Diabetic ketoacidosis (DKA) is a medically fatal condition in poorly controlled hyperglycemia or newly diagnosed diabetes mellitus. Severe hypertriglyceridemia (HTG) is an uncommon complication of DKA and can be associated with acute pancreatitis (AP). We present the clinical manifestations, laboratory findings, and management of AP associated with HTG in a 14-year-old girl with DKA. The patient, with a 7-year history of type 2 diabetes presented with epigastric pain, 1 month after stopping insulin injection. DKA, severe HTG, and AP were diagnosed based on the laboratory and imaging tests. She recovered from DKA after conventional treatment for DKA, and her triglyceride (TG) level was reduced from 10,867 mg/dL to the normal range after 7 days of admission without antilipid medication. Given that her C-peptide level was not too low and considering her negative diabetes-related antibodies and high TG level, targeted gene panel sequencing was performed on the genes associated with diabetes and HTG. We identified a heterozygous mutation, c.4607C>T (p. Ala1537Val), in \( ABCC8 \) related to maturity-onset diabetes of the young (MODY) 12. To our knowledge, this is the first reported case of HTG-induced AP with DKA in a patient with MODY. In addition, we reviewed the literature for pediatric cases of HTG with DKA. In patients with DKA, timely awareness of severe HTG related to insulin deficiency is crucial for improving the consequences of AP. We recommend considering AP in all DKA patients presenting with severe HTG to ensure early and proper management.

**Keywords:** Hypertriglyceridemia, Acute pancreatitis, Diabetic ketoacidosis

### Highlights
- Severe HTG is an uncommon complication of DKA and can be associated with AP. In patients with DKA, timely awareness of severe HTG related to insulin deficiency is crucial for improving the consequences of AP.

### Introduction

Diabetic ketoacidosis (DKA) is a medically fatal condition that may occur in patients with poorly controlled hyperglycemia or newly diagnosed diabetes mellitus (DM). Cerebral edema is its most devastating complication and causes >20% of deaths among DKA cases.\(^1\) Severe hypertriglyceridemia (HTG, triglyceride [TG] > 1,000 mg/dL) is an uncommon complication of DKA and can be associated with acute pancreatitis (AP).\(^2\) The combination of DKA, HTG, and AP has been discussed in adults. While severe HTG was identified in around 8% of adult DKA cases, data of this combination in children have remained limited.\(^3,4\) Here, we present the clinical manifestations, laboratory findings, and management of AP associated with HTG in a 14-year-old girl with DKA. In addition, literature on HTG with DKA in pediatric cases was reviewed.
Case report

A 14-year-old girl presented to Samsung Medical Center owing to severe epigastric pain, nausea, and fever for 1 day. She was diagnosed with type 2 DM at another hospital at the age of 7 years and 10 months, when her hemoglobin A1c (HbA1c) was 10.1% and postprandial C-peptide level was 7.2 ng/mL, while her diabetes-related antibodies were all negative. She was treated with metformin (≤2 g/day) in the early stage of DM; however, basal insulin (glargine) was added to metformin owing to the poor control of hyperglycemia (HbA1c level, 14.0%). It was 1 month before this episode that she discontinued blood glucose testing and regular insulin injections. When she presented to our hospital, her mental status was alert and vital signs included a blood pressure of 132/70 mmHg, heart rate of 157 bpm, respiratory rate of 24 breaths/min, and body temperature of 38.2°C. Her body weight, height, and body mass index were 60.1 kg (standard deviation score [SDS], 1.18), 157.4 cm (SDS, -0.07), and 24.3 kg/m² (SDS, 1.38), respectively. She showed a dry mouth and decreased skin turgor. Her abdomen was soft and distended, and the bowel sounds were normal. She complained of tender epigastrum on palpation. Her laboratory findings were suggestive of DKA, such as a glucose level of 311 mg/dL, venous blood gas with a pH of 7.2, pCO₂ of 21 mmHg, HCO₃⁻ of 8.2 mmol/L, base excess of -17.8 mmol/L, and β-hydroxybutyrate level of 3.4 mmol/L (normal reference < 0.4–0.5 mmol/L). Her HbA1c level was 14.2%, and urinalysis revealed 3+ glucose and 3+ ketones. Other laboratory findings included the following results: white blood cell count of 12,380/μL, hemoglobin level of 13.5 g/dL, platelet count of 205,000/μL, total cholesterol level of 336 mg/dL, high-density lipoprotein (HDL) level of 14 mg/dL, TG level of 10,867 mg/dL, low-density lipoprotein (LDL) level of 32 mg/dL, aspartate aminotransferase level of 16 U/L, alanine aminotransferase level of 19 U/L, amylase level of 711.4 U/L (normal reference, 28–100 U/L), lipase level of 2,403.2 U/L (normal reference, 13–60 U/L), sodium level of 133 mmol/L, potassium level of 3.9 mmol/L, chloride level of 97 mmol/L, and C-reactive protein (CRP) level of 1.61 mg/dL. Antiglutamic acid decarboxylase antibody and anti-insulin auto-antibody tests were negative. Eruptive xanthoma or xanthelasma was not observed. There were no abnormalities, such as lipemia retinalis, found on an ophthalmologic examination. Abdominal computed tomography (CT) imaging revealed a diffuse edematous pancreas with adjacent fluid collection, which suggested AP of grade D (Fig. 1A). In addition, she had a fatty liver. No gallbladder involvement was seen.

Immediate management included intravenous rehydration therapy, continuous intravenous insulin infusion (6 units/hr), experimental antibiotics (piperacillin and tazobactam) for AP, and an analgesic (1 g of propacetamol) for pain control. On the second day of admission, her CRP level had increased to 33.47 mg/dL and the abdominal pain had persisted. She did not complain of steatorrhea. Follow-up CT imaging of the abdomen showed an increased volume of peripancreatic fluid collection relative to the previous examination suggesting AP of grade D (Fig. 1B). Her antibiotics were changed to broad-spectrum antibiotics (meropenem and vancomycin). Four days after admission, her TG level had declined to 305 mg/dL, and her CRP level was 16.41 mg/dL. The abdominal pain had also resolved. Her blood culture was negative, and antibiotics were changed to piperacillin and tazobactam. She recovered from DKA, and her TG level decreased to 197 mg/dL without antilipid medication 7 days after admission. Because her abdominal pain had resolved and the serum amyrase and lipase were nearly normal (27.2 and 68 U/L, respectively), she commenced with a normal diet. Repeated ultrasonography showed resolution of pancreatic inflammation. She did not have complications of diabetes, including retinopathy, nephropathy, or neuropathy. Serial laboratory results related to HTG and AP during hospitalization are summarized in Table 1.

Table 1. Serial laboratory results

| Hospital day     | TG (mg/dL) | TC (mg/dL) | HDL (mg/dL) | LDL (mg/dL) | Amylase (U/L) | Lipase (U/L) | CRP (mg/dL) |
|------------------|------------|------------|-------------|-------------|---------------|--------------|-------------|
| At admission     | 10,867     | 336        | 14          | 32          | 711.4         | 2,403.2      | 1.61        |
| 9 Hours after admission | 4,589 | 559        | 13          | 25          | 734.9         | 1,787.9      | -           |
| 2 Days           | 652        | -          | -           | -           | 180.9         | 401.5        | 33.47       |
| 4 Days           | 305        | -          | -           | -           | 59.4          | 107.2        | 16.41       |
| 7 Days           | 197        | -          | -           | -           | 27.2          | 68           | 12.6        |
| 10 Days          | 227        | -          | -           | -           | 40.4          | 114.2        | 5.16        |

TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.
Table 2. Pediatric cases of acute pancreatitis associated with hypertriglyceridemia in diabetic ketoacidosis

| Study                          | Age (yr) | Peak TG (mg/dL) | Peak amylase (U/L) | Peak lipase (U/L) | Management with antilipid medication | Time to normal TG (day) |
|-------------------------------|----------|-----------------|-------------------|------------------|--------------------------------------|-------------------------|
| Cywinski et al, 1965          | 12       | >1,000          | 175               | NA               | No                                   | 7 (232)                 |
| Slyper et al, 1994            | 14       | 3,119           | 627               | 3,680            | No                                   | NA                     |
| Hahn et al, 2010              | 20       | 15,000          | 443               | 615              | No                                   | 3 (506)                 |
| Lufti et al, 2012             | 10       | 16,334          | NA                | 3,537            | Fenofibrate, plasmapheresis          | 1.5 (1,100)             |
| Aboulhosn and Arnason, 2013   | 18       | 1,724           | 319               | NA               | No                                   | NA                     |
| Wolfrum and Macdonald, 2013   | 10       | 8,300           | NA                | 2,950            | No                                   | NA                     |
| Singla et al, 2015            | 19       | 4,009           | 408               | 1,714            | Fenofibrate                          | 1 (NA)                 |
| Sharma et al, 2017            | 4        | 13,846          | 150               | 442              | No                                   | 28 (90)                |
| Zaher et al, 2019             | 14       | 6,400           | NA                | 1,000            | Fenofibrate, unsaturated oils        | 7 (332)                |
| Yagnik et al, 2019            | 16       | 2,515           | 612               | 5,387            | Fenofibrate                          | 14 (170)               |
| Our case                      | 14       | 10,867          | 711.4             | 2,403.2          | No                                   | 6 (197)                |

TG, triglyceride; NA, not available.
subunit of the ATP-sensitive potassium (K_{ATP}) channel, can regulate the secretion of insulin. ABCC8 mutations have been shown to cause congenital hyperinsulinism (CHI), type 2 DM, gestational DM, neonatal diabetes, and MODY.\(^{13}\) CHI is associated with the blindness of pancreatic β-cells responsible for insulin secretion, causing severe and persistent hypoglycemia. CHI is classified histologically into diffuse hyperinsulinism or focal islet-cell hyperplasia. Diffuse hyperinsulinism appears in an autosomal recessive manner, and entire β-cells in the pancreas are affected. On the other hand, its focal form is a heterozygous paternally inherited K_{ATP} mutation of chromosome 11p15 region, which is confined to the islet cells of focal lesions.\(^{14}\) It is challenging to differentiate MODY from other types of diabetes depending on clinical manifestations. In patients with MODY, β-cell function is generally conserved, and insulin is not required in the early stage of the disease.\(^{15}\)

Kapoor et al.\(^{16}\) reported a dominant ABCC8 mutation, A1537V, identified in our patient, which causes an asymptomatic carrier, hyperinsulinemic hypoglycemia, and gestational DM within 3 generations of a single family. Mutations in ABCC8 can be associated with both hyperactivity and underactivity of the K_{ATP} channel. Slow and progressive damage to β-cells owing to increased β-cell apoptosis can lead to both remission of hyperinsulinism and progression to diabetes.\(^{17}\)

Considering the clinical variability of ABCC8 mutations, the mutation identified in our patient is suspected to be related to MODY 12. As the result of target gene panel sequencing was classified as a VUS, family segregation analysis can enforce the pathogenicity of this variant. However, it was not possible to collect the detailed family history and conduct genetic testing of relatives in this case. This is the limitation of our case and thus, further validations in additional patients and functional studies are needed to prove the pathogenicity of this variant. Patients with MODY 12 respond to sulfonylurea therapy.\(^{18}\) Thus, switching our patient from insulin to sulfonylurea is under consideration.

In this study, we presented a 14-year-old girl with AP related to severe HTG in DKA. To our knowledge, this is the first report of HTG-induced AP with DKA in a patient with MODY. In patients with DKA, timely awareness of severe HTG related to insulin deficiency is crucial for improving the consequence of AP. Based on our experience and the review of pertinent literature, we recommend considering AP in all DKA patients presenting with severe HTG to ensure early and proper management.

**Ethical statement**

Informed consent was obtained from the parents of the patient.

**Notes**

**Conflicts of interest:** No potential conflict of interest relevant to this article was reported.
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