Hypertriglyceridemia induced acute pancreatitis: 4 years’ experience from a tertiary care institute and quick literature review

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ABSTRACT

Hypertriglyceridemia (HTG) is infrequent but an established etiology that can trigger recurrent episodes of acute pancreatitis. The risk of acute pancreatitis is significant when serum triglycerides levels surpass >1000 mg/dL. Although the severity of HTG-induced acute pancreatitis (HTG-AP) may be correlated to higher HTG levels in the early stages, the overall clinical outcomes are similar to other aetiologies. The initial management also differs from the routine recommendations with additional diagnostic and therapeutic challenges. This retrospective case series includes a 4-year experience with HTG-AP at our facility and a brief literature review.

Keywords: Hypertriglyceridemia, insulin, novel therapeutics, pancreatitis, plasmapheresis

Introduction

Acute pancreatitis (AP) is a life-threatening medical condition, which usually occurs due to the acute inflammation process of the pancreas. Diagnosis and severity of AP are given by revised Atlanta classification of AP 2012.[1] Various risk factors and aetiologies have been described in the literature. However, gallstones and heavy alcohol consumption are the most common aetiologies, accounting for up to 40% and 30% cases, respectively.[2] AP owing to hypertriglyceridemia (HTG-AP) is another well-known etiology for AP, accounting for nearly 7% of all AP cases. However, the frequency may reach up to 50% during pregnancy and the presence of familial HTG syndromes.

HTG is defined as an increase in fasting serum triglyceride (TGs) levels above 150 mg/dL. HTG is only considered a risk factor for the development of pancreatitis when serum TGs surpass 1000 mg/dL.[3] Apart from keeping the patient nil per oral, aggressive hydration and pain management form the mainstay of therapy. Aggressive TG lowering therapies are also the cornerstone of initial management. This article contributes a four-year experience with HTG-AP at our centre and a comprehensive literature review. This experience helps in creating knowledge in primary and family care physicians about the clinical characteristics of this not so rare disease and helps in early identification and management.

Materials and Methods

This is a 4-year retrospective case series diagnosed with HTG-AP between 2017 and 2020 at All India Institute of Medical Sciences Rishikesh (AIIMS-R), India. The diagnosis of AP was made...
using modified Atlanta classification 2012 (clinical, biochemical, and imaging features of AP). The BISAP score and Modified marshal score were used to determine AP severity. The results were expressed as a mean and standard deviation (SD).

**Case series**

A total of five patients were included in the study. The clinical characteristics and presentation of the patients have been described in Table 1. The mean (± SD) age in the study was 33.6 ± 8.1 years. Three out of the five patients were chronic alcohol consumers, one patient had Type 2 diabetes, and one patient was a primigravida. Two patients had a prior history of AP. Acute pain abdomen radiating to the back and vomitings were the most common clinical symptoms at the time of presentation. The biochemical parameters have been described in Table 2. The mean (± SD) amylase and lipase levels are 1060 (± 1197) and 1695 (± 2170) IU/mL, respectively. The mean (± SD) TG levels at the baseline were 1483.4 (± 653.1) mg/dL. The mean (± SD) BISAP score at the time of presentation was 1.2 (± 1.09). In terms of AP severity, four patients had mild pancreatitis episodes and one patient developed severe AP with persistent organ failure (shock and acute lung injury requiring mechanical ventilation) and local complications in the form of peripancreatic necrotic collections [Figure 1]. Initial conservative management is done in all patients. In addition, two patients received combined insulin and heparin therapy for high levels of TG at the baseline. Following combination insulin and heparin administration, we saw a dramatic drop in TG levels, even reaching safe levels (TGs <1000 mg/dL) by day 2 of infusion [Figure 2].

Further, one patient with severe pancreatitis with multiple peripancreatic necrotizing collections required insertion of pigtail drainage followed by surgical necrosectomy (video-assisted retroperitoneal debridement). In this patient, the length of hospital stay is unusually prolonged. At the time of discharge, all of the patients had made a complete clinical recovery. The severity and outcomes in these patients were described in Table 3.

**Discussion**

AP is a life-threatening medical condition due to acute inflammation of the pancreas causing local injury, systemic inflammatory response syndrome, and organ failures.[8] Diagnosis and severity are given by the revised Atlanta classification.[9] Various risk factors have been mentioned in the literature. Gallstones and alcohol abuse are the two most common causes of AP, with incidence up to 70%.[3] HTG is considered the third most common etiology, with incidence up to 7%.[6] HTG is defined as an increase in fasting serum TG levels >150 mg/dL. Based on the latest Multi-society Cholesterol Guidelines (2018), normal fasting TG levels is defined as <150 mg/dL, mild-to-moderate HTG 175–885 mg/dL, severe >885 mg/dL or very severe >1770 mg/dL. Several epidemiological studies have attempted to establish an appropriate cut-off point for the TG level that can cause AP.[7] However, there is no definitive proof that an HTG-AP occurs beyond certain threshold serum TG levels. Frequently, TG levels >1000 mg/dL was linked to AP with a lifetime risk of up to 5%.[8] The presence of additional risk factors can trigger AP even at lower TG levels (<1000 mg/dL).[9] In our case series, the mean (± SD) baseline TG levels were 1483.4 ± 653.1 mg/dL that has triggered HTG-AP. Sandhu et al.[10] reported recurrent AP episodes at TG levels of >1771 mg/dL. Zafrir et al.[11] observed that AP risk was linked to peak TG levels of >1771 mg/dL. Amblee et al.[12] found that having a TG level of 2,000 mg/dL had higher HTG-AP prevalence among ethnic minorities.

The risk factors of HTG were classified into two groups: primary and secondary (Table 4). Primary HTG is most often associated with Familial hyperlipidaemia syndromes (particularly Fredrickson Type I, IV, and V), which usually presents in infancy and early adulthood.[13,14] Alcohol abuse, metabolic syndrome, uncontrolled blood sugars, hypothyroidism, cirrhosis, end-stage renal diseases, and drugs like Corticosteroids, Tamoxifen and High-dose thiazides are all secondary factors linked to HTGP.[15,16]

**Figure 1:** A contrast enhanced CT abdomen (axial) performed in the third week of pancreatitis reveals numerous necrotic collections with air foci. Pre (a) and post pigtail drainage (b) in a patient with hypertriglyceridemia induced severe acute pancreatitis

**Figure 2:** Graphical trend of serum triglyceride levels after intravenous insulin infusion therapy
Frankly, Secondary factors alone may not raise the risk of AP. However, the interaction of several secondary factors or a combination of both primary and secondary factors might result in severe HTG levels. Elevated serum TGs (up to 300 mg/dL) can also be detected during pregnancy (during 3rd trimester), which serves as an important etiology of AP during pregnancy.\(^{17,18}\) In our case series, underlying risk factors such as alcohol abuse were observed in three of our patients, and diabetes in one patient.

The specific pathophysiology behind HTG triggered pancreatic injury is unclear. Normally, TGs in our body are packaged and transported via VLDLs and chylomicrons, which are large-sized

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**Table 1: Clinical presentation**

| Case No. | Age/Gender | Addictions | Co-morbidity | Prior history of pancreatitis | Clinical presentation                          | BISAP score |
|----------|------------|------------|--------------|-------------------------------|-----------------------------------------------|-------------|
| 24/F     | 0          | 0          | 0            | 0                             | Abdominal pain, Vomiting, shortness of breath | 3           |
| 41/M     | Alcohol    | 0          | 0            | 0                             | Abdominal pain, vomiting                       | 1           |
| 43/M     | Alcohol    | 0          | yes          | 0                             | Abdominal pain                                 | 1           |
| 29/M     | 0          | 0          | 0            | 0                             | Abdominal pain, nausea, vomiting               | 1           |
| 31/M     | Alcohol    | DM         | yes          | 0                             | Abdominal pain                                 | 0           |

*Bedside index for severity in acute pancreatitis (BISAP) score

**Table 2: Biochemical parameters and management**

| Case No. | Amylase (IU/mL) | Lipase (IU/mL) | Baseline TG level (mg/dL) | Treatment of HTG | TG level at discharge (mg/dL) |
|----------|-----------------|----------------|---------------------------|------------------|-------------------------------|
| 2800     | 4200            | 2200           | 2200                      | Regular insulin (0.07 IU/Kg/Hr) Infusion and 5000 IU heparin SC thrice daily | 455        |
| 249      | 130             | 1600           | 1600                      | Regular insulin (0.07 IU/Kg/Hr) Infusion and 5000 IU heparin SC thrice daily | 492        |
| 281      | 118             | 835            | 835                       | Fibrates and ω-3 fatty acids                       | 468        |
| 1830     | 3940            | 782            | 782                       | Fibrates and ω-3 fatty acids                       | 322        |
| 140      | 87              | 2000           | 2000                      | Fibrates and ω-3 fatty acids                       | 780        |

*SC - subcutaneous, Hypertriglyceridemia (HTG)

**Table 3: Severity and outcome**

| Case No. | AP severity | Modified Marshal score | Complications | Duration of hospital stay | Outcome |
|----------|-------------|------------------------|---------------|---------------------------|---------|
| Severe   | 2           | Walled of pancreatic necrosis | 105           | Recovered                 |         |
| Mild     | 0           | None                   | 6             | Recovered                 |         |
| Mild     | 0           | None                   | 7             | Recovered                 |         |
| Mild     | 0           | None                   | 5             | Recovered                 |         |
| Mild     | 0           | None                   | 8             | Recovered                 |         |

**Table 4: Risk factors for hypertriglyceridemia**

| Severe hypertriglyceridemia | Mild to moderate hypertriglyceridemia |
|-----------------------------|--------------------------------------|
| **Primary causes** | FLP Type 1 (Monogenic chylomicronemia) | FLP Type 4 (Polygenic HTG) |
| Lipoprotein lipase deficiency | Lipoprotein lipase deficiency | FLP Type 3 (DysbetaIoproteinemia) |
| Apo C-II deficiency | Apo C-II deficiency | FLP Type 2 B (LDL-C polymorphisms) |
| Apo A-V deficiency | Apo A-V deficiency | Combined hyperlipoproteinaemias |
| Lipase maturation factor 1 deficiency | Lipase maturation factor 1 deficiency | | |
| FLP Type 5 (Polygenic chylomicronemia) | FLP Type 5 (Polygenic chylomicronemia) | |
| **Secondary causes** | Excessive alcohol intake | Metabolic syndrome |
| Diabetes mellitus | Diabetes mellitus | Cirrhosis |
| Hypothyroidism | Hypothyroidism | Nephrotic syndrome |
| Hypercortisolism | Hypercortisolism | End-stage renal diseases |
| Obesity | Obesity | Pregnancy |

**Medications**

| Hormonal | Immune-Related | Others |
|----------|----------------|--------|
| Oestrogen related drugs | Cyclophosphamide | fl- Blockers |
| Clomiphene | Interferon | High-dose thiazide |
| Tamoxifen | Tocilizumab | Quetiapine |
| Isotretinoin | Calcineurin inhibitors | Rosiglitazone |
| All-Trans Retinoic Acid | Everolimus | L-asparaginase |
| Corticosteroids | Capecitabine | Propofol |
| | | Ritonavir |

*Familial hyperlipoproteinemia (FLP)
low density molecules. Breakdown of excess TGs by pancreatic lipase results in the generation of FFAs (as three FFA are linked to glycerol to generate one TG), which has a pro-inflammatory and cytotoxic potential. Also, These generated excess FFAs can activate and convert acinar cell trypsinogen into trypsin leading to acinar cell injury.[9] The second mechanism lectured were the intrinsic toxicity of TGs to the pancreatic parenchyma. Non-esterified TGs can act as pro-inflammatory substrates leading to an increase in interleukin (IL) 1, IL6, IL 10 and tumour necrosis factor-α, thus SIRS. Thirdly, intracellular lipid accumulation leads to a faulty intracellular scavenging mechanism and mitochondrial dysfunction. Further mechanisms such as increased plasma viscosity by hyperchylomicronaemia leading to decreased capillary blood flow causing local pancreatic ischemia and necrosis were also advocated.[10] Pathophysiology of HTG-induced pancreatitis is explained in a graphical abstract [Figure 3]

Clinical presentation is similar to that of any other aetiologies of AP, with high incidence in males sex and younger population.[20] Important distinguishing characteristics from other aetiologies were the presence of lipemic blood [Figure 4] and history of recurrent pancreatitis episodes. Two patients in our case series had a prior history of AP. Although there are inconsistent data regarding the correlation of TG levels with pancreatitis severity and clinical outcomes in HTG-AP[21-23] Multicentre APPRENTICE consortium showed baseline characteristics and clinical outcomes were similar to other aetiologies of pancreatitis.[24] Pascual et al.[25] observed that the number of organ failures, pancreatic necrosis and mortality increased with increments of 100 mg/dL of TGs (P < 0.05). However, In a recent meta-analysis of seven studies, two studies revealed no difference in severity, whereas the other five showed HTG-AP patients may have higher severity when compared to other aetiologies of pancreatitis.[26] The initial management focuses on supportive care, including prompt fluid resuscitation, analgesia, and transfer to intensive care units should be made in patients with severe acute pancreatitis (BISAP ≥2, APACHE-II ≥8, and CRP at 24 h (> 210 mg/L) or any organ failure) similar to other aetiologies of AP.[27] Furthermore, the initial treatment in HTG-AP also includes specific plasma TG lowering therapies such as insulin, Heparin, Apheresis, hemofiltration and, anti-hyperlipidaemic drugs. Each therapy has its advantages and disadvantages depending on the severity of HTG-AP.

Insulin is one of the advocated older therapies that has been considered effective in lowering serum TG levels when given as a continuous intravenous infusion. The main rationale behind its use was that insulin activates lipoprotein lipase activity to accelerate chylomicron breakdown.[28] Data from various case series and retrospective analyses have shown the TG lowering effects of insulin infusion up to 75%. [29,30] In a comparative Review, Insulin therapy combined with careful blood glucose monitoring was effective, especially when apheresis is not an option.[30] For patients receiving insulin infusion (0.07 IU/kg/H), serum TG levels should be checked every 12 hourly. Additionally, Serum glucose levels must be checked on an hourly basis, and insulin must be adjusted accordingly. Insulin infusion can be stopped once TG levels are below <500 mg/dL (5.6 mmol/L). Heparin also can be utilized either alone or in conjunction with insulin therapy. Although the pharmacological role of heparin is anticoagulation, heparin also promotes the release of endothelial LPL, thereby decreasing serum TG levels with uncertain benefit.[29,31] Two patients in our case study underwent combined insulin and heparin therapy and experienced a dramatic decrease from their baseline TG levels in concordance with earlier studies.

Aggressive modalities plasma TG lowering may be required in some patients with high baseline TG levels. Plasmapheresis is a preferable acute TG lowering therapy that has been recommended by the American Society for Apheresis (ASFA), especially in patients with very high TG levels (>2000 mg/dL).[32] Kandemir et al.[33] observed that following two sessions of PLEX,

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**Figure 3:** The pathophysiology of hypertriglyceridemia-induced acute pancreatitis. (VARD - video-assisted retroperitoneal debridement)
serum TG reduction was noted up to 80% with minimal side effects. A retrospective study by Biberci et al.\(^4\) showed that apheresis significantly decreased plasma TG levels with no decrease in overall mortality or recurrences. Studies using double filtration PLEX significantly reduced TGs, cholesterol, and very-low-density lipoprotein levels, with high-density lipoprotein levels exhibiting an inverse relationship with hospital stay.\(^5\) A systematic review of 74 studies found that apheresis is an efficient way to lower serum TG levels but not the severity of pancreatitis. Moreover, when compared to insulin, neither of them proved to be superior.\(^6\) Jin et al.\(^7\) compared the combination of insulin and heparin to PLEX therapy. In this study, he noted that combined Insulin and heparin was non-inferior to plasma exchange in rapidly lowering TG levels. Araz et al.\(^8\) Highlighted the safety of PLEX but with no clear advantage over insulin infusion. Similarly, Frankova et al.\(^9\) observed that neither IV insulin nor apheresis was better for treating severe HTG, but their combination exhibited synergistic effects. High-volume hemofiltration (HVHF) is another controversial extracorporeal method that can effectively remove Excess TGs (also downregulate systemic inflammatory response by lowering plasma cytokines) more efficiently than PLEX or any other conventional therapies. Despite this fact, HVHF therapy was not superior in patient outcomes and cost reduction across various studies. In a Prospective study by Sun et al.\(^10\) comparing conventional treatment and HVHF, the HVHF therapy dramatically decreased the APACHE II score, systolic blood pressure, serum creatinine, blood TGs and cholesterol but not the mortality. An RCT of 66 HTGP patients receiving HVHF (n = 32) or heparin plus insulin (n = 34) therapy. HVHF was able to eliminate TG (target <500 mg/dL) from the plasma in around 9 h, but the heparin plus insulin therapy did not accomplish this in 48 h (P < 0.05). However, there were no changes in clinical outcomes, such as local pancreatic complications (P > 0.05) and survival (P = 0.49).\(^11\)

Recurrent attacks of HTG-AP can be minimized by keeping TG levels less than 200 mg/dL. This necessitates long-term HTGP care with improved lifestyle choices such as weight reduction, alcohol abstinence, diabetic control, and dietary modifications.\(^12\) Pharmacologic management includes lipid-modifying drugs such as fibrates, statins, ezetimibe, ω-3 fatty acids, and niacin acting with different lipid-lowering efficacy. Statin and ezetimibe have a limited influence on TGs (5–15%), whereas fibrates decrease TGs by 25–50%. Current guidelines urge an early use of drugs that primarily target high TG to decrease the risk of HTGP. Fibrates, high-dose long-chain ω-3 fatty acids, or niacin, combined with a very low fat diet, is recommended by the majority of guidelines.\(^13\) Although fibrates were recommended first-line therapy, it is said to be associated with gallstone formation. According to a recent meta-analysis, statin use was linked to a reduced risk of pancreatitis in patients with mild to moderately increased TG levels.\(^14\) Alipogene tiparvovec, Pemafibrate, Pradigastats, Volanesorsen and Evinacumab are some novel anti-HTG drugs currently in phase 2-3 clinical trials. Alipogene tiparvovec is an adeno-associated virus (AAV) serotype 1-based gene therapy that normalizes TG in 12 weeks by targeting lipoprotein lipase.\(^15\) Pemafibrate, a PPAR modulator, reduces TG levels by 35%–45%. Pradigastats are oral TG synthesis inhibitors. Volanesorsen, an inhibitor of Apolipoprotein CIII mRNA and Evinacumab, a monoclonal antibody against the angiopoietin-like protein (ALP) 3, were designed to treat familial HTG syndromes.\(^16\) More extensive clinical research is needed before recommending these novel therapies. This knowledge of HTG-AP helps the primary care physicians and family physicians to identify the disease early and prevent the development of grave consequences.

In summary, HTG is infrequent but an established etiology that can trigger recurrent episodes of AP. Mild pancreatitis can be treated conservatively. However, the severe disease requires aggressive TG reduction. As per previous studies, insulin infusion is a safe and cost-effective therapy with TG lowering efficiency and clinical outcomes comparable to PLEX. Novel therapies are not yet validated and require further research.

Points to remember

- HTG is considered the third most common etiology for AP, with incidence up to 7% across various studies.
- The exact mechanism of HTG-induced pancreatic injury is unclear; however, specific pathophysiology is attributed to free fatty acid-induced acinar cell damage and pancreatic ischemia by hyperchylomicronaemia.
- The initial treatment includes specific plasma TG lowering therapies such as insulin, Heparin, Apheresis, hemofiltration, anti-hyperlipidaemia drugs, along with best supportive care.
- HTG-AP disease severity may correlate with serum TG levels in the early stages, but the overall clinical outcomes are similar to any other aetiologies of AP.
- Plasmapheresis is a preferable acute TG lowering therapy that the American Society has recommended for Apheresis (ASFA). However, insulin infusion is also an effective modality in resource-limited settings.
• Long-term management includes lifestyle changes such as weight reduction, alcohol abstinence, diabetes control, dietary modifications and pharmacotherapy with fibrates and ω-3 fatty acids.

• Alipogene tiparvovec, Pemafibrate, Pradigastals, Volanesorsen and Evinacumab are some novel anti-HTG drugs currently in phase 2-3 clinical trials, which require further validation.

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**Abbreviations**
AP - acute pancreatitis

APACHE II - acute physiology and chronic health evaluation II score

BISAP - bedside index for severity in acute pancreatitis score

FFA - free fatty acids

HTG - hypertriglyceridemia

HTG-AP - hypertriglyceridemia induced Acute Pancreatitis

HVHF - high-volume hemofiltration

NPO - nil per oral

PLEX - plasmapheresis

SIRS- systemic inflammatory response syndrome

TGs - serum triglycerides

VLDL - very-low-density lipoproteins.

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