /μL |       | Cortisol  | 37.9 μg/dL |       |
| Neut      | 91.5 %  |       | CFR       | 3.57 ng/mL |       |
| Lymph     | 4.0 %   |       | GADAb     | <5.0 μU/mL |       |
| Mono      | 4.5 %   |       | TSH       | <0.005 μU/mL |       |
| Baso      | 0 %     |       | FT3       | 25.0 pg/mL |       |
| Eosino    | 0 %     |       | FT4       | 7.1 ng/dL  |       |
| Hgb       | 14.7 g/dL |       | TRAb      | >40.0 μU/mL |       |
| HCT       | 45.8 %  |       | TSAb      | 549 % |       |
| PLT count | 41.5 ×10⁹/μL |       | TPOAb     | 401 IU/mL |       |
| PT-1NR    | 1.19    |       | Tg        | 17.3 ng/mL |       |
| aPTT      | 20.3 s  |       |           |        |        |
| D-dimer   | 32.4 μg/mL |       |           |        |        |

*Under medium-concentration oxygen mask 7 L inspiration (FIO₂ level 0.30). ALB: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; T-Bil: total bilirubin; AMY: amylase; CK: creatine kinase; UA: urine acid; Posm: plasma osmolality; BUN: blood urea nitrogen; Cre: creatinine; Na: sodium; K: potassium; Cl: chloride; Ca: calcium; IP: inorganic phosphorus; CRP: C-reactive protein; BNP: brain natriuretic peptide; WBC: white blood cell; Neut: neutrophil; Lymph: lymphocyte; Mono: monocyte; Baso: basophil; Eosino: eosinophil; Hgb: hemoglobin; HCT: hematocrit; PLT: platelet; PT-1NR: prothrombin time-international normalized ratio; aPTT: activated partial thromboplastin time; PaCO₂: partial pressure of carbon dioxide; PaO₂: partial pressure of oxygen; HCO₃⁻: bicarbonate; AG: anion gap; Lac: lactic acid; PG: plasma glucose; HbA1c: glycated hemoglobin; AcAc: acetoacetic acid; β-OHBA: β-hydroxybutyric acid; ACTH: adrenocorticotropic hormone; CPR: C-peptide immunoreactivity; GADAb: glutamic acid decarboxylase antibody; TSH: thyroid-stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TRAb: thyroid-stimulating hormone receptor antibody; TPOAb: thyroid peroxidase antibody; Tg: thyroglobulin.

**Case 1**

A 67-year-old woman presented with complaints of weight loss, fatigue, decreased appetite, nausea, and diarrhea. She had been diagnosed with type 2 diabetes mellitus at 57 years old and treated with 25 mg empagliflozin, 5 mg linagliptin, 2,000 mg metformin, and 1.5 mg repaglinide. Empagliflozin therapy had been initiated five years prior to the hospital visit. The patient had no history of thyroid disease. Her weight had decreased by 7 kg in the 3 months prior to the visit. She developed the symptoms described above, had difficulty moving, and had been unable to eat for three days prior to the visit but continued all of her medications. She was brought to our hospital by ambulance and admitted on the same day.

On admission, the patient (height: 158.0 cm; weight: 51.0 kg; body mass index: 20.43 kg/m²) had impaired consciousness, with a Japan Coma Scale score of 1-2. Her body temperature, resting heart rate, blood pressure, respiratory rate, and peripheral oxygen saturation were 38.4°C, 174 beats/min, 162/83 mmHg, 47 breaths/min, and 90% (room air), respectively. She had Kussmaul breathing, and her face appeared pained. The thyroid gland was diffusely enlarged, elastic, and soft, with no palpable nodules. She had a clear respiratory sound and grade 3/6 systolic ejection murmur. No other abnormalities were found during the physical examination.

The laboratory findings are shown in Table 1. Elevated transaminase and brain natriuretic peptide levels indicated damage to various organs. Her glycated hemoglobin (HbA1c) level was 7.8%, and her random blood glucose level was 259 mg/dL. An arterial blood gas analysis revealed severe metabolic acidosis and a large anion gap. Elevated ketone body levels were observed in plasma and urine samples. The insulin secretion ability was preserved. She had thyrotoxicosis and was strongly positive for thyroid-stimulating hormone receptor antibody (TRAb).

Electrocardiography (ECG) revealed severe tachycardia with a heart rate of 175 beats/min. Chest radiography revealed no cardiomegaly or pulmonary congestion. Transthoracic echocardiography showed diffusely increased wall motion with no wall motion abnormalities. Thyroid echography revealed diffuse enlargement of the thyroid gland and increased blood flow. D-dimer elevation suggested the presence of pulmonary embolism or deep vein thrombus, but contrast-enhanced CT showed no obvious thrombosis; thus, the D-dimer elevation might have been caused by hypercoagulability due to hyperthyroidism (8).

Based on these clinical findings, the patient was diagnosed with thyroid crisis caused by Graves’ disease (9, 10) as well as euDKA (11). The Acute Physiology and Chronic Health Evaluation II score (12), an index of systemic complications, was 24 points, suggesting high disease severity.

The clinical course of the patient is shown in Fig. 1. After admission, the patient was managed in the intensive-care unit. The thyroid crisis was treated with thiamazole (MMI), potassium iodide (KI), and dexamethasone (DEX). EuDKA was treated with continuous intravenous insulin and glucose supplementation. On the seventh day, the patient suddenly...
developed right hemiplegia and aphasia. Cerebral magnetic resonance imaging revealed a cerebral infarction in the left middle cerebral artery region, although no obvious atrial fibrillation was observed on ECG. Carotid artery echocardiography and magnetic resonance angiography found no indication of an atherothrombotic mechanism and thus no obvious cause of the cerebral infarction; however, hypercoagulability due to hyperthyroidism may have contributed to the development of the infarction. The patient’s free triiodothyronine (FT3) level decreased but increased before and after the stroke. After the onset of cerebral infarction, MMI was changed from 20 mg orally to 60 mg intravenously for the strict management of thyrotoxicosis. Despite emergency thrombus retrieval and continuous heparin infusion, the neurological prognosis was poor, and the patient sustained right hemiplegia and aphasia.

The patient’s glucose level and thyroid function stabilized, and she was transferred to a convalescent hospital on the 64th day for rehabilitation. The patient provided her written informed consent for the publication of this case report. The present case was originally reported in a Japanese article (7).

Case 2

A 27-year-old man presented to our emergency department with complaints of thirst, palpitations, fatigue, and weight loss. He had no family history of endocrine disorders or diabetes mellitus. He had been diagnosed with Graves’ disease at 21 years old and started treatment with 5 mg MMI on alternate days, which stabilized his thyroid function. The patient’s plasma glucose level had been elevated for six months prior to his visit. Three days before his visit, he was diagnosed with diabetes mellitus, with a plasma glucose level of 250 mg/dL and an HbA1c level of 9.4%. He started taking 10 mg of empagliflozin and began limiting his carbohydrate intake at his own discretion. Thereafter, he developed symptoms of thirst, palpitations, and fatigue. In addition, his weight decreased by 5 kg within 1 month. The patient felt very ill, called for an ambulance, and was admitted to our hospital on the same day. At the time of admission, he was administered 10 mg empagliflozin, 5 mg MMI, and 20 mg febuxostat.

On admission, the patient (height: 169.0 cm, weight: 63.1 kg, body mass index: 22.10 kg/m²) was conscious and alert. His body temperature, resting heart rate, blood pressure, respiratory rate, and peripheral oxygen saturation were 36.8°C, 125 beats/min (regular), 116/89 mmHg, 20 breaths/min, and 98% (room air), respectively. The thyroid gland was diffusely enlarged, elastic, and soft with no palpable nodules. No other abnormalities were found during the physical examination.

The laboratory findings are shown in Table 2. The patient had thyrotoxicosis and TRAb positivity. His HbA1c level was 8.9%, and his plasma glucose level was 99 mg/dL. An arterial blood gas analysis revealed severe metabolic acidosis and a large anion gap. Elevated ketone body levels were ob-
Table 2. Laboratory Findings on Admission of Case 2.

| Parameter | Value | Unit | Parameter | Value | Unit |
|-----------|-------|------|-----------|-------|------|
| ALB       | 5.4 g/dL |       | Venous blood gas analysis |       |      |
| AST       | 44 U/L |      | pH | 7.177 |       |
| ALT       | 83 U/L |      | PaCO2 | 29.7 mmHg |       |
| ALP       | 240 U/L |      | PaO2 | 51.7 mmHg |       |
| LDH       | 196 U/L |      | HCO3⁻ | 10.6 mmol/L |       |
| T-Bil     | 0.63 mg/dL |     | AG | 21.4 meq/L |       |
| AMY       | 40 U/L |      | Lac | 1.00 mmol/L |       |
| CK        | 60 U/L |      |       |       |      |
| UA        | 7.8 mg/dL |     |       |       |      |
| Posm      | 287 mOsm/kg |     | Protein | (1+) |      |
| BUN       | 13.1 mg/dL |    | Glucose | (4+) |       |
| Cre       | 0.76 mg/dL |     | Ketone | (3+) |       |
| Na        | 134 mEq/L |      |       |       |      |
| K         | 4.8 mEq/L |      |       |       |      |
| Cl        | 102 mEq/L |      | PG | 99 mg/dL |       |
| Ca        | 10.3 mg/dL |     | HbA1c | 8.9 % |       |
| IP        | 4.1 mg/dL |      | AcAc | 2,080 μmol/L |       |
| CRP       | 0.04 mg/dL |     | β-OHBA | 7,580 μmol/L |       |
| BNP       | 16.2 pg/mL |     | ACTH | 28.0 pg/mL |       |
| WBC count | 6,900 /μL |     | Cortisol | 11.1 μg/dL |       |
| Neut      | 66.9 % |      | CRP | 1.72 ng/mL |       |
| Lymph     | 28.4 % |      | GADAb | 725.8 U/mL |       |
| Mono      | 4.4 % |      | TSH | 0.006 μIU/mL |       |
| Baso      | 0.3 % |      | FT3 | 8.5 pg/mL |       |
| Eosino    | 0 % |      | FT4 | 4.0 ng/dL |       |
| Hgb       | 16.8 g/dL |     | TRAb | 11.9 μg/mL |       |
| HCT       | 47.2 % |      | Tg | 1.72 ng/mL |       |
| PLT count | 25.8 x10⁹/μL |   |       |       |      |
| PT-INR    | 1.00 |      |       |       |      |
| APTT      | 32 s |      |       |       |      |
| D-dimer   | 1.4 μg/mL |     |       |       |      |

ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, AMY: amylase, CK: creatine kinase, UA: urine acid, Posm: plasma osmolality, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, IP: inorganic phosphorus, CRP: C-reactive protein, BNP: brain natriuretic peptide, WBC: white blood cell, Neut: neutrophil, Lymph: lymphocyte, Mono: monocyte, Baso: basophil, Eosino: eosinophil, Hgb: hemoglobin, HCT: hematocrit, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, PaCO2: partial pressure of carbon dioxide, PaO2: partial pressure of oxygen, HCO3⁻: bicarbonate, AG: anion gap, Lac: lactic acid, PG: plasma glucose, HbA1c: glycated hemoglobin, AcAc: acetoacetic acid, β-OHBA: β-hydroxybutyric acid, ACTH: adrenocorticotropic hormone, CPR: C-peptide immunoreactivity, GADAb: glutamic acid decarboxylase antibody, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, TRAb: thyroid-stimulating hormone receptor antibody, Tg: thyroglobulin.

In our study, we observed that glucagon loading tests (baseline and 6-min C-peptide values were 2.15 and 4.18 ng/mL, respectively). ECG showed a heart rate of 90 beats/min with normal sinus rhythm. Chest radiography revealed no cardiomegaly or pulmonary congestion. Thyroid echocardiography revealed diffuse goiter enlargement and increased blood flow. Based on these clinical findings, the patient was diagnosed with exacerbation of Graves’ disease and euDKA. Although depletion of insulin secretion was not observed, slowly progressive insulin-dependent diabetes mellitus (SPIDDM) was suspected because of the strong positivity for anti-GAD antibody (13).

The clinical course of the patient is shown in Fig. 2. For the exacerbation of Graves’ disease, the dose of MMI was increased to 15 mg/day, and treatment with KI was initiated. To treat euDKA, SGLT2i was discontinued, and an appropriate amount of carbohydrate intake and frequent subcutaneous insulin injections were administered. Consequently, his thyroid function, acidemia, and blood glucose levels gradually stabilized. Since SPIDDM was suspected, the patient was instructed to undergo self-administration of insulin and self-monitoring of blood glucose levels. On the eighth day after admission, the patient was discharged after receiving a daily dose of 7 units of insulin degludec, 18 units of insulin lispro, 15 mg MMI, and 20 mg fexofenadate. The patient provided his written informed consent for the publication of this case report.

Discussion

We herein report two rare cases of euDKA and thyrotoxicosis after treatment with SGLT2i. The patient in Case 1 developed thyrotoxicosis during the course of type 2 diabetes mellitus, whereas the patient in Case 2 was suspected of having developed SPIDDM during the course of Graves’ disease. As the frequency of SGLT2i treatment is increasing, there is concern that the frequency of similar cases may also increase.

EuDKA was first described by Munro et al. (1973). It is defined by a blood glucose level of <300 mg/dL and HCO₃⁻ level of <10 mEq/L (11). Excessive carbohydrate restriction, heavy alcohol consumption, chronic liver disease, glycoprotein storage disorders (glycogenosis), pregnancy, and sepsis have been reported as etiological factors (14, 15).

The possible mechanisms underlying euDKA development in our study are shown in Fig. 3. Thyrotoxicosis leads to abnormal glucose tolerance owing to accelerated gluconeogenesis, increased insulin resistance, and increased glucose absorption in the gut (16-20). Blood glucose levels predominantly increase after meals, a phenomenon known as oxyhyperglycemia (21). However, the negative regulation of sterol regulatory element-binding protein-1c and angiopoietin-like protein 3 enhances fat catabolism and ketone body production (22, 23). In addition, the activation of the sympathetic nervous system via the β-adrenergic system induces excess cation (24-28).

Under fasting conditions, ketone body production may predominantly increase after meals, a phenomenon known as oxyhyperglycemia (21). However, the negative regulation of sterol regulatory element-binding protein-1c and angiopoietin-like protein 3 enhances fat catabolism and ketone body production (22, 23). In addition, the activation of the sympathetic nervous system via the β-adrenergic system induces excess cation (24-28). Under fasting conditions, ketone body production may predominantly increase after meals, a phenomenon known as oxyhyperglycemia (21). However, the negative regulation of sterol regulatory element-binding protein-1c and angiopoietin-like protein 3 enhances fat catabolism and ketone body production (22, 23). In addition, the activation of the sympathetic nervous system via the β-adrenergic system induces excess cation (24-28).
increasing insulin secretion and increasing glucagon secretion (29). In addition, ketone body reabsorption in the kidneys increases (30). Through these mechanisms, the use of SGLT2is can lead to euDKA. Pancreatic β-cell dysfunction present in a patient can increase the risk of euDKA (30-32). As such, the Japanese Diabetes Society has issued recommendations on the use of SGLT2is to reduce the risk of DKA development due to inappropriate use (33).

In Case 1, SGLT2i treatment was continued despite a poor dietary intake, and in Case 2, the patient chose to restrict his carbohydrate intake after starting SGLT2i treatment. Therefore, it is important to teach patients how to manage their condition effectively and to avoid excessive carbohydrate restriction. In case 2, euDKA may have occurred as a result of increased fat catabolism due to hyperthyroidism and continued use of an SGLT2i despite a poor diet and carbohydrate intake.

The association between thyroid disease and diabetes mellitus was also notable. In Case 1, Graves’ disease may have occurred incidentally during the course of type 2 diabetes mellitus. Care should be taken, as it may not be uncommon for both diseases to occur together, as neither disease is rare. The complication rate of hyperthyroidism in patients with type 2 diabetes was 0.8% in men and 1.3% in women (5). Because DKA can trigger thyroid crisis (9), inappropriate use of SGLT2is may increase the risk of developing thyroid crisis via the development of DKA when thyrotoxicosis is present. In addition, thyrotoxicosis can cause gastrointestinal symptoms, and if a patient is taking SGLT2is, it is necessary to discontinue the medication in the event of gastrointestinal illness.

In Case 2, the onset of SPIDDM was suspected during the course of Graves’ disease. The coexistence of thyroid disease and type 1 diabetes mellitus is not rare because of autoimmune mechanisms (34). The complication rate of hyperthyroidism in patients with type 1 diabetes was 1.1% in men and 6.4% in women (5). The insulin secretion ability was not depleted but may have been decreased compared to the secretion ability before the onset of diabetes mellitus. The combination of exacerbation of Graves’ disease, relative insulin hyposecretion, carbohydrate restriction, and the use of an SGLT2i may have led to the development of euDKA in Case 2. Therefore, the onset of diabetes mellitus during the treatment of thyroid disease should be differentiated from that of type 1 diabetes mellitus, and the use of SGLT2 is should be carefully considered.

Only a few cases of euDKA accompanied by thyrotoxicosis have been reported. For example, a case of DKA with a blood glucose level of <300 mg/dL accompanied by type 1 diabetes mellitus and painless thyroiditis (35) and a case of euDKA accompanied by type 2 diabetes mellitus and Graves’ disease under antithyroid drug treatment (36) have been reported. To our knowledge, there has been only one report of ketosis (not euglycemic) in a patient with type 2 diabetes mellitus complicated by hyperthyroidism under SGLT2i treatment (37), aside from our cases. Whether or not using SGLT2is increases the incidence of euDKA or DKA in patients with type 2 diabetes complicated by hyperthyroidism is unclear, but this possibility cannot be ruled out, considering the mechanisms described above.
Figure 3. Mechanism underlying the euDKA onset in our cases; effects of thyrotoxicosis and SGLT2 inhibitor treatment on glucose and lipid metabolism. *Oxyhyperglycemia caused by thyrotoxicosis increases the postprandial blood glucose level but may not increase the fasting blood glucose level. ANGPTL3: angiopoietin-like protein 3, euDKA: euglycemic diabetic ketoacidosis, SGLT2: sodium-glucose transport protein 2, SPIDDM: slowly progressive insulin-dependent diabetes mellitus, SREBP-1c: sterol regulatory element-binding protein-1c

In conclusion, we reported two cases of euDKA and thyrotoxicosis following SGLT2i treatment. SGLT2is have been approved for the treatment of heart failure or chronic kidney disease without diabetes mellitus, and the proportion of their usage will likely increase in the near future. Therefore, cases similar to ours may have occurred. When thyrotoxicosis is observed, the possibility of DKA should be considered, even in cases without a high blood glucose level, especially under SGLT2i treatment.

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

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