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Hypertriglyceride Induced Acute Pancreatitis

Joshua Lebenson and Thomas Oliver
Uniformed Services University of the Health Sciences, United States

1. Introduction

Pancreatitis is a common clinical entitiy with multiple contributing etiologies[1]. Triglyceride (TG) levels greater than 1000 mg/dL are seen in a small but significant number of cases of acute pancreatitis (AP), with estimates ranging between 1-7% of all cases and perhaps slightly higher in patients who present during pregnancy[2-4]. The clinical presentation of hypertriglyceridemic pancreatitis (HTGP) is similar to other causes of acute pancreatitis, but some evidence suggests that there may be an increased severity and risk of complications[5,6]. Multiple etiologies of highly elevated TG levels have been implicated, including congenital disorders, metabolic perturbations and certain medications but a definitive treatment regimen for profoundly elevated serum TG in association with acute, and often severe, pancreatitis has yet to be demonstrated[7-10].

Dietary restriction is the cornerstone of therapy. Additional treatment modalities have included insulin and heparin to stimulate the synthesis, release and activation of lipoprotein lipase (LPL) from capillary endothelial cells to promote TG degradation into free fatty acids for further metabolism or storage[11]. We present a case of HGTP managed with insulin, heparin and octreotide with dramatic results; a logarithmic decrease in serum TGL magnitude and a significant reduction in the time to resolution as compared with previous reports of treatment with insulin and heparin alone. Recent advances in the management of HGTP, including proposed mechanisms, will be reviewed. Adjunctive therapies, including plasmapheresis and more chronic therapy with lipid lowering agents and dietary modification will be discussed.

2. Case report

A 51-year-old Hispanic man presented to the emergency department with 2 days of epigastric pain radiating to the back. The patient reported one episode of emesis but denied fever, chills, dyspnea, diarrhea, or constipation. His past medical history was significant for asthma and gastroesophageal reflux disease. Medications included omeprazole daily and as needed acetaminophen, ibuprofen, and albuterol. Social history was significant for tobacco use, one pack per month, and ethanol use, two cans of beer daily.

Temperature was 97.6°F. Blood pressure was 117/72 mm Hg, heart rate 80 min, regular, and respiratory rate was 18/min. Examination of the cardiopulmonary and nervous system was unremarkable. The abdomen was diffusely tender without rebound, guarding or discoloration. No xanthelasmas, eruptions, arcus, or xanthomas were noted. Relevant

laboratory measurements from lipemic serum are listed in Table 1. The urine toxicology screen was positive for barbiturates. Cardiac screening (enzymes, electrocardiogram) was negative and ultrasound imaging revealed no abnormalities of the gall bladder, common bile duct, or pancreas. A CT scan performed on the second hospital day was remarkable for peripancreatic fat stranding without necrosis or hemorrhage.

Analyte	Reference Range	Admission	24 h	48 h
Amylase	25-125 U/L	80	126	141
Lipase	23-203 U/L	179	166	96
Glucose	74-118 mg/dL	100	83	93
Triglycerides	30-190 mg/dL	20891	1423	355
Cholesterol	60-160 mg/dL	862	997	594
Sodium	136-144 mmol/L	111	121	140
AST	<40 IU/L	737	186	74
ALT	<33 IU/L	227	135	39

Table 1. Laboratory Values at Presentation and While Hospitalized

The patient was diagnosed with HTGP and initial management included elimination of enteral intake, aggressive fluid repletion, and opiate analgesia. Subsequent therapy included a continuous insulin infusion, a 10% dextrose infusion titrated to maintain euglycemia, 60 U/kg unfractionated heparin intravenous (IV) bolus every 4 hours, and 100μg octreotide bolus subcutaneously every 8 hours. TG fell by 2 orders of magnitude in 2 days, falling from 21,000 to 355 mg/dL, the rest of the laboratory values were improved (Table 1), and the lipemia resolved. The clinical course was uncomplicated and the patient was discharged after 4 days.

3. Clinical presentation of hypertriglyceridemic pancreatitis

The clinical features of acute HTGP are similar to that of other causes of pancreatitis[12]. Patients may present with sudden and severe epigastric abdominal pain often accompanied by anorexia and profound nausea lasting hours to days[13]. Other less common findings, more indicative of chronic hyperlipidemia, include the presence of eruptive xanthomas over the extensor surfaces, lipemia retinalis, arcus and hepatospenomeglay due to fatty infiltration of the liver.[14] Frequently, those presenting with significant TG elevations and pancreatitis have an underlying metabolic abnormality in lipid metabolism[15,16]. Patient presentations where HTGP is encountered include poorly controlled diabetics with or without a history of HTG, alcoholics with hypertriglyceridemia or lactescent serum on admission, non-diabetic, non-obese patients with drug or diet-induced HTG and patients presenting with AP without secondary risk factors; the first three of these comprise the majority of clinical presentations of HTGP[12,17,18].

Following the onset of HTGP, TGL tend to fall rapidly over 72 hours in the fasting state as a result of decreased supply and absorption of chylomicrons[19]. In addition, VLDL secretion from the liver is reduced secondary to the administration of hypocaloric intravenous fluids, thus leading to a direct reduction in TGL[20].

4. Lipid physiology

Lipoproteins are macromolecules containing both organic proteins and bound lipids that are found in plasma in varying proportions and can be separated by density via ultracentrifugation. In increasing order of density, these separate into layers of chylomicrons, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density proteins (LDL) and high density lipoprotein (HDL)[21].

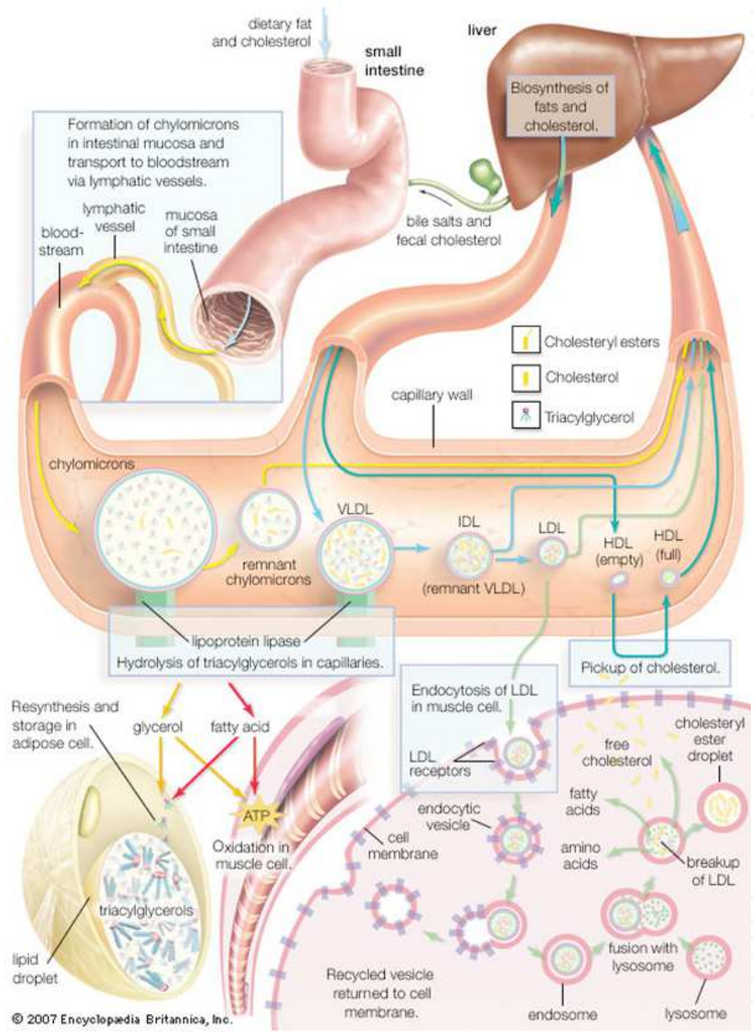

Fig. 1. Fat metabolism
http://www.britannica.com/bps/media-view/92255/0/0/0

TG are a major lipid constituent of chylomicrons and VLDL. The former contains Apo B-48 and is derived from dietary sources while the latter contains Apo B-100 and is liver generated[22,23]. Cholesterol is the primary component of IDL and LDL[24].
Dietary TG are absorbed through the brush border of intestinal enterocytes, incorporated into chylomicrons and pass through the basolateral aspect where they enter the lymphatics before entering the venous circulation via the thoracic duct, ultimately acquiring apolipoprotein C-II, a critical cofactor for lipoprotein lipase (LPL)[25].

Both chylomicrons and VLDL are transported to muscle and adipose tissue where they are metabolized by LPL to meet energy demands or stored for future use[26,27]. LPL is secreted into the venous circulation by parenchymal cells in many tissues, migrates through the vasculature and anchors to the capillary endothelium via a heparan sulfate chain. Upon activation, it facilitates lipoprotein binding and TG degradation[28]. This process results in the release of fatty acids and acylglycerols which can then be utilized directly by myocytes to meet metabolic demands or be reincorporated into triglyceride for storage in adipocytes[29].

5. Diagnosis and laboratory evaluation

The clinical presentation and course of HTG pancreatitis does not differ greatly from other causes of AP[30]. Lipemic serum, frequently associated with an underlying metabolic abnormality or compromising medications, is the single most reliable clue that the pancreatitis is associated with or precipitated by hyperlipidemia[31]. Although the serum triglyceride threshold for considering HTGP is generally considered to be in the range of 1000 mg/dL, the severity, clinical course and complication rate do not correlate with lipid levels. In a study of 43 patients with HTGP, no correlation was observed between admission HTG and APACHE II score, nor was there a relation between TG level and pancreatic inflammatory complications or ultimate patient outcome[32].

Historically, clinicians have relied on increases in levels of serum amylase, and/or lipase to secure the diagnosis of acute pancreatitis. Newer diagnostic modalities, such as urine trypsinogen, procarboxypeptidase A and carboxypeptidase A, are becoming more available and may become more relevant[33-35]. Some patients with HTG pancreatitis and lipemic serum present with spurious laboratory values that can complicate the diagnosis[36] but a serum lipase sensitivity and specificity of 67% and 97% respectively, argue that this test remains a valuable diagnostic tool[37].

6. Pathophysiology of hypertriglyceridemic pancreatitis

The mechanism by which elevated levels of plasma TG lead to the development of AP is not fully understood. It is generally accepted that levels greater than 1000 mg/dL are required to precipitate an episode of pancreatitis, but such levels of TG do not always cause HTGP.[38] The most recent ATP III guidelines suggest that a normal TG level is considered to be less than 150 mg/dl, while those greater than 500 mg/dl are considered very high[39]. Pancreatic lipase, a digestive enzyme concentrated in the exocrine pancreas which participates in TG degradation, may be liberated in AP and act in an unregulated fashion to contribute to tissue breakdown[40]. Additionally, if the local plasma TG level increases beyond the enzymatic capacity of the pancreas, free fatty acids begin to accumulate and can lead to injury of pancreatic acinar cells and surrounding tissues[41,42]. Altered pancreatic blood flow, perhaps aggravated by the hyperviscosity of chylomicronemia, may also create a more acidic environment in which free fatty acids become more toxic to the surrounding tissue[43-46]. The resultant cellular injury leads to further pancreatic inflammation, injury and destruction.

7. Causes of hypertriglyceridemia

Primary Causes: Primary causes of HTG consist of a series of genetic disorders leading to abnormalities in lipid metabolism and patients presenting with HTG or lipemic serum

should be evaluated for Frederickson classification dyslipidemias types I, IV and V as they are strongly associated with highly elevated serum TG[47,48].

Secondary Causes:

Diabetes – Poorly controlled, or uncontrolled, diabetes is a common cause of HTGP[49]. In type 1 diabetes mellitus, the paucity of insulin reduces LPL synthesis and thus compromises effective TG hydrolysis and release of free fatty acids. The latter are already accumulating in the absence of insulin-facilitated storage[50,51]. Similarly, in type 2 diabetes mellitus, increased insulin resistance leads to enhanced production and reduced clearance of TGs[52]. The causal role of diabetic ketoacidosis (DKA) in HTG was evaluated in a prospective study of 100 patients with DKA, 11 of whom had AP, and of these, HTG was the only attributable cause in 4 cases[53]. Serum TG levels normalized in these patients after control of the acidosis.

Primary HTG
Genetic: Frederickson type I, IV, V
Secondary HTG
Diet: alcohol excess, weight gain/obesity
Drugs: exogenous estrogens, tamoxifen, retinoids, thiazides, beta blockers, protease inhibitors, propofol, parenteral lipid infusions
Disorders of Metabolism: Diabetes, pregnancy, chronic renal failure, hypothyroidism, porphyria
*Adapted from Ref [12]

Table 2. Common Etiologies of HTG

Alcohol – Ethanol compromises fuel and energy metabolism, thereby resulting in decreased serum glucose levels with elevated levels of lipids due to increased production and decreased utilization of energy sources. Alcohol can aggravate HTG and the liberated free fatty acid esters can promote calcium influx which leads to calcium-mediated pancreatic necrosis[57]. Nutritional deficiencies, including hypoglycemia, activated counterregulatory mechanisms and reduced cofactor availability reduce or inhibit insulin secretion, thus further compromising energy metabolism and exacerbating hyperlipidemia[58].

Medications- Several medications are known to increase plasma TG levels, including isotretinoin[59], propofol[60], protease inhibitors[61] and furosemide[62]. Estrogens and Tamoxifen are two well studied drugs in which the tendency to promote HTG and steatohepatitis is well described[63].

Estrogen – Exogenous estrogens increase serum TG and fatty acids primarily by reducing levels of lipoprotein and hepatic lipases which subsequently decreases clearance and aggravates insulin resistance, perhaps by as much as 40%[64-66]. Goldenberg et al., evaluated 56 female patients at a Cholesterol Center because of TG >400 mg/dl and/or HTGP, and/or failure of TG-lowering therapy. Of that cohort, 17 females (30%) had a history of AP and of those, 9 (53%) had taken, or were concurrently taking exogenous steroid hormones[67]. The authors concluded that hormone therapy remain relatively contraindicated with plasma TG>300mg/dl and strictly contraindicated when TG greater than >500 mg/dl in order to avoid an episode of pancreatitis.

Tamoxifen – Tamoxifen is a non-steroidal anti-estrogen commonly used in the treatment of patients with breast cancer and has shown the ability to decrease LDL and total cholesterol levels. There is frequently an increase in VLDL synthesis and subsequent rise in plasma TG

levels due to reductions in lipoprotein lipase activity[68,69]. Elisaf, et al., reported 12 patients with serum TG >1000 mg/dl who were observed after administration of 20mg/day of tamoxifen[70]. Four of these patients, two of whom had a personal or family history of hyperlipidemia, developed HTGP. This led them to the conclusion that, like synthetic estrogens, the tamoxifen-mediated rise in TGs may be either contributory or causative in the development of AP.

Pregnancy – Gestational AP is an uncommon condition, with studies ranging incidence between 1 in 3,500-4,000 pregnancies[71]. Most cases of AP during pregnancy are mild and are most often attributable to biliary disease, while severe AP most commonly results from hypertriglyceridemia and tends to occur in the second and third trimesters[72]. During pregnancy there is a physiologic increase in plasma lipids. Cholesterol and TG increase due to an increased production of VLDL and the decreased actions of LPL and hepatic lipase[73].

HTGP tends to develop in women with an underlying disorder in lipid metabolism, such as LPL[74] or apolipoprotein C-II deficiency[75]. Maternal mortality in cases complicated by HGTP is estimated to be near 20% and cause of death has been linked to the pancreatitis itself, or, rarely, has been associated with HELLP syndrome.[76] The mainstay of treatment, as in the non-pregnant state, is early recognition and intervention[77,78]. A major difference in long term management is that the use of HMG-CoA reductase inhibitors (statins) is contraindicated in pregnancy as they are a teratogenic category X pharmaceutical[79].

	Type I	**Type IV**	**Type V**
Elevated lipoproteins	Chylomicrons	VLDL	VLDL Chylomicrons
Cholesterol	Normal	Normal or Increased	Normal
Triglycerides	+++	++	+++
Plasma appearance †	Clear plasma, creamy supernatant	Turbid	Turbid plasma, creamy supernatant
Genotype	LPL deficiency Apo C-II deficiency	FCH Sporadic HTG	Familial HTG
Age of onset (primary form)	Infancy or childhood	Usually adulthood	Usually adulthood
Xanthomas ‡	Eruptive or tuberous	None usually	Eruptive or tuberoeruptive
Other clinical features	Recurrent abdominal pain Pancreatitis Lipemia retinalis Hepatosplenomegaly	Premature CAD Pancreatitis Obesity Glucose intolerance Arthritic symptoms Gall bladder disease Hyperuricemia	Recurrent abdominal pain Pancreatitis Lipemia retinalis Hepatosplenomegaly Peripheral paresthesis Glucose intolerance Hyperuricemia

*Adapted from Reference 12
† Plasma obtained after 12 hours of fasting, left undisturbed in refrigerator overnight
‡Seen only in a minority of patients, frequency increases as plasma lipid levels rise
LPL, lipoprotein lipase; HTG, hypertriglyceridemia; Apo C-II, apolipoprotein CII; CAD, coronary artery disease; FCH, familial combined hyperlipidemia.

Table 3. Familial Hyperlipidemias*

Hypothyroidism – HTG is common in hypothyroidism, having been reported in up to 35% of cases[80]. Decreased free thyroid hormone increases the synthesis of LPL and decreases hepatic lipase activity with a net tendency toward increased plasma TG levels, perhaps further complicated by the down-regulation of LDL receptors[81-84]. One patient with central hypothyroidism secondary to a craniopharyngioma developed HTG with a level of (3,300 mg/dL) which precipitated an episode of AP[85].

8. Treatment

Initial Management – Initial management of patients presenting with HTGP mirrors that of other causes of AP[86]. Patients should be placed on bowel rest, receive nothing by mouth and undergo aggressive fluid resuscitation due to third space losses[87]. Adequate pain control is essential, often through the use of opioid narcotics[88-90]. Some controversy still remains about the potential for medication-induced sphincter of Oddi dysfunction aggravating the clinical picture although low dose transdermal fentanyl patches appear do not to compromise sphincteric function[91,92]. Meperidine has been used as an alternative analgesic to treat pain in those suffering from acute pancreatitis, but concern for the production of toxic metabolites has altered prescribing practices[93-95]. Enteral nutrition should be resumed as soon as is practical, recognizing that the reintroduction of fats, the building blocks of chylomicrons, may be deleterious[96-100]. Assessment of exocrine function prior to refeeding may be prudent, given that pancreatic destruction has the potential to compromise secretion of digestive enzymes[101].

Beyond initial management, HTGP therapy must include measures to reduce serum TG, both acutely and following the episode to minimize the risk of recurrence[102]. Laboratory tests including liver function tests, glucose, renal function, thyroid stimulating hormone and urine protein should be obtained to rule out secondary causes of HTG[103]. Specific tests documenting LPL or Apo C-II deficiency should be obtained if type I hyperlipidemia is suspected[104-107]. No standard treatment guidelines yet exist in the specific treatment of HTGP although a rational treatment strategy should include rapidly lowering serum TG, blocking the induction of pro-inflammatory mediators that lead to pancreatic destruction and reducing the likelihood of recurrence by eliminating offending agents, as is possible, and through the use of antihyperlipidemic medications[108-111].

Insulin – Intravenous insulin administration is an effective therapy for patients diagnosed with HTG induced pancreatitis, including those with and without diabetes mellitus[112,113]. VLDL is a triglyceride-rich lipid moiety and the use of insulin decreases hepatic production of apolipoprotein B-100 rich VLDL1 and intestinal production of VLDL2, rich in apoprotein B-48 while also increasing hydrolysis of TG by LPL[114,115]. Insulin promotes storage of both glucose and fatty acids, thus a continuous infusion of insulin should reduce serum levels of both of these fuels[116,117]. Intravenous (IV) insulin may be considered more effective and easier to titrate than subcutaneous (SQ) administration based upon absorption and delivery kinetics, although both have been used with some success[104,118,119]. Insulin has been used alone, but is commonly used in conjunction with other TG lowering modalities[120,121]. Mikhail et al. reported lowering TG from 7,700 mg/dL to 246 mg/dL in one patient using only intravenous insulin at 3-9 units per hour for 4 days while maintaining euglycemia[122]. In the same report, a second patient treated in a similar fashion saw TG levels drop from 10,500 mg/dL to 656 mg/dL over 4 days using 4 units SQ insulin (Lispro) every four hours.

Although no standard protocol for insulin administration in the context of HTGP has been defined, the authors have achieved success with insulin doses titrated from an initial rate of

0.1-0.4 units/kg per hour. Once an effective insulin infusion dose has been achieved, we have kept this constant while the dextrose infusion is titrated to maintain euglycemia, contrary to what is usually done when insulin is infused.

Heparin – Heparin is an effective treatment in the management of elevated TG in the presence of HTGP[123]. LPL, the enzyme which hydrolyzes TG rich lipoproteins, is normally bound by a heparan sulfate proteoglycan chain to the capillary endothelium[124]. Heparin, when administered in a bolus dose, has a stronger affinity for the LPL binding site than does the heparan sulfate, leading it to dissociate from the endothelium tissue into the plasma as a heparan-LPL complex.[125] This surge of "free" LPL is then able to bind and metabolize lipoproteins at an accelerated rate, thus lowering serum TG levels[126]. Although there is an initial rise in available LPL, there is also a peaking of activity, after which, LPL activity begins to wane as the enzyme is transported and degraded in the liver[127]. This heparin-stimulated increase and then reduction in LPL activity can be minimized by the use of intermittent heparin dosing and results in an initial drop in serum TGs, but then followed by a gradual increase[128,129]. This phenomenon tends to be more pronounced with the use of LMW heparin, versus un-fractionated heparin, although studies have shown both preparations capable of lowering severely elevated TG in the setting of HTGP.[130]

Heparin has been used as successful monotherapy in treatment of profound HTG in previous studies[131-133]; however, more dramatic results have been achieved when used in combination with other modalities (Table 4). At present, no studies have been conducted as to the best route of administration (IV or SQ) or dosage in the treatment of HTGP. It is the opinion of the authors that bolus dosing of IV heparin 18 units/kg[134] dosed every 4-6 hours is more effective than continuous administration.

Patient	**Trig Level (mg/dL) at Admission**	**IV Insulin U/h: IV Heparin Units; SC Octreotide μg**	**Triglyceride Results**
41-year-old female ETOH abuse	7037	Insulin 1-5 U/h for 5d; heparin 500-900 U/h for 3d	5111 mg/dL by day 3
51-year-old male ETOH abuse	7900	Insulin 12 U/h; heparin 5000 U b.i.d	670 mg/dL by day 4
31-year-old female at 30 wk gestation	4445	Insulin 20 U/h; heparin 10,000 U/24h	880 mg/dL by day 3
51-year-old* ETOH abuse	21,000	Insulin 2 U/h minimum; heparin 60 U/kg every 4h; octreotide 100 μg subcutaneously every 8 h	355 mg/dL in 48 hr

*Our patient.
Adapted from Ref 122

Table 4. Published Reports of Management of Hypertriglyceridemia With IV Insulin and Heparin: Comparison to Case Patient

Octreotide™ – Somatostatins, also called somatotropin release inhibitory factors (SRIFs) are cyclic peptide hormones which exist in 2 forms, SRIF14 (14 amino acids) and SRIF28 (28 amino acids)[135], and are synthesized in several sites within the body, including the central

nervous system, pituitary, gastrointestinal (GI) tract, liver, pancreas, and urogenital system[135,136]. SRIFs bind to 6 subpopulations of somatostatin receptors (sstrs) (1, 2_A, 2_B, 3, 4, 5) located both peripherally and centrally[137]. The sstr 2_B receptor has been demonstrated in rodents but not unequivocally in humans[138]. Binding of somatostatins to each of these receptors leads to the inhibition of adenylate cyclase via a pertussis toxin sensitive G-protein$_{(G\alpha i)}$ and, at agonist concentrations greater than 1-nM, there is stimulation of phospholipase C which increases calcium ion mobilization[139]. In neuroendocrine cells, sstrs 2,3,4 and 5 bind to inward rectifying potassium channels[140].

SRIFs inhibit the secretion of several GI tract hormones including insulin, glucagon, gastrin, cholecystokinin, vasoactive intestinal peptide and secretin and also inhibit exocrine gastric acid, pepsin, pancreatic enzymes, bile and intestinal fluid secretions [141]. The pancreas expresses sstrs on both acinar cells (sstr4, sstr5)[142] and islet cells (sstr1 > sstr5 > sstr2 > sstr3 > sstr4)[143]. In rodents, sstr2 in the dorsal vagal complex exerts some control of pancreatic exocrine secretion[144].

Octreotide, a somatostatin analog, has particular affinity for types 2_A, 2_B and somewhat for sstr5[145]. Octreotide has been used in the treatment of pancreatitis with varying degrees of success[146]. The evidence that pancreatic sstrs are down-regulated in acute pancreatitis suggests that the mechanisms of action of octreotide therapy may include both receptor and non-receptor mediated mechanisms[147]. Secretion of insulin and glucagon are inhibited by agonists of sstr2, sstr5, and sstr1[148]. 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[149]. Octreotide's effect on the hypoglycemic counter regulatory system, notably the hyperglycemic actions of glucagon, necessitates the co-administration of dextrose and frequent monitoring of glucose levels to maintain euglycemia.

Study	No. of patients	No. of patients with complete recovery (%)	Mortality (%)
Yeh et al.	17	13(76.5)	2 (11.8)
Kyriakidis et al.	10	9 (90)	1 (10)
Kadikoylu et al.	7	7 (100)	0
Lennertz et al.	5	5 (100)	0

* Adapated from Ref 5

Table 5. Apheresis in hypertriglyceridemic pancreatitis *

Plasmapheresis – Although the primary methods of treating HTGP are dietary fat restriction and lipid lowering medications, these treatments may be inadequate in the setting of severe acute HTGP[150,151]. Plasmapheresis has been used with some measure of success and is thought to work through two mechanisms: the removal of serum TG from the patient's serum and the supplementation of LPL and apolipoprotein found in the fresh frozen plasma of the donor plasma[152,153]. Yeh, et. al found that a single exchange removed 66.3% of TG, while a second exchange removed 83.3% of serum TG[154]. The number of sessions, however, did not correlate with clinical outcome. Syed et al., evaluated patients with HTGP receiving plasmapheresis and observed an average reduction in TG levels of 89.3% with the first

treatment, but found no clear relationship between APACHE II scores or length of hospital stay[155].

Plasmapheresis is not without risk, and at this time its use in HTGP remains undefined. Potential complications or adverse reactions include allergic reaction and transfusion related infections. One patient undergoing plasmapheresis was reported to develop anaphylactoid shock[154,156]. At present the American Society for Apheresis Guidelines of 2007 places apheresis in its role for HTGP as a category three due to limited data and conflicting reports[157].

Apheresis Recommendations*

Category	Recommendation
I	First line therapy
II	Second line therapy
III	Specific role not determined
IV	Not recommended

*Journal of Clinical Apheresis, Special Issue(Vol 25, 2010)

9. Long-term management

Diet and General Precautions –Primary causes of hyperlipidemia often require medications but, where possible, reducing the impact of secondary causes with therapeutic lifestyle changes such as reducing alcohol intake, weight reduction, improved diabetic control and discontinuing precipitating medications are all vital steps[158]. Dietary advice should be obtained through a certified nutritionist, but fat consumption should be reduced to 7% of total caloric intake, cholesterol limited to 200mg and trans fatty acid intake should be limited[159]. Medium chain TG are an improved source of fat calories as they are absorbed directly into portal circulation and do not require chylomicrons for hepatic uptake and lower TG levels at the cost of a slightly elevated cholesterol level[160]. A meta-analysis performed by Dattilo and Kris-Etherson observed a strong correlation between weight loss and decrease in plasma TG levels.[161]

Medications:

Fibrates - Fibric acid derivatives are a class of medications which bind to peroxisome proliferator alpha (PPARα) receptors and are capable of increasing serum HDL while simultaneously lowering TG and are an effective adjunct in treating patients with HTGP who cannot be managed with diet alone[162]. They are typically used in treating primary HTG and include drugs such as gemfibrozil, bezafibrate and fenofibrate[163]. Fibrates lower serum TG by increasing the levels of LPL and hepatic lipase, reducing levels of Apo CIII, which down-regulates LPL activity, and by increasing fatty acid uptake by the liver[164,165]. Toxicities include elevated liver enzyme levels, cholelithiasis, myalgias and rhabdomyolysis; the last two of these are more common when used in patients with impaired renal function[166]. Two cases have been reported where patients developed pancreatitis while taking fibrate or fibrate-statin combinations.[167, 168] It is unclear whether the cause of the pancreatitis was directly related to the drug itself, a failure of treatment or possibly through the formation of biliary sludge or gallstone formation.

Niacin – Niacin, a B vitamin somewhat less potent than the fibric acids, decreases TG levels by reducing hepatic secretion of VLDL and TG while raising HDL and lowering LDL levels,

an overall positive impact on the lipid profile[169]. When used as doses of 1,500mg/day, no adverse impact on glucose metabolism is seen but significant prostaglandin D2-mediated flushing limits the clinical utility of this drug[170].

Statins – HMG-CoA reductase inhibitors (statins) are not the preferred method for lowering serum TG as their role in lipid management remains in prevention (primary and secondary) of coronary artery disease in the presence of elevated cholesterol, but only mild to moderate triglyceride elevations[171]. Statins are not suitable monotherapy for long-term management of HTG, however, they may have some synergistic benefit when combined with fibrates[172,173].

Omega 3 Fatty Acids – Fish oils and omega-3 fatty acids are effective adjuncts to other drug therapy as they lead other drug therapy as they lead to a decrease in VLDL and lower endogenously derived TG-rich lipoproteins[174,175]. Active TG lowering molecules in these supplements include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)[176]. Omega-3 fatty acids were studied in a prospective, double-blinded trial and were able to lower TG levels, ranging from 500-2,000 mg/dL, by an average of 45%[177]. The minimum effective dose is approximately 1 g/d; however, a dose of 3 to 4 g/d has shown to reduce serum TG by 30-50% in hyperlipidemic patients[178].

10. Conclusion

HTG is a significant cause of AP, with most estimates ranging from 1-7% of all cases. Presentation is often similar to other forms of AP, with lipemic serum usually the only distinguishing initial sign. Clinicians should routinely test TG levels in patients with suspected or confirmed AP, especially those who have a history of diabetes, alcoholism, obesity, are taking a known precipitating medication, are pregnant or display normal amylase in the presence of elevated lipase.

To date, there are no official guidelines for the treatment of HTGP, although a number of different treatment modalities have been employed to rapidly lower the serum TG, including insulin, heparin, fibric acids and omega 3 fatty acids. Plasmapheresis can also rapidly lower serum TG levels, but significant potential side effects and lack of rigorous proof of efficacy have yet to clarify its role in treatment of HTGP. Long term management with diet modification and anti-hyperlipidemic medications such as statins, niacin and omega-3 fatty acids are excellent adjuncts in controlling TGs in patients with HTGP and preventing potential recurrences.

We have achieved dramatic effects with the combination of insulin, heparin and octreotide, a reduction in TG levels of two orders of magnitude in 48 hours, results unprecedented in the literature. These results, while impressive, have yet to be reproduced and one must remain appropriately circumspect when interpreting this case report. It is also important to note that the positive barbiturate level may have unmasked an inducible porphyria and that rapid resolution of HTGP was aided by the removal of this compound from the metabolic milieu. No clear treatment algorithm exists for the management of HTGP and well-designed, controlled, prospective studies are needed to clearly delineate the ideal regimen.

11. Disclaimer

The views expressed in this manuscript are those of the authors and do not reflect the official policy or position of the Department of the Armed Forces, Department of Defense, or the U.S. Government

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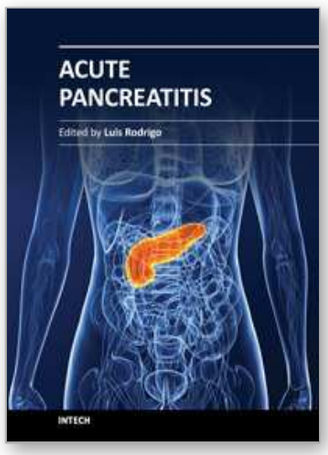

Acute Pancreatitis

Edited by Prof. Luis Rodrigo

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Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example... This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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