Severe Hypertriglyceridemia in Diabetic Ketoacidosis Accompanied by Acute Pancreatitis: Case Report

Suk Jae Hahn, Jung-hyun Park, Jong Ho Lee, Jun Kyu Lee, and Kyoung-Ah Kim

Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University School of Medicine, Goyang, Korea

Received: 22 July 2009
Accepted: 29 October 2009

Address for Correspondence:
Kyoung-Ah Kim, M.D.
Department of Internal Medicine, Dongguk University Ilsan Hospital, 29 Donggung-ro, Ilsandong-gu, Goyang 410-773, Korea
Tel: +82.31-961-7136, Fax: +82.31-961-9469
E-mail: kyoung-ah.kim@duih.org

DOI: 10.3346/jkms.2010.25.9.1375

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute metabolic complication that occurs mainly in type 1 diabetes mellitus (1). The risk factors are omission of insulin, infection, trauma and acute pancreatitis (2, 3). Insulin deficiency increase free fatty acid (FFA) and amino acids release from adipose tissue and muscle, respectively and increased counter-regulatory hormones causes increased gluconeogenesis and glycogenolysis in the liver (4, 5). Elevated FFA taken up by liver leads to increased production of very low density lipoprotein (VLDL), which causes hypertriglyceridemia (2-4). Hypertriglyceridemia is an uncommon cause of acute pancreatitis accounting for 1-4% of cases, especially when the serum triglycereide (TG) level exceeds 1,000 mg/dL (5). In Korea, 13 cases of hypertriglyceridemia-induced acute pancreatitis have been reported. In two cases, where hypertriglyceridiemia was noted along with DKA, the serum TG levels were severely elevated (12,864 and 11,929 mg/dL) but it did not cause acute pancreatitis (6, 7) (Tables 1, 2). The present case also involved DKA and an extremely high TG level (15,240 mg/dL), which ultimately culminated in the development of acute pancreatitis. DKA, hypertriglyceridemia and acute pancreatitis were successfully resolved by insulin and hydration therapy.

CASE REPORT

A 20-yr-old female visited the emergency department because of a 1-day history of vomiting (10 times) and was experiencing epigastric pain with diarrhea on March 23, 2009. The upper gastrointestinal pain was continuous without radiation. The patient had been drinking almost daily alcoholic beverages soju (alcohol concentration in the range of 19-22%) for 5 days prior to admission. The patient had a smoking history of one pack-year. Two years previously, the patient experienced DKA accompanied by acute pancreatitis. At that time, the patient had been diagnosed with type 1 diabetes mellitus. Insulin treatment began at that time. However, 7 months prior to the current admission, the patient ceased taking insulin.

Upon admission, the patient was determined to be 161 cm in height, 55 kg in weight with a body mass index of 21.2. On admission, the patient was alert but appeared acutely ill. Initial vital signs were blood pressure 90/60 mmHg, pulse rate of 88 beats/min, respiratory rate of 20/min and body temperature of 36.5°C. Physical examination revealed a dehydrated tongue and skin turgor. There was no evidence of xanthoma, xanthelasma or eruptive xanthoma. No palpable lymph node enlargement was apparent on head and neck examination, and no abdominal tenderness on abdominal examination. Bowel sound was normoactive.

Initial laboratory findings were ABGA (pH 7.148, pCO₂ 12.9 mmHg, pO₂ 126 mmHg, HCO₃⁻ 8.4 mM/L, SaO₂ 98.0%), glucose level 281 mg/dL, hemoglobin A1c 13.8%, C-peptide (premeal) 0.441 ng/mL (normal reference: 1.1-4.4 ng/mL), total cholesterol 1,640 mg/dL, TG 15,240 mg/dL, measured low density lipoprotein cholesterol (LDL-C) 246 mg/dL (determined by homogeneous enzymatic colorimetry method assay), high density lipo
poprotein cholesterol (HDL-C) 69 mg/dL, serum ketone body 3.1 mM/L (normal reference 0–0.05 mM/L), total bilirubin 1.2 mg/dL, AST 19 IU/L, ALT 14 IU/L, total protein 8.4 g/dL, serum albumin 4.1 g/dL, alkaline phosphatase 147 IU/L, serum amylase 81 U/L, serum lipase 108 U/L, WBC 13,310/μL, hemoglobin 13.9 g/dL, hsCRP 5.616 mg/dL, BUN 14.0 mg/dL, creatinine 0.6 mg/dL, sodium 125 mEq/L, potassium 4.4 mEq/L and chloride 95 mEq/L. There were no abnormalities in the coagulation test. Serum sample was milky and turbid, which suggested a lipemic state (Fig. 1). Anti-glutamic acid decarboxylase (GAD) antibody was 0.12 U/mL (normal reference 0–0.9 U/mL), and anti-islet antibody-2 (IA-2) antibody was <0.4 U/mL (normal reference 0–0.4 U/mL). Apolipoprotein E genotyping assessed by polymerase chain reaction revealed ε2/ε3.

The patient was aggressively hydrated and treated with intravenous insulin in the intensive care unit. On admission, serum sodium was 125 mEq/L and serum osmolality was 317 mOsm/kg. We suspected pseudohyponatremia caused by hyperlipidemia and hyperglycemia, and tried normal saline infusion. In spite of significant improvement in glucose level for the first 12 hr, sodium level dropped to 115 mEq/L. After correcting the hyponatremia with 3% NaCl solution, continuous insulin infusion and hydration for next 12 hr, serum sodium level rose to 121 mEq/L.

On the second day of hospitalization, the patient complained of aggravated epigastric pain. Follow-up laboratory analyses revealed a serum amylase level of 443 U/L and a serum lipase level of 615 U/L. On abdominal computed tomography (CT) scan, the pancreas was diffusely swollen with peripancreatic fat infiltration and fluid collection, which suggested acute pancreatitis.

Table 1. Sequential laboratory results

| Parameters          | Initial | After 7 hr | After 12 hr | 2 day | 3 day | 4 day | 5 day | 8 day | 22 day |
|---------------------|---------|------------|------------|-------|-------|-------|-------|-------|--------|
| Triglycerides       | 15,240  | -          | -          | 5,590 | 506   | 328   | -     | 642   | 309    |
| HDL-cholesterol     | 69      | -          | -          | 57    | 36    | -     | -     | 34    | 66     |
| Total cholesterol   | 1,640   | -          | -          | 900   | 281   | 494   | -     | 308   |        |
| Glucose             | 281     | 233        | 211        | 214   | 198   | 210   | 231   | -     | 127    |
| K⁺                  | 4.4     | 4.9        | 4.1        | 3.7   | 3.1   | 2.9   | 3.5   | -     | 4.0    |
| Na⁺                 | 125     | 121        | 115        | 122   | 129   | 132   | 136   | -     | 137    |
| Cl⁻                 | 95      | 99         | 93         | 100   | 108   | 106   | 101   | -     | 97     |
| HCO₃⁻               | 8.4     | 11.1       | 10.3       | 12.4  | 15.8  | 20.5  | -     | -     |        |
| pH                  | 7.148   | 7.228      | 7.210      | 7.277 | 7.334 | 7.415 | -     | -     |        |
| Serum Ketone        | 3.1     | -          | -          | 2.3   | 0.1   | -     | -     | -     | -      |
| Amylase             | 81      | -          | -          | 443   | 98    | 50    | -     | 107   |        |
| Lipase              | 108     | -          | -          | 615   | 281   | 36    | -     | -     | 48     |
| BUN                 | 14.0    | 10.5       | -          | 6.2   | 4.8   | 25    | -     | -     | -      |
| Creatinine          | 0.6     | 0.5        | -          | 0.1   | 0.2   | 0.2   | -     | -     | -      |

Triglycerides (mg/dL), HDL-cholesterol (mg/dL), Total cholesterol (mg/dL), Glucose (mg/dL), K⁺ (mEq/L), Na⁺ (mEq/L), Cl⁻ (mEq/L), HCO₃⁻ (mEq/L), pH, Serum ketone (mmol/L), Amylase (U/L), Lipase (U/L), BUN (mg/dL), Creatinine (mg/dL).

Table 2. Summary of severe hypertriglyceridemia in DKA in Korea

| Ref. | Year | Sex/Age | Past history | Initial TG (mg/dL) | Follow-up TG (Time) | Associated conditions | Treatment | Outcome  |
|------|------|---------|--------------|-------------------|---------------------|-----------------------|-----------|----------|
| (5)  | 1999 | F/25    | T1D, without treatment | 12,864 | 72 (after 72 hr) 83 (after 5 month) | Non-specific | Conservative with insulin | Survival |
| (20) | 2002 | M/38    | T2D on insulin, Acromegaly | 1,488 | 427 (after 72 hr) 80 (after 5 month) | Acute pancreatitis | Conservative with insulin | Survival |
| (6)  | 2008 | M/26    | T1D on OHA (omit insulin) | 11,929 | 1,316 (after 72 hr) 77 (after 45 days) | Lipemia retinalis | Conservative with insulin | Survival |
| Present | 2009 | F/20    | T1D, omit insulin | 15,240 | 506 (after 72 hr) 309 (after 22 days) | Acute pancreatitis | Conservative with insulin | Survival |

OHA, oral hypoglycemic agent; TG, triglyceride; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus.
grade D, according to the Balthazar CT severity index (Fig. 2). The Ranson’s score was 4 at this point. There was no lipidemia retinalis on an ophthalmologic exam.

On the third day of hospitalization, the TG was 506 mg/dL, total cholesterol 281 mg/dL, LDL-C 101 mg/dL and HDL-C 36 mg/dL. The epigastric pain had diminished. The patient commenced oral intake, multiple subcutaneous insulin injection and fibrate medication.

On the fourth day of hospitalization, the serum amylase level was 50 U/L and lipase level was 36 U/L. The patient was discharged without any complication on post-admission day 8. Fourteen days after discharge, analyses revealed total cholesterol 308 mg/dL, TG 309 mg/dL, LDL-C 184 mg/dL, HDL-C 66 mg/dL, serum amylase level 107 U/L and serum lipase level 48 U/L. Lipoprotein electrophoresis performed after recovery showed a normal pattern.

DISCUSSION

In DKA, the deficiency of insulin activates lipolysis in adipose tissue releasing increased FFA, which accelerates formation of VLDL in the liver. In addition, reduced activity of lipoprotein lipase in peripheral tissue decreases removal of VLDL from the plasma, resulting in hypertriglyceridemia (8). Moderate hypertriglyceridemia is common during episodes of DKA (9). However, severe hypertriglyceridemia, which is defined as a TG level >2,000 mg/dL, is rare. Although morbidity is <1%, clinicians should be aware that devastating consequences such as acute pancreatitis or lipidemia retinalis are possible (8). In extreme cases, co-existence of genetic mutations in lipoprotein lipase should be suspected (10).

During treatment of DKA with severe hypertriglyceridemia, pseudohyponatremia or pseudonormoglycemia due to laboratory interference may lead to delay of proper management. Frier et al. suggested that if serum triglyceride concentration exceeds 2,500 mg/dL, measured electrolyte can decrease by over 5% because of the intracellular movement of serum lipid components. Therefore, in the hyponatremic state, the clinician should consider the possibility of pseudohyponatremia and avoid overtreatment with hypertonic saline (11). We presently observed a decreased sodium level of 125 mEq/L to 115 mEq/L during the recovery phase, which necessitate temporary correction with 3% hypertonic saline.

In severe hypertriglyceridemia, there is an increased risk of developing acute pancreatitis. The mechanism is related to high plasma chylomicrons or TGs, which are hydrolyzed by lipase in the pancreatic capillaries and subsequently trigger FFA release (12) that, in turn, causes activation of trypsinogen and commences pancreatic capillary damage by free radical damage (13, 14). The common clinical scenario of hypertriglyceridemia-induced acute pancreatitis involves poorly-controlled diabetes mellitus with type IV hyperlipidemia (5), or chronic alcoholism (15). In contrast, moderate hyperlipidemia (usually <400 mg/dL) can be observed secondary to acute pancreatitis and should not be confused with the marked hypertriglyceridemia that causes acute pancreatitis (16), as in the present case.

Of note, normoamylasemia is possible in about 50% of patients with hypertriglyceridemia-induced pancreatitis. The mech-
anism is believed to be the interference with in vitro determination of the actual amylase level by disturbance of the calorimetric method. Serial dilutions of the sample could reduce interference of light transmission by hyperlipidemic serum (17). In the present case, increased amylase occurred parallel to the decreased TG level, which might have delayed the diagnosis of acute pancreatitis at initial presentation.

Although acute pancreatitis can initiate DKA, DKA itself may mask a co-existing acute pancreatitis that occurs in 10–15% of cases due to ambiguous clinical presentations (16). Even worse, nonspecific elevations of amylase and/or lipase without clinical evidence of pancreatitis have been reported in 24.7–79.0% of DKA cases (17). At least in those patients with continuous abdominal pain, it is prudent to seek further laboratory evaluation or a CT scan of the abdomen. In our case, not surprisingly, because of the severe dehydration secondary to DKA, the initial and 48 h Ranson’s score was 4 points each, which is relatively high. In a previous study, the clinical course of acute pancreatitis with DKA seemed to be mild, although the mean Ranson’s score was 1.36±0.5 and the mean CT severity index (total 20 point) score was 4.6±1.2; none of the patients developed systemic complication (17).

In the present case, hypertriglyceridemia was controlled with insulin without lipid lowering agents. However, in severe hypertriglyceridemia, physicians should consider the application of plasma exchange to avoid complications (18). The present patient has since been administered fibrate, which is the first-line drug of hypertriglyceridemia, and insulin treatment, in order to prevent recurrence of pancreatitis (19).

To our knowledge, this is the first report of a case in Korea of DKA and severe hypertriglyceridemia, complicated by acute pancreatitis. Although moderate hypertriglyceridemia in DKA is common, if the TG level exceeds 1,000 mg/dL, the clinician should consider the devastating consequences such as acute pancreatitis or lipemic retinails, which might benefited from insulin administration and conservative management, unless otherwise necessitating the plasma exchange.

REFERENCES

1. Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am 2006; 35: 725-51.
2. Chiasson JL, Aris-Ilwan N, Belanger R, Bertrand S, Beauregard H, Ekoe JM, Fournier H, Havrankova J. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. CMAJ 2003; 168: 859-66.
3. Kitabchi AE, Unsuprieryez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JJ, Wall BM. Hyperglycemic crises in diabetes. Diabetes Care 2004; 27 Suppl 1: S94-102.
4. Exton JH. Mechanisms of hormonal regulation of hepatic glucose metabolism. Diabetes Metab Rev 1987; 3: 163-83.
5. Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol 1995; 90: 2134-9.
6. Choi DS, Oh JH, Park IB, Kim JW, Choi KM, Kim YH, Kim NH, Kim SI, Baik SH. A case of severe hypertriglyceridemia with diabetic ketoacidosis. J Korean Diabetes Assoc 1999; 23: 715-21.
7. Choi SH, Sohn TS, Lee JI, Kim ES, Choi WH, Shin J, Son HS. A case of severe hypertriglyceridemia in diabetic ketoacidosis. Korean Clin Diabetes 2008; 9: 336-40.
8. Fulop M, Eder H. Severe hypertriglyceridemia in diabetic keto. Am J Med Sci 1990; 300: 361-5.
9. Fulop M, Eder HA. Plasma triglycerides and cholesterol in diabetic ketoacidosis. Arch Intern Med 1989; 149: 1997-2002.
10. Karagianni C, Stabouli S, Roumeliotou K, Traeger-Synodinos J, Kavazarakis E, Gourgiotis D, Lambrou J, Kanavakis E. Severe hypertriglyceridemia in diabetic ketoacidosis: clinical and genetic study. Diabet Med 2004; 21: 380-2.
11. Friet BM, Steer CR, Baird JD, Bloomfield S. Misleading plasma electrolytes in diabetic children with severe hyperlipidaemia. Arch Dis Child 1989; 55: 771-5.
12. Havel RJ. Pathogenesis, differentiation and management of hypertriglyceridemia. Adv Intern Med 1969; 15: 117-54.
13. Havel RJ. Approach to the patient with hyperlipidemia. Med Clin North Am 1982; 66: 319-33.
14. Tsuang W, Navaneethan U, Ruiz L, Palascak JB, Gelrud A. Hypertriglyceridemic pancreatitis: presentation and management. Am J Gastroenterol 2009; 104: 984-91.
15. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. J Clin Gastroenterol 2003; 36: 54-62.
16. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol 2000; 95: 2795-800.
17. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasaemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. Am J Gastroenterol 2000; 95: 3123-8.
18. Furuya T, Komatsu M, Takahashi K, Hashimoto N, Hashizume T, Wajima N, Kubota M, Itoh S, Soeno T, Suzuki K, Enzan K, Matsuo S. Plasma exchange for hypertriglyceridemic acute necrotizing pancreatitis: report of two cases. Ther Apher 2002; 6: 454-8.
19. Huang DB, Raskin P. Diabetic hypertriglyceridemia-induced acute pancreatitis masquerading as biliary pancreatitis. J Diabetes Complications 2002; 16: 180-2.
20. Lee CY, Lee MK, Lee SY, Hong SN, Kim HH, Kang BH, Kang HW, Lee BW, Park YJ, Min YK, Lee MS, Kim KW, Kim JH. A case of acromegaly with diabetic ketoacidosis and hypertriglyceridemia-induced acute pancreatitis. J Korean Soc Endocrinol 2002; 17: 110-6.