

Very severe hypertriglyceridemia in children with diabetic ketoacidosis

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Abstract: Hypertriglyceridemia can be observed in up to 50% of patients with diabetic ketoacidosis (DKA), but a condition for DKA with very severe hypertriglyceridemia is uncommon. The objective of this case report is to present and describe the clinical features, laboratory investigations, case management, and natural course of hypertriglyceridemia in DKA.

Key words: hypertriglyceridemia, diabetic ketoacidosis

Case summary: A 9-year-old girl referred by district hospital with DKA and hypertriglyceridemia. Chief complaint was a decreased in consciousness for 16 hours before the admission. Patient has been known to suffer from diabetes mellitus within these 9 months. At ER patient looked severely ill, GCS 7, Kussmaul breathing. Random blood glucose was 255 mg/dL. Glycosuria and ketone urine tests were positive. Triglyceride level was 16.200 mg/dL. She had diagnosed with diabetic encephalopathy, DKA and very severe hypertriglyceridemia due to DKA. We treat DKA with standard guidelines, and on the 15th day we gave additional therapy fibrates and omega oil to treat the very severe hypertriglyceridemia. The level of triglyceride decreased gradually with hydration and insulin in standard guideline for DKA but didn't achieve the normal level. With additional treatment, normal level of triglyceride achieved without any clinical side effects.

Conclusion: Triglyceride level should be monitored in DKA patients. The hypertriglyceridemia can be treated by hydration, insulin, fibrates, and omega oil. The use of these treatment need to be evaluated for side effects.

Hypertriglyceridemia is defined as an increased plasma fasting triglyceride concentration above 95th percentile for age and sex.¹ The triglyceride concentrations are considered greater or equal to 100 mg/dL for children ages 0 to 9 years, and greater or equal to 130 mg/dL for children ages 10 to 19 years.² Very severe hypertriglyceridemia is defined as an increased triglyceride concentration above 2000 mg/dL in children. Based on the etiology, hypertriglyceridemia can be categorized as primary and secondary. In primary hypertriglyceridemia, there is genetic defect in triglyceride synthesis or metabolism, while the secondary hypertriglyceridemia commonly happens as the result of mix complications of poorly controlled diabetes mellitus (DM), obesity, metabolic

syndrome, and the use of some medications such as estrogen.³

Hypertriglyceridemia can be observed in up to 50% of patients with diabetic ketoacidosis (DKA), but a condition for DKA with very severe hypertriglyceridemia is uncommon. The clearance of very low-density lipoprotein (VLDL) and chylomicrons from plasma is restricted due to a transient decrease of lipoprotein lipase (LPL) activity, which is attributed to insulin deficiency. In a very severe hypertriglyceridemia, its pathogenesis cannot only be attributed to insulin deficiency, but may also be exacerbated by a co-existing genetic predisposition to hyperlipidemia.⁴

The recommended treatment for DKA includes intravenous fluid and insulin administration based on the DKA treatment guidelines.⁵ Lifestyle modification and some pharmacological agents can be used to manage a severe hypertriglyceridemia in DKA children.⁷

The case

A 9 years and 2 months old girl was admitted to M. Djamil Hospital with diabetic ketoacidosis. Chief complaint was a decreased in consciousness for 16 hours before the admission. Patient has been known to suffer from diabetes mellitus within these 9 months. Before the admission, the associated symptoms included epigastric pain and vaginal discharge for 2 days, followed by twice vomiting, fever for 1 day, and decrease in consciousness for 16 hours. Urine volume had decreased and had cloudy appearance. Patient started to lose weight since last year, the previous weight was 30 kg and her present weight is 27 kg. Patient and family members were uneducated. She was referred from District Hospital after being hospitalized for 1 day and had been diagnosed with diabetic ketoacidosis. She had been given insulin drip for 16 hours before admission. History of dyslipidemia in family was unknown.

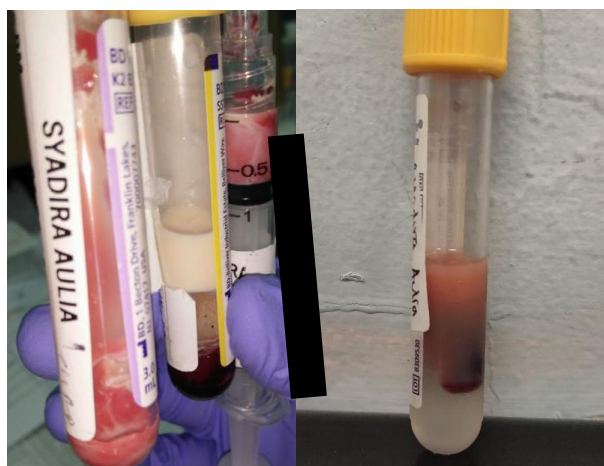


Figure 1. Milky plasma on first day (left) and 15th day (right)

Patient looked severely ill, Glasgow Coma Scale (GCS) 7, pulse rate 148 times per minute with good perfusion, body temperature was 36,8°C, Kussmaul breathing, respiratory rate was 38 times per minute, blood pressure was 115/70 mmHg (P50 102/63 mmHg), body height was 139 cm, body weight was 27 kg; undernourished. There was no papilledema and no retinal lipemia. Tanner stage was A1M1P1. There was desquamation on the inguinal with satellite lesion.

Laboratory examinations revealed hemoglobin 13,9 gr/dl, white blood cell count 16.650/mm³, hematocrit 30% vol, and platelet count 262.000/mm³. The differential counts were 0/0/17/60/20/2. Random blood glucose was 255 mg/dL. Glycosuria and ketone urine tests were all positive. Blood gas

analysis (BGA) pH 7,02, pCO₂ 15, pO₂ 245, HCO₃⁻ 3,8, BE -25, and oxygen saturation 100%. The milky plasma caused electrolyte serum became difficult to interpret. Triglyceride level was 16.200 mg/dL. Brain CT scan showed no cerebral edema.

The patient had been diagnosed with diabetic encephalopathy, diabetic ketoacidosis (DKA) with moderate dehydration, uncontrolled diabetes mellitus, candidiasis vulvovaginal, very severe hypertriglyceridemia due to DKA, and undernourished. The patient was given oxygen, sodium bicarbonate, fluid resuscitation, insulin drip 0.1u/BW/hour, antibiotic, and miconazole cream. The parents and patient had been given education about basic information of diabetes mellitus and treatments.

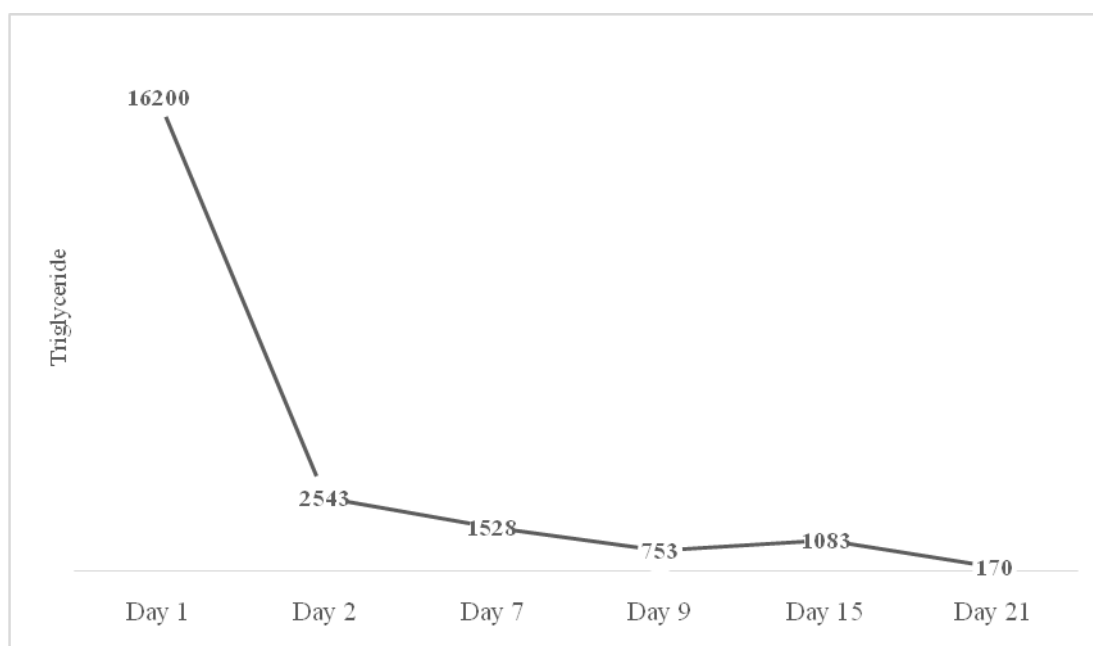


Figure 2. Triglyceride level during hospitalization

The laboratory result on second day, total cholesterol 422 mg/dL, HDL 5 mg/dL, triglyceride 2.543 mg/dL,

and ketonuria was still present. Patient was fully alert on the 4th day. Blood glucose level was stable, total

cholesterol 755 mg/dL, HDL 23 mg/dL, and triglyceride 1.528 mg/dL. On the 7th day, triglyceride level was still high and we started gemfibrozil 2x300 mg. On the 9th day, patient felt pain at the right epigastric area. There was no abdominal tenderness, supple, and murphy sign was negative. Pancreatic amylase was 16U/L and lipase 25U/L. Based on these data, the diagnosis of acute pancreatitis was excluded. Because the patient still had high triglyceride levels on 15th day at 1083 mg/dL, omega-3 fatty acid was given as an adjunctive therapy combined with gemfibrozil 2x300 mg. These medications were tapered off from 21st day.

Discussion

Insulin deficiency in DKA activates lipolysis, increasing free fatty acid (FFA) in circulation. It accelerates the formation of very low-density lipoprotein (VLDL) in the liver. Reduced activity of lipoprotein lipase in peripheral tissue decreases removal of VLDL from the plasma, resulting in hypertriglyceridemia. Moderate hypertriglyceridemia is common during the episodes of DKA, while very severe hypertriglyceridemia is rare.⁸

There have been reports of the incidence of severe hypertriglyceridemia in DKA (table 3). Most of them were managed with fluid resuscitation and insulin drips. Triglyceride level was gradually reduced to less than 500 mg/dL within 3-17 days at most cases. In some cases with organ failure such as renal

insufficiency or failure after conservative treatment, plasmapheresis is needed to decrease the triglyceride levels.⁹ In this case, we started insulin infusion at 1 hour after starting fluid resuscitation at dose 0,1 u/kg/hour. By administering the fluid resuscitation and insulin infusion, the blood glucose levels decreased and triglyceride level dropped to 2.543 mg/dL on the second day of hospitalization. But this level decrease did not significantly happen on the days after, and on the 15th day of hospitalization, the level of triglyceride still remained high. Failure in conservative therapy on the 15th day led us to start using the fibrates as anti-lipid agent and supplement of omega 3 fatty acids.

Zaher et al had ever reported a similar case previously and by giving the insulin, hydration, fibrates, and omega oil, they successfully reduced the triglyceride level to the normal level in 5 days.⁴ Gemfibrozil acts as an agonist for peroxisome proliferator-activated receptor-alpha (PPAR-alpha) that upregulates lipoprotein lipase (LPL) causing an increase in the degradation of very low density lipoprotein (VLDL) and triglyceride, thus reducing triglyceride level up to 60%.^{10,11} Close follow-up when initiating this medication is recommended if the side effects develop, such as rhabdomyolysis, myopathy, or kidney injury. Gemfibrozil can be discontinued after triglyceride level has reached the normal value.¹² In this case, we didn't found any of these sides effect to the patient.

Table 1. Cases of severe hypertriglyceridemia in DKA

Ref.	Year	Age	Initial TG (mg/dL)	Therapy
Cywinski et al ¹⁶	1965	12,5	>1 000	Hydration, insulin
Slyper et al ¹⁷	1994	14	3.119	Hydration, insulin
Kadota-Shinozaki et al ¹⁸	1997	19	3.386	Hydration, insulin
Fortson et al ¹⁹	1999	25	12.864	Hydration, insulin
Lee et al ²⁰	2002	38	1.488	Hydration, insulin
Choi et al ²¹	2008	26	11.929	Hydration, insulin
Hahn et al ²²	2009	20	15.240	Hydration, insulin
Lutfi et al ⁹	2012	10	16.334	Plasmapheresis
Kota et al ²³	2012	12	1.020	Hydration, insulin
Aboulhosn and Arnason ²⁴	2013	18	1.724	Hydration, insulin

Wolfgang and Macdonald ²⁵	2013	10	8.300	Hydration, insulin
Saengkaew T et al ²⁶	2016	13	9.810	Hydration, insulin
Sharma et al ²⁷	2017	4	13.846	Hydration, insulin
Zaher FZ et al ⁴	2019	14	64.000	Hydration, insulin, fibrate, omega oil

Omega-3 fatty acid can be used as an adjunctive therapy when triglyceride level is more than 500mg/dL.⁷ It works by reducing hepatic secretion of VLDL cholesterol and enhancing chylomicron metabolism. It reduces triglyceride level up to 35% in adult,¹³ and up to 39% in pediatric.¹⁴ Supplementation with 3g/day of omega-3 fatty acids in pediatric patient is considered safe.¹⁵ However, in order to establish the efficacy and safety in this population, it needs larger trials that recruit children/adolescent.¹³

The common complication of hypertriglyceridemia is acute pancreatitis. Based on study observed by Richardson et al, the lowest plasma triglyceride observed in patients at the onset of pancreatitis was 1,041mg/dL. Several factors which contributed to this pancreatitis are multiple DKA admissions, poor glycemic control, and infrequent clinic visits.²⁸ We suspected acute pancreatitis in our patient on the 10th day of hospitalization and evaluated the pancreatic enzyme, however the result was normal. The diagnosis of acute pancreatitis can be made based on INSPPIRE criteria. It requires at least 2 out of 3 criteria of the following: (1) abdominal pain compatible with acute pancreatitis, (2) serum amylase and/ or lipase level ≥ 3 times upper normal limits, (3) imaging finding is consistent with acute pancreatitis.²⁹ In this case, abdominal pain was not compatible with acute pancreatitis and serum

amylase and lipase were normal, so we excluded acute pancreatitis.

It has been suggested that genetic studies might be necessary in patients with hypertriglyceridemia in DKA to rule out the presence of coexisting mutations in LPL gene.¹⁸ Mutation in LPL gene can lead to severe and persistent hypertriglyceridemia in DKA that does not improve with insulin alone.³⁰ On the other hand, a severe but not persistent hypertriglyceridemia may be caused by abnormality in lipoprotein cofactors.³⁰ It is possible that subtle abnormality in lipid metabolism in usual conditions may contribute to the development of hyperlipidemia under stress such as DM. Karagianni et al have reported a case with similar severe hyperlipidemia in DKA. They observed the S447X mutation in exon 9 which could produce a premature termination codon truncating the LPL protein by two amino acids and the D9N mutation on exon 2 which substitutes the aspartic acid by asparagine at amino acid residue 9.³¹ Matern et al have reported a case of a boy who also had heterozygote for the same LPL genotype. However the heterozygosity for the mutation was only under the state of DKA.³²

Conflict of interest

None declared.

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