

Hypertriglyceridemia Induced Recurrent Pancreatitis: Successfully Managed with Insulin and Heparin in Community Hospital Settings

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Abstract

Hypertriglyceridemia is a well-known cause of acute pancreatitis. A serum triglyceride level of more than 1000 mg/dl is the identifiable risk factor. Clinical presentation of hypertriglyceridemic pancreatitis is similar to other causes. Treatment is conservative with measures to rapidly lower triglyceride levels by plasmapheresis; insulin and heparin, or purified apo C II. Once acute attack of pancreatitis resolve, subsequent control of hypertriglyceridemia with dietary restriction of fatty meals, antihyperlipidemic agents and even regular apheresis is required to prevent further episodes of acute pancreatitis. Yet there are no clear guidelines for the management of hypertriglyceridemic pancreatitis to follow. Limited literature is available about the efficacy of intravenous insulin and heparin. We are presenting a case of 17 year old male with recurrent episodes of hypertriglyceridemic pancreatitis, successfully managed with insulin and heparin therapy.

Keywords: *Pancreatitis; Hypertriglyceridemia; Insulin and Heparin Therapy*

Introduction

Although gall stones and alcohol are most common causes and account for 75 - 80% of cases of pancreatitis [1]. Metabolic, structural, and iatrogenic causes accounts for 20 - 25% of the cases [2]. Hyperlipidemia in the form of hypertriglyceridemia or chylomicronemia causes 1 - 7% cases of acute pancreatitis [3]. Usually hypertriglyceridemia-induced pancreatitis occurs in a patient with a pre-existing lipid abnormality, along with the presence of a secondary precipitating factor like poorly controlled diabetes, alcohol or medication. Type I, IV, and V hyperlipoproteinemia's (Friedrickson's classification) are associated with severe hypertriglyceridemia and predispose to acute pancreatitis [4]. Genetic factors determine over 60% of the variability in serum lipids [5]. Insulin, heparin and apheresis have an important role to play during the acute attack of pancreatitis with the aim to rapidly lower the triglycerides [6,7].

Case Report

A 17-year old male normotensive, nondiabetic, nonsmoker, non-alcoholic with no significant past medical history presented to our emergency department with complaints of epigastric pain and recurrent vomiting -24 hour duration. No significant family history. On examination patient was conscious and mucous membranes were dry. Pulse was 120/min, blood pressure 100/70 mmHg, respiratory rate 30/min and temperature 101 F. Abdominal examination revealed marked tenderness and guarding in epigastric region with sluggish bowel sounds. Rest of systemic examination was unremarkable.

Serum was lipemic (Figure 1); Laboratory parameters revealed normal complete blood count, electrolytes, calcium, liver function tests, renal function test, lactate dehydrogenase, coagulation profile, blood glucose and thyroid function test. Serum amylase was 209 mg/dl (normal 25 - 125); lipase 333U/L (normal 13 - 60), triglycerides 1742 mg/dl (normal < 150), cholesterol 262 mg/dl (normal < 200), low density lipoprotein 86 mg/dl (normal 100 - 129), very low density lipoprotein 233 mg/dl (normal 2 - 30), high density lipoprotein 48 mg/dl (> 40) and chylomicrons were present. Ultrasound of abdomen showed inflammatory changes in the pancreas with normal gall-

bladder and biliary tree. Contrast enhanced computed tomography findings were consistent with acute pancreatitis (Figure 2). In view of high triglycerides, very low density lipoproteins and presence of chylomicrons diagnosis of type V hyperlipoproteinemia's (Friedrickson's classification) was made. Based on clinical, laboratory and imaging studies final diagnosis of Type V hyperlipoproteinemia with hypertriglyceridemia induced pancreatitis was made.



Figure 1: Lipemic serum.

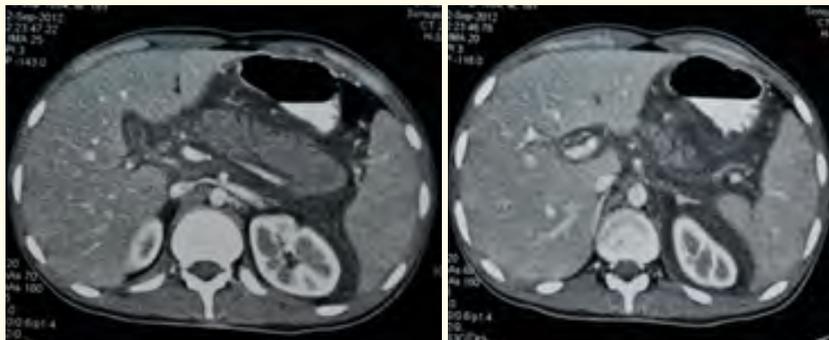


Figure 2: CECT showing inflamed pancreas with peripancreatic fat stranding and peripancreatic fluid extending into the left pararenal space. Fluid also noted posterior to pancreas.

Patient was started on regular insulin infusion at a rate of 0.1U/kg per hour in 5% dextrose along with subcutaneous heparin at a dose of 5000 units twice daily and blood glucose was maintained between 151 - 200 mg/dl. Blood glucose levels were measured 2 - 4 hourly and triglycerides 12 - 24 hourly. Insulin and heparin was continued for 3 days till triglycerides dropped to 251 mg/dl. Serial triglyceride levels and corresponding appearance of serum samples during these three days are shown in (Figure 3). Patient was also kept nil per oral and was given intravenous fluids, analgesics and antiemetics. After four days patient was discharged on finofibrate 160 mg daily and was advised to follow up. On follow up after four weeks his triglycerides were increased to 302 mg/dl so dose of finofibrate was increased to 200mg per day. However patient did not follow after that and 3 months later he presented again with clinical, laboratory and imaging findings of severe pancreatitis. Serum was again lipemic with amylase 220 mg/dl (normal 25 - 125), lipase 290 U/L (normal 13 - 60), triglycerides 1469 mg/dl (normal < 150), very low density lipoproteins 207 mg/dl (normal 2 - 30). Ultrasound abdomen and Contrast enhanced computed tomography again revealed evidence of acute pancreatitis (Figure 4). Patient was again managed with insulin infusion, heparin,

intravenous fluids, analgesics and antiemetics. After resolution he was discharged on finofibrate 200 mg per day and advised to take low fat diet. On follow after 6 weeks his triglycerides were again high 387 mg/dl. Nicotinic acid 500 mg per day was added to treatment and 8 weeks latter his lipid profile was normal with cholesterol 121 mg/dl, triglycerides 83 mg/dl and very low density lipoproteins 16 mg/dl. Patient is on regular follow up and doing well on treatment.

Time Interval	0 hours	12hours	36 hours	60 hours
TG levels	1742 mg/dl	1122 mg/dl	541 mg/dl	251 mg/dl
Serum Appearance				

Figure 3: Showing duration of insulin infusion, serial triglyceride levels and corresponding serum sample appearance during first episode of pancreatitis.

Graphical representation of serum triglycerides and duration of insulin infusion.

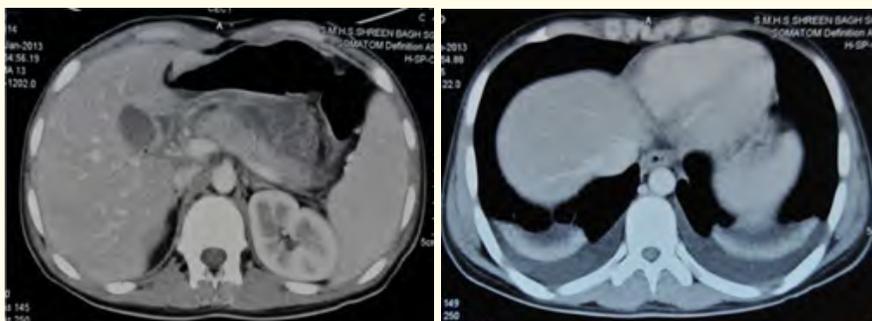
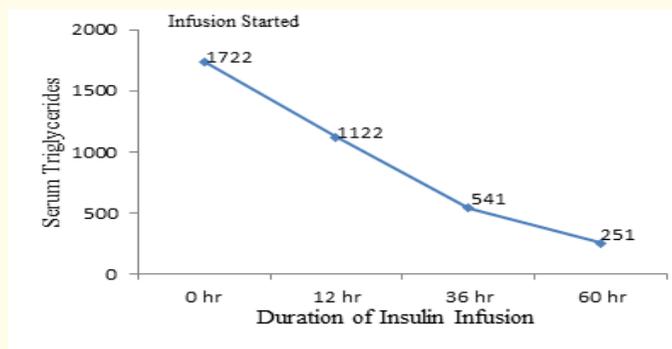


Figure 4: Axial Contrast enhanced Computed tomography CECT of the same patient after 3 months, showing evidence of fresh episode of pancreatitis with peripancreatic fluid collection and phlegmon, bilateral pleural effusion, basal atelectasis.

Lipid Profile, Amylase and Lipase During Course of Illness

Investigations	First Episode	Second Episode	Follow Up on Fibrates	On Fibrates and Niacin
Amylase	209 mg/dl	220 mg/dl	N.D	N.D
Lipase	333 U/l	290 mg/dl	N.D	N.D
Triglycerides	1742 mg/dl	1469 mg/dl	387 mg/dl	83 mg/dl
Cholesterol	262 mg/dl	212 mg/dl	190 mg/dl	121 mg/dl
LDL	86 mg/dl	98 mg/dl	90 mg/dl	82 mg/dl
VLDL	233 mg/dl	207 mg/dl	81 mg/dl	16 mg/dl
HDL	48 mg/dl	42 mg/dl	46 mg/dl	50 mg/dl
Chylomicrons	Present	Present	N.D	N.D

N.D Not Done

Discussion with Review of Literature

Hypertriglyceridemia (HTG) is the third most common cause of acute pancreatitis (AP) after alcohol and gallstones [1,5]. The association of severe hypertriglyceridemia and pancreatitis was first postulated by Speck [8] in 1865. It is reported to cause 1 to 7 percent of all cases of acute pancreatitis and up to 56 percent of pancreatitis cases during pregnancy [9]. Hypertriglyceridemia is defined by fasting serum triglyceride level of > 150 mg/dl and is classified as mild (150 to 199 mg/dl), moderate (200 to 999 mg/dl), severe (1000 to 1999 mg/dl) and very severe > 2000 mg/dl [10]. A serum triglyceride level of 1000 mg/dl or greater increases the risk of acute pancreatitis, although some patients have developed acute pancreatitis at lower levels. Usually levels less than < 500 mg/dl do not significantly increase the risk of acute pancreatitis. Hypertriglyceridemia can be primary (genetic) or secondary to diabetes, obesity, pregnancy, excess carbohydrate intake, hypothyroidism, alcohol, hepatitis, sepsis, renal failure, and drugs like estrogen, glucocorticoids, β blocker, bile acid binding resins, thiazide, tamoxifen cyclosporine protease inhibitors, and isotretinoin [11]. Frederickson’s class I (high chylomicrons), IV (high very low density lipoprotein), and V (high chylomicrons and high very low density lipoprotein), dyslipidemias are associated with severe hypertriglyceridemia and predispose to acute pancreatitis [4]. Types I and V can present with acute pancreatitis without an exacerbating factor, whereas type IV usually requires another factor to raise serum triglyceride levels. The initial presentation of hypertriglyceridemic pancreatitis is similar to that of acute pancreatitis of other causes; abdominal pain, nausea, and vomiting are the major complaints. Poorly controlled diabetes, alcoholism, obesity, pregnancy, prior pancreatitis, and a personal or family history of hyperlipidemia help in diagnosis [1,5,9,12]. Certain features on the physical examination can help identify hypertriglyceridemia as the cause of acute pancreatitis which include eruptive xanthomas over the extensor surfaces of the arms, legs, buttocks, and back [13,14]; lipemia retinalis [13,15]; and hepatosplenomegaly from fatty infiltration of the liver [13]. The severity and complication rates associated with hypertriglyceridemic pancreatitis have been reported to be higher compared to acute pancreatitis from other etiologies, however overall mortality does not differ.

Pathogenesis of hypertriglyceride-induced pancreatitis

The exact mechanism involved in hypertriglyceridemia-induced pancreatitis is unclear. Chylomicrons which are triglyceride-rich lipoprotein particles are believed to be responsible for pancreatic inflammation. They are present in the circulation when serum triglyceride levels exceed 1000 mg/dl and are large enough to occlude the pancreatic capillaries, leading to ischemia and subsequent acinar structural alteration leading to exposure of these triglyceride-rich particles to pancreatic lipase. The pro-inflammatory non-esterified free fatty acids generated from the enzymatic degradation of chylomicron-triglycerides causes further damage of pancreatic acinar cells and microvasculature. Subsequent amplification of the release of inflammatory mediators and free radicals may ultimately lead to necrosis, edema, and inflammation [16,17].

Treatment

The management of hypertriglyceridemic pancreatitis includes conventional treatment of acute pancreatitis, and treatment of serum triglyceride levels with an initial goal of < 500 mg/dl. Maintenance of triglyceride levels below 500 mg/dl has been shown to accelerate clinical improvement [1]. There are no definitive guidelines for management of severe hypertriglyceridemia in acute pancreatitis. However various modalities which have been used to lower triglycerides are insulin and heparin to enhance lipoprotein lipase activity, and apheresis to remove triglycerides. To date no randomized trials have been done to compare the efficacy of apheresis with that of insulin and heparin. Further studies are needed to develop optimal treatment.

Apheresis

Apheresis for lowering triglyceride levels was first reported in 1978 by Betteridge, *et al* [18]. Since then many case reports and series have utilized apheresis for hypertriglyceridemic pancreatitis (Table 1). The beneficial effect of plasmapheresis is believed to be due to a rapid decrease in triglyceride levels, yet removal of excessive proteases from the plasma and replacement of consumed protease-inhibitors might play an additionally beneficial role.

Reference	Patients included	Results (Reduction in TG level)
Stefanutti, <i>et al.</i> [19]	17	By 61%
Gubensek, <i>et al.</i> [20]	50	Significant reduction
Kyriakidis, <i>et al.</i> [21]	10	By 62%
Chen, <i>et al.</i> [22]	54	Not available
Yeh, <i>et al.</i> [7]	18	By 66% (first setting) and by 83% (second setting)
Yeh, <i>et al.</i> [23]	17	Significant reduction
Kadikoylu, <i>et al.</i> [24]	7	Significant reduction
Lennertz, <i>et al.</i> [25]	5	By 70%

Table 1: Overview of the currently available studies on the use of apheresis.

For better results apheresis has to be started early after diagnosis. Kyriakidis, *et al.* [21] started it within 48 hours of diagnosis and found it very effective. On the other hand Chen, *et al.* [22] found it less effective which they contributed to delay in initiation of apheresis. After every cycle, a serum triglyceride level is re-checked and, if less than 500 mg/dl, apheresis is stopped. Limitations of apheresis include high cost, lack of availability, anaphylactic reactions, hypotension, hypocalcaemia, transfusion-related infections.

Insulin and heparin

Combination of Insulin and Heparin has been used in many case reports [26,27] and series [28,29] to rapidly lower triglycerides in hypertriglyceridemic pancreatitis. Insulin activates lipoprotein lipase, an enzyme that accelerates chylomicron degradation into glycerol and fatty free acids [30,31]. Insulin also inhibits hormone-sensitive lipase in adipocytes, which is the key enzyme for breaking down adipocyte triglycerides and releasing free fatty acids into the circulation. Heparin stimulates the release of endothelial lipoprotein lipase into circulation [32], and has been used without insulin to successfully manage hypertriglyceridemia [33-35]. Although used successfully in some studies the use of heparin as a monotherapy has been questioned because of its transient benefits. Heparin causes an initial rise in circulating lipoprotein lipase levels that is followed by increased hepatic degradation [36]. This degradation may result in further depletion in plasma stores of lipoprotein lipase and results in the accumulation of circulating chylomicrons [37]. Insulin alone has been used in many case series to rapidly lower triglycerides. Mikhail, *et al.* [38] used intravenous insulin to lower triglyceride levels from 7,700 mg/dl to 246 mg/dl over 4 days in one patient, and subcutaneous insulin every 4 hrly for 4 days to lower triglycerides in another patient from 10,500 to 656 mg/dl. Tamez-Perez, *et al.* [39] utilized intravenous insulin to lower triglycerides from > 1,000 mg/dl to below 400 mg/dl over 2.5 days in seven patients. There are no clear cut guidelines for dosage and route of administration for insulin and heparin use.

However based on published literature so far we suggest to use insulin as infusion in 5% dextrose, starting with 0.1 - 0.3 U/kg per hour to maintain blood glucose levels between 150 - 200 mg/dl. Heparin can be used 5000 U twice daily subcutaneously/intravenously. Treatment should be stopped when triglyceride levels are < 500 mg/dl, which typically occurs within several days.

Purified apoC- II infusion, used in some studies has also been found to transiently normalise triglycerides and improved clinical status of pancreatitis patients with apoC- II deficiency [40].

Once the acute attack of pancreatitis settles, the aim of further treatment is to keep TG under control so as to prevent subsequent attacks. Persistence of hyperlipidemia on a fat-reduced diet should prompt the institution of lipid-lowering agents. The fibrates are the drugs of first choice. They effectively lower triglyceride levels by 40 - 60% and raise high density lipoprotein levels [41,42]. Niacin is less potent than fibrates, can be used alone or in combination with a fibrate. It lowers triglyceride levels by 30 - 50 % [42]. Omega-3 fatty-acids are capable of lowering triglyceride by 45% [43]. Anti-oxidant therapy (selenium, beta-carotene, vitamin C and α -tocopherol) has been used with success in the reduction of recurrent pancreatitis episodes in patients with familial lipoprotein lipase deficiency who remained markedly hypertriglyceridemic after medical therapy [44]. Anti-oxidants protect from the free radicals which are generated in pancreatic acinar cells as a result of ischemia induced by chylomicrons.

Gene therapy is another useful treatment modality for cases of hypertriglyceridemia with documented lipoprotein lipase deficiencies [45]. This treatment consists of local intramuscular application of a viral vector containing a lipoprotein lipase gene. Lipoprotein lipase gene therapy may become a useful tool for achieving permanent control of hypertriglyceridemia in the future.

Proposed approach based on available literature, to patient with hypertriglyceridemic pancreatitis

To date no guidelines exists regarding the management of hypertriglyceridemic pancreatitis. However based on published literature so far, we suggest that patients with hypertriglyceridemic pancreatitis should be managed as conventional pancreatitis besides measures to rapidly lower TG to less than 500 mg/dl. Apheresis should be initiated within 48 hr if readily available at the medical centre, and the patient has no contraindications. Apheresis should be continued in several sessions until end-of-session serum triglyceride levels are < 500 mg/dl. If apheresis is delayed or unavailable, the patient cannot tolerate apheresis, or the patient's glucose is > 500 mg/dl, the clinician can initiate intravenous insulin at a rate of 0.1 - 0.3 U/kg per hour. Most studies have used regular insulin in 5% dextrose infusion to maintain blood glucose levels between 150 and 200 mg/dl. Fingerstick glucose levels should be done every 4 hrly to ensure good glucose control and triglyceride levels every 12 - 24 hrly to verify appropriate decreases with intravenous insulin. Intravenous insulin should be continued until triglyceride < 500 mg/dl, which typically occurs over several days. Oral anti-hyperlipidemics should be initiated as adjuvant therapy when the patient can tolerate. Although the patient is undergoing treatment, the clinician should investigate the etiology of the hypertriglyceridemia, such as reviewing patient medications, medical history, or obtaining a detailed family history looking for familial hyperlipidemia. The treatment plan must be tailored to each patient.

Conclusion

Hypertriglyceridemia can present as recurrent pancreatitis. The initial clinical presentation of hypertriglyceridemic pancreatitis is similar to that of acute pancreatitis of other causes, but history, physical examination and biochemical features can suggest the diagnosis. Clinicians should routinely test triglyceride levels in patients who present with acute pancreatitis to accurately identify the need for specialized management. In addition to the conventional treatment of acute pancreatitis, management of hypertriglyceridemic pancreatitis focuses on decreasing triglyceride levels to < 500 mg/dl. Several modalities like insulin, heparin and apheresis are available to rapidly lower triglycerides. However no trials are available to compare efficacy between these modalities. Oral antihyperlipidemics, dietary fat restriction, and even regular apheresis have been used with success to prevent further episodes of pancreatitis. Since no clear-cut guidelines exist for management of hypertriglyceridemic pancreatitis, further studies and formulation of guidelines are needed to improve the management of acute hypertriglyceridemic pancreatitis.

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Khalid Rasheed: Reviewed and Edited final draft.

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