Futility of plasmapheresis, insulin in normoglycaemic individuals, or heparin in the treatment of hypertriglyceridaemia-induced acute pancreatitis

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There is a well-established link between the severity of hypertriglyceridaemia and acute pancreatitis and long-term triglyceride-lowering therapies known to prevent episodes of acute pancreatitis. Therefore, it has been assumed, without firm evidence, that rapid lowering of plasma triglycerides would be an effective strategy for reducing the clinical severity of acute pancreatitis and improving health outcomes. Therapies, such as intravenous heparin, intravenous insulin in normoglycaemic individuals (with glucose to prevent hypoglycaemia), and plasmapheresis, continue to be widely used as therapeutic interventions to rapidly reduce serum triglyceride concentration. These therapies are all associated with a risk of adverse reactions, require increased resources, and increase health-care costs. Randomised controlled clinical trials of these therapies have generally shown more rapid reductions in plasma triglycerides than conventional supportive care with the patient made nil by mouth. However, these three therapies alone or in combination, have failed to show effectiveness in improving substantial health benefit outcome measures. While we recognise the theoretical basis for rapidly reducing plasma triglycerides in hypertriglyceridaemia-induced pancreatitis—based on our review of studies using heparin, insulin, plasmapheresis, or a combination of these—these strategies overall do not reduce complications associated with acute pancreatitis or the rapidity of disease resolution. Therefore, we do not advocate the use of triglyceride-lowering therapies at this time, pending more convincing evidence.

Introduction

Acute pancreatitis is a complex inflammatory disease of the exocrine pancreas and is associated with considerable morbidity and mortality.[1,2] Li and colleagues reported a 62·9% increase in incidence rate from 2010 to 2019,[3] establishing acute pancreatitis as one of the most common gastrointestinal-related causes of hospitalisation, resulting in up to US$2·6 billion in annual health-care expenditure.[1,4] In terms of severity, the disease ranges from mild to severe, as defined by the Revised Atlanta Classification.[5] Whereas mild disease is characterised by the absence of systemic complications and organ failure, moderate disease presents with temporary organ failure (lasting less than 48 h), the presence of local complications (eg, tissue injury, oedema, or necrosis), or the development of comorbidities.

Although most cases of acute pancreatitis (65–70%) are considered mild, approximately 20–25% are moderate, and approximately 10% are diagnosed with a severe form of acute pancreatitis,[1] with this 10% of cases associated with failure of multiple organs (eg, renal, cardiac, and respiratory) lasting more than 48 h, and the presence of systemic or local complications.[5,6] In severe cases, patients require a complex, high-dependency hospital course, and present a high-risk mortality rate of 30–50%.[1,7] Notably, 20–30% of patients who develop acute pancreatitis are at risk of experiencing recurrent attacks of acute pancreatitis[8,9] and can develop chronic pancreatitis resulting in long-term debility, pancreatic exocrine and endocrine insufficiency, reduced quality of life, socioeconomic consequences of prolonged hospitalisation, and an increased risk of pancreatic cancer.[1,9]

Hypertriglyceridaemia-induced acute pancreatitis

Hypertriglyceridaemia is defined as mild (1·7–5·6 mmol/L), moderate (>5·6–11·2 mmol/L), severe (>11·2–22·4 mmol/L), or very severe (>22·4 mmol/L) depending on serum triglyceride concentrations.[10] An increase in serum triglyceride concentration by every 100 mg/dL (around 1·12 mmol/L) above 1000 mg/dL (around 11·2 mmol/L) is associated with a relative increase in the incidence rate of acute pancreatitis by 4%, after controlling for demographic factors and lifestyle habits, making it the third leading cause (after gall stone and alcohol-induced pancreatitis) of acute and recurrent pancreatitis and accounting for about 1–9% of cases.[8,11–13] Moreover, hypertriglyceridaemia-induced pancreatitis (either as a sole factor or a co-factor) has been shown to be more severe than the other aetiologies[14,15] and can increase the risk of recurrent attacks four-fold than other aetiologies.[16] Guda and colleagues in their consensus article suggest that recurrent attacks of acute pancreatitis occur mostly in individuals who continue with their lifestyle (eg, drinking and smoking) or those with chronic calcific pancreatitis.[17] Despite the number of attacks, long-term triglyceride control in those with hyperlipidaemia-associated pancreatitis has been shown to prevent relapse.[17]

In a study by Nawaz and colleagues, the proportion of persistent organ failure increased linearly with the severity of hypertriglyceridaemia in individuals developing acute pancreatitis.[18] Similar results were presented by Lu and colleagues showing that serum triglycerides correlated directly with the severity of

hypertriglyceridaemia-induced acute pancreatitis.[19] Furthermore, Zhang and colleagues conducted univariate and multivariate regression analyses between serum triglycerides and persistent organ failure, acute peripancreatic fluid collection, and acute necrotic collection, and reported a significant increase in all three factors with an increment of 100 mg/dL in triglyceride concentrations.[20] Lastly, in a rodent model, Kimura and colleagues perfused varying concentrations of triglycerides and quantified amylase and lipase in portal veins, as an indicator of pancreatic injury.[21]

Consistent with clinical studies, increasing concentrations of triglycerides increased pancreatic enzyme levels in a dose-dependent manner in rats,[21] which leads to an understanding that high triglyceride concentrations induce acute pancreatitis and worsen disease pathology to a more severe form. Recently published results from prospective, randomised, placebo-controlled, double-masked clinical trials of novel triglyceride-lowering therapies targeting apolipoprotein C-III have provided the first conclusive data that effective chronic treatment of marked hypertriglyceridaemia reduces the occurrence of acute pancreatitis events in those with the rare genetic condition, familial chylomicronaemia syndrome.[22–24] It is not known whether these novel therapies can also be effective in ameliorating the severity of pancreatitis if first administered in this acute setting. Based on phase 1 clinical trial data, the ability of these therapies to rapidly and robustly lower plasma triglycerides has been shown to be less than the known effects of plasmapheresis.[25–27] Many national guidelines for the treatment of hypertriglyceridaemia have settled on a plasma triglyceride concentration of 10 mmol/L and higher as a threshold for treatment to prevent acute pancreatitis. For example, both Canadian Cardiovascular Society guidelines and the European Society of Cardiology and European Atherosclerosis Society recommend treatment of plasma triglycerides greater than 10 mmol/L to prevent pancreatitis.[28,29] However, no national or societal guidelines advocating specific therapy for treatment of hypertriglyceridaemia in the setting of acute pancreatitis were found in the literature.

In light of the link between the severity of hypertriglyceridaemia and the proven effectiveness of chronic triglyceride-lowering in preventing episodes of acute pancreatitis, it has been assumed, without firm evidence, that rapid lowering of plasma triglycerides in the setting of acute pancreatitis could be effective in reducing its clinical severity and improving health outcomes. Currently there are several pharmaceutical investigational drugs that are being tested for the management of hypertriglyceridaemia-induced acute pancreatitis. An extract of relevant interventional studies from the ClinicalTrials.gov website is listed in the appendix (p 2). Therapies, such as intravenous heparin, intravenous insulin in individuals with normoglycaemia (with glucose to prevent hypoglycaemia), and plasmapheresis continue to be widely used as therapeutic interventions to rapidly reduce serum triglyceride concentration (figure 1).[30] These therapies are all associated with risk of adverse reactions, require increased nursing and other resources, and add to health-care costs. Furthermore, plasma triglycerides decline rapidly over 48–72 h when the patient with marked hypertriglyceridaemia is fasted (as is commonly the case in the care of a patient presenting with acute pancreatitis) with either no or only slightly more rapid triglyceride decline when these therapies are instituted.[31] However, it is important to appreciate that the reduction observed in triglyceride levels in multifactorial chylomicronaemia syndrome might not occur in those with primary familial chylomicronaemia syndrome, in which triglyceride concentrations might remain persistently elevated even with fasting.[32] The important point; however, is not the rapidity of the decline of plasma triglycerides, but

See Online for appendix

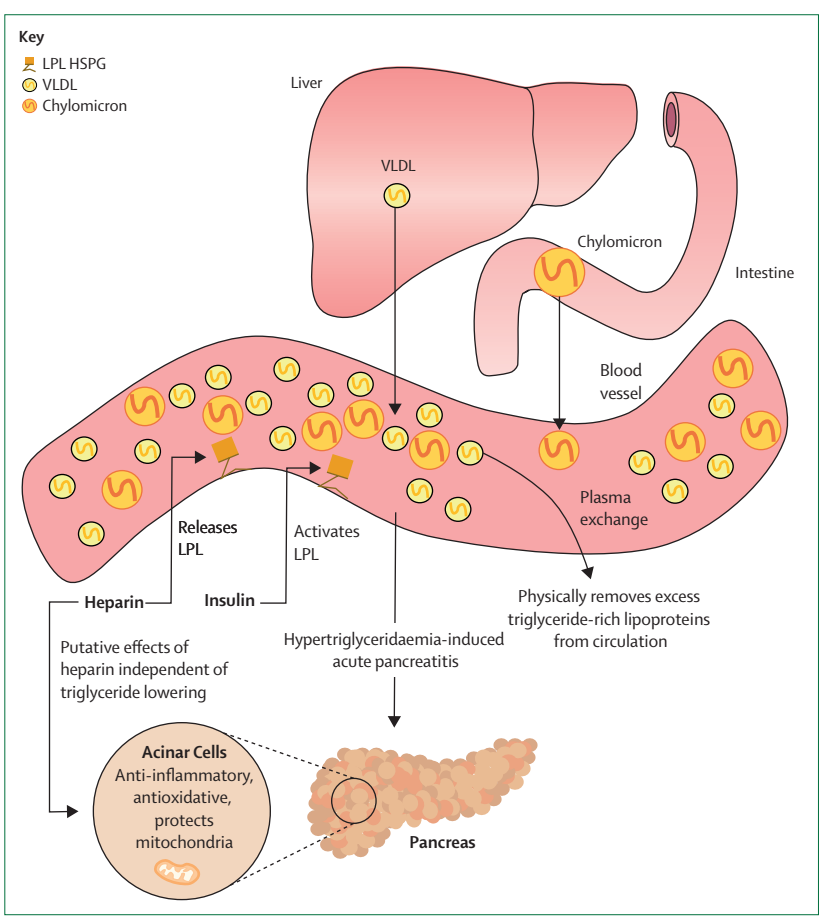

Figure 1: **Therapies currently used to treat hypertriglyceridaemia-induced acute pancreatitis**
Intravenous insulin activates LPL, which increases the clearance of triglycerides from the circulation. Heparin binds to HSPG and releases LPL, leading to a reduction in plasma triglycerides. Heparin also reduces inflammation, oxidative stress, and protects mitochondria in acinar cells of the pancreas. These effects are independent of the triglyceride-lowering effect of heparin. Plasma exchange (plasmapheresis) removes triglycerides directly from circulation. HSPG=heparan sulphate proteoglycan. LPL=lipoprotein lipase.

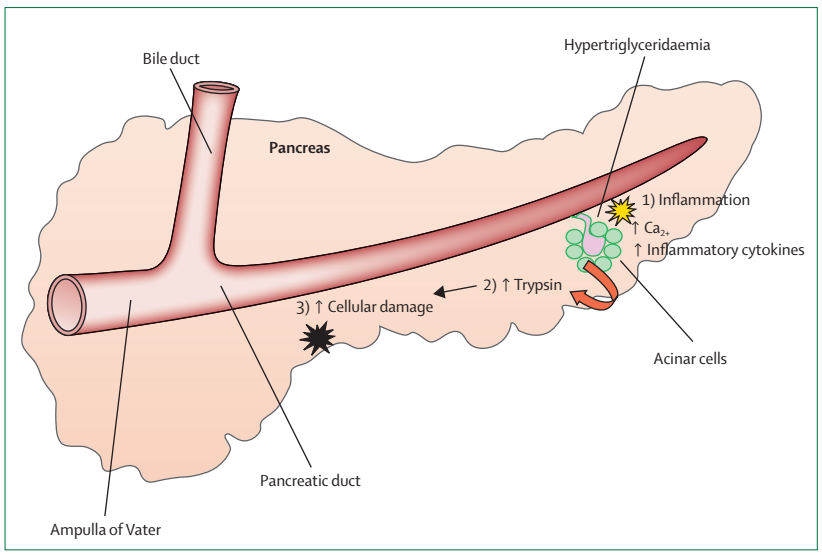

Figure 2: **Pathogenic mechanisms of hypertriglyceridaemia-induced acute pancreatitis**
Hypertriglyceridaemia due to elevated levels of plasma triglyceride-rich lipoproteins (particularly chylomicrons) within pancreatic capillaries might promote local injury of acinar cells with ectopic release of exocrine pancreatic lipase leading to abnormal metabolic products and stimulate local perturbed calcium flux and inflammatory cytokines (1). Injured pancreatic cells release digestive enzymes, such as trypsin (2), which further propagate inflammation and cell damage (3).

whether these therapies are effective in improving hard clinical outcome measures, such as disease severity, length of intensive care unit (ICU) or hospital stay, complications, progression to chronic pancreatitis, or mortality. As we will discuss later, insufficient high-quality studies have been conducted to quantify hard health outcomes for us to advocate the use of these therapies.

Proposed pathogenic mechanisms of hypertriglyceridaemia-induced acute pancreatitis

As shown in figure 2, the initial stages of acute pancreatitis involve a series of events that begin with the development of inflammation within the pancreatic acinar cells causing them to prematurely activate and release pancreatic enzymes (eg, trypsin) within pancreatic tissue rather than into the pancreatic duct that leads to the intestine and causes cellular damage.[33,34] Amylases and lipases secreted in the bloodstream are used as diagnostic tests, but can also result in fatty necrosis of the pancreas.[34,35] In the severe form of the disease, fluid retention, systemic inflammatory response syndrome, and sepsis are observed and eventually lead to pancreatic ascites, pancreatic effusion of the lungs, acute renal failure, and infected pancreatic necrosis.[35,36] In a more recent review, calcium signalling in acinar cells has also been recognised as a key initiating factor in the pathophysiology of acute pancreatitis.[36] Acinar cell concentrations of calcium (within cytosolic or mitochondrial compartments) are 5–20 fold higher than physiological levels either due to increased efflux or to a defect in calcium homoeostasis transporters induced by toxins (ie, bile acids, fatty acids, and hormones).[36,37] A persistent increase in cytosolic calcium levels is an initiating event commonly observed in human and rodent acute pancreatitis models,[19] which can result in opening of the mitochondrial permeability transition pore.[36,37] Hydrogen enters through this pore, which disrupts the energy gradient required for ATP production, leading to reduced calcium clearance and mitochondrial dysfunction.[36–38] Persistent increase in calcium (intracellular and mitochondrial) can also be observed due to high pressure calcium channels, which again results in impaired ATP production and subsequent cascade of events resulting in systemic inflammation.[39]

Two leading theories of the potential mechanisms that contribute to the triggering of hypertriglyceridaemia-induced acute pancreatitis have been proposed, although the mechanism remains poorly defined. First, the release of free fatty acids due to excess hydrolysis of triglycerides[40] and second, increased viscosity of blood due to high concentrations of triglycerides and chylomicrons in the blood.[39,41] The contribution of triglyceride-induced viscosity in aggravating acute pancreatitis via ischaemia-induced inflammation appears to be less convincing since the prevalence of acute pancreatitis is low in hypergammaglobulinaemia and polycythaemia (conditions of hyperviscosity syndrome).[39] Regarding the release of free fatty acids due to excess triglycerides, hydrolysis by pancreatic lipase appears to contribute to several pathways at the molecular level that might induce and progress disease severity. Excess triglycerides reach the pancreatic vasculature in the form of triglyceride-rich lipoprotein particles and acinar cells release exocrine pancreatic lipase in response.[42] These changes result in the lipolysis of free fatty acids and the fatty acids exceed albumin binding sites and might bind directly to the vasculature, resulting in damage at the microcirculatory level—ie, endothelial cell dysfunction, leakage, and activation of coagulation factors.[39,40,42] Furthermore, high concentrations of free fatty acids in microcirculation and tissues can also result in the formation of micelles, which leads to ischaemia, acidosis, and trypsin activation.[42] In addition to vascular damage, free fatty acids transported within the acinar cells activate protein kinase C, reduce ATP production due to endoplasmic reticulum stress, and increase the release of proinflammatory cytokines.[39] The combined increase of protein kinase C and reduction of ATP results in elevated concentrations of intracellular calcium, inhibition of ductal function, and greater endoplasmic reticulum stress.[39,42] Calcium overload has also been observed as a cause of excess lipase secretion, reduced antioxidants, and increased reactive oxygen species generation, which eventually leads to tissue necrosis.[36,37,39,42] Additionally, fatty acids from the pancreatic and peripancreatic regions have been shown

to inhibit mitochondrial complexes I and V in the acinar cells. Of note, increased levels of fatty acids (unsaturated) derived from peripancreatic fat necrosis have been shown to independently worsen the disease, possibly by increasing calcium release, cytoplasmic leakage of lactate dehydrogenase, and cytochrome C, and might upregulate inflammatory mediators by inducing multisystem organ failure.[40,42,43]

Summary of available therapies

The conventional supportive therapies used in the management of acute pancreatitis primarily include intravenous fluid resuscitation, analgesia, and enteral nutrition (nil by mouth approach). Moreover, in the severe form of the disease, critical care, organ support, parenteral nutrition, antibiotics, pancreatic exocrine and endocrine replacement therapy are used depending on the individual's needs.[1] However, when serum triglycerides are markedly elevated, one of the three approaches is commonly used to attempt to rapidly reduce serum triglyceride concentrations (ie, heparin, insulin or glucose, or plasmapheresis). We extensively searched the literature on PubMed for randomised controlled trials (RCTs) using these treatments in hypertriglyceridaemia-induced acute pancreatitis and discuss them later.

Intravenous heparin

Heparin is an anticoagulant that also releases lipoprotein lipase from heparan sulphate proteoglycans that tether it to the endothelial surface, thus increasing its physical access to triglyceride-rich lipoproteins (ie, VLDL and chylomicrons) and hydrolysing triglycerides in these lipoproteins. To date, only case studies have been conducted that have reported a reduction in triglyceride concentration after heparin infusion. No randomised, placebo-controlled, masked study has been conducted for the use of heparin in treating hypertriglyceridaemia-induced acute pancreatitis. Only one retrospective study conducted by Altinkaya and colleagues in 2021 showed that heparin treatment caused a reduction in triglyceride concentration on the third day of treatment but was not as significant as observed in the control group (insulin infusion). However, reduced triglyceride concentration did not result in hard health benefits related to disease resolution.[44]

RCTs that were conducted to evaluate the effect of heparin in cases of pancreatitis were either examining post-endoscopic retrograde cholangiopancreatography[45,46] or moderate to severe cases of acute pancreatitis that were induced by other causes.[47–50] Therefore, the primary outcomes of these studies did not include the rate of decline of plasma triglycerides, nor can they necessarily be extrapolated to pancreatitis secondary to hypertriglyceridaemia. However, these studies evaluated heparin's effect on some of the factors that are commonly associated with hypertriglyceridaemia-induced acute pancreatitis and although these findings might provide insights, the evidence regarding their clinical benefit remains inconsistent. For example, heparin infusion appeared to be effective in resolving pancreatic necrosis,[47,48] pancreatic encephalopathic incidence,[49] Balthazar computed tomographic score for pancreatitis risk,[47–49] systemic complications,[48] blood biomarkers,[50–52] curative rate,[49] aggravation rate, and secondary operation rate.[52] In contrast, no differences were observed in the rate of post-endoscopic retrograde cholangiopancreatography pancreatitis and number of days without organ failure (organ failure-free days).[53] Furthermore, there are scarce data on adverse events. Ung and colleagues reported an increase in leucocytes after heparin treatment and no differences in C-reactive protein and alanine aminotransferase concentrations.[51]

Of note, mixed findings appear for mortality rates and hospitalisation rates. For example, Patil and colleagues, Tozlu and colleagues, Lu and colleagues, and Jiao and colleagues reported a significant reduction in mortality rates and hospitalisation rates, whereas Chen and colleagues reported no changes in Acute Physiology And Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA), and Ranson scores. Similarly, Lu and colleagues and Jiao and colleagues reported a reduction in hospital stay or hospitalisation rates, respectively;[49,52] however, Patil and colleagues reported no differences.[47] Studies on heparin also revealed no reduction in the number of ICU admissions or number of days needed for relief from symptoms. In fact, Zhou and colleagues reported a greater number of ICU admissions with heparin-induced rapid reduction of triglycerides.[53] Lastly, the use of heparin for the treatment of hypertriglyceridaemia has been controversial due to a rebound in triglycerides and chylomicron concentrations after 4 days (starting as early as 4 h) of heparin.[54–56] Thus, heparin treatment has been recommended only when conventional or insulin therapy fails.[57] These data suggest that heparin treatment-induced benefits in some, but not all, factors related to acute pancreatitis resolution are potentially due to the anticoagulant and antithrombotic characteristics of heparin.[58] Therefore, the use of heparin in treating hypertriglyceridaemia-induced pancreatitis cannot be justified until adequately powered, placebo-controlled, double blinded, RCTs are conducted.

Intravenous insulin with glucose

Insulin is a known activator of lipoprotein lipase, and it lowers triglyceride concentrations by enhancing lipoprotein lipase activity.[59] However, insulin can also induce hypoglycaemia, therefore, glucose is infused simultaneously to maintain blood glucose levels. We emphasise that diabetic lipaemia (ie, marked hypertriglyceridaemia that results from insulin

deficiency in insulin-deficient diabetes) unquestionably should be treated with insulin and is not a topic of discussion here. To our knowledge, only one randomised parallel-design controlled clinical trial[60] has been conducted that evaluated the effect of insulin on hypertriglyceridaemia and disease-related factors (ie, mortality, number of days to reduce triglycerides <10 mmol/L, and adverse effects). Although insulin was able to successfully reduce triglycerides to lower than 10 mmol/L within 24 h, no meaningful differences were observed in mortality rates or the course of the disease. Berberich and colleagues reported a marked reduction in triglycerides with insulin therapy in patients with hyperglycaemia; however, this reduction was not different from conventional therapy (nil by mouth) in patients with normoglycaemia.[61] Three other studies that were conducted retrospectively also reported a significant reduction in triglycerides with insulin infusion.[60,62–64] Araz and colleagues reported a 44% reduction in plasma triglycerides but no differences in mortality risk (calculated using APACHE II scores), hospital stay (days), rates of respiratory failure, hypotension, or disease prognosis.[62] Frankova and colleagues also reported a reduction in triglycerides but no changes in hospital stay and mortality rates (calculated using bedside index for severity in acute pancreatitis [BISAP] scores).[64] Zhou and colleagues reported a rapid reduction in plasma triglycerides with insulin therapy; however, no differences were observed for organ failure-free days. Furthermore, the use of therapy for rapid reduction in triglycerides was associated with a greater number of ICU admissions. Moreover, compared with the diet-only group, a BISAP score of 2 or higher (an indicator of greater risk of mortality) was present in 13 (52·0%) of 25 individuals who received insulin or glucose therapy compared with 14 (23·7%) of 59 in the diet-only group. Lastly, Yu and colleagues compared two different modes of insulin infusion—ie, treatment that only infused insulin and treatment that infused insulin with glucose.[63] Both therapies reduced triglyceride levels by more than 60%; however, the infused insulin approach took 49 h to cause this reduction whereas the infused insulin with glucose approach took 72 h. Neither of these two therapies resulted in any difference in mortality rates, length of hospital stay, or the need for surgery. Moreover, 13 (30·2%) of 43 patients of the insulin with glucose group and 19 (41·3%) of 46 patients of the insulin group reported local complications post-therapy.

These data indicate that insulin therapy can only reduce triglycerides within 24–72 h of infusion when given alone or in combination with glucose, but does not reduce them rapidly.[65] It is noteworthy that four of five cited insulin treatment studies included some patients with diabetes, yet none of these studies showed benefits to hard health outcomes (ie, substantial health benefits). However, we acknowledge the necessity of insulin treatment in individuals with diabetes to control glycaemia. Based on the limited data presented here, despite more rapid reductions in triglyceride concentrations, no changes were observed in clinical outcomes associated with the disease resolution. Therefore, insulin therapy cannot be recommended in treating patients with hypertriglyceridaemia-induced acute pancreatitis but without diabetes.

Plasmapheresis

Plasmapheresis or plasma exchange can rapidly and physically remove triglycerides from the blood. Although studied extensively using retrospective data,[62–64,66–70] only two prospective randomised control trials were found in the literature.[60,71] Gubensek and colleagues compared plasma exchange with a control group, which received insulin therapy, and He and colleagues compared the effects of high-volume haemofiltration (HVHF) with heparin and insulin combined therapy (control). Although HVHF reduced plasma triglycerides to lower than 500 mg/dL (<5·6 mmol/L) within 9 h, plasma exchange was able to reduce the concentration to less than 10 mmol/L within 24 h. Despite these rapid reductions, both studies reported either no differences or worse results compared with control groups, let alone meaningful benefits to hard health outcomes. Gubensek and colleagues reported no differences between the groups for mortality rates, inflammatory markers such as C-reactive protein levels, or a severe course of pancreatitis.[60] Similarly, He and colleagues reported no differences between the groups for mortality risk (APACHE II scores), days in hospital, local pancreatic complications, or the need for surgery during treatments. Although inflammatory markers, such as C-reactive protein (four-fold) and procalcitonin (ten-fold) were significantly reduced, these reductions were no different from the control group. Moreover, in the HVHF group, 50% of the patients reported persistent organ failure, 44% with persistent respiratory failure, and 50% with severe acute pancreatitis, as opposed to the control group (20% for all). In three studies, Cao and colleagues, Wang and colleagues, and Zhou and colleagues reported no differences between plasmapheresis and conventional treatment regarding organ failure-free days or rate of organ failure resolution. Instead, these studies reported a higher number of ICU admissions in groups receiving plasmapheresis compared with conventional medical treatment.[53,72,73]

When compared with the aforementioned clinical trials, other retrospective analyses of plasma exchange therapy also reported a significant reduction in triglyceride concentrations.[62–64,66–70] Conflicting data were obtained when mortality rates and inflammatory

markers were assessed, with several studies reporting no differences.[68–70] Moreover, Araz and colleagues and Jin and colleagues reported patient fatalities despite reductions in plasma triglyceride levels.[62] Regarding the duration of hospital stay, no differences were noted, rather, apheresis was shown to prolong ICU stay compared with other treatments.[62,64] Of note, the lack of benefit to clinical outcomes remained unchanged even after double-filtration plasmapheresis, which sought to reduce triglycerides to lower concentrations.[74] Lastly, studies also reported cases of hypotension, tachycardia, intra-abdominal abscesses, and acute renal failure with plasmapheresis.[62,66] Although these data do support the use of plasmapheresis to rapidly achieve lower triglyceride levels, they do not show improved resolution of direct and indirect complications of acute pancreatitis and therefore cannot be recommended.

Combined therapies

Only one RCT used a combination of heparin and insulin, possibly to overcome several limitations observed with individual therapies.[71] While triglycerides were significantly reduced, no differences were observed in local pancreatic complications, surgical needs, mortality, prognosis, or the duration of hospitalisation.[71] In contrast to plasma exchange, a combination of heparin and insulin was reported to have more complications than benefits, except for the cost of the treatment. For example, in a retrospective observational study conducted by Jin and colleagues, persistent organ failure (43%) and mortality (10%) were reported despite a significant reduction in triglyceride levels. They also reported adverse events in 21% of their patients with no differences in inflammatory markers or APACHE II scores. These data do not support the notion of using multiple therapies to overcome individual challenges of acute pancreatitis.

Overall recommendations

Although we recognise the rationale for rapidly reducing plasma triglycerides in hypertriglyceridaemia-induced pancreatitis, it could also be argued theoretically that once pancreatic inflammation has been triggered, the rapidity of plasma triglyceride-lowering might no longer be an effective therapeutic strategy. Therefore, we emphasise that currently the most effective treatment approach is the prevention of hypertriglyceridemia-induced acute pancreatitis by treating marked hypertriglyceridaemia. Recent advances in the development of highly effective triglyceride-lowering therapies, such as apolipoprotein C-III and possibly ANGPTL3 inhibitors greatly improve the efficacy of our current therapeutic options. Based on our review of studies using heparin, insulin in patients without diabetes, plasmapheresis, or a combination of these, these strategies overall appear to lower triglycerides more rapidly than nil per mouth and supportive care, but do not reduce complications associated with acute pancreatitis or the rapidity of disease resolution. While some studies report specific benefits of each therapy, methodological issues and inconsistencies were observed between studies. Larger, randomised, well-controlled, clinical trials mostly revealed no differences in hard health outcomes of these therapies in disease resolution. Since these therapies increase the risk of off-target complications and raise medical care costs (requiring considerable nursing and other resources), we do not advocate their use at the present time, pending more convincing evidence from future research. However, we do acknowledge that there are instances in medicine in which specific therapies are not currently supported by RCT evidence, and yet the illness is one that poses extreme risk to the patient and the available therapy might not have been specifically tested in a subgroup of patients. Use of such therapy, in the absence of proven benefit, could be regarded as an unproven desperation measure in which there are no therapeutic alternatives. Although we do not wish to endorse unproven therapies, we acknowledge the need to leave a small opening for physician judgement in occasional specific instances, such as that of patients with proven familial chylomicronaemia syndrome during pregnancy, in the hope that future RCTs might show some benefit. Other therapies directed toward treating disease complications observed in the early stages of acute pancreatitis (similar to inflammation) should be targeted for future research.

Conclusion

In summary, hypertriglyceridaemia-induced acute pancreatitis is a complex inflammatory disease that requires immediate medical attention and supportive care. Current treatment options, including heparin, insulin (with glucose), and plasma exchange, do not provide hard health outcome-related benefits, aside from rapidly reducing elevated serum triglyceride concentrations. However, no prospective, double-masked, placebo-controlled, randomised studies have provided any evidence that rapid reduction in serum triglycerides can improve hard health-care outcomes in these patients. Although there is currently no convincing evidence showing the clinical effectiveness of intravenous insulin (with glucose in patients with normoglycaemia), heparin, and plasma exchange for the treatment of hypertriglyceridaemia-induced acute pancreatitis, we advocate for future adequately powered, prospective, double-blinded, placebo-controlled, randomised studies of these therapeutic modalities, with particular attention given to their effects on hard health-care outcomes. Lastly, since the mechanism of acute pancreatitis involves other systemic abnormalities affecting calcium homoeostasis, ATP production, endoplasmic reticulum stress, endothelial dysfunction,

Search strategy and selection criteria

References for this Personal View were identified from searches of PubMed for articles published from Jan 1973, to Dec 2024, using the term "acute pancreatitis" combined with: "heparin", "insulin", "plasmapheresis", "plasma exchange", "apheresis", or "hypertriglyceridemia". Articles lacking full texts in PubMed were requested from the University of Toronto Libraries Online Archives Collection. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English were included. A brief overview of these studies is presented in the appendix (pp 3–5).

microvascular damage, mitochondrial dysfunction, systemic inflammation, and tissue necrosis in addition to hypertriglyceridaemia, treatment options should include nil by mouth and supportive care. Experimental strategies that potentially regulate calcium homoeostasis, mitochondrial function, endothelial and vascular repair, and systemic inflammation are being tested.

Contributors

MMS-A was responsible for data curation, formal analysis, funding acquisition, investigation, methodology, visualisation, writing the original draft, and reviewing and editing the manuscript. LT wrote, reviewed, and edited the manuscript. RAH was responsible for conceptualisation, methodology, validation, and writing, reviewing, and editing the manuscript. GFL was responsible for conceptualisation, funding acquisition, investigation, methodology, software use, supervision, validation, and writing, reviewing, and editing the manuscript.

Declaration of interests

RAH received consulting fees from Amgen, Arrowhead, Ionis, Novartis, Pfizer, Sanofi, and UltraGenyx; and payment or honoraria from Amgen, HLS Pharma, Novartis, and Pfizer. GFL received consulting fees from Amgen. MMS-A and LT declare no competing interests.

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