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REVIEW ARTICLE

Mechanisms linking hypertriglyceridemia to acute pancreatitis

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Abstract

Hypertriglyceridemia (HTG) is a metabolic disorder, defined when serum or plasma triglyceride concentration (seTG) is >1.7 mM. HTG can be categorized as mild to very severe groups based on the seTG value. The risk of acute pancreatitis (AP), a serious disease with high mortality and without specific therapy, increases with the degree of HTG. Furthermore, even mild or moderate HTG aggravates AP initiated by other important etiological factors, including alcohol or bile stone. This review briefly summarizes the pathophysiology of HTG, the epidemiology of HTG-induced AP and the clinically observed effects of HTG on the outcomes of AP. Our main focus is to discuss the pathophysiological mechanisms linking HTG to AP. HTG is accompanied by an increased serum fatty acid (FA) concentration, and experimental results have demonstrated that these FAs have the most prominent role in causing the consequences of HTG during AP. FAs inhibit mitochondrial complexes in pancreatic acinar cells, induce pathological elevation of intracellular Ca^{2+} concentration, cytokine release and tissue injury, and reduce the function of pancreatic ducts. Furthermore, high FA concentrations can induce respiratory, kidney, and cardiovascular failure in AP. All these effects may contribute to the observed increased AP severity and frequent organ failure in patients. Importantly, experimental results suggest that the reduction of FA production by lipase inhibitors can open up new therapeutic options of AP. Overall, investigating the pathophysiology of HTG-induced AP or AP in the presence of HTG and determining possible treatments are needed.

KEYWORDS
acute pancreatitis, fatty acid, hypertriglyceridemia

1 | INTRODUCTION

Triglycerides (TGs) are essential for efficiently storing excess energy. Whenever an excess of nutrients is present, this energy is stored as TG, regardless of whether the nutrient is carbohydrate, protein, or fat. TGs are transported in the circulation by chylomicrons (CMs), which carry exogenous dietary fat from the small intestine, and very low-density lipoproteins (VLDLs), which contain endogenous liver-related lipids.[1] The general amount of circulating fat depends on the balance between the endogenous and exogenous lipid production and the lipolytic removal of lipoproteins and their remnants.

Dietary fat is predominantly composed of TGs. These TGs are digested by lipases to mainly glycerol and fatty acids (FAs). FAs have different carbon chain lengths and are categorized based on the extent of saturation (Figure 1). The most prevalent saturated FAs include palmitic and stearic acids. Among monounsaturated FAs which contain only one double-bond oleic acid, and polyunsaturated FAs (two or more double bonds), linoleic acid (LA) is the most prevalent.

In the first part of this review, we will cover the pathophysiology of hypertriglyceridemia (HTG), which is a common form of dyslipidemia that is characterized by elevated (>1.7 mM) fasting plasma/serum triglyceride concentrations (seTGs). Interestingly, HTG can not only cause acute pancreatitis (AP) but can also modify its severity. Our main focus is to reveal the relationship between HTG and AP. The review will connect the current knowledge about the effects of HTG on the initiation and severity of AP with a focus on clinically relevant pathomechanisms. We will discuss evidence on how pancreatic lipase may play a significant role in AP. Furthermore, AP-related cellular mechanisms during HTG will be presented, including mitochondrial injury, Ca^{2+} signaling, endoplasmic reticulum (ER) stress, and impaired autophagy. We will emphasize the pathophysiological relevance of TG-derived FAs, the significance of FA types (saturated/unsaturated), and the possible AP-related therapeutic targets during HTG. The literature was screened by using the following terms in PubMed (two different searches): (a) acute pancreatitis AND (hypertriglyceridemia OR "fatty acid") and (b) hypertriglyceridemia AND (acute pancreatitis OR "fatty acid" OR lipids). Relevant publications and their references were checked.

2 | PATHOPHYSIOLOGY OF HTG

Depending on the degree of seTG elevation, the Endocrine Society defines HTG as mild (1.7–2.3 mM), moderate (2.3–11.3 mM), severe (11.3–22.6 mM), or very severe (>22.6 mM).[2] Independent of the degree of elevation, HTG resembles a metabolic disorder with both genetic and lifestyle factors playing significant roles in its pathophysiology. Basic pathophysiological views of HTG as well as certain genetic determinants, risk factors, and associated conditions are described below.

Regardless of their origin, the key component of lipolytic removal of circulating TG-rich lipoproteins is the lipoprotein lipase (LPL). LPL is predominantly synthesized in

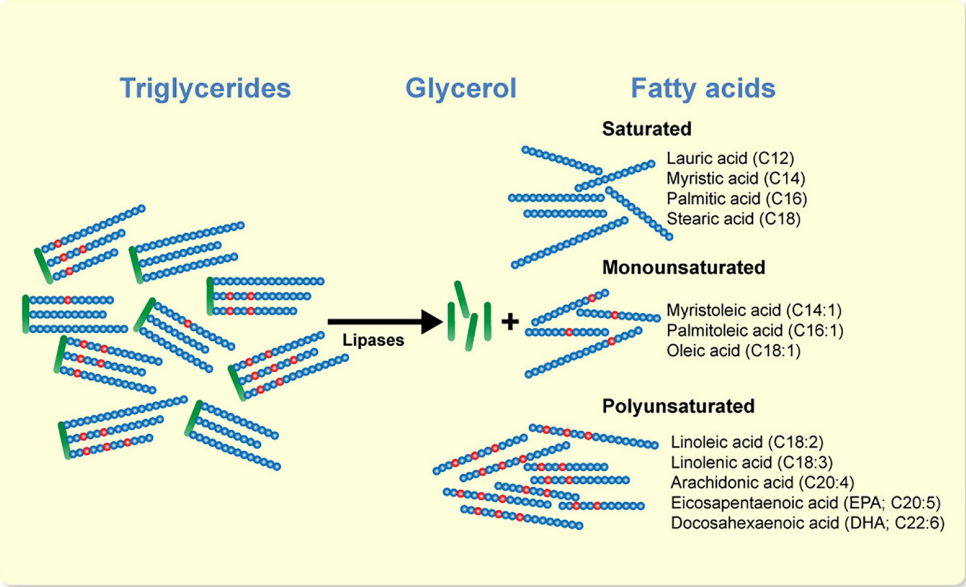

FIGURE 1 Hydrolysis of triglycerides (TGs). TGs can be hydrolyzed to glycerol and fatty acids (FAs) by lipases (e.g., pancreatic, hepatic, and hormone-sensitive lipases). FAs can be categorized as saturated, monounsaturated, and polyunsaturated based on their saturation level (some examples of FAs are shown).

adipocytes and myocytes as an immature protein. Lipase maturation factor 1 (LMF1) promotes its maturation which is then secreted in the interstitial space, transported transendothelially, and finally bound to its anchoring protein, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), on the luminal surface of the endothelium. The LPL binds to circulating TG-rich lipoproteins and hydrolyzes TG.[3] The activity of LPL is regulated by various apolipoproteins (APOs) and angiopoietin-like proteins (ANGOTLs). Among these, APOC2, APOC3, APOA5, APOE, and ANGPTL3, ANGPTL4, and ANGPTL8 are worthy to be mentioned. Whereas APOC2 is an essential cofactor for LPL activity, APOC3 is believed to inhibit LPL activity. APOA5 is believed to play a crucial role in stabilizing the LPL–lipoprotein complex. APOE is a critical ligand activating the hepatic clearance of TG-rich lipoproteins.[4,5] ANGPTLs mostly inhibit LPL activity, either in paracrine or endocrine ways, and seem to be regulated by systemic nutritional, metabolic, and endocrine factors.[5] Therefore, the general amount of circulating fat depends on the balance between endogenous and exogenous lipid production and the lipolytic removal of endogenous and exogenous lipoproteins and their remnants.

Primary (genetic) and secondary (acquired, see Table 1) factors can cause elevated seTG, and these factors coexist in most patients with severely elevated seTG.

2.1 | Primary factors

Polygenic and monogenetic determinants are present among patients with severe HTG. However, polygenetic determinants are much more common than monogenic ones.[6] Only a very small subset of patients have a rare form of monogenetic HTG called familial chylomicronemia syndrome (FCS). FCS resembles an autosomal recessive disorder characterized by homozygous or compound heterozygous variants in one of five canonical FCS genes (LPL, APOC2, APOA5, LMF1, and GPIHBP1) leading to non-function or low function of LPL.[7]

However, most HTG cases are polygenic in nature. Here, several genetic factors contribute to the susceptibility toward HTG, including rare heterozygous variants in the abovementioned canonical TG genes, and/or accumulated common variants associated with elevated TG levels, and/or variants in non-canonical TG genes.[8–10] The polygenic HTG is mostly a clustering of multiple gene variants.

2.2 | Secondary factors

Almost all patients with severe HTG have a genetic predisposition and an additional condition or factor known to raise seTG (secondary factor). This is often referred to as multifactorial HTG or multifactorial chylomicronemia syndrome and represents the most common form of severe HTG.

Secondary factors aggravating impaired TG metabolism include a fat- and simple carbohydrate-rich diet, reduced activity levels, obesity, metabolic syndrome, alcohol intake, TG-increasing medications, chronic renal disease, and uncontrolled diabetes.[11–13] Among these patients, CM and VLDL are increased in the circulation due to LPL activity impairment and hepatic overproduction of VLDLs and their reduced clearance. Furthermore, demographic and sociocultural factors have significant effects.[14] In very rare cases, severe HTG is also observed as a result of autoimmune hyperlipidemia (e.g., anti-GPIHBP1 antibodies in patients with lupus erythematosus) or multiple myeloma.[15] Table 1 shows acquired conditions and factors known to increase the risk of HTG.

The significance of insulin-resistant conditions must be stressed. These conditions mainly include (visceral) obesity, metabolic syndrome, and type 2 diabetes mellitus.[16] However, it is also present in pregnancy, chronic renal failure, human immunodeficiency virus infection, hepatocellular disease, and chronic inflammatory diseases. In these insulin-resistant states, HTG is believed to be due to TG-rich lipoprotein overproduction as a result of the increased release of free FAs (FFAs) from the adipose tissue, enhanced hepatic lipogenesis, and increased TG-rich lipoprotein secretion by the liver and intestine.[17] LPL activity is known to be decreased in insulin-deficient states.[18] However, recent data on LPL regulation have also shown that insulin resistance leads to increased APOC3 and ANGPTL4, thereby reducing LPL activity and remnant clearance.[19,20] The effect of obesity on TG metabolism is believed to be more strongly related to visceral obesity than to total adiposity.

Alcohol consumption is another prominent cause of secondary HTG. Alcohol is known to stimulate VLDL secretion through enhanced production, combined with an increased hepatic delivery of FFAs as a result of increased lipolysis in adipose tissue and decreased LPL activity.[21,22]

3 | AP

AP is a potentially fatal gastrointestinal disease that requires emergency hospitalization. The etiology of AP is mostly related to massive alcohol consumption or biliary disease. The third or fourth (depending on regions) leading cause of AP is HTG, which will be referred to as HTG-induced AP (HTG-AP). Less frequent causes of AP include post-endoscopic retrograde cholangiopancreatography, drugs, hypercalcemia, or mutations in certain

TABLE 1 Important secondary factors/conditions contributing to severe HTG

Insulin-resistant conditions, including: • Type 2 diabetes mellitus • (Visceral) obesity • Metabolic syndrome
Excessive alcohol intake
Diet with excess calories, high glycemic load, and/or sucrose- or fructose-containing beverages and/or high oral fat intake
Chronic renal disease
Hypothyroidism
Multiple myeloma
Systemic lupus erythematosus
TG-increasing medications, including: • Glucocorticoids • Beta-blockers • Thiazide diuretics • Bile acid sequestrants • Certain antineoplastic agents (cyclophosphamide and L-asparaginase) • Certain immunosuppressants (e.g., cyclosporine and mechanistic target of rapamycin kinase inhibitors, such as everolimus and sirolimus) • Tamoxifen, raloxifene, and clomiphene • Retinoic acid derivatives: isotretinoin, acitretin, and bexarotene • Second-generation antipsychotic medications, such as clozapine and olanzapine • Antiretroviral regimens, particularly for human immunodeficiency virus

genes (e.g., cationic trypsinogen [*PRSS1* gene] and serine protease inhibitor Kazal type 1 [*SPINK1*]).

Interestingly, several causes of AP seem to have no consistent relation to clinically relevant parameters of AP severity, except for HTG-AP, where different clinical and basic evidences support that HTG worsens AP severity. Most experimental AP models (e.g., caerulein, or bile acid infusion) study how these agents initiate or perpetuate signaling in the exocrine pancreas and often focus on local (autophagy and necrosis) or intermediary endpoints, including inflammatory cell infiltration or cytokine elevation. However, the severity of clinical AP is strongly related to organ failure (discussed below). We will therefore cover how HTG-AP may be initiated and how TGs make pancreatitis severe.

According to the Revised Atlanta Classification, the severity of AP can be mild, moderately severe, and severe.[23] Patients with mild AP have no organ failure. The presence of transient (<48 h) or persistent (>48 h) organ failure determines the moderately severe and severe groups, respectively. Most of the mortality happens in the severe group. Unfortunately, there is no specific treatment for the disease, and only supportive care with fluid resuscitation, pain control, and nutrition are available.

Long-term consequences can also develop because of AP. Fluid collections, including pseudocyst or walled-off necrosis, may be observed in the pancreas or peripancreatic region.[23] These conditions appear more than 4 weeks after the onset of AP in a subset of patients. AP can progress to recurrent AP and/or chronic pancreatitis which increases the risk of pancreatic cancer.[24] Further sequelae of AP is endocrine dysfunction, which manifests as post-pancreatitis diabetes mellitus.[25] Exocrine dysfunction is another significant consequence of AP, which may lead to exocrine pancreatic insufficiency.[25]

4 | HTG-INDUCED AP

HTG-AP is unique and can have several causes. Moreover, it may be a risk factor for severe AP. Overall, it is widely accepted that seTG ≥11.3 mM defines HTG-AP.[26] However, some authors define HTG-AP when seTG is >5.6 mM[27] or >5.6 mM with lactescent serum presentation in the absence of other causes of AP.[28] Here, we will examine the evidence of HTG-AP as an AP etiology in relation to TG levels in different populations and patient demographics, along with HTG-AP-associated geographic and temporal patterns.

4.1 | Demographics

The age of presentation of patients with HTG-AP is typically 10–15 years younger than that of other etiologies. Males comprise two-third of patients with HTG-AP compared with approximately 50% for other AP etiologies. Furthermore, patients with HTG-AP may have higher body mass indexes (BMIs) than those due to other etiologies.[29,30] This is likely because the prevalence and severity of HTG increase with BMI, as previously discussed. The first and largest systematic review on the impact of age and sex on HTG-AP examined 34 studies (including 23 case series and 11 case–control studies) from 15 countries with a total of 1340 cases[27] with HTG-AP.[27] The results showed that the average age of presentation of patients with HTG-AP was 42 years, with two-third of patients being males.[27] Similar results were reported in subsequent multinational studies. For example, a study from the Hungarian Pancreatic Study Group conducted between 2012 and 2017, with 219 patients with HTG-AP, reported that more than 80% of patients with AP with seTGs of >5.6 mM were males.[30] Moreover, the peak prevalence of HTG-AP in males occurred in the 30–50-year-old age group, and after which, the proportion of males and

females with HTG-AP became similar. Another study by the APPRENTICE consortium including 22 international centers conducted between 2015 and 2018 with 69 patients with HTG-AP showed that 67% of the patients were males with an average age of 40 years.[29] In contrast, males contributed to approximately 50% of AP from other etiologies, wherein their average age were 10 years higher than in HTG-AP group. Similarly, a recent large study from China[31] conducted between 2016 and 2020 with 614 patients with HTG-AP reported that approximately 70% of the patients were males and the average age of presentation was in the mid-40s. Again, the age of presentation with non–HTG-AP was significantly higher, with an average of 60 years and males comprising 43%–52% of the non–HTG-AP group. Overall, the typical age of presentation of patients with HTG-AP is young to middle-aged and males are more exposed than females.

4.2 | Relationship of HTG-induced AP to seTGs

The initial clinical course of HTG-AP and the diagnostic criteria for the disease are similar to other AP etiologies. There is no international guideline that defines the HTG concentration threshold that induces AP; however, the risk of disease development progressively increases with increasing seTG. When seTG exceeds 11.3 mM, the risk of AP is approximately 5%, and this risk increases to 10%–20% when the seTG is >22.6 mM.[32]

The risk of HTG-AP in relation to seTGs depends on whether these are collected in a fasted or fed state. In a prospective Danish population-based study of 116 550 individuals over 6.7 years,[33] the multivariate hazard ratio of AP significantly increased with non-fasting mild-to-moderate HTG. Compared with seTGs of <1 mM, patients with seTGs of 2–4.1 mM had a hazard ratio of 2.3 (95% confidence interval [CI]: 1.3–4.0). The hazard ratio increased to 8.7 (CI: 3.7–20.0) for seTGs of >5 mM, with this translating to 12 AP episodes/10000 person-years.[33] In a follow-up study from the same geographic area, with a fixed cut-off set at >10 mM, 75 of the 2146 (3.5%) patients developed pancreatitis over a 12-year period (2008–2019), resulting in a risk of 29/10000 person-years.[34] Interestingly, fasting HTG has a higher risk for AP for similar seTGs. For example, in 5550 patients with fasting seTGs of >11.3 mM followed for 1 year, 301 (5.4%) developed pancreatitis,[35] resulting in a rate of 542/10000 person-years. At this point, it is important to realize that biochemically, TGs form 90% of CMs, which are increased in the non-fasted state. However, TGs typically form 50% of VLDLs, which are synthesized by the liver,[36] and thus are a smaller proportion than in CMs, particularly in the fasted state. This, along with the higher mean HTG levels (approximately equal to 16 and 28.25 mM reported in two different studies), may explain the higher HTG-AP risk (>2000/10000 person-years) noted in FCS.[37,38] As previously discussed, APOs and ANGPTLs regulate the LPL pathway, and certain variants of these genes can increase seTG. In a one-sample Mendelian randomization analysis, variants of *LPL, APOA5, APOC3, ANGPTL3*, and *ANGPTL4* genes were used as markers of seTG, and these were associated with elevated seTG, which increased the risk of AP development.[39] Other two Mendelian randomization studies also supported the causal association of HTG with the increased risk of AP.[40,41] Interestingly, a study by Yuan et al. reported a more profound relationship between moderate HTG and chronic pancreatitis.[40]

4.3 | Changes in HTG-induced AP patterns with time

Over the last few decades, the proportion of HTG-AP has increased. This is based on the finding that the temporal changes in HTG-AP come in populations from the same geographic area. While studies from Africa,[42] Asia,[43–47] and Central and South America[48,49] reported that the proportion of HTG-AP among other AP etiologies come from different centers and are largely after year 2000, some studies from Europe and North America come from the same area or span long periods. For example, a study using the Danish nationwide health registry data reported an increase in HTG-AP from 0.7/100000 person-years in 2008 to 1.7/100000 person-years in 2019.[34] Similarly, two reports from the University of Pittsburgh showed that HTG-AP significantly increased from 12 of 401 patients with AP (3.0%) in 1996–2005[50] to 25 of 400 patients with AP (6.3%) in 2003–2014 ($p = 0.03$).[51] Other studies from Europe and North America supported these trends, with four studies (approximately equal to 4100 patients) initiated before the year 2000 reported that HTG-AP accounts for only 1%–3% of all AP cases,[50,52–54] whereas six studies initiated after the year 2000 (approximately equal to 4100 patients) showed HTG-AP rates of 2.3%–7.7%.[30,51,55–58] Interestingly, a recent systematic review also showed an increase in all causes of AP in Europe and North America[59] over time, whereas the incidence in Asia and South America remained stable. The exact reasons for these trends in the west remain unknown. Potential explanations include an increase in unsaturation of the western diet over the later part of the 20th century[60] with a corresponding increase in unsaturated FAs in fat stores[61] or perhaps a parallel increase in common risk factors of both HTG and AP, including obesity[29,30] and diabetes mellitus.[62,63]

4.4 | Serum TG-lowering therapies in HTG-induced AP

The initial treatment of HTG-AP is similar to that of other AP etiologies (e.g., aggressive intravenous hydration, pain control, and consideration of early enteral nutrition). Additionally, the management of patients with HTG-AP includes acute seTG-lowering treatment. Intravenous insulin and/or heparin or plasmapheresis are utilized to reach a seTG of <5.6 mM.[64–66] Insulin and heparin enhance LPL activity, which is present in endothelial cells, and this effect leads to seTG hydrolysis and subsequent seTG reduction in a matter of days. Moreover, insulin is present endogenously and participates in fat metabolism. Importantly, it enhances the uptake of FAs in adipocytes, muscles, and livers. Therefore, it not only reduces the seTG but also the serum FA concentrations.[67] Plasmapheresis can rapidly reduce seTG[68]; however, some studies demonstrated that it does not lead to improved outcomes compared with treatments with insulin or heparin.[69,70] For further details on the acute treatment of HTG-AP, please check some recent reviews on this topic.[64–66]

A long-term management of HTG is very important to prevent pancreatitis development. Well-known HTG treatment strategies include the use of fibrates and long-chain omega-3 FAs in addition to dietary measurements and strict alcohol abstinence. Novel TG-lowering molecular therapies are also currently investigated in clinical trials and can be highly effective in severe HTG (e.g., FCS) and seTG of >5.6 mM, which reduces the risk of AP development.[71] These therapies include ANGPLT3 and APOC3 inhibitors via monoclonal antibodies, antisense oligonucleotides, and small interfering RNA silencers.[72,73] ANGPLT3 inhibition reduces both serum cholesterol and TG concentrations, whereas APOC3 inhibition affects only seTG. In case of LPL deficiency, gene delivery via adeno-associated virus can also be effective.[37] In the future, it would be interesting to investigate the potential use of these novel drugs during the acute phase of HTG-AP with insulin and/or heparin.

5 | CLINICAL COURSE OF AP WITH ELEVATED SETG AND HTG-INDUCED AP

SeTG is not only related to the initiation of AP but also affects its course, even in cases of non-HTG-AP. The risk of organ failure and severity increases with elevated seTG. Zhang et al[43] proposed that seTG at a 2.06-mM cut-off threshold value measured 3–4 days after admission can be an accurate predictor of severe AP development. Both Nawaz et al[51] and Wan et al[44] presented that HTG is independently and proportionally correlated with persistent organ failure and admission to intensive care unit apart from AP etiology.[38] The incidence of severe AP increased in patients with elevated seTG. Additionally, several studies found that the risk of organ failure or severe AP increases with elevated seTG.[45,57,74–78] Furthermore, the ratio of seTG measured at 48 h and admission (0 h) can predict AP severity, indicating the direct relationship between seTG and disease outcome.[79] With respect to AP etiology, Goyal et al[80] observed that HTG-AP severity is higher and causes more complications than that in alcoholic AP. When HTG-AP was compared with biliary AP,[81] respiratory distress syndrome, acute kidney injury, deep venous thrombosis, and multiple organ dysfunction were more frequent in the earlier AP group. Interestingly, infected pancreatic necrosis was typical for biliary AP.[81] Moreover, severe HTG-AP was associated with diabetes mellitus, and HTG-AP is a predictor for recurrent AP.[82] Therefore, the impact of seTG on AP from different etiologies and long-term outcomes require more work.

Interestingly, a few clinical studies could not find correlations between seTG and AP severity. Balchandra et al[83] presented that seTG did not correlate with pancreatic complications or the APACHE II score. Another research group reported two distinct results.[29,84] Their first international and multicenter prospective cohort did not show a relationship between seTG and AP severity,[29] whereas their further international multicenter cohort did.[84]

Furthermore, the published data are heterogenous regarding the impact of seTG on mortality in AP. In most studies, no correlation between mortality and seTG was found,[51,57,74] whereas some studies found an association between these parameters.[45,84] However, the low AP-associated mortality should be interpreted with caution due to small number of involved patients.

Recently, three meta-analyses of clinical data investigated the relationship between HTG and AP.[85–87] Our previous study[87] showed that even a seTG of 1.7–11.3 mM increases AP severity and the risk of persistent organ failure compared with a normal seTG. Moreover, a significant difference in AP severity was noted when seTGs of <5.6 versus >5.6 and <11.3 versus >11.3 mM were compared with each other. Regardless of AP etiology, higher seTGs increased the disease severity, mortality, and the risk of intensive care unit admission. Wang et al[85] compared the outcomes of AP in the following two groups: TG-related and non-TG-related AP; they reported that elevated seTG increased the occurrence of renal failure, respiratory failure, shock, mortality, systemic inflammatory response, and APACHE II scores compared with non-HTG-related AP. Similarly, Bálint et al[86] investigated how different etiologies affect the course of AP and showed that severe AP, moderately severe AP, pulmonary failure, and mortality

are more frequent in HTG-AP than those in other etiological groups. Therefore, clinical studies strongly support that the risk of severe AP increases with the elevation of seTG. The mechanisms by which this may occur are described below.

5.1 | Other important factors that can affect the clinical course of AP during HTG

Excess alcohol consumption and HTG frequently interact to cause AP. Alcohol intake results in elevated seTG and increased FFA release.[88] Moreover, it should be noted that the effects of alcohol and HTG on exocrine pancreatic cells are similar. These adverse effects are presumptively due to increased FFA levels, which will be discussed later in detail. Furthermore, ethanol exerts several toxic responses in pancreatic cells, such as affecting calcium signaling and zymogen secretion, impairing autophagy and cellular regeneration, evoking the unfolded protein response, and damaging mitochondrial membrane integrity. Ethanol is metabolized via oxidative and non-oxidative pathways, which all cause pancreatic damage. In pancreatic acinar cells, the non-oxidative pathway is more prominent.[88] FA ethyl esters, the non-oxidative metabolites of ethanol, have marked adverse effects on the pancreas (toxic sustained intracellular Ca^{2+} elevation and mitochondrial dysfunction). The inhibition of non-oxidative ethanol metabolism reduced acinar cell toxicity and the ethanol-induced AP severity.[89,90]

HTG is often accompanied by an increased waist circumference, which is termed as hypertriglyceridemic waist phenotype. This phenotype is associated with an increased risk of AP and non-alcoholic fatty liver disease (NAFLD).[91–94] There is clinical evidence based on a meta-analysis that the risk of severe AP may be higher in patients with NAFLD.[95] The mechanism of this relationship can be explained by the decreased albumin production in the liver due to NAFLD. Albumin binds FAs in the serum[96] and decreased albumin levels can lead to increased FFA concentration, which is responsible for different detrimental effects and may aggravate AP during NAFLD. In fatty liver diseases, the production of serum alpha-1-antitrypsin is also decreased.[97] This inhibitor has a protective role during AP regardless of the disease etiology; therefore, fatty liver disease may directly aggravate AP severity.

Diabetes mellitus often causes HTG and gallstone disease, which are both etiological factors for AP. Furthermore, Li et al. described that diabetes mellitus is an independent risk factor for HTG-AP development.[98] A meta-analysis demonstrated that the presence of diabetes mellitus during AP increases the risk of complications, including renal failure and intensive care unit admission.[99] Interestingly, no significant differences were found in cardiovascular, neurological, and respiratory complications. In a recent large international prospective study, no significant relationship was found between AP severity and preexisting diabetes mellitus.[100] The cause of these discrepancies should be clarified, and the exact effect of diabetes on HTG-AP needs to be elucidated.

5.2 | Contribution of HTG on the long-term sequelae of AP

Studies reported that the group of AP with severe HTG was readmitted more frequently than the non- or mild HTG groups.[101] This indicates that HTG-AP increases the risk of recurrent AP attacks more than other etiologies.[82,86,101] Additionally, recurrent AP can lead to the development of chronic pancreatitis; therefore, HTG-AP can contribute to the development of chronic pancreatitis. Pseudocyst and walled-off necrosis are also late complications of AP. In a meta-analysis, three articles were included to investigate and compare the effects of HTG-AP and biliary AP on pseudocyst formation.[86] The results showed no significant effect of these etiological factors. Jiang et al. compared patients with AP with or without HTG and found that pseudocyst formation was significantly more frequent in AP group with HTG.[78] Although diabetes and pancreatic insufficiency are also significant AP consequences, there is a knowledge gap regarding how HTG affects the incidence of these sequelae, which is necessary to reveal in the future.

6 | MECHANISMS ON HOW HTG INDUCES OR AGGRAVATES AP

The following are the two main theories on how HTG initiates and/or aggravates AP: via (a) the release of FFAs during excess hydrolysis of TGs by lipases and (b) the increased blood viscosity in HTG. Regarding the first theory, it was previously shown that perfusion of an ex vivo-isolated pancreas with unsaturated TGs caused a large increase in serum FAs, with the pancreas becoming oedematous and hemorrhagic.[102] This occurred faster with oleic acid perfusion. However, mineral oil, which is viscous, did not cause the abovementioned changes.[102] Moreover, it was demonstrated that TG administration into the pancreas perfusate causes dose-dependent elevation of serum amylase and lipase activities during AP,[103] which can lead to further TG hydrolysis and FFA release. Recent studies[104,105] wherein TG was delivered directly into the pancreas also showed hemorrhage and an increase in serum FA concentrations,

which were prevented by inhibiting lipolysis (Figure 2). These results strongly support TG lipolysis to underlie the severe AP phenotype observed during HTG.

Another theory regarding the mechanism of HTG, which increases disease severity, focuses on plasma hyperviscosity (Figure 2).[102,103,106] The high seTG increases blood viscosity, reduces tissue microcirculation, and leads to brain or cardiovascular system ischemia.[107,108] Furthermore, hyperviscosity can cause pancreatic ischemia leading to cellular acidosis.[109] The acidosis may increase the potential for trypsinogen activation by cathepsin B[109] and initiate or aggravate inflammation. However, the risk of pancreatitis in hyperviscosity syndromes is low. A detailed examination of the two common causes of hyperviscosity that is, hypergammaglobulinemia and polycythemia support this. For example, while a PubMed search of "hypergammaglobulinemia" retrieves >7300 articles, adding "pancreatitis" to it reduces the search results to 130 articles. Among these, the few reports we found on pancreatitis associate autoimmune pancreatitis with hypergammaglobulinemia. Excluding "autoimmune" and "IgG4" reduces this to 22 reviews and reports of pancreatic involvement by the tumor-associated with hyperglobulinemia, and no clear association with pancreatitis. Similarly, literature searches do not show evidence of "polycythaemia" leading to "pancreatitis," since the case reports retrieved on PubMed using these search terms showed polycythaemia to follow pancreatitis,[110] local vascular complications from pancreatitis,[111,112] and share common risk factors, including obesity hypoventilation syndrome.[113] Moreover, the inability of mineral oil to reproduce the deleterious effects of TG and FFA in the abovementioned ex vivo studies reduced the likelihood of viscosity contributing to HTG-AP.

Based on these theories, the production of FFAs from TGs by lipases presumably aggravates or induces AP. In Sections 6.1.1 and 6.1.2, how pancreatic lipases may be released from acinar cells into the pancreatic parenchyma and counteract with pancreatic adipocytes, wherein the process results in increased FFA levels in the pancreas and blood, will be presented. Subsequently, the detailed mechanisms of FFA actions (Section 6.2) on pancreatic cells (acinar and ductal) and different organs will be discussed. Moreover, the roles of unsaturated and saturated FAs during AP will be highlighted.

6.1 | How TG may be exposed to pancreatic lipase

6.1.1 | Redirection of pancreatic acinar exocytosis to the basolateral side during AP

As pancreatic lipase seems to play a central role in the production of toxic unsaturated FAs, how it interacts with TG-containing CMs or VLDLs remains unclear. During

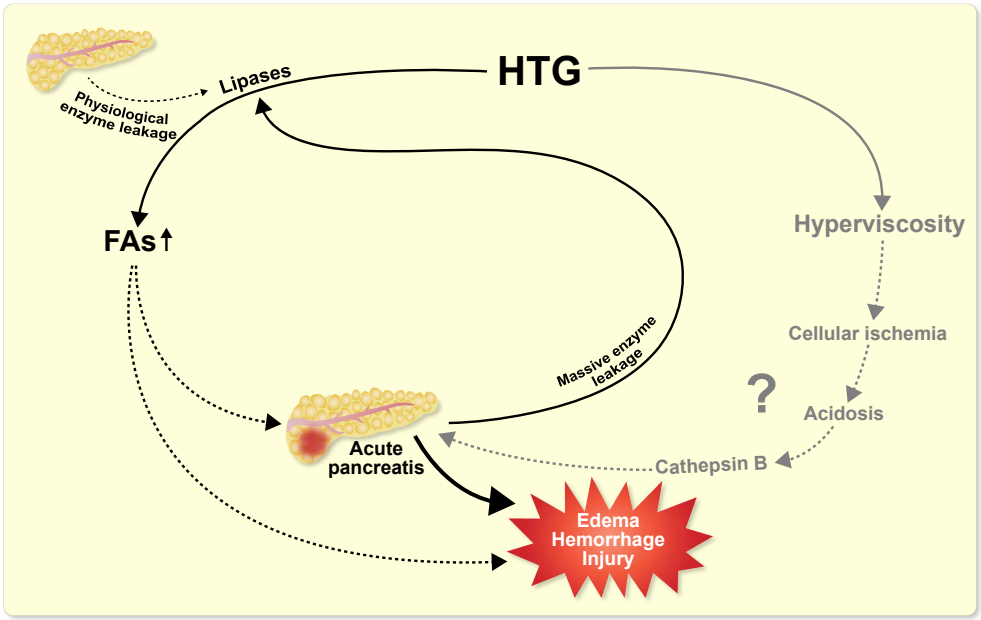

FIGURE 2 The possible mechanism of hypertriglyceridemia (HTG)-induced pancreatic injury. There are two theories on how HTG results in acute pancreatitis (AP) or aggravates this disease: (A) the release of FAs during excess hydrolysis of TGs by lipases (black text) and (B) the increased blood viscosity in HTG (gray text). FAs can induce AP and aggravate AP-related tissue injury. The role of HTG-induced hyperviscosity is questionable. Theoretically, it could contribute to HTG-related adverse effects; however, experimental data using mineral oil and hyperviscosity syndromes do not support this hypothesis. FAs, fatty acids; HTG, hypertriglyceridemia.

physiological conditions, pancreatic acinar cells release lipase into the ductal lumen through their apical membrane. In this case, the enzyme cannot interact with TG in the serum or adipocytes in the pancreatic parenchyma. However, the exocytosis of zymogen granules is redirected in pathophysiological conditions. Scheele et al[114] indirectly showed that exocytosis can occur in the basolateral side of the cells during stimulation of guinea pigs or rats with a supramaximal dose of the cholecystokinin (CCK) analog, caerulein (5 μg/kg/h), or the acetylcholine receptor agonist, carbamylcholine (5 μmol/kg/h). After stimulation, the intraductal release of amylase decreased, whereas the serum amylase activity increased. In vitro studies on isolated pancreatic acinar cells showed that the administration of supramaximal concentration of 10-nM caerulein reorganizes the acinar actin cytoskeleton, which may change the secretory response or the site of exocytosis[115] perhaps due to vacuole fusion with the basolateral membrane (Figure 3). Furthermore, it has been shown that the normal apical enrichment of filamentous actin in the pancreatic acini changes to a more basolateral location under supramaximal states.[116] This, along with the increased myosin-II phosphorylation, results in the contraction of the basolaterally enriched cytoskeleton with consequent formation of large plasma membrane blebs.[116,117] While such blebs are reversible in the early state, their rupture may lead to the basolateral release of zymogen granules under periods of sustained stimulation.[118] The mechanisms linking stimulation with supramaximal caerulein to actin reorganization include the activation of Src family tyrosine kinases, among which Yes and c-Src are present in pancreatic acinar cells.[119,120] This can cause the phosphorylation of cortactin, which has been shown to be responsible for actin reorganization.[119] Therefore, a potential mechanism to explain the basolateral leakage of pancreatic enzymes from the pancreatic acini includes Src-mediated cortactin phosphorylation, which together with myosin-II phosphorylation can mediate the actin rearrangement and consequently deleterious basolateral blebbing.

Various protein kinase C (PKC) isoforms play a prominent role in the regulation of events, including zymogen granule release from acinar cells. It has been described that the physiological stimulation of PKCδ mediates amylase secretion through the apical membrane (Figure 3). However, under pathophysiological stimulation, PKCα activation redirects exocytosis to the basolateral membrane, and PKCδ and ε activation initiate the generation of inflammatory mediators via the nuclear factor-κB pathway.[121]

Another important participant in the process of zymogen exocytosis is the family of SNARE proteins, which are responsible for membrane bridging and intracellular membrane fusions.[122–125] Among them, acinar cells express the syntaxin-4. The membrane bridging function of syntaxin-4 with zymogen granules at the basolateral membrane of pancreatic acinar cells is inhibited by Munc18c protein. Munc18c is one of the targets of PKC. Previous studies demonstrated that PKC activation by supramaximal CCK, submaximal CCK with 20 mM ethanol, or TG leads to Munc18c phosphorylation.[126–128] This will release Munc18c from syntaxin-4, which can bridge the zymogen granules and plasma membrane and promote basolateral zymogen exocytosis.

6.1.2 | AP triggers TG or FFA release from pancreatic adipocytes

During AP, regardless of etiology (e.g., biliary, alcoholic, or HTG), TG-containing pancreatic and peripancreatic adipocytes are also affected. Basolaterally secreted pancreatic enzymes can interact with or damage pancreatic adipocytes. It was shown that pancreatic adipocytes that necrosed during pancreatitis contain the enzyme pancreatic lipase, which is normally absent in the adipose tissues.[129] This entry can result from the concurrent release of phospholipases and be exacerbated by FA-induced adipocyte damage.[129] The resulting interaction between lipase and TG can cause fat necrosis of the involved adipocytes[129–132] and adipocyte receptor-associated TG release. This release, which may be mediated via G-protein coupled protease-activated receptor 4,[133] is triggered proteolytically by trypsin.[134,135] Furthermore, trypsin enhances the lipolytic response of adipocytes to catecholamines.[136] These phenomena can further contribute to the increased TG and FA levels in the interstitium of the pancreas and cause a vicious cycle, resulting in excess FA generation (Figure 3). The relevance of FAs in AP is described below.

6.2 | Pathophysiological effects of FAs on AP

Notably, Navina et al.[130] reported that unsaturated FFAs can trigger an increase in intracellular Ca^{2+} concentration (ic[Ca^{2+}]), inhibit mitochondrial complexes I and V, and promote necrosis in the pancreatic acinar cells and tissue inflammation, whereas saturated FAs had no such effects (Figure 4). Furthermore, unsaturated FAs are abundant (73%–75%) among non-esterified FAs (NEFAs) in human pancreatitis debridement fluid. Moreover, visceral adipose TGs in obese mice contain more unsaturated FAs than those in lean mice.[137] Recently, it was demonstrated that the dietary unsaturated/saturated composition determines the FA composition in adipocyte TG, which in

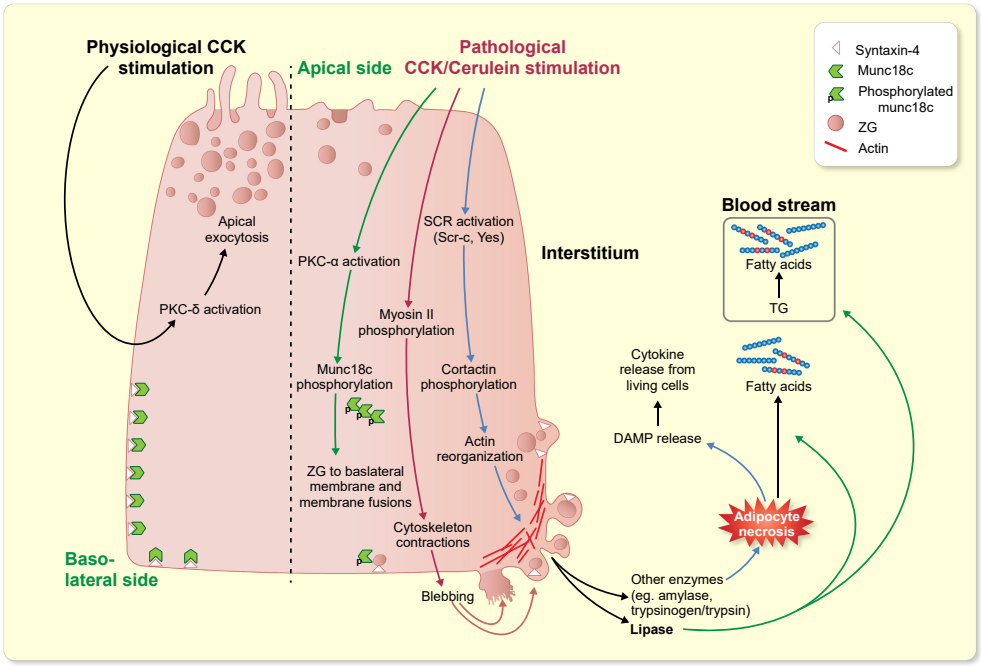

FIGURE 3 Redirection of pancreatic acinar exocytosis. During the physiological stimulation of acinar enzyme secretion, the δ isoform of protein kinase C (PKC) is activated, leading to apical exocytosis of zymogen granules (ZGs). Syntaxin-4, which anchors ZGs, is normally bound to Munc18c. In pathophysiological conditions, including supramaximal CCK/caerulein stimulation, PKCα is activated, which phosphorylates Munc18c, leading to uncovering syntaxin-4. ZGs can attach to syntaxin-4 at the basolateral side of the acinar cells. Furthermore, the pathological stimulation of the cells causes myosin-II phosphorylation and activation of Src family tyrosine kinases, leading to cytoskeleton contractions, Actin reorganization, and blebbing. All these processes contribute to the release of pancreatic lipases and other enzymes at the basolateral side of the cells. Theoretically, these enzymes may enter into the bloodstream or remain at the interstitium, where they can degrade TGs into FAs, induce adipocyte necrosis, or stimulate adipocytes to release TGs. CCK, cholecystokinin; DAMP, damage-associated molecular pattern.

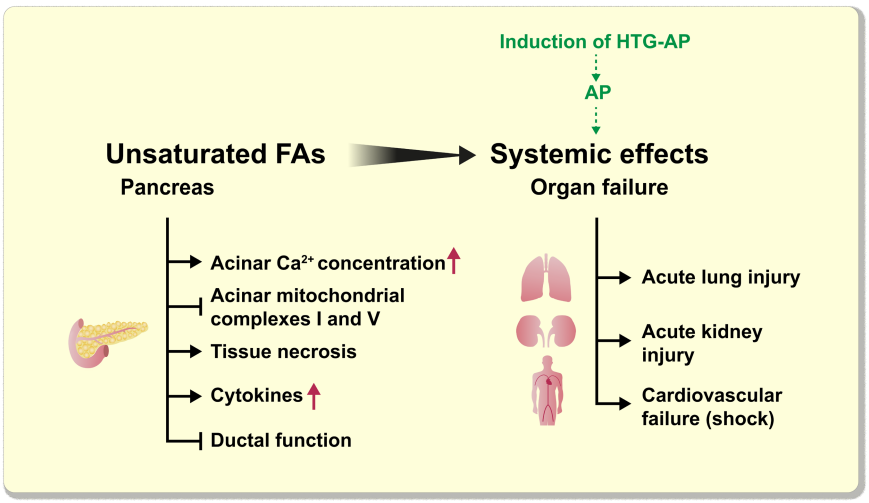

FIGURE 4 The pancreatic and systemic effects of unsaturated FAs. In the pancreas, unsaturated FAs induce ic[Ca^{2+}] increase in acinar cells, inhibit mitochondrial complexes, evoke pancreatic tissue necrosis, and cytokine release (IL-1β, IL-6, IL-18, MCP-1, and TNF-α), and suppress ductal functions. Furthermore, unsaturated FAs may cause kidney, lung, and cardiovascular failure.

turn can influence AP severity.[131] Unsaturated long-chain FAs in a TG make it more prone to lipolysis by pancreatic lipase, whereas saturated long-chain FAs in a TG interfere with this interaction.[131] Therefore, an unsaturated TG may be hydrolyzed more and generate more NEFAs than a saturated TG. Moreover, unsaturated long-chain NEFAs are more aqueous stable than saturated ones. This aqueous stability allows them to exist as monomers at higher concentrations than saturated NEFAs.[131] Consequently, unsaturated NEFA monomers are more effective in initiating cellular signaling than saturated NEFAs.[131] Several reports indicated that unsaturated FAs have a key role in the development of severe AP. In vitro studies have shown their toxic effect on pancreatic cells.[130,132,137,138] Furthermore,

clinical investigations in humans revealed the significant role of lipotoxicity caused by unsaturated FAs.[104,132] Unsaturated FAs released during fat necrosis can reach a millimolar concentration in the pancreatic necrotic collection and high concentration in the serum.[139,140] These FAs bind to extracellular Ca^{2+} causing hypocalcemia during severe AP.[141] This hypocalcemia may be pathophysiologically relevant since early Ca^{2+} supplementation delays organ failure in severe AP models,[141] and calcium is a component of lactated Ringer's solution, which is commonly used for fluid resuscitation. However, clinical studies of Ca^{2+} supplementation have not shown clear benefits, suggesting that other factors may also contribute to AP severity.[142] In the following Sections 6.2.1–6.2.5, the detailed pathological effects of FAs on acinar (inflammatory response, intracellular Ca^{2+} signaling, mitochondrial toxicity, ER stress, and autophagy) and ductal cells (ion channel/transporter function) and on the kidneys, lungs, and cardiovascular system will be presented (Figure 4).

6.2.1 | Effects of FAs on the inflammatory response

The strongest evidence supporting the role of TGs and their lipolysis in worsening inflammation during AP is noted when using cytokines and adipokines as a readout of FA toxicity. Cytokines, including interleukin-6 (IL-6),[143–146] monocyte chemoattractant protein-1 (MCP-1),[147] and tumor necrosis factor α (TNF-α),[144] along with adipokines, including resistin and visfatin,[148,149] are elevated during clinical AP and may correlate with disease severity[143–147,150–152] or organ failure.[23] Recent studies have shown that such a cytokine response may follow the generation[129,132,137] or administration of FAs[129,131,153] that are released in severe AP. The evidence supporting hydrolysis of TGs to FAs in causing the cytokine response initially came from genetically obese mice with pancreatitis induced by IL-12 and IL-18 injection, which had marked increases in serum IL-6, MCP-1, and TNF-α and unsaturated FA concentrations, all of which were decreased by lipase inhibition.[130] This was again noted when studying caerulein-induced AP in obese mice, which also showed a remarkable increase in these serum cytokines and unsaturated FAs compared with lean mice.[137] Direct evidence of the significance of unsaturated TG lipolysis in the remarkable increase in cytokine response of severe pancreatitis came from the injection of the TG of LA, that is, glyceryl tri-linoleate (GTL) into the pancreatic duct of rats, which resulted in approximately equal to 70% pancreatic necrosis and 10- to 1000-fold increases in serum concentrations of IL-6, IL-1β, IL-18, and keratinocyte chemoattractant/growth-regulated oncogene (KC/GRO).[104] Similarly, intraperitoneal administration of the TG of oleic acid (glyceryl tri-oleate; GTO) converted the classically mild model of caerulein pancreatitis in rats to a hyperinflammatory lethal model with IL-1β and KC/GRO elevations.[132] TG lipolysis inhibition with orlistat reduced AP severity from both GTL and GTO and prevented the increase in cytokine and serum FA levels.[104,132] These studies support the lipolytic generation of FAs from TGs to be the mechanism underlying the cytokine response in severe pancreatitis. Since IL-1β[150] and IL-8[143,146,154] (the homolog of KC/GRO) levels are also increased in human severe pancreatitis, along with oleic acid and LA levels, which are also increased in human pancreatic necrotic collections,[132] their increase due to GTL and GTO lipolysis in animal models of AP is clinically significant.

The various lines of evidence supporting a lipotoxic source of cytokines and adipokines during AP include the following: (1) unsaturated FAs, such as LA, but not saturated ones, such as palmitic acid, increase the mRNA expression of cytokines, including TNF-α and CXCL-1 and -2, in primary cultured acini.[130] (2) The adipokine, resistin, is released exclusively from adipocytes.[155] Moreover, when co-cultured with pancreatic acini, the release of resistin was increased,[130,155] which was completely prevented by inhibiting lipolysis.[130] (3) In the comparison of obese mice whose visceral fat TG was either predominantly saturated or unsaturated,[131] the mice group with predominantly unsaturated visceral fat TG had 10- to 100-fold higher IL-6, TNF-α, MCP-1, and CXCL-1 and -2 mRNA levels in their adipose tissues during AP.[131] (4) TG lipolysis may increase circulating (non-adipokine) cytokine levels in the absence of adipose tissues, as observed in lean mice which hydrolyzed the intraperitoneally injected GTL during AP.[131] This resulted in approximately equal to 10-fold higher serum levels of IL-6, TNF-α, and MCP-1 than those administered with a saturated TG, glyceryl tri-palmitate.[131,132] (5) The increase in cytokine levels may result from extensive necrosis. For example, the intraductal GTL models cause severe pancreatic necrosis,[104,105] along with increasing serum LA concentration,[105] and releasing circulating damage-associated molecular patterns (DAMPs), including ds-DNA and histone-DNA complexes.[105] Such DAMP release from the extensive necrosis may underlie the marked increase in serum cytokine levels, since DAMPs cause hypercytokinemia when directly administered to mice.[156–158]

6.2.2 | Intracellular Ca^{2+} overload and mitochondrial injury

There are several potential roles of intracellular Ca^{2+} in FA-induced responses. The earliest studies demonstrated

a dose-dependent, global, and sustained increase in ic[Ca^{2+}] in response to palmitoleic acid (POA, C16:1) administration.[159] The increase in concentration was because of the release from intracellular stores since it could be inhibited by pretreatment and depleting ER stores with the Ca^{2+} ATPase inhibitor, thapsigargin.[159] Subsequent publications showed POA to reduce mitochondrial membrane potential (ψ_m) and NADH levels.[160] Repletion of ATP[160,161] rescued the cells from the increase in ic[Ca^{2+}] induced by the intracellular delivery of POA. While ATP repletion, caffeine, and intracellular Ca^{2+} chelation using BAPTA-AM reduced cell injury over a short time,[159] subsequent studies[130] showed the protective effects of Ca^{2+} chelation to be short-lived and non-sustainable over 3 h. This was noted as progressively reduced protection from LA-induced lactate dehydrogenase leakage[130] and LA-induced leakage of mitochondrial cytochrome c into the cytoplasm (suggesting concurrent Ca^{2+}-independent mitochondrial injury) despite Ca^{2+} chelation. Specifically, a reduction in the activities of mitochondrial complexes I and V was noted with the unsaturated FA LA (C18:2) although not with pamitic acid (C16:0).[130] Recent live imaging studies using fluorescent LA show that its uptake into cells results in mitochondrial depolarization[153] both of which can be rapidly reversed by extracellular albumin.[131,153,162] The pathophysiological relevance of this mitochondrial dysfunction in AP was supported by electron microscopy demonstrating lamellar inclusions and injury in obese mice developing organ failure from increased FA levels.[130] Notably, this mitochondrial injury is highly similar to that found in LPL-deficient minks, which have HTG.[163] Interestingly, this mitochondrial injury can explain the previously reported decrease in NADH levels and increase in ic[Ca^{2+}], which was rescued by ATP repletion.[160] Furthermore, similar results were obtained by another research group[164] who also presented that unsaturated FAs cause high or pathological ic[Ca^{2+}] as well as trypsin and PKC activations, whereas saturated FAs had no effect on acinar cells.

While the abovementioned studies may support the increase in ic[Ca^{2+}] to at least partly resulting from mitochondrial injury, recent studies have reported the mitochondrial injury to be independent of the increase in ic[Ca^{2+}] induced by unsaturated FA administration.[141] For example, in mouse pancreatic acini dually loaded with the ratiometric intracellular Ca^{2+} sensor Fura-2 AM and ψ_m sensor JC-1, BAPTA-AM completely prevented the LA-induced increase in ic[Ca^{2+}] while minimally affecting the loss of ψ_m.[141] Similarly, while dantrolene, a ryanodine receptor antagonist, and thapsigargin reduced the LA-induced increase in ic[Ca^{2+}] to approximately half of those in the presence of LA alone, these had no effect on the loss of ψ_m.[141] Therefore, since the principal site of damage induced by unsaturated FAs is mitochondrial, the short-term protection from necrosis provided by intracellular Ca^{2+} chelation does not translate to longer durations.

6.2.3 | ER stress and autophagy

Pancreatic acinar cells have the highest rate of protein synthesis among human cells; therefore, they contain a strongly developed and active ER.[165] Acinar cells are more susceptible to perturbation in their function and homeostasis[166] because of their rich ER network.[166] Such ER stress has been noted in classically mild, self-limited AP models induced by caerulein and L-arginine.[167] It has been revealed that saturated FAs cause ER stress, whereas unsaturated FAs have no such effect or even protective role. Zeng et al[168] demonstrated that palmitic acid, a saturated FA, induces ER stress by the increased expression of unfolded protein response elements (GRP78/Bip, XBP-1, and GADD153/CHOP). In these studies, palmitate seems to cause an instant increase in cytosolic calcium concentration, unlike the steady increase noted with caerulein alone. Such changes can be noted owing to optical interference or turbidity from an incompletely dissolved FA. Danino et al[169] compared the effects of saturated (palmitic acid) and unsaturated FAs (oleic acid, LA, and docosahexaenoic acid [DHA]) on acinar cells. Interestingly, palmitic acid treatment evoked the highest ER stress, whereas linoleic and DHAs had less effect on ER. Treatment of AR42J and primary rat acinar cells with oleic acid exerted protection against ER stress. Moreover, it was revealed how unsaturated and saturated FA exposure increases fat accumulation in acinar cells, which may make acinar cells susceptible to further insults.[169] Subsequently, the same group showed that palmitic acid dose-dependently enhances unfolded protein response and increases the inflammatory cytokine release and pancreatic lipase levels in pancreatic acinar cells.[170] The combination of palmitic acid with the AP-inducing caerulein synergistically increased ER stress. However, oleic acid reduced the caerulein-evoked cytokine release without aggravating ER stress. Furthermore, oleic acid decreased the effect of palmitic acid on acinar ER. Furthermore, it should be noted that in these studies,[169,170] FAs were fed to cells following conjugation with albumin. Albumin-bound FAs do not mirror the acute lipotoxicity relevant to the large FA increase in severe AP,[140,171] which is associated with hypoalbuminemia.[172,173] This causes an increase in aqueous stable (largely unsaturated) albumin-unbound FAs[131] that are taken into cells and induce mitochondrial damage.[153,162] A recent review highlighted that oleic acid has a protective role in type 2 diabetes mellitus and other diseases, whereas palmitic acid causes lipotoxicity and

lipoapoptosis and enhances insulin resistance development.[174] Wu et al[175] investigated the pathomechanism of palmitic acid-induced inflammation. This FA induces ER stress, which will lead to the activation of the pro-inflammatory transcription factor, nuclear factor-κB, via CCAAT-enhancer-binding protein activation. These results seem to show the opposite to what was discussed earlier when the effect of FAs on ic[Ca^{2+}], ψ_m, or lung and kidney injury measurements were demonstrated. Therefore, it would be imperative to further investigate and compare the effects of saturated and unsaturated FAs.

Effective autophagy helps to eliminate misfolded, damaged proteins and organelles and inhibits inflammation; however, autophagy is dysregulated during AP.[167,176] Impaired autophagy causes ER stress and induces inflammation. Mei et al. reported that a high-fat diet elevates autophagic flux.[177] However, this flux is defective and induces ER stress. Additionally, they provided evidence that palmitic acid blocks autophagy in pancreatic acinar cells.

6.2.4 | How FAs affect pancreatic ductal cells

In the last two decades, different studies indicated that beyond acinar cells, pancreatic duct dysfunction also plays a significant role in the development or aggravation of AP.[178,179] The main ductal function is the secretion of HCO_3^-, which alkalinizes the pancreatic juice and contributes to keeping the digestive enzymes inactive inside the pancreas. Several ion transporters participate in the HCO_3^- secretion, such as cystic fibrosis conductance transmembrane regulator (CFTR), SLC26A3, SLC26A6, or Na^+/HCO_3^- co-transporter. It was demonstrated that POA, an unsaturated FA, markedly influences the pancreatic ductal cell function.[180] The HCO_3^- secretion of guinea pig pancreatic ducts was decreased by the administration of 200 μM POA. POA significantly reduced CFTR Cl^- currents in isolated guinea pig ductal cells and inhibited the apical SLC26A3 and SLC26A6 Cl^-/HCO_3^- exchangers and CFTR in Capan-1 human pancreatic ductal cells. POA administration induced pathologically high Ca^{2+} signals, reduced the ψ_m, and depleted ATP in Capan-1 ductal cells. Interestingly, Ca^{2+} chelation abolished the effects of POA on apical transporter function (CFTR, SLC26A3, and SLC26A6), suggesting that POA-induced Ca^{2+} signaling has immediate and prominent effects on pancreatic ductal cells. Furthermore, the expression and protein folding efficacy of CFTR were reduced in Capan-1 cells by POA treatment for 48 h. Overall, these results indicate that unsaturated FAs can have direct effects on pancreatic ductal function and ion channel protein expression.

However, saturated FAs can also affect pancreatic ductal cells. Long-term overexposure to saturated FA may cause the differentiation of ductal cells into adipocytes or β-cells.[181] Additionally, lipotoxic stimulus (long-term high concentration of FAs) can evoke insulin production in ductal cells. Furthermore, rat pancreatic ductal cell line treatment with palmitate-induced fat accumulation and leptin release. Gezginci-Oktayoglu et al[181] demonstrated that the suppression of Erk1 during saturated FA treatment can be the background mechanism for ductal cell adipogenesis. A high-fat diet induces TG and FFA elevation in the serum of experimental animals,[182,183] and it can affect pancreatic ductal function. Similarly, Huang et al[184] found that a high-fat diet can induce the transdifferentiation of pancreatic ducts to insulin-producing cells. They suggested that intracellular F-box/WD repeat-containing protein 7 ubiquitination plays part in this effect.

Fat accumulation in the pancreas can increase the risk of pancreatic cancer. Takahashi et al[185] reported that a pancreas with fatty infiltration increases the susceptibility of pancreatic ducts to the development of pancreatic ductal adenocarcinoma.[185] They collected pancreata from mice and human patients who had undergone pancreatoduodenectomy. The degree of fatty infiltration in the tissue had a positive association with pancreatic ductal adenocarcinoma development. Furthermore, pancreatic ductal cell replication is increased in individuals with obesity.[186] This increased replication is a characteristic of obstructive pancreatitis and pancreatic cancer.[187–189]

6.2.5 | How FAs affect extrapancreatic organs

In contrast to experimental models of AP that often equate disease severity to the extent of pancreatic inflammation and necrosis, the severity of clinical AP is measured by the duration and extent of systemic injury (e.g., organ failure).[23] Therefore, HTG-AP is interesting owing to its uniquely higher propensity of being more severe. The lipotoxicity from FAs generated from TG lipolysis, which has been shown to cause systemic injury in most AP models, may contribute to HTG-AP severity. Evidence supporting the role of FA lipotoxicity comes from comparing AP-associated systemic injury and organ failure in lean rodents with those that are obese or are administered an excess of TG. For example, while lean mice[137] with cerulein-induced AP have a transient and small increase in serum blood urea nitrogen and unsaturated FA levels, the unsaturated FA and blood urea nitrogen increase in obese mice with AP is significantly higher and more sustained and is associated with renal failure, which is due to tubular injury (detected by TUNEL staining).[137] The ubiquitous nature of unsaturated FA-induced tubular injury contributing to renal failure in AP is supported by TUNEL-positive tubular cells that are present in biliary

pancreatitis and are exacerbated by the co-administration of unsaturated TG[104,190] and systemic administration of LA.[105,191] Similarly, TUNEL-positive cells in the lungs that support acute lung injury are noted in severe AP. Alveolar TUNEL positivity is one of the histological parameters noted during acute lung injury in humans.[192] The lipolytic breakdown of TGs into unsaturated FAs in the abovementioned studies underlies both renal and alveolar injuries. The administration of orlistat, a lipase inhibitor, prevented the unsaturated FA increase and TUNEL positivity in these organs as well as in caerulein- or IL12/18-induced mouse AP models.[131] Similarly, TUNEL-positive tubules and alveoli were noted in rats with caerulein pancreatitis co-administered with the TG of oleic acid, triolein,[132] wherein serum oleic acid was increased. Here, the renal tubules were dilated with loss of epithelial lining, and the remaining tubules showed an increase in TUNEL-positive cells or expressed the kidney injury molecule-1.[132] Additionally, triolein dose-dependently increased lactate dehydrogenase activities in the bronchoalveolar lavage of rats with caerulein-induced AP.[132] Similarly, propidium iodide-positive cells increased in the bronchoalveolar lavage, as did the leakage of high molecular weight fluorescent dextran from the vascular compartment into the alveoli.[132] All these changes were prevented when orlistat was co-administered with triolein during AP. These findings support that excessive unsaturated FA generation from TG hydrolysis during AP can lead to renal failure and acute lung injury. In animal models of severe AP, shock is observed as a reduction in carotid arterial pulse distention.[105,129,131] This reduction in pulse distention is noted in caerulein- and IL12/18-induced AP models, which are severe owing to excessive TG lipolysis,[131] obesity,[129] or unsaturated FA administration, including linoleic or oleic acid.[105,129,131,141] Similar to renal tubular injury, this lipotoxic shock is noted in the mechanistically distinct models of caerulein,[141] IL12/18,[141] and biliary AP, which themselves are mild and self-limited. Lipotoxicity causes organ failure and shock and thus aggravates the outcome of COVID-19 infection.[153] Mechanistically lipotoxic systemic injury is best noted on electron microscopy of renal tubules in obese mice with IL12/18-induced severe AP.[130] These results demonstrated mitochondrial swelling, the appearance of inclusion bodies, and the loss of mitochondrial cristae[130] that were prevented by lipase inhibition.

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Our knowledge regarding the relationship between HTG and AP remains far from complete. Several studies have proven that HTG worsens AP severity regardless of the etiology and HTG-AP has more severe outcomes than other types of AP. The pathomechanism that links HTG to AP is relatively complex and involves ic[Ca^{2+}] increase, mitochondrial damage, tissue injury, pro-inflammatory cytokine release, ductal function inhibition, ER stress, defective autophagy, and respiratory, kidney, and cardiovascular failure. These adverse effects are induced by the increased unsaturated FA concentration (derived from the hydrolysis of TGs by different types of lipases, including LPLs, pancreatic lipases, and hormone-sensitive lipase) in the blood and most probably in the pancreatic and peripancreatic interstitium.

For decades, there were two theories about how HTG worsens the AP. One of the theories was blood hyperviscosity, which can lead to ischemia and local acidosis. Here, it was demonstrated in different ways that there is no experimental or observational evidence supporting this hypothesis.

The release of pancreatic lipases into the pancreatic and peripancreatic interstitium has been less studied during AP. It was demonstrated that pancreatic and peripancreatic fat necrosis contributes to the increased disease severity, which is caused by proteases and lipases.[130,132] However, the detailed process remains unknown. Most probably, the basolateral enzyme secretion during AP is one of the first steps; however, it should be proven by direct evidence.

Our current knowledge about the effect of saturated and unsaturated FAs is somewhat contradictory to what has been hypothesized in chronic diseases. Researchers in the field of cardiovascular diseases have suggested the consumption of a Mediterranean diet with reduced saturated and increased unsaturated FAs. This results in decreased low-density lipoproteins (LDLs) and LDL-cholesterol levels in serum, which decreases the incidence of cardiovascular diseases.[193–195] However, unlike what we have shown in AP, the effect of these diets on cardiovascular outcomes (e.g., death and acute organ failure) remains unclear. Interestingly, while such diets decrease the BMIs at which severe AP occurs, the risk of severe AP does not decrease but rather may increase,[131] which is dubbed as the "obesity paradox." In this review, several presented literature data showed the basis of this phenomenon and why the results seem opposite with saturated/unsaturated FA in the case of AP. Unsaturated FAs significantly worsen AP and induce pathological signaling in pancreatic acinar, endothelial, and renal tubular cells (relevant to vascular leak, hypotension, and renal failure), whereas saturated FAs have no or less severe effect (except in case of ER stress). Dietary unsaturated fat consumption leads to unsaturated visceral fat accumulation, which worsens AP more than the amount of saturated fat.[131] Based on these findings,

it appears that both saturated and unsaturated FAs may have differential effects on the risks of development and severity of different diseases. Therefore, in the future, it is significant to have a discussion between cardiologists, gastroenterologists, and dieticians and improve the current recommendations regarding dietary fat consumption while balancing disease risk with disease severity. Furthermore, in the clinical setting, measuring not only the seTG on the admission of patients with AP but also revealing the composition of TGs (the proportion and type of FAs) may be useful.

As previously mentioned, several literature data support the observation that unsaturated FAs worsen the outcome of AP. However, in the case of ER stress investigation, unsaturated FAs have no or even protective effect on the ER of pancreatic acinar cells, whereas saturated FAs cause ER stress. Further investigating these effects and performing a more detailed comparison of different FAs is essential. Creating subgroups within unsaturated FAs based on the unsaturation level and the double-bond position will be reasonable. Subsequently, the effect of these subgroups could be compared with each other and with saturated FAs using pancreatic cells.

Pathological ic[Ca^{2+}] increase is one of the most important initiating processes of AP.[178,196,197] It is widely accepted that this ic[Ca^{2+}] increase will lead to mitochondrial damage and NF-κB translocation to the nucleus. Interestingly, during HTG, the mitochondrial toxicity is independent of the ic[Ca^{2+}] increase. Therefore, reevaluating the pathophysiological mechanisms of AP and balancing the focus on etiological factors while taking severity and outcomes into consideration are necessary.

The administration of the lipase inhibitor, orlistat, exhibited protection against high seTG in in vivo and in vitro models of AP.[104,130,132,198] In clinical settings, insulin and/or heparin therapies are available to decrease the seTG in patients with HTG-AP; however, it takes days. In the case of patients with obesity and/or HTG with AP, the administration of lipase inhibitors could also be beneficial and supplement the available therapies. Lipase inhibitors may exert their effect more rapidly and can also reach the pancreatic and peripancreatic interstitium, not just the blood. Disadvantages of orlistat treatment include its adverse effects[199] and poor oral absorption, which cannot be avoided by other administration routes as they remain prohibited by authorities. Therefore, new administration routes for orlistat should be tested and the development of novel lipase inhibitors could have greater potential as a specific treatment for this disease.

Overall, investigating the pathophysiology of HTG-induced AP or AP in the presence of HTG and determining a more specific therapy to prevent or reduce the occurrence of worse disease outcomes are needed.

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CONFLICT OF INTEREST

We have no conflict of interest to declare.

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