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Diabetes mellitus-associated severe hypertriglyceridemia causing pancreatitis: Experience with 2 cases

Pooja Sachdeva*; Rohit; Willis G Christopher; D'Souza M Jason; Pawar Manjit; Tavintharan Subramaniam

***Pooja Sachdeva**

Sengkang General Hospital, 110 Sengkang East way, Singapore 544886

Phone: 0065-9617 0342, Fax: 0065-6379 4149; Email: pooja.sachdeva@singhealth.com.sg

Abstract

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Insulin deficiency also causes dyslipidemia by releasing free fatty acids from adipose tissue that are taken up by the liver to produce excessive Very Low Density Lipoproteins (VLDL). This dyslipidemia may cause acute or chronic complications. An acute complication of mixed hyperlipidemia is Pancreatitis. In the setting of Diabetes Mellitus-associated hypertriglyceridemia causing pancreatitis, emergency treatment is required involving intravenous insulin in addition to conventional treatment. Plasmapheresis is considered where triglycerides levels are not responding to insulin infusion or when complications such as multi-organ failure ensue. We managed two patients who presented with DM-associated hypertriglyceridemia causing pancreatitis whose responses to insulin were different. The first patient presented with severe ketoacidosis precipitated by pneumonia. He had delayed response to insulin infusion hence was considered for plasmapheresis. The second patient who presented with DM-associated hypertriglyceridemia and pancreatitis responded to subcutaneous insulin injections. Both patients had good recovery and were followed up in outpatient clinic. Insulin is the mainstay in the management of hypertriglyceridemia-induced pancreatitis, however the route of administration is not necessarily intravenous. Clinically stable patients may respond to subcutaneous insulin.

Keywords

diabetes mellitus; hypertriglyceridemia; pancreatitis; plasmapheresis

Introduction

Severe hypertriglyceridemia can cause acute pancreatitis in 1-4% of cases when levels exceed 1,000 mg/dL (11.2 mmol/l) [3]. Diabetes Mellitus is a metabolic disease that results from either Insulin deficiency or defects in its secretion, or both [1]. Insulin deficiency increases Free Fatty Acids (FFA) and amino acids release from adipose tissue and muscle, respectively. . In addition, increased counter-regulatory hormones increase gluconeogenesis and glycogenolysis in the liver. Elevated FFA taken up by the liver leads to increased production of Very Low Density Lipoprotein (VLDL), which causes hypertriglyceridemia. The most common dyslipidemia in patients with Diabetes Mellitus is combined elevated triglyceride and cholesterol levels, with reduced High-Density Lipoprotein (HDL) cholesterol

(mixed hyperlipidemia) [2]. This hypertriglyceridemia if severe, can cause Pancreatitis. Pancreatitis is an acute inflammation of the Pancreas that is mostly caused by gall stones or alcohol use. Other less common causes of pancreatitis include trauma, drugs, autoimmune destruction and post procedural like post ERCP (Endoscopic Retrograde Cholangio-Pancreatography).

Case Reports

A 24-year-old nonsmoker, nondrinker Bangladeshi male with known past medical history of Diabetes Mellitus but non-compliant to medications, presented with one day history of abdominal pain and painful urination with no other systemic complaints. On examination, he was lethargic and afebrile with HR 101/min, BP 119/89 mm Hg, and RR 20/min with oxygen saturation of 98% on room air. His systemic examination was unremarkable. Blood investigation showed raised total white count of 16,000 due to high neutrophils; hemoglobin (Hb) 10.9 g/dL; platelets 153; Sodium 133mmol/L; Potassium 4.3mmol/L; Bicarbonate 4 mmol/L, Chloride 93 mmol/L, Anion Gap of 36 mEq/L. His arterial blood gas revealed: pH 7.024, pCO2 15.4 mmHg, Bicarbonate 6.2 mmol/L; a random plasma Glucose was 24.6 mmol/L, with Beta-hydroxybutyrate 6.0mmol/l ; Amylase 48 mmol/L; Lactate 0.7 mmol/L; Urea 4.9 mmol/l; and Creatinine 81 mmol/L. This was consistent with severe and incompletely compensated Diabetic Ketoacidosis precipitated by sepsis. Computed Tomography (CT) imaging showed evidence of pneumonia in the left lower lobe and early Pancreatitis with no gall stones. The patient required endotracheal intubation and mechanical ventilation for severe metabolic acidosis. Patient was initiated on supportive and definitive treatment of Diabetes Ketoacidosis according to current practice guidelines. He was treated with intravenous hydration 20ml/kg isotonic normal saline over the first hour and, intravenous insulin infusion 0.1units/kg /hr. He was started on Piperacillin-Tazobactam for treatment of Pneumonia. Maintenance normal saline of 10ml/kg/hr was given over the next 6 hours and 2.5 ml/kg/hr over the next 18 hours. However despite having intravenous Actrapid insulin and IV hydration with good urine output of 50-70mls/hour, metabolic acidosis worsened over the next four hours with pH 7.01, Bicarbonate 5.9 mmol/L, and pCO2 13.0 mmHg and elevated lactate. The subsequent biochemistry showed elevated Amylase of 143 mmol/L and Lipase of 200 mmol/L. Continuous Renal Replacement Therapy (CRRT) was initiated but there was repeated clotting of filters from severe lipemia and hypertriglyceridemia. Patient was considered for Therapeutic Plasma Exchange (TPE) in view of elevated Lactate, refractory acidosis and severe hypertriglyceridemia causing Pancreatitis. His initial lipid panel was "invalid" as it was out of laboratory measurement range and the first measured value after 24 hours treatment showed total Cholesterol of 12.0 mmol/L and Triglycerides (TG) 32.0 mmol/L. The Glycosylated Hemoglobin was (HBA1c) 9.3%.

A left femoral catheter was inserted. However just before the TPE was initiated, repeat biochemistry showed improving metabolic acidosis and TG values and it was with held. His serum beta hydroxybutyrate levels gradually became normal suggesting the resolution of ketoacidosis. The patient continued on IV hydration and IV Insulin. The metabolic acidosis and TG levels were gradually improving with ongoing treatment and resolved within 48 hrs. The patient was extubated uneventfully and was converted to subcutaneous NPH insulin 10 units twice a day with regular Actrapid 6 units three times a day pre-meals. He was observed closely in the general ward and was discharged with Insulin therapy and combined therapy for his hypertriglyceridemia with Atorvastatin 40 mg at bedtime, Omega-3 Fish Oil 4 gm three times a day and Fenofibrate 300 mg every morning. His discharge biochemistry revealed TG of

10 mmol/L and total Cholesterol 9.2 mmol/L. Anti-Islet cell antibodies and anti-Glutamate Dehydrogenase (GAD) antibodies were negative. His C-peptide was 203 pmol/L. He was followed upas an outpatient and his biochemistry showed TG 0.3 mmol/L and total cholesterol 2.7 mmol/L after six months of treatment.

A 31 year-old nonsmoker nondrinker Chinese male with no known past medical history presented with left sided abdominal pain for one day with no other symptoms. On examination his temperature was 37.9 C, HR 121/min, BP 141/99 mm Hg with O2 saturation of 98% on room air. He had epigastric tenderness with no rebound tenderness or guarding. The rest of the physical examination was unremarkable. His laboratory studies showed an elevated total white count of 13.98 x 106 /L due to neutrophilia; Hb 15.7 mmol/L; Platelets 276 x 109 /L; Sodium 136 mmol/L; Potassium 3.8 mmol/L; Chloride 94 mmol/L; Bicarbonate 17.0 mmol/L; random blood Glucose 15.6 mmol/L; Amylase 154 mmol/L; Lipase 471 mmol/L. Arterial Blood gas showed pH 7.40, pCO2 32.6 mmHg, Bicarbonate 21.5 mmol/L. Computed Tomography (CT) of the abdomen showed evidence of pancreatitis with no cholelithiasis. Etiologic work up showed markedly raised triglycerides of 32.95 mmol/L; total Cholesterol 10.95 mmol/L; Glycosylated Hemoglobin (HbA1c) 9.3%. The patient was treated for pancreatitis and the TG improved with subcutaneous insulin. There was no laboratory evidence of ketoacidosis suggesting underlying marked insulinopenia hence he was responsive to subcutaneous Actrapid Insulin injection and the TG showed an improved trend over the next 72 hours. The patient was closely monitored for further complications, but recovered uneventfully and was discharged with subcutaneous Glargine insulin 8 units at bedtime, Metformin 250 mg twice a day, Atorvastatin 80 mg at bedtime and Fenofibrate 300 mg every morning. On discharge his biochemistry showed a total Cholesterol of 8.52 mmol/L and TG of 6.19 mmol/L. He was followed up in the outpatient department for Diabetes mellitus and hyperlipidemia management. Outpatient biochemistry showed further reduction in the TG levels to 4.05 mmol/L and total cholesterol of 3.46mmol/L.

Discussion

Diabetic Ketoacidosis (DKA) is an acute metabolic complication and a medical emergency that arises from insulinopenia [4]. The risk factors are omission of insulin, infection, trauma, acute myocardial infarction and acute pancreatitis [5,6]. In DKA, the deficiency of insulin activates lipolysis in adipose tissue releasing increased FFA, which accelerates formation of VLDL in the liver and also associated with a reduced activity of lipoprotein lipase in peripheral tissue, resulting in decreased removal of VLDL from the plasma leading to hypertriglyceridemia [7]. Severe hypertriglyceridemia increases the risk of acute pancreatitis by causing pancreatic capillary injury. High plasma chylomicrons are hydrolyzed by lipase in the pancreatic capillaries which triggers FFA release [8]. These FFA, in turn, causes activation of trypsinogen and produce free radicals which ensues damage leading to pancreatitis [9,10].

The hypertriglyceridemia of diabetes can be classified as mild to moderate (triglycerides between 1.7-5.64 mmol/L) and severe hypertriglyceridemia (triglycerides ≥5.65 mmol/L) [12]. Management of hypertriglyceridemia associated with DM in hospitalized patients requires aggressive treatment to avoid complications such as pancreatitis. Various emergency treatment modalities have been discussed in the literature including Insulin therapy, Heparin therapy, Plasmapheresis and Octreotide [3,14]. Outpatient management includes weight reduction where appropriate, physical activity, Medical Nutrition Therapy (MNT) [13] and pharmacological agents for diabetic control along with combination therapy of statins

and fibrates with or without Niacin and fish oil. The aim is to reduce long term cardiovascular morbidity and mortality resulting from dyslipidemia.

Insulin decreases serum triglyceride levels by enhancing lipoprotein lipase activity which accelerates chylomicron and VLDL metabolism to glycerol and free fatty acids. It also inhibits hormone-sensitive lipase in adipocytes, which is the key enzyme for breaking down adipocyte TG and releasing FFA into the circulation [14,15]. Heparin therapy releases endothelial lipoprotein Lipase (LPL) that metabolizes TG containing lipoproteins [14,15]. Octreotide, a somatostatin analogue, binds to receptors in the pancreas and modulates its exocrine and endocrine function by inhibiting secretion of Insulin and Glucagon. Inhibition of glucagon secretion with Octreotide therapy may potentiate the fatty acid storing action of insulin and lead to a greater reduction of serum TG [15]. Plasmapheresis is a successful and safe alternative for treatment of hypertriglyceridemia resistant to conventional management [15]. The mechanisms of action are thought to be removal of cholesterol-containing lipoproteins, removal of excess proteases from the plasma, and replacement of consumed protease inhibitors with the donor's plasma. Indications for Therapeutic Plasma Exchange (TPE) are TG >11.3 mmol/L with elevated Lipase more than three times the upper limit or hypocalcaemia or lactic acidosis or signs of multi-organ dysfunction syndrome (MODS) [15].

The two patients had Hypertriglyceridemia-induced-Pancreatitis associated with poorly controlled DM but responded differently to insulin. Our first patient presented with severe ketoacidosis that represents severe insulin deficiency and decreased responsiveness to insulin from severe inflammation in sepsis as compared to our second patient who was not in hyperglycemic crisis. It is evident that not all patients require intravenous insulin. Stable patients may be tried with subcutaneous insulin provided there are no other indications for intravenous insulin.

Figures

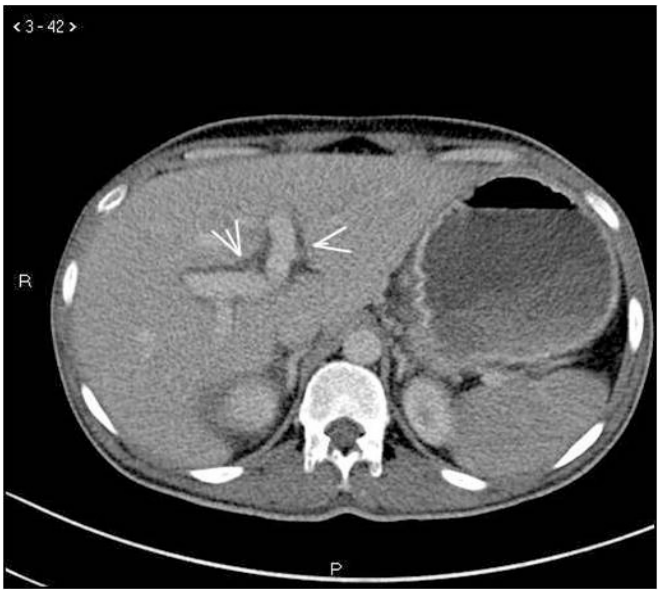

Figure 1: CT demonstrates periportal edema (arrowheads) suggestive of early pancreatitis in patient 1

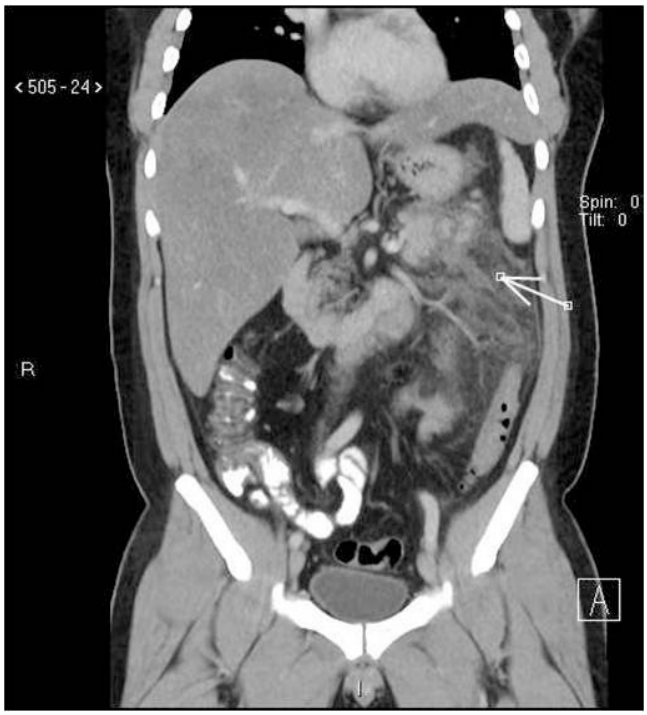

Figure 2: CT (Coronal Section) demonstrates pancreatitis (arrow) in Patient 2

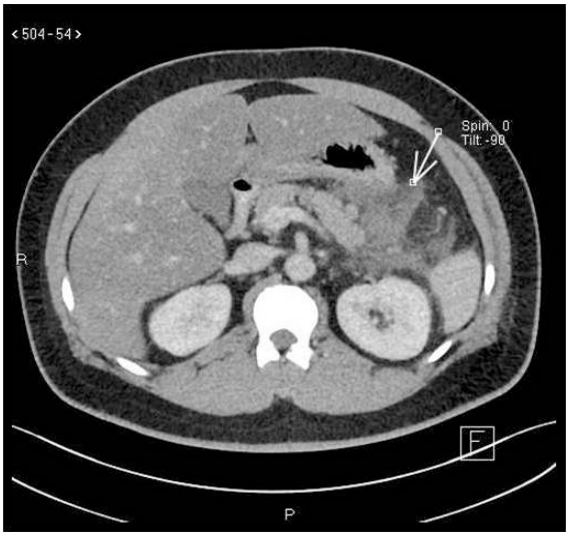

Figure 3: CT (Axial) demonstrates Pancreatitis (arrow) in patient 2.

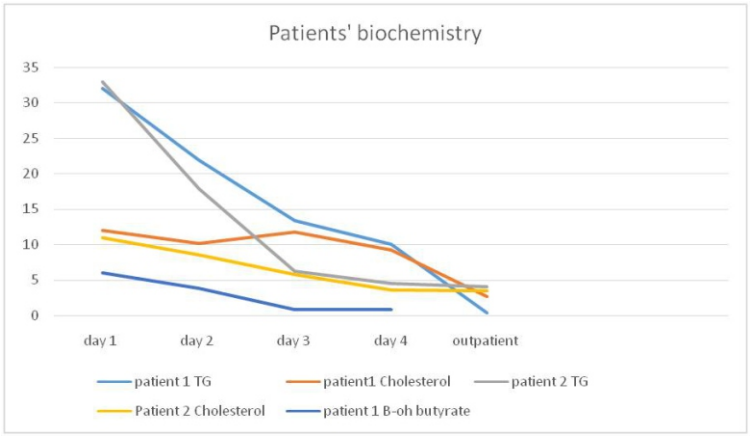

Chart 1: CBiochemistry of two patients showing trend of TG, Total cholesterol and Beta-hydroxybutyrate for first patient.

Conclusion

It is evident from our cases that insulin remains the mainstay for emergency management of hypertriglyceridemia, however the route of administration depends on the severity of the clinical presentation. Plasmapheresis should be considered if the patient shows evidence of pancreatitis or if TG levels are not responding to conventional therapy.

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Authors Information: Sachdeva Pooja[1]*; Rohit[2]; Willis G Christopher[3]; D'Souza M Jason[3]; Pawar Manjit[3]; Tavintharan Subramaniam[3]

[1]Sengkang General Hospital, 110 Sengkang East way, Singapore 544886
[2]Department of Diagnostic Radiology, KK women and Children Hospital, Singapore
[3]Department of General Medicine, Khoo Teck Puat Hospital, Singapore

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