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Review Article

Current knowledge of hypertriglyceridemic pancreatitis ☆

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ABSTRACT

Severe hypertriglyceridemia (HTG) is a well established and the most common cause of acute pancreatitis (AP) after alcohol and gall stone disease. It is alleged to account for up to 10% of all pancreatitis episodes. Studies suggest that in patients with triglyceride (TG) levels > 1000 mg/dL (>11.3 mmol/L), hypertriglyceridemia-induced acute pancreatitis (HTGP-AP) occurs in approximately 15–20% of all subjects referred to Lipid Clinics. Until now, there is no clear evidence which patients with severe HTG will develop pancreatitis and which will not. Underlying pathophysiological concepts include hydrolysis of TG by pancreatic lipase and excessive formation of free fatty acids with inflammatory changes and capillary injury. Additionally hyperviscosity and ischemia may play a decisive role. The clinical features of HTG-AP patients are supposed to be no different from patients with AP of other etiologies. Yet, there are well-conducted studies suggesting that HTG-AP is associated with a higher severity and complication rate. Therapeutic measurements in HTG-AP include dietary modifications, different antihyperlipidemic agents, insulin and/or heparin treatment. The beneficial use of plasmapheresis is repeatedly reported and suggested in many studies. Yet, due to the lack of randomized and controlled trials, it is currently unknown if plasmapheresis may improve morbidity and mortality in the clinical setting of HTG-AP. Since there are no commonly accepted clinical guidelines in the management of HTG-AP, there is a definite need for an international, multicenter approach to this important subject.

1. Introduction

Acute pancreatitis (AP) is a potentially life threatening acute inflammatory condition of the pancreas with a worldwide rising incidence [1]. Though most cases are rather mild, there is a subset of patients with severe pancreatitis where mortality may reach up to 30% [2]. To determine the etiology of acute pancreatitis is crucial to the management of this potentially fatal condition.

The most common etiology of acute pancreatitis is gallstone disease and alcohol [3]. However, hypertriglyceridemia (HTG) is a well known cause of AP and hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is not a rare condition. In series of cases with AP, HTG was considered causative of the attack ranging from 1% up to 10% [4–10]. Some studies on gestational pancreatitis even report HTG as the underlying cause in more than half of all cases [11].

Several hyperlipoproteinemia (HLP) phenotypes show HTG, i.e. types I, III, IV and V, but only high chylomicron concentrations may trigger an attack of AP. Occasionally, subjects with type IV (VLDL) may become type V (VLDL plus chylomicrons) HLP under circumstances such as a fatty meal, alcohol ingestion, hypothyroidism, estrogens or pregnancy, retinoids or uncontrolled diabetes mellitus [12–14]. Less common is primary HLP type I due to abnormalities in the catabolic pathways of TG-rich lipoprotein, a syndrome named "Familial Chylomicronemia Syndrome" [15]. Nevertheless, these rare cases provide the evidence that chylomicrons by itself may trigger AP, as it is shown by pediatric cases [16,17].

2. Epidemiology of HTG-AP

As stated above HTG is ascribed causative in up to 10% of all pancreatitis episodes.

There is no clear threshold by which HTG triggers AP, but the general rule says that "the higher the levels of TG, the higher the probability to suffer from AP". Because high concentrations of chylomicrons are needed, severe HTG is usually defined by TG levels > 1000 mg/dL (>11.3 mmol/L). Chylomicrons increase almost lineally as total TG increases, yet they are even present with lower TG levels [17].

In a specialized Lipid Clinic, the prevalence of HTG-AP was 15% in those with TG > 20.0 mmol/L as compared to 3% of those having TG 10–20 mmol/L [18]. A French cohort of 129 subjects with severe HTG

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(TG > 1000 mg/dL), showed that 20% of them had had AP; the OR for AP was 4.0 (CI 95%: 1.3–12.6) for those in the third tertile vs. those in the first tertile of serum TG [19].

Data from the *German Lipid League* (*DGFF*) showed that among 306 patients referred to specialized Lipid Centers with severe HTG (TG > 1000 mg/dL), there were 19% (58/306) with HTG-AP [20]. Among participants who were included in the *Spanish Registry of Hypertriglyceridemia*, the prevalence of AP was 10% in those who were referred with total TG > 1000 mg/dL, but only 3% in those referred with TG < 500 mg/dL [21].

Population studies additionally support the view that severe HTG increases the risk of AP. Using large databases, Christian et al. identified 41,210 persons with severe HTG (in that case defined as TG > 500 mg/dL). During follow-up, 8493 remained uncontrolled (TG persisted above 500 mg/dL); in that group, the OR for AP was 1.79 (CI: 95% 1.47–2.18) and therefore even greater than that for a cardiovascular event (OR: 1.19 [CI 95%: 1.10–1.28]). Murphy et al. conducted a population-based study. Taking individuals with TG < 150 mg/dL as the reference, the hazard ratio for AP was 1.5 for subjects with TG 150–500 mg/dL and 3.2 (CI 95%: 1.99–5.16) for those in the group with TG > 500 mg/dL. Interestingly, the risk of incident AP increased by 4% for every 100 mg/dL increase in TG concentration (after adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease) [22].

3. Pathophysiological concepts of HTG-AP

To date, the exact pathophysiological mechanism of HTG causing AP still remains unclear and is a topic of controversial discussion. Several studies on animal models, have suggested some commonly accepted theories. According to the most common theory initially put forward by Havel [23], the excess of TG is hydrolyzed by high levels of pancreatic lipase released in the vascular bed of the pancreas. Thus free fatty acids (FFAs) are formed in high concentrations, which overwhelm the binding capacity of albumin and they self-aggregate to micellar structures with detergent properties. Hence acinar cell and pancreatic capillary injury is promoted. The resultant ischemia creates an acidic environment, which further triggers FFA toxicity [23–25]. Additionally, the elevated levels of chylomicrons increase the viscosity of blood and therefore impair the blood flow in the pancreas causing ischemia and acidosis within the pancreas. Furthermore, endoplasmic reticulum stress is also discussed as a pathophysiological concept contributing to HTG-AP [26].

Data suggests that there are additionally specific genes associated with HTG-AP. A Chinese study, e.g., found a Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation/variant/haplotype and a Tumor Necrosis Factor promoter polymorphism as independent risk factors for HTG-AP. The CFTR gene mutation rate in patients with HTG and AP was 26.1% (12 of 46), whereas in patients with HTG without AP only 1.3% (1 of 80) showed this specific CFTR gene mutation in this study [27]. A Spanish study by Ivanova et al. finds the ε4 allele of the apolipoprotein E (APOE) gene more frequent in patients with HTG-AP, also suggesting a genetic background [7].

Most probably all of the described theories contribute to some degree to the development of HTG-AP. Yet, further research efforts in this area will be needed to spread more light into the exact pathophysiology of HTG-AP.

4. Clinical presentation and severity of HTG-AP

The clinical presentation of patients suffering from HTG-AP is generally no different from patients with AP of any other etiology. Some studies show, however, that patients with HTG-AP might generally be of younger age than patients with AP due to other causes [28].

There are some other special features of HTG-AP different from AP of other etiology that are frequently discussed. This holds especially true for the severity of HTG-AP.

According to several animal studies, HTG seems to intensify the course of acute pancreatitis. The available studies demonstrate greater lipase activity and more severe histological damage in the setting of experimental HTG-AP [29–32].

Despite some older studies suggesting that HTG may play a pivotal role in the development of respiratory failure and other severe complications associated with acute pancreatitis [33,34], it is generally believed that there is no significant difference concerning morbidity and mortality of patients with HTG-AP vs. patients with AP of any other cause [5]. Supporting this view, a prospective study in 43 British patients with pancreatitis of different etiologies (14/43 with alleged HTG-AP), did not find a more severe disease in patients with HTG-AP as compared to AP of any other cause [35]. However, it is important to realize that the authors chose a very low cut-off value for HTG (>175 mg/dL, >2 mmol/L) in this study. This does not represent the typical HTG-AP patient. Additionally, mild-to-moderate HTG can frequently be found as an epiphenomenon secondary to pancreatitis of any cause [36]. Therefore this study bears major flaws.

Other studies seem to favor a more severe course of the disease with HTG as the underlying cause of AP. A French cohort study showed that the severity of HTG-AP was higher than that of AP induced by gallstones or alcohol. Severe pancreatitis (defined as: need for intensive care, C-reactive protein > 150 mg/L, or Balthazar score > C) was observed in 71.5% of the HTG-AP study collective [19]. A prospective Chinese study also suggests higher morbidity (rate of complications, shock, infection, renal failure, etc.) and mortality in patients with HTG-AP as compared to patients with pancreatitis of any other etiologies [37]. Furthermore a Hungarian study of 351 patients with pancreatitis (among those 23 patients with HTG-AP) also showed a more severe prognosis, longer hospitalization, more frequent pancreatic necrosis, sepsis and local complications in patients with HTG-AP [29]. However, the absolute TG levels do not correlate with the severity of the disease in several studies [19]. Therefore the more severe course of the disease seems to be due to the mere fact, that AP is HTG-induced.

Concluding, there seems to be rising evidence for a more severe course in HTG-AP as compared to AP of any other etiology.

5. Treatment options

Initial diagnostic and therapeutic procedures of HTG-AP should adhere to the same practice recommendations as established for AP in general (including intensive intravenous hydration, analgetic treatment and a fastening state).

Earliest possible determination of serum TG levels is crucial, as TG levels are well known to rapidly decrease within the first 48 h of onset of pancreatitis [38]. A thorough medical history and examination are obligatory in order to identify possible secondary causes of HTG (e.g. drug associated HTG, uncontrolled diabetes mellitus, hypothyroidism).

5.1. Diet and initial management

Restriction of oral intake, intravenous fluids and analgesia are the basis for the therapy of AP. Patients should be categorized according to severity, using the APACHE II scale [39] or the Balthazar grade [40,41]. Subjects with an APACHE II score of >8 and/or grade E in Balthazar score should be offered to the intensive care unit. If clinical course prolongs or worsens, then naso-enteral tube feeding or parenteral nutrition should be started with a fat-free diet.

Most patients with uncomplicated HTG-AP have a good prognosis; usually serum TG levels decrease in 24 to 48 h to a level in which the risk of AP is really low and reach values below 500 mg/dL at the fourth or fifth day [6,7]. Once pain disappears and intestinal transit is normalized, then an oral fat-free diet can be begun again.

5.2. Pharmacological options

Heparin and insulin infusions have been used for a long time as main therapy for HTG-AP. Most of the evidence for both drugs come from isolated cases [42–48] or short series of cases [49]. Infusion of unfractionated heparin is able to release lipoprotein lipase (LPL) attached to the endothelial cells, which is followed by a transient reduction in serum TG. In pre-heparin serum samples, the amount and activity of LPL are almost undetectable. In fact, post-heparin serum samples must be taken in order to assay the mass and activity of LPL [50,51]. However, there are some concerns with heparin in the management of severe HTG and AP [52]. Long-term infusion is able to deplete LPL on the surface of endothelial cells, allowing serum TG to be raised again [53,54]. Watts et al. published a case of a pregnant woman who develops a HTG-AP after long-term use of heparin, inducing LPL deficiency [55]. Furthermore, some authors are reluctant to use heparin in patients with pancreatic necrosis due to the risk of hemorrhage into the pancreas [6]. There is no contraindication to use low-molecular weight heparin as prophylaxis for deep-vein thrombosis in the clinical setting of HTG-AP.

The rationale for the use of insulin is linked with the synthesis of LPL from adipose and muscle cells. There is no clear evidence of the benefit of insulin in HTG-AP for those patients who are not diabetic. By contrast, intravenous insulin is mandatory for those patients with type 1 diabetes mellitus who develop diabetic ketoacidosis and severe HTG with AP, which is not an uncommon association [56–59]. Nevertheless, insulin is also mandatory for patients with severe HTG and uncontrolled type 2 diabetes mellitus with [60] or without AP [61,62].

In summary, although frequently used in clinical practice, there is no evidence coming from randomized and controlled clinical trials supporting the use heparin or insulin infusions, unless indicated for diabetes mellitus.

5.3. Plasmapheresis

Because HTG-AP is a life-threatening condition, some centers apply plasmapheresis in order to reduce the levels of circulating chylomicrons in a very short time thus removing the causative agent for continuing pancreatic damage. Table 1 summarizes main demographic data, comorbidities, type of replacement, serum TG before plasma exchange is done, the percentage of reduction and the in-hospital mortality for those papers published including more than five patients [63–71]. One single session of plasma exchange is able to reduce serum TG from 49 to 80%, although few patients need two or more sessions to reach a TG level below 1000 mg/dL. Some centers perform plasma exchange at admission, just before 24 h, while others include patients between 24 and 72 h of admission. Some studies emphasize the importance of an early start of apheresis [64], while other studies were not able to detect any difference in morbidity or mortality concerning an early or late start of apheresis [70]. Additionally there is controversy on the technical details of plasmapheresis in HTG-AP. A recent study on 111 episodes of HTG-AP treated with plasmapheresis, for example, found a significantly reduced mortality using citrate anticoagulation as compared to heparin anticoagulation [70].

Due to the lack of randomized and controlled trials, it is currently unknown if plasmapheresis may improve morbidity and mortality in the clinical setting of HTG-AP in general. In some centers, plasmapheresis is only used in severe AP [63], but other centers even treat patients with low APACHE II scores [66,70]. The only paper comparing subjects with conservative managements vs. plasma exchange, showed no benefits in terms of mortality [64]. The lack of availability of plasmapheresis in any center as well as the rather high costs limits its use further. This results in the latest guidelines from the American Society for Apheresis, which considers HTG-AP as category III indication (disorders for which the optimum role of apheresis therapy is not established, individualized decision is necessary) [72].

5.4. Long-term management

Once the HTG-AP attack has been resolved, prevention of a next episode is compulsory. Lifestyle changes and dietary modifications are the key features in long-term management of HTG. Dietary advice by a nutritionist is obligatory in patients having suffered an episode of HTG-AP. There are several additional approaches, based on the underlying HTG phenotype. For subjects with HLP type I, most of them young and suffering from mutations at LPL, GPIHBP1 or C-II gene, the only treatment available is to adhere strictly to a low fat diet, approximately 15% of total calories and between 10 and 15 g of fat daily. Both unsaturated and saturated fats should be limited. Medium-chain triglycerides (MCT), which are also capable of decreasing TG levels effectively [73–75], should be added in order to give sufficient calories [15]. There are isolated cases indicating that inhibition of pancreatic lipase with Orlistat can reduce TG and avoid recurrent abdominal pain and AP [76]. Lomitapide, a drug that blocks microsomal transfer protein, is able to reduce VLDL and chylomicron synthesis and has been recently approved for the treatment of homozygous familial hypercholesterolemia [77]. Lomitapide has been also used for thirteen years to control very severe HTG in a young woman and prevent recurrent AP due to familial LPL deficiency, although liver steatosis progressed to steatohepatitis and liver fibrosis [78]. Finally, Alipogene-Tiparvovec, an adeno-associated viral vector of serotype 1 coding for the LPLS447X gene variant, given intramuscular simultaneously at several places was able to reduce fasting TG almost to 40% in more than half of patients with LPL deficiency at 3–12 weeks, then TG returned to baseline levels but overall incidence of HTG-AP was reduced [79]. Regular

Table 1
Main data from studies of HTG-AP treated with plasmapheresis, reporting more than 5 patients.

Author	Number (men/women)	Age (years-old)	Severity (APACHE II)[a]	Diabetes N (%)	Alcohol N (%)	Replacement[b]	Baseline TG (mg/dL)	Drop TG (%)	Mortality N (%)
Yeh et al. [65]	17 (10/7)	40 ± 6	NA	7 (41)	6 (35)	FFP or Alb	2104 ± 679	−67 (−85)[c]	2 (12)
Chen et al. [64]	60 (NA)	42 ± 9	NA	30 (55)	17 (28)	FFP or Alb	2109 ± 780[d]	−66[d]	4 (6.7)[e]
Kyriakidis et al. [68]	9 (7/2)	43 ± 13	14 (11–16)	NA	NA	FFP	1486 ± 458	−84	1 (10)
Al-Humoud et al. [67]	8 (6/2)	35 ± 9	NA	3 (37)	NA	Alb	9743 ± 12,932	−69	0
Gubensek et al. [66]	40 (37/3)	46 ± 8	5 (0–15)	NA	NA	Alb	4505 ± 3614	−79 ± 22	6 (15)
Kadikoylu et al. [69]	7 (5/2)	47 ± 3	NA	3 (43)	NA	Alb	1406 ± 498	−48	0
Ramirez-Bueno et al. [63]	11 (3/8)	40 ± 8	13 (9–18)	2 (18)	8 (72)	Alb	2260 ± 1101	−78	3 (27)
Gubensek et al. [70]	111 (97/14)	47 ± 9	4 (2–7)	34 (31)	24 (22)	Alb	4900 ± 2975	−59	6 (5)

NA = not available.
[a] Data shown as median (interquartile range).
[b] FFP = Fresh frozen plasma, Alb = 5% albumin.
[c] Data collected for those with 1 session (two sessions).
[d] Data collected for only those 22 patients who were treated with plasmapheresis.
[e] Data reported for the whole group of 60 patients.

plasmapheresis can also be used in severe HLP type I or type V to avoid recurrent HTG-AP [69,71,80,81].

For patients with HLP type IV or V, it is compulsory to control all environmental factors that are associated with poor TG control, such as alcohol consumption, uncontrolled diabetes mellitus, estrogens, retinoid and if possible antiretroviral agents. If obesity is present, as habitual, body weight reduction is suggested with a low-calorie diet [82]. Most patients after an episode of HTG-AP need a combination of drugs, such as fibrates [83] and omega-3 fatty acids [74,84,85] to reduce fasting TG. Omega-3 fatty acids reduce serum TG in a dose-dependent manner, and doses as high as 12 g per day are prescribed [86]. A recent meta-analysis of five trials reported that fibrates may increase the risk of AP [87]. However, it should be noted that in all trials included in the meta-analysis, the clinical end-points were cardiovascular events and the criteria for entry to the studies were to have <445 mg/dL of fasting TG, far away from those levels usually seen in patients suffering from HTG-AP. Furthermore, the rates of AP in the fibrate trials were low, as expected given the fact that these trials largely excluded those at high risk of the condition (known hepatobiliary disease, alcohol excess and marked hypertriglyceridemia) [88]. Overall, fibrates are of great value to reduce high TG levels and therefore are indicated, jointly with lifestyle changes to prevent HTG-AP, as suggested by the Endocrine Society [89].

Some authors suggest that the prescription of lipid-lowering drugs to reduce fasting TG in asymptomatic persons to prevent AP is not justified due to the absence of evidence and should not be encourage in clinical guidelines [90]. Although there are no randomized clinical trials supporting that notion, clinical practice clearly indicates that severe HTG-AP tends to recur if preventive measures are not strictly implemented. Recently, Christian et al., gathering data from two large US healthcare databases, have demonstrated that lowering TG from >500 mg/dL to less than 200 mg/dL is able to reduce the incidence of AP from 1.1 per 100 person-year to 0.4 per 100 person-year (adjusted OR 0.45 [CI 95%: 0.34–0.60]) [91]. For this reason, fasting TG should be as low as possible, ideally below 200 mg/dL, in order to avoid a postprandial peak of chylomicrons greater than 1000 mg/dL.

Lipid self-monitoring might additionally be a beneficial option in the long-term management of HTG-AP. A German study describes a positive effect of self-monitoring of TG levels by patients at home. Subjects were able to influence their diet individually, stabilized their TG levels and hence avoided further episodes of severe HTG-AP [75].

Unfortunately there are no commonly accepted clinical guidelines on the treatment of HTG-AP so far. However, there are some frequently cited reviews proposing valuable treatment algorithms for HTG-AP [92,93].

6. Conclusion

Since HTG seems to account for approximately 10% of all pancreatitis cases and for even up to 50% of all cases in pregnancy, it is important to routinely test patients presenting with signs and symptoms suggestive of AP for TG levels on admission. This holds especially true if medical history or physical examination is suggestive of primary or secondary HTG. Early testing for elevated TG levels is even more important as they usually rapidly decrease within the first 48 h of the onset of AP [38]. Determining the exact cause of AP is important since HTG-AP bears some special considerations and therapeutic options. Among these, plasmapheresis is probably the most discussed topic. Since evidence is rising that HTG-AP is associated with a more severe course of AP and hence with a higher morbidity and mortality, effectively removing the causative agent for continuing pancreatic damage by means of plasmapheresis seems a reasonable approach. Therefore plasmapheresis is commonly used in certain centers. Since there is a lack of randomized and controlled trials, however, it is currently unknown if plasmapheresis may improve morbidity and mortality in the clinical setting of HTG-AP. More studies in the promising area of plasmapheresis are therefore urgently needed and strongly encouraged to adequately judge the value of this therapeutic option in HTG-AP. Future research efforts should also focus on determining which patients with severe HTG will develop AP and which of them will not. This could be crucial to our understanding of HTG-AP.

Concluding one has to state that there are still no generally accepted guidelines for the treatment of HTG-AP to date. International efforts in taking this further step in developing such guidelines are strongly suggested and encouraged.

Core tip

Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is the most common cause of pancreatitis after alcohol and gall stone disease and accounts for up to 10% of all pancreatitis episodes. Triglyceride levels > 1000 mg/dL are considered necessary to ascribe causation for pancreatitis, yet this threshold is arbitrary. Presentation of patients with HTG-AP seems generally no different from patients with acute pancreatitis of any other cause, yet a more severe course of the disease is reported. Dietary intervention, different pharmacological options, insulin, heparin and plasmapheresis resemble valuable therapeutic options.

Learning points

- Hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is the most common cause of pancreatitis after alcohol and gall stone disease and accounts for up to 10% of all pancreatitis episodes.
- Triglyceride levels > 1000 mg/dL are considered necessary to ascribe causation for pancreatitis, yet this threshold is arbitrary.
- Presentation of patients with HTG-AP seems generally no different from patients with acute pancreatitis of any other cause, yet a more severe course of the disease is reported.
- Dietary intervention, different pharmacological options, insulin, heparin and plasmapheresis resemble valuable therapeutic options.

Conflict of interest

The authors declare no conflict of interest.

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