Type 2 diabetes presenting with DKA and severe hypertriglyceridaemia

SING YEE SIM,[1] MARIE-FRANCE KONG,[2] FAIZANUR RAHMAN[3]

Introduction

Diabetic ketoacidosis (DKA) is a common metabolic complication of diabetes which occurs not only in patients with type 1 diabetes but also in those with other types of diabetes, especially in ketosis-prone type 2 diabetes. In about 6% of all cases DKA can be the first presentation of diabetes. Immediate management of DKA with intravenous fluids, insulin and potassium is vital regardless of the type of diabetes. Identifying the type of diabetes can be confirmed at a later stage in the outpatient setting.

Hypertriglyceridaemia is defined as a fasting plasma triglyceride of ≥2.3 mmol/L according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). Chylomicronaemia is present when the triglyceride level is ≥11.3 mmol/L. Hypertriglyceridaemia has become more common due to an increased incidence of obesity as a result of sedentary lifestyle. Markedly elevated triglycerides can cause pancreatitis. We describe a case where a patient who was not known to be diabetic presented with DKA and severe hypertriglyceridaemia. His triglyceride level was >100 mmol/L. It is important to recognise that DKA, hypertriglyceridaemia and pancreatitis can co-exist.

Key words: diabetic ketoacidosis, hypertriglyceridaemia, ApoE2, lipoprotein lipase, pancreatitis

Case report

In May 2018 a 46-year-old Caucasian man was referred to the emergency department with a history of lethargy, polyuria and polydipsia. On the day of admission he had visited his GP who found a capillary blood sugar of 26.7 mmol/L. A blood test done at the surgery the day before had shown HbA_{1c} 93 mmol/mol

[1] Specialist Registrar in Diabetes & Endocrinology, University Hospitals of Leicester NHS Trust, Leicester, UK
[2] Marie-France Kong, Consultant Diabetologist, University Hospitals of Leicester NHS Trust, Leicester, UK
[3] Faizanur Rahman, Consultant in Metabolic Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK

Address for correspondence: Dr Faizanur Rahman
Chemical Pathology and Metabolic Disorders, Room 409, Sandringham Building, Level 4, Leicester Royal Infirmary, Leicester LE1 5WW, UK
Tel: +44 (0)116 258 6550
E-mail: Faizanur.Rahman@uhl-tr.nhs.uk

(10.6%), cholesterol 25.6 mmol/L, triglycerides 100.58 mmol/L. He denied any weight loss but had blurring of vision. He also complained of nausea and abdominal pain. There was no history of alcohol consumption. He was found to have fatty liver disease on an ultrasound scan in April 2018. He reported that his father has impaired glucose tolerance and he has an aunt who has diabetes (unsure if type 1 or type 2). He also had an obese sister who died at the age of 25 and he was told that she died from diabetic complications in the form of renal failure. The patient had a history of depression for which he was taking mirtazapine. He was found to have mixed hyperlipidaemia in 2012 and was started on atorvastatin. He admitted stopping taking the atorvastatin in late 2016 (see lipid results in Table 1).

On examination he was obese with a BMI of 37.4 kg/m² (weight 120 kg, height 1.79 m). There were no stigmata of hyperlipidaemia. He was not examined for lipaemia retinalis. His abdomen was soft but he had some tenderness in the epigastrium. There was no hepatosplenomegaly. Initial blood results showed normal U+Es apart from pseudohyponatraemia, normal liver function test and full blood count (see Table 2). Blood gas analysis showed a normal sodium of 133 mmol/L, venous pH of 7.27, bicarbonate 15.7 mmol/L and blood glucose 30 mmol/L. Near patient testing revealed blood ketones of 4.2 mmol/L. Serum amylase was normal at 32 IU/L (normal range 30–110). The urine albumin-creatinine ratio and thyroid function test were also checked and were normal.

He was treated for DKA with intravenous fluids and fixed rate insulin infusion and received antibiotics for a lower respiratory tract infection. He made an uneventful recovery. He was discharged home on basal bolus insulin regimen and fenofibrate 160 mg once daily, atorvastatin 20 mg once daily and Omacor 1 g twice daily. Apolipoprotein E2 genotyping showed the patient to be heterozygous for E2 allele.

When reviewed in the outpatient clinic three weeks later his cholesterol was 3.2 mmol/L and triglycerides 3.2 mmol/L. His blood sugars were mostly in single figures and he reported feeling hungry during the day. His anti-GAD antibodies, IA2 antibodies and islet cell antibody were negative. On further questioning he reported symptoms of postprandial hypoglycaemia for many years and his GP had checked him for diabetes over the years. His insulin doses were reduced and he was started on metformin. As his HbA_{1c} improves we plan to cut back on his lipid-lowering medications. He may eventually only need atorvastatin if good glycaemic control is achieved.

Table 1 Blood results from 2012 until last reviewed in the outpatient clinic

Date	HbA$_{1c}$ (mmol/mol)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	LDL-calc (mmol/L)	HDL (mmol/L)
03/10/2012		6.4	7.94		1.0
16/3/2016*	38 (5.6%)	3.0*	1.48*	1.6	1.0
05/02/2018	46 (6.3%)	6.3	7.15		1.1
30/05/2018	93 (10.6%)	25.6	100.58		
31/05/2018		26.9	98.85		
02/06/2018		15.6	42.92		
29/06/2018		3.2	3.2	0.8	0.9

LDL, low density lipoprotein; HDL, high density lipoprotein. *Patient was on atorvastatin but stopped it later that year.

Table 2 Other blood results

	31/05/2018		01/06/2018		31/05/2018
Sodium (mmol/L)	123*	Albumin (g/L)	35	Haemoglobin	156 g/L
Potassium (mmol/L)	4.8 mmol/l	ALP (IU/L)	110	WCC	11.4x10^9/L
Urea (mmol/L)	5.0	ALT (IU/L)	29	Platelets	318x10^9/ L
Creatinine (µmol/L)	136	T bilirubin (µmol/L)	2	CRP	240 mg/L
T cholesterol (mmol/L)	26.9	Amylase (IU/L)	32	TSH (mIU/L)	0.94
Triglycerides (mmol/L)	98.85			Free thyroxine (pmol/L)	21

ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; WCC, white cell count.
 *Low sodium due to pseudohyponatraemia (see text).

Discussion

This patient presented with DKA and has negative GAD antibodies, which are present in 75–90% of type 1 diabetic patients at diagnosis.[1] He has features of type 2 diabetes with abdominal obesity and mixed dyslipidaemia and has a family history of impaired glucose tolerance and presumed type 2 diabetes. In addition, he reported symptoms of postprandial hypoglycaemia for several years. Postprandial hypoglycaemia has been reported in patients with insulin resistance or pre-type 2 diabetes mellitus. Ketosis-prone type 2 diabetes is a well-recognised entity. More than three-quarters of patients with ketosis-prone type 2 diabetes present with DKA.[2] Males are affected more than females, which is in contrast to DKA in type 1 diabetes. Some patients with ketosis-prone type 2 diabetes are able to come off insulin. Long-term insulin independence can be predicted by absence of autoimmune markers of β-cell destruction (such as GAD antibody) and positive β-cell function.

In DKA there is increased release of free fatty acids from adipose tissue from lipolysis resulting in production of ketones. There is also increased production of very low density lipoprotein (VLDL) from the liver resulting in hypertriglyceridaemia. Lipoprotein lipase (LPL) is an enzyme which metabolises triglycerides into fatty acids and becomes less effective in type 1 diabetes due to insulin deficiency.[3] Some degree of hypertriglyceridaemia is seen in all cases of DKA, but it is unusual to see such marked hypertriglyceridaemia as in our patient.

Lipoprotein electrophoresis is a useful investigation for pa-
tients with severe hypertriglyceridaemia. It separates lipoprotein in the serum due to their different electrophoretic mobility and is widely available. This was the basis of the Frederickson's classification. The severity of hypertriglyceridaemia in this case suggests these are mainly coming from chylomicrons. This happens in Frederickson's type I and type V hyperlipoproteinaemia (HLP). Type V HLP is more prevalent. In this condition not only chylomicrons but also the VLDL portion is increased. In type V HLP, a serum sample left standing overnight will have a creamy layer of chylomicrons on top with turbid milky infranatant due to the VLDL, while in type I HLP there will just be a creamy layer with a clear infranatant.[3]

The type V HLP pattern is seen in patients with both a genetic background along with acquired causes such as diabetes and excess alcohol intake.[3] Among genetic abnormalities seen in type V HLP, familial combined hyperlipidaemia which usually shows type IIb or IV HLP, monogenic familial hypertriglyceridaemia which shows type IV HLP and heterozygosity of LPL gene abnormalities are considered important. These usually present as type IV HLP but, under the influence of environmental factors, can change to type V.[3]

Familial chylomicronaemia syndrome is a much rarer autosomal recessive monogenic cause of severe hypertriglyceridaemia. This presents as a type I pattern on electrophoresis. Here there is defective LPL activity or deficiency of other factors required for its function. The proteins which affect LPL activity are apolipoprotein C2, apolipoprotein A5, GP1HBP1 (glycosylphosphatidylinos-

itol-anchored high-density lipoprotein-binding protein 1) and LMF1 (lipase maturation factor 1).[4] Homozygous monogenic disorders usually present in childhood with pancreatitis and have a type I pattern, while heterozygous mutations on more than one of the genes encoding the above proteins may have a variable presentation. A panel of genetic tests has been sent to assess for the above but will not impact on this patient's management.

Apo E mediates the metabolism of chylomicrons, chylomicron remnants, VLDL, intermediate density lipoprotein and a subclass of high density lipoprotein particles. Patients who are homozygous for apolipoprotein E2 in the presence of secondary genetic or environmental factors like hypothyroidism, obesity and diabetes can present with Frederickson's type III HLP, which gives a broad-beta pattern on electrophoresis. This is due to an increase in predominantly chylomicron remnants and intermediate density lipoprotein in the serum. Serum samples of such patients when left standing have a very thin cream layer with a turbid milky infranatant. The expression of type III HLP in E2/2 subjects is elicited to a large extent by fasting hyperinsulinaemia.[5] Our patient was heterozygous for apolipoprotein E2, which should not have an adverse effect on his lipid metabolism.

In cases of significantly elevated triglycerides, electrolyte values may be affected causing pseudohyponatraemia. This happens with routine analysers but not with blood gas analysers. Routine analysers use indirect ion-specific electrode (ISE) and the increase and decrease in plasma water volume distort the results of this method, as there is a dilution step, which does not take into account the real percentage of plasma water of the patient in the determination of the concentrations. By contrast, blood gas analysers use the direct ISE. With this method the sample is not diluted and the results are accurate even if the volume of plasma water is modified.[6] This was seen in the current case.

One of the complications of severe hypertriglyceridaemia is pancreatitis, but serum amylase is an unreliable test in this setting. Melnick *et al* reported a case of a woman with acute pancreatitis and hypertriglyceridaemia (>112 mmol/L) with a normal amylase level.[6] If acute pancreatitis is strongly suspected in this setting, blood tests should not be relied on to rule it out. Instead, imaging (such as CT scan) should be used. Hypertriglyceridaemia is indeed the third most common cause of acute pancreatitis after gallstones and alcohol, contributing to around 5% of cases.[7]

The initial management of patients with hyperglycaemia and hypertriglyceridaemia is intravenous insulin as it activates LPL activity. This is also effective in normoglycaemic patients with severe hypertriglyceridaemia for preventing acute pancreatitis.[8] The next step would be to commence lipid-lowering therapy such as fibrates as first line together with statins. Fibrates reduce the triglyceride level by up to 50%,[9] and statins reduce the triglyceride level by up to 30%.[10] Atorvastatin is as effective as rosuvastatin in reducing triglycerides, although this has not been checked in the setting of severe hypertriglyceridaemia.[10] Omacor, which has omega-3 fatty acid ethyl esters, also reduces triglycerides by up to 45%,[11] and is particularly useful in patients with renal impairment in whom fibrates may be contraindicated. The

Key messages

- Ketosis-prone type 2 diabetes is a well-recognised entity
- In the acute setting insulin therapy is the first-line treatment for severe hypertriglyceridaemia, not only in people with diabetes but also in people without diabetes
- Fibrates are the most effective oral medication for severe hypertriglyceridaemia

primary goal is to lower the triglyceride level to <5.0 mmol/L to ensure a good clinical outcome.[12] Although fibrates achieve a greater reduction in triglycerides compared with statins, they should be reserved for patients with severe hypertriglyceridaemia (>10 mmol/L) as fibrates may increase the risk of pancreatitis, possibly due to its effect on gallstone formation.[13]

Heparin is well known to cause release of LPL, but it also accelerates hepatic degradation of LPL. Administering intravenous heparin alone results in increasing circulating chylomicrons eventually. Intravenous heparin has been used along with insulin in hypertriglyceridaemia-induced pancreatitis, but it is still debatable whether heparin alone is sufficient in treating severe hypertriglyceridaemia.[14]

Studies have shown apheresis to be an effective tool in lowering triglycerides and the first documented use was in 1978.[15] Data from Yeh *et al* demonstrated a reduction in triglyceride levels of up to 70% with clinical and biochemical improvement.[16] Performing plasma apheresis early offers the best possible outcome in patients, but this is not routinely available in most centres in the UK.

The general consensus in the management of severe hypertriglyceridaemia is initiating intravenous insulin followed by starting lipid-lowering therapy. While treating DKA with insulin will also take care of triglycerides, insulin therapy can be a challenge in normoglycaemic patients. There are no consensus guidelines on the management of severe hypertriglyceridaemia causing pancreatitis. More experience is needed in the use of apheresis to guide us in managing difficult cases of severe hypertriglyceridaemia.

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