Review Article

Management of hypertriglyceridemia-induced pancreatitis – A review of updates from the past decade

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ABSTRACT

Hypertriglyceridemia-induced acute-pancreatitis (HTG-AP) is an important etiology of acute pancreatitis (AP). The treatment includes general management of AP with bowel rest, analgesia, and venous thromboembolism prophylaxis. Specific treatment of HTG-AP focuses on reducing serum triglyceride (TG) levels. Various modalities have been used, including heparin infusion, insulin infusion, plasmapheresis, and double filtration plasmapheresis (DFPP). However, the extent to which TG reduction translates into a clinical response remains unclear. This review highlights the emerging evidence on the management of HTG-AP. Insulin therapy and plasmapheresis remain treatment options to reduce TG. DFPP is an emerging treatment modality to reduce TG levels in patients with AP. However, to what extent this translates into a better clinical response is yet to be answered in large and prospective study designs.

Key words: Hypertriglyceridemia, Pancreatitis, Triglycerides, Hypertriglyceridemia-induced acute pancreatitis

Acute pancreatitis (AP) is one of the most common gastrointestinal issues leading to medical admissions [1]. It is a medical emergency with a broad spectrum of triggering factors ranging from socioeconomic and geographically dependent to independent factors. Around 0.2 million people in the United States of America (USA) and around 25 thousand in the United Kingdom (UK) are admitted with pancreatitis annually [2]. In North America, the prevalence of AP is increasing, although it appears to be steady in Asian countries [3], and lower in African countries [4]. The estimated annual health-care cost is around 2.5 billion USD in the USA alone [5]. Despite extensive research on AP and technical progress, the mortality rate associated with AP has only slightly decreased (1.7/100,000 in 1990 to 1.4/100,000 in 2019), and the pathophysiology and management of hypertriglyceridemia-induced AP (HTG PA), one of the growing etiologies of PA, remain unclear [6]. The true prevalence of HTG-AP is not well established. Valdivielso *et al*., in their review in 2014, reported a prevalence from 1 to 10% among all patients with AP [5], Elzouki *et al*. [7] reported a prevalence of 5.8% of all patients with AP, while Olesen *et al*. found HTG to be the cause of AP in 35% of patients [8]. This discrepancy can be owed to under-recognition or a rapidly rising prevalence of HTG-AP. The prevalence of HTG with varying severity is estimated to be present in approximately 10% to 27% of adults [9,10]. The importance of HTG-AP lies in the fact that it has shown a growing incidence worldwide as a consequence of the increased prevalence of metabolic syndrome and diabetes mellitus, and because there is no evidence-based therapy for this clinical entity [11,12].

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CLINICAL PRESENTATION

Although the clinical presentation of HTG-AP is similar to that of other causes, the amylase level at presentation may be normal and should be interpreted with caution due to calorimetric interference of lipemic serum, and repeat amylase levels should be performed with severe dilutions [13].

RISK FACTORS OF HTG-AP

The risk of HTG-AP increases with rising TG levels, especially when above 500 mg/dL (5.6 mmol/L), where the risk of AP increased by 4% with every 100 mg/dl (1.13 mmol/L) increase in triglycerides (TG) [14]. TG level >500 mg/dL (5.6 mmol/L) is usually found in patients with primary or genetic abnormalities in lipid metabolism. Recently, Zhang *et al.* identified two common differentially expressed genes associated with AP and hypertriglyceridemia along with seven miRNAs that may regulate AP. Typically, hypertriglyceridemia-induced pancreatitis occurs in a patient with a pre-existing lipid abnormality, along

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with the presence of a secondary precipitating factor (e.g., poorly controlled diabetes, alcohol abuse, or medication such as estrogen, tamoxifen, and corticosteroids) [15].

A major modifiable risk factor of HTG-AP, which has seen a rising trend in the past years, is alcohol consumption. Alcohol has been shown to stimulate very-low-density lipoprotein (VLDL) secretion possibly through enhanced assembly of VLDL, combined with elevated hepatic delivery of free fatty acids as a results of enhanced adipose tissue lipolysis [16,17].

PATHOPHYSIOLOGY

Although the high levels of chylomicrons are necessary to trigger an attack of HTG-AP [6], the exact mechanism of HTG-AP is not clearly understood. Most accepted theories are based on animal models which revealed a detrimental effect of lipids on the pancreas. Chowdhury *et al*. compared the effects of a high-fat diet with a high-carbohydrate diet on exocrine pancreatic function in rats. Pancreatic acinar cells isolated from fat-fed rats showed reduced exocrine function and histopathological changes consistent with inflammation [18]. One of the proposed mechanisms has suggested that the release of excess free fatty acids from the TG by pancreatic lipases causes damage leading to AP [19]. Recent studies have confirmed the pathophysiological role of unsaturated fatty acids (UFAs) in inflammation and associated damage to pancreatic cells. The toxic effects of UFAs on the pancreas are multimodal. UFAs generally bind to calcium to get neutralized, which is why hypocalcemia is sometimes a feature of AP [20]. The primary mechanism of induction of injury by the unbound UFAs is through ATP depletion and initiation of an inflammatory cascade through activation of tumor necrosis factor (TNF-α), CXC ligand 1 (CXCL1), and CXCL2, which results in necrosis [20]. Fatty acids also directly cause endothelial damage, coagulopathy, and vascular leakage in the pancreatic acinar cells [21]. Thus, reducing fatty acids are an integral treatment modality in patients with HTG-AP.

HTG is common in pregnancy due to physiological changes. These changes are integral to providing appropriate nourishment and a favorable atmosphere for the growth of the fetus [22]. AP is more prevalent in pregnant females than in the general population. The added hypertriglyceridemia translates into a higher prevalence of HTG-AP in pregnancy as high as 47%, making it the most common cause of AP in pregnancy. In their retrospective study, Sheng *et al*. also reported a positive correlation of serum TG levels with significant outcomes such as maternal and perinatal mortalities [23].

MANAGEMENT

Management of HTG-AP can be broadly divided into two aspects. One is focused on managing pancreatic inflammation similar to any other type of AP; aggressive fluid resuscitation, bowel rest, analgesia, and thromboprophylaxis [1]. The other part comprises TG reduction. The most of the controversies and knowledge gaps concerning HTG-AP lie in this half of its management. Various treatment options have been tried and reported with variable success rates. These include fasting, heparin, or insulin infusion, hemoperfusion, hemofiltration, and therapeutic plasmapheresis.

Insulin and heparin infusion has been used in TG reduction since 1999 [24]. Both effectively reduce He *et al*. conducted a prospective study on 66 HTG-AP patients who received hemofiltration or a combination of insulin and heparin [25]. Compared to hemofiltration, patients in the heparin and insulin group (n=34) had considerably less persistent organ failure (POF). However, pancreatic complications were not significantly different among the two groups. Although insulin is a therapeutic option in most centers managing HTG-AP, heparin is generally avoided. The main reason lies in its adverse effects. Heparin causes lipoprotein lipase (LPL) mediated breakdown of lipoproteins enriched with TG, releasing toxic FFA [26]. This also causes depletion of LPL, shifting the balance toward more VLDL, and chylomicrons [27]. Bleeding is an additional risk with heparin.

Multiple studies have evaluated the effectiveness of plasmapheresis in TG reduction and AP resolution in the past few years. Lu *et al*. studied 242 HTG-AP patients and reported an association of high TG with POF. Multivariate logistic regression showed an association of TG level of above ≥5.6 mmol/L at 48 h with POF (OR 3.316 [1.256–8.755] p = 0.016). The patients were given insulin or plasmapheresis for TG reduction. However, a subgroup analysis was not performed to compare the effectiveness of these treatments, probably due to a small sample size which would limit validation of the results [28].

The TG reducing effect of plasmapheresis has been consistent across multiple studies; however, its correlation with clinical outcomes of AP shows inconsistent results. Plasmapheresis showed worse clinical outcomes despite TG reduction [29]. Patients with plasmapheresis had considerably higher rates of acute respiratory distress syndrome (30.4% vs. 7.4%), acute kidney injury (19.5% vs. 2.2%), and sepsis (2.17% vs. 0.74%). In addition, a more extended median hospital stays (12.5 vs. 8 days) and higher healthcare costs (41 vs. 12.1 Yuan) were associated with the plasmapheresis group [29]. The difference may be attributed to the likelihood of patients with a more severe HTG-AP to have received plasmapheresis, and milder cases may have received conservative therapy. A well-organized prospective study can only establish the true efficacy and safety profile of plasmapheresis in HTG-AP. PERFORM study (a multicenter, prospective, observational, and cohort study which intends to enroll 300 HTG-AP patients) is underway, which may answer some of the questions related to the effectiveness and safety profile of TG reduction in the context of clinical outcomes in HTG-AP patients [30].

Double filtration plasmapheresis (DFPP) is a current area of research interest in the context of TG reduction and AP resolution. Amid limited literature with controversial results, the initiation of plasmapheresis is recommended in severe AP with an APACHE score of at least 8 or Marshasls score of at least 2, reflecting higher mortality risks [31]. However, the current science is devoid of guidelines-based indications of DFPP. As with other treatments

Table 1: Suggested management protocol of hypertriglyceridemia-induced acute pancreatitis

Management of HTG-AP						
Initial management	**Aggressive fluid resuscitation, bowel rest, analgesia, and thromboprophylaxis**					
Plasmapheresis	**To be considered in cases of severe pancreatitis (APACHE II >8, Marshall's criteria >2)**					
IV Insulin	Known to have Diabetes Mellitus	Initiate IV insulin 0.05–0.3 units/kg/hr	Give usual subcutaneous long-acting insulin.	Withhold oral hypoglycemic agents.	Check blood glucose hourly.	Titrate IV insulin to maintain target serum glucose: 150–200 mg/dl (8.3–11.1 mmol/L)
	Non-diabetic	Consider a lower initial dose of 0.03 units/kg/hr of IV Insulin with hourly glucose monitoring to ensure insulin titration to maintain serum glucose of 150–200 mg/dl (8.3–11.1 mmol/L)				
IV Fluids	If initial RBS >200 mg/dl (11.1 mmol/L)		Once RBS <200 mg/dl (11.1 mmol/L)		If RBS <150 mg/dl (8.3 mmol/L)	
	0.45% or 0.9% NaCl depending on serum sodium		Add Dextrose 5% to NaCl (0.45% or 0.9%)		Increase fluid rate or switch to Dextrose 10% in NaCl	
Potassium	Serum potassium to be followed every 6 h and replaced intravenously to keep between 4-5 mmol/L.					
Follow-up	1. Serum TG to be rechecked every 12 h. 2. If serum TG falls <20% from initial reading, consider increasing insulin infusion up to 0.1 units/kg/hr. 3. Stop insulin infusion once serum TG < 500 mg/dl (5.6 mmol/L). 4. Commence pharmacological/non-pharmacological treatment of hypertriglyceridemia before discharge.					

HTG-AP: Hypertriglyceridemia-induced acute pancreatitis; RBS: random blood sugar; IV: intravenous; hr: hour

of HTG-AP, the available evidence is scarce and inconsistent concerning the use of DFPP in HTG-AP [31-33]. In DFPP, two layers of filters are applied, one separates plasma from blood, and then the plasma is passed through the second filter to avoid passage of high-molecular-weight molecules. Despite being less effective in TG reduction when compared to traditional plasmapheresis, it may be a preferred method due to its ease of application and potentially fewer complications [33]. Chang *et al*. conducted a study on 25 patients with HTG-AP who received DFPP as a treatment. They reported decreased recurrence and shorter length of stay in patients with DFPP than without [32]. However, a small sample size limits the generalizability and validation of their results. In a recent study on 249 HTG-AP patients, Lu *et al*. have reported a rapid reduction in TG level in patients with DFPP compared to those without DFPP in a propensity score-matched analysis [31]. However, their study failed to show any correlation of this reduction with improved clinical outcomes. This might be due to a reduction in already small sample size by the propensity matching, which reduced their sample size to 100 (50 in each group). Studies on a larger cohort are required to analyze the effects of DFPP on HTG-AP resolution, recurrence, and other clinically significant outcomes. A randomized and controlled multicenter trial (ELEFANT) is being conducted and we can expect better and more precise answers in the future [34]. Although there are few studies with variable results on the effect of TG reduction on the progression of HTG-AP, controversies and knowledge gaps still exist, requiring further studies to resolve this debate. PERFORM study, which is ongoing, aims to assess the effect of TG reduction on organ failure in the HTG-AP patient population and may help strengthen the available guidelines [30].

Given the current paucity of validated data on the management of this disease entity, we hereby propose a protocol that standardizes the management of HTG-AP (Table 1). This recommendation is based on protocols in place at various hospitals across the globe [13,35,36].

CONCLUSION

Management of HTG-AP remains controversial despite considerable effort to find the best treatment. Uncertainty in the available studies is mainly due to the retrospective nature of the studies and small sample sizes, reflecting the disease's rarity. Insulin therapy and plasmapheresis remain treatment options to reduce TG. However, to what extent this translates into a better clinical response is yet to be answered in large and prospective study designs. The current management should focus on adequate hydration, sufficient analgesia, and bowel rest with the early but safe diet reintroduction. TG reduction should be started early on with insulin infusion or plasmapheresis, depending on availability.

AUTHORS' CONTRIBUTIONS

Ata F aided in conceptualization, methodology, literature review, manuscript preparation, critical review, and revisions of the manuscript. Khan AH, Yousaf Z, and Chopra A aided in the literature review, manuscript writing, critical review, and revisions of the manuscript. All the authors reviewed and approved the final version of the manuscript.

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