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Review

Pancreatitis Secondary to Dyslipidemia: An Understudied Condition

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Abstract: Dyslipidemia (DL), defined by dysregulated levels of lipids in the bloodstream, is an ever-growing problem in modern society. In addition to those with congenital defects in lipid metabolism, the pervasive nature of high-fat and high-calorie diets in modern industrialized societies has led to a meteoric increase in its incidence. Patients who suffer from this condition subsequently are at a higher risk of developing other co-morbid conditions, most notably diabetes mellitus and coronary artery disease. This review explores another arguably lesser-known consequence of DL, pancreatitis, which is an inflammatory disease of the pancreas. The goal of this article is to review the intersection of these two conditions by briefly highlighting the proposed pathophysiology and exploring the impact of DL (specifically hypertriglyceridemia) on acute, acute recurrent, and chronic pancreatitis. This paper additionally examines the long-term risks of developing pancreatic cancer in patients with pancreatitis secondary to DL and presents unique clinical scenarios that result in DL-associated pancreatitis. Finally, we discuss potential treatment options for hypertriglyceridemia which can potentially mitigate the risk of DL-associated pancreatitis.

Keywords: triglyceride; pancreatitis; lipid dysfunction; inflammation; high calorie; obesity; pancreatic cancer; COVID-19

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1. Introduction

Pancreatitis is a complex inflammatory disease process of the pancreas, a glandular intra-abdominal organ that plays a dual exocrine and endocrine function. It is characterized and managed based on the duration of inflammation and symptoms, with three interrelated types: acute pancreatitis (AP), acute recurring pancreatitis (ARP), and chronic pancreatitis (CP). AP is defined as a short-lived episode of inflammation of the pancreas and classically presents with epigastric abdominal pain that often radiates to the back. It is characterized by elevated serum levels of pancreatic exocrine enzymes, amylase and lipase, as well as inflammatory changes in the pancreatic parenchyma seen radiographically with cross-sectional imaging [1,2]. The illness can be further defined as mild or severe based on symptomatology and whether it is complicated by the involvement of surrounding structures, local necrosis, fluid collections, and local/systemic infections [3].

The most common etiologies for AP include alcohol and gallstone, followed by hypercalcemia, hypertriglyceridemia (HTG), trauma, genetic disorders, auto-immune disorders, drug-induced, and post-endoscopic retrograde cholangiopancreatography [1]. Globally, the incidence of AP continues to grow with recent studies demonstrating a steady increase since 1961, and the greatest increases seen in the United States and Europe [1]. Mortality from an episode of AP is generally about 1% but can increase to an estimated 30–40% secondary to complications associated with severe cases [1]. When at least two independent episodes of AP occur, this is defined as ARP. Compared to AP, the multiple insults to the pancreas seen in ARP is associated with increased morbidity, more severe and persistent abdominal

pain, maldigestion of fats secondary to exocrine insufficiency, and a greater risk for severe complications [3].

CP is a more insidious form of pancreatitis, secondary to recurrent or persistent inflammation of the pancreas [3], leading to increased cellular regeneration, progressive morphological changes, increased tissue fibrosis. and an overall decline in both endocrine and exocrine function [4]. A wide range of clinical presentations of CP exists, with some being asymptomatic, diagnosed incidentally by imaging or enzymatic changes alone, while others presenting with severe pain. Estimates of CP prevalence range from 25.4 to 98.7 per 100,000 people and incidence of 4–5 new cases per 100,000 per year in the United States from 2001 to 2013 [5]. Patients who experience AP and ARP can eventually progress to CP. Common etiologies associated with CP include excessive alcohol use, chronic tobacco use, hereditary pancreatitis (e.g., in families with *PRSS1* gene mutations), auto-immune pancreatitis (e.g., immunoglobulin G4-related disease), and metabolic disorders/dyslipidemia (DL) [4,5]. Due to chronic inflammation and high rates of tissue turnover, patients with CP are also at increased risk of developing pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC). Pancreatic cancer is the 12th most common malignancy and the 7th leading cause of cancer mortality in the world [6]. This form of cancer is known to have high mortality rates, with a 5-year survival rate estimated to be about 10% [4]. The incidence of this type of cancer is also growing globally, with the greatest rise in incidence occurring in countries of higher socioeconomic standing [6].

DL, while less commonly discussed, not only plays a significant role in the development of pancreatitis but also contributes to pancreatitis severity after the onset [7–11]. Common etiologies of DL include obesity and metabolic syndromes, lipid storage diseases, pregnancy, acute infections, and drug-induced disorders of lipid metabolism [12–16]. In this review, we delve into the complex interplay of these two entities through a discussion of DL pathophysiology with emphasis on HTG, the role of DL in the three types of pancreatitis (AP, ARP, and CP), how DL contributes to the development of pancreatic cancer (specifically, PDAC), and some of the unique clinical scenarios of DL-associated pancreatitis (Figure 1). The final section of this paper summarizes current therapies in use to treat HTG.

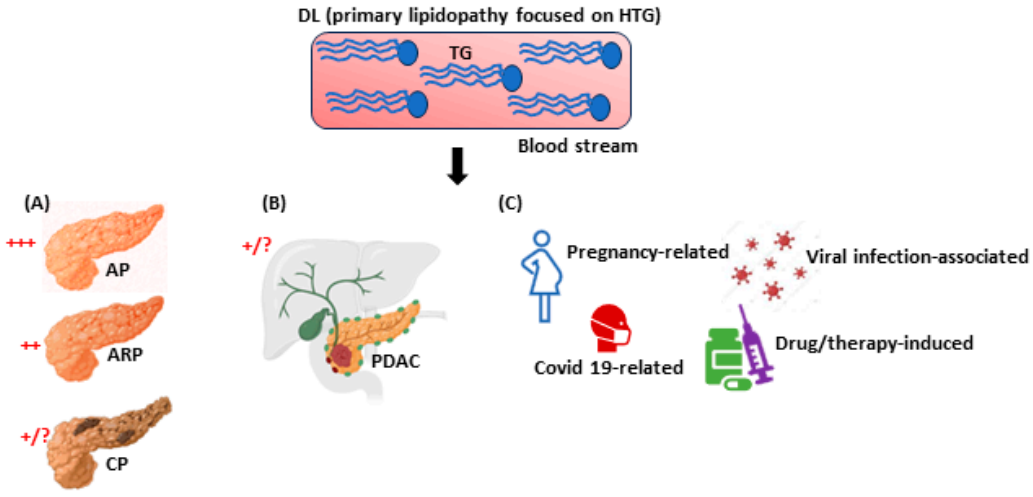

Figure 1. Clinical Evaluations of Dyslipidemia (DL)-associated Pancreatitis: The aim of this review is to present a consolidated clinical assessment of the effects of dyslipidemia (DL) on pancreatitis, with primary emphasis on hypertriglyceridemia (HTG)-associated pancreatitis. The clinical evaluations within this review are structured into 3 arms: (**A**) A detailed literature analysis on the association of DL and its relationship with acute pancreatitis (AP, +++ denoting the extensive literature-based supporting evidence), acute recurrent pancreatitis (ARP, ++ denoting moderate literature-based evidence currently available), and chronic pancreatitis (CP, +/? referring to lack of definitive evidence, and thereby warranting more research in determining DL's direct association with CP). (**B**) The second

arm of this article examines the long-term risks of developing pancreatic cancer (focus on pancreatic ductal adenocarcinoma, PDAC, in patients diagnosed with DL), again with overall limited information on the topic, and therefore necessitating further investigations. (**C**) The third arm presents unique clinical scenarios that result in DL-associated pancreatitis.

2. Dyslipidemia Pathophysiology with a Focus on Hypertriglyceridemia

The pathophysiology by which DL can contribute to pancreatitis is complex, the result of dysregulated intra- and extra-cellular processes, and remains a major focus of research today. Some of the established mechanisms by which the triglycerides (TGs) are shuttled throughout the body via the circulatory system are detailed within previous work [17–20]. Briefly, TGs are transported through plasma via very low-density lipoproteins (VLDL), which transport TGs primarily made in the liver, and as chylomicrons (CMs), which transport dietary, exogenous fat [18]. These carrier molecules are composed of a combination of lipids and proteins, called lipoproteins. There are multiple lipoproteins which comprise these carrier molecules—apoB-100 is the predominant lipoprotein component of VLDL. while apoB-48 is the predominant lipoprotein of CMs [21]. The interaction of several other lipoproteins, including apoA-I, apoA-IV, apoC-I, apoC-II, apoC-III, apoE, and apoF, facilitate catabolism of these carriers by TG hydrolysis through lipoprotein lipase (LPL). It is the interaction with these lipoproteins and several others which intricately act to regulate LPL activity [22]. The hydrolysis of core TGs from VLDL and CMs result in remnant particles, which are cleared through a host of proteins involved in remnant clearance processes [18]. Aberration of the catabolism of these carrier molecules plays a significant role in the dysregulation of TGs, leading to HTG.

The dysregulation of TG levels stems from defects in its metabolism. Plasma TG levels reflect the TG content of multiple lipoprotein particles, mainly VLDL and CM. TG saturation in plasma occurs when its levels exceed ~500–700 mg/dL. According to the Endocrine Society guidelines, HTG is defined as serum TG levels >150 mg/dL (>1.7 mmol/L) [17,23]. The degree of HTG is further stratified into four groups based on serum TG levels, including mild HTG [150–199 mg/dL (1.7–2.3 mmol/L)], moderate [200–999 mg/dL (2.3–11.3 mmol/L)], severe [1000–1999 mg/dL (11.3–22.6 mmol/L)], and very severe [>2000 mg/dL (>22.6 mmol/L)] [23].

Primary HTG is defined as HTG stemming from genetic disorders of TG metabolism, like familial HTG, familial chylomicronemia syndrome (FCS), or multifactorial chylomicronemia syndrome (MCS) [17,23]. Alternatively, secondary causes of HTG are often associated with insulin-resistant etiologies such as diabetes mellitus (DM), chronic kidney disease, metabolic syndrome, alcohol use disorder, medications, or chronic high fat and high carbohydrate diet with sedentary lifestyle [17,24,25]. These disease-states tend to lead to decreased lipolysis by LPL intrinsically and via the upregulation of apolipoprotein C3 (apoC-III) and angiopoietin-like 4 proteins [17,26–29]. Additionally, these factors cause the reduced hepatic clearance of lipoproteins, the increased generation of free fatty acids from adipose tissue, and the increased generation of TG-rich lipoproteins from the liver.

Clinically relevant abnormalities of plasma TG levels appear to require a polygenic foundation of common or rare genetic variants [30]. The polygenic accumulation of common (rather than rare) variants was shown to be the most prevalent genetic feature underlying severe HTG [31]. The term chylomicronemia syndrome (CS) refers to a set of clinical findings such as abdominal pain, AP, eruptive xanthoma, and lipemia retinalis, which occur in association with very high TG levels [18,20]. FCS is a form of CS and is predominantly a monogenic disorder where the TG levels exceed 1000 mg/dL, the risk of pancreatitis is increased, and these patients are highly resistant to treatment [32,33]. The MCS occurs in individuals where genetic predisposition and secondary forms of HTG co-exist and typically manifests with moderately elevated TG levels (500–999 mg/dL) [20]. The risk of pancreatitis in MCS is higher (~10–20%) than in other polygenic HTG but less than in FCS. In FCS, pancreatitis is the most serious clinical consequence which can be life-threatening. It is typically diagnosed in childhood (infancy to adolescence). As stated

above, the primary lipoprotein of CMs is apoB-48, which is a shortened protein, compared to apoB-100, due to mRNA editing leading to the truncation of the protein [21]. Therefore, measuring apoB-100 levels in these patients will be expectedly low, potentially acting as a useful test to differentiate excess VLDL from CMs.

Regardless of the cause of HTG, elevated circulating TG levels can worsen or incite pancreatitis, which is generally seen with TG levels >500 mg/dL (5.6 mmol/L) and with no other discernable cause of AP [17,34,35]. There are two hypotheses for how elevated TG levels can influence AP. The first relates to the exposure of pancreas to significantly increased TG levels, in the form of CMs, large TG-rich lipoproteins. The hydrolysis of CMs within the microcirculation of the pancreas leads to a surge of lipolysis by pancreatic lipases and the subsequent release of free fatty acids. These free fatty acids exceed the binding capacity of albumin and in turn lead to pancreatic edema and hemorrhage [17,36–38]. Resulting in a vicious cycle of lipolysis and damage, pancreatic injury leads to a further local leak of the pancreatic enzymes amylase and lipase. The second hypothesis is related to the concept that elevated CMs, rich in TG, in plasma leads to increased plasma viscosity [17,36,37]. This increased viscosity in turn causes occlusion of pancreatic microcirculation, and leads to parenchymal ischemia, acidosis, and the subsequent activation of pancreatic enzymes, which in turn cause further pancreatic damage and inflammation. For the purposes of clinical discussion, elevated TG levels should be understood to imply elevated TG bound to large lipoproteins such as VLDL or CMs. This point is to underscore the importance of CS in the pathogenesis of DL-associated pancreatitis. At present, the former theory is the most widely accepted as increasing blood viscosity is not well correlated with AP, either clinically or in ex-vivo studies [17,36]. A detailed and current understanding of the cellular and molecular mechanisms related to the pathophysiology of HTG-associated pancreatitis is beyond the scope of this review and has been covered in other recent reviews [17,39,40].

3. Dyslipidemia and Acute Pancreatitis

Cases of AP have been increasing throughout the world, with the third most common etiology being DL, specifically HTG [1]. A retrospective study by Qureshi et al. evaluated 3746 patients with AP and identified 57 patients with AP and HTG [41]. Of these patients with AP and HTG, 55 patients had secondary causes of HTG, including DM, alcohol use disorder, chronic kidney disease, obesity, and metabolic syndrome. In addition, high-fat and simple carbohydrate diets combined with sedentary lifestyle increase the risk of HTG [17]. Other rare etiologies of DL include pregnancy-associated, auto-immune (such as systemic lupus erythematosus or chronic inflammatory diseases), medication-induced, multiple myeloma-associated, and infectious causes of HTG [17]. It is the increased prevalence of these co-morbid chronic conditions that has led to a rise in DL in modern society and the subsequent increase in DL-associated pancreatitis.

Several reports have substantiated a significant relationship between elevated TG levels and AP incidence [14,35,42], with studies concurrently associating HTG as a modulator of pancreatitis severity [10]. Similar conclusions have been drawn from multiple other studies which have evaluated the impact of blood or serum TG elevations on the outcomes and severity of acute biliary pancreatitis [43,44]. Evaluating TG levels during the early hospitalization phase after an episode of AP might be prognostic-bearing in determining the degree of AP severity and can help ascertain other patient- or hospital-associated risk parameters. Multiple studies have confirmed that patients admitted for AP have worse outcomes if also found to have severe HTG (>1000 mg/dL) [11,45–49]. Additionally, severe HTG has been associated with an increased risk of persistent organ failure, multiple organ dysfunction syndrome, pancreatic necrosis, and mortality secondary to AP. Similar outcomes have been identified when comparing HTG-associated pancreatitis compared to other causes of pancreatitis [50]. These studies highlight that there is a strong correlation between the levels of HTG and degree of AP severity. Mild levels of HTG may not play a role in determining AP severity, whereas patients presenting with severe to very severe HTG (>1000–2000 mg/dL) are at a much higher risk for developing moderate to severe AP.

Patients with a primary etiology for HTG are also at increased risk for HTG-associated AP, requiring more stringent medical and lifestyle management. A retrospective cross-sectional study by Paquette et al. used next-generation sequencing in 103 patients with HTG and screened them for five canonical genes associated with TG metabolism (*LPL*, *APOC2*, *GPIHBP1*, *APOA5*, and *LMF1*) [51]. These genes are commonly tested to diagnose FCS (or type I hyperlipoproteinemia) or MCS (or type V hyperlipoproteinemia). FCS is an exceedingly rare condition, with a prevalence of 1 per 1,000,000, and is associated with homozygous or compound heterozygous variants of one or multiple genes of the five canonical genes. While MCS is less rare, with a prevalence of 1 in 600, it is associated with a heterozygous variant and/or several single nucleotide polymorphisms of one of the canonical five genes. It tends to have a less severe phenotype of HTG and is more variably dependent on environmental factors. After next-generation sequencing, their study identified 53 patients with HTG who were negative for aberrations to the five canonical genes (non-MCS), 22 patients who were diagnosed with MCS, and 28 patients who were diagnosed with FCS. The study compared the demographics and incidence of pancreatitis between the groups. They found that those in the FCS and MCS groups had a greater prevalence of patients with at least one episode of pancreatitis and patients with multiple episodes of pancreatitis when compared to the FCS or MCS-negative group. Those in the FCS group also had a significantly lower average age of presentation for their first episode of pancreatitis. Medical management with fibrates and statins has variable effect in reducing TG levels in these patients but an antisense oligonucleotide against *APOC3* mRNA has showed improved efficacy in patients suffering from these genetic conditions [51]. Several additional studies, including case reports and a prospective cohort study have also demonstrated a link between genetic aberrations in lipid metabolism leading to HTG and increased incidence of AP [52–54]. In addition to aberrant TG levels acting as a catalyst for AP, derivations of other elements of lipid metabolism have also been associated with severe AP. For example, in a study of 678 patients with severe AP between 2018 to 2020, decreased serum apoA-I and high-density lipoprotein cholesterol (HDL-C) were independently associated with an increased rate of severe AP [55].

4. Dyslipidemia and Acute Recurrent Pancreatitis

Patients with HTG-associated AP, are at an increased risk for ARP [56–58]. In a recent single-center retrospective analysis, HTG was identified as the most common etiology for ARP [59]. This study also indicated that smoking history, infected pancreatic necrosis, and high low-density lipoprotein cholesterol (LDL-C) levels were critical risk factors for ARP [59]. Patients with extreme cases of HTG (peak TG levels of >3000 mg/dL) strongly correlate with an increased risk of ARP [60,61]. Conversely, some studies offer an interesting observation that even a modest elevation in TG levels can be associated with ARP in patients with HTG-associated pancreatitis [62].

Akin to other AP etiologies, HTG-associated ARP considerably enhances overall disease burden due to repeated hospitalizations, thereby significantly impacting quality of life and increasing the risk of disease progression to CP [57]. In a recent study, based after sentinel admission for HTG-induced AP, the most frequent readmission diagnosis was for ARP (45.2%), followed by CP (6.3%) [63]. Additionally, these readmitted patients were found to have significantly worse outcomes including increased mortality rate and longer length of stay, compared to patients who only experienced the index AP event [63]. With ARP, there is an increased risk of long-term damage to the pancreas which leads to endocrine and exocrine dysfunction, and in a subset of cases, it can progress to CP. Aggressive medical treatment of DL after an episode of AP should be at the forefront of outpatient management.

5. Dyslipidemia and Chronic Pancreatitis

It is controversial at present whether DL can cause CP or not [64]. A study by Agawa et al. found that in addition to elastography studies and studies of exocrine pancreatic

function, HDL-C was significantly lower in patients with CP compared to controls and could be a useful predictive measure [7]. A separate retrospective case–control study by Ni et al. found that HDL-C was significantly decreased in patients with CP and that increased LDL-C, hyperglycemia, and elevated total cholesterol may act as risk factors for CP development [65]. Limited cases have been reported of patients with HTG and signs or symptoms of CP including the presence of exocrine or endocrine insufficiency and pancreatic calcifications. In one of these reported patients, a multifactorial source for CP was reported, including the use of alcohol [66], and in the other, a familial cause was identified (familial HTG) [67]. A single-center retrospective study of patients with a primary etiology of HTG, specifically FCS, found that these patients had an increased number of AP episodes, higher rate of splenic vein thrombosis and developed CP at a younger age compared to other patients with CP. This demonstrates that the chronicity of DL and recurrent insult to the pancreas can be a nidus for chronic damage. To that end, a retrospective study of 121 patients with TG levels $\geq$500 mg/dL over a thirteen-year period demonstrated that those with elevated TG levels had an increased rate of ARP and found a 16.5% prevalence of CP, with an incidence during the 13-year period of 9% within the cohort [56]. HTG and CP may also co-exist in the context of metabolic syndrome as suggested in case reports, but this correlation warrants further investigations [68].

6. Dyslipidemia and Pancreatic Adenocarcinoma

In general, DL is thought to be a risk factor for the development of a variety of cancers [69]. Specific to pancreatic cancer, increased cholesterol levels have been shown to be associated with pancreatic cancer development [70,71] and altered lipid metabolism may even play an important role in chemotherapy resistance [72]. Pre-clinical models have also identified that a high fat diet can activate K-Ras, part of the RAS/MAPK oncogenic pathway, through the enzyme cyclooxygenase 2 (COX2) and results in a clear progression from pancreatic inflammation/fibrosis to PDAC [73].

Fat infiltration within the pancreatic tissue has also been found to have a significant association with PDAC in both animal and human studies [74]. A post-mortem study of pancreatic ductal proliferation in humans found that obese patients (BMI > 27 kg/m^2) and patients with type 2 DM had significantly increased ductal proliferation compared to lean and non-diabetic controls. This effect was further magnified in patients with both obesity and type 2 DM [75]. A separate study of patients with type 1 DM also demonstrated increased pancreatic duct gland proliferation compared to non-diabetic controls; these findings aligned with ongoing inflammation [76]. Higher cellular replication poses an increased risk for obstructive processes and dysplastic tissue generation. A meta-analysis of seven cohort and case–control studies evaluating the relationship between PDAC, and metabolic syndrome found that metabolic syndrome had a significant association with an increased risk of PDAC [9]. Additionally, the analysis found that decreased levels of HDL-C, hypertension, and hyperglycemia were significantly associated with an increased risk of PDAC but no direct association with pancreatic cancer and obesity or HTG [9]. In the largest study to date on this topic, 260 patients with PDAC were compared to 172 patients with non-pancreatic cancer tumors (defined as pancreatic neuroendocrine tumor or intraductal papillary mucinous neoplasms) [77]. Patients with PDAC were found to have higher levels of serum TG, cholesterol, and LDL, in addition to a lower level of HDL. However, DL was not found to significantly impact survival in those with pancreatic cancer [77]. More work is needed to establish the importance of DL on PDAC development and whether this is a modifiable risk factor in patients at high risk for cancer development.

7. Unique Etiologies of Dyslipidemia Causing Dyslipidemia-Associated Pancreatitis

In addition to the more well-known causes mentioned previously, there have been other less common etiologies of DL resulting in DL-associated pancreatitis observed in the literature. These include pregnancy, COVID-19 viral infection, and drug/therapy-related cases.

In pregnancy, several physiologic changes inherent to pregnancy can result in the development of pancreatitis, among which are gallstone formation and HTG. Gallstone formation in pregnancy is a result of a variety of factors, including elevations in both estrogen and progesterone, hormonal changes supportive of fetal growth, and increasing body mass index (BMI) [78–81]. Progesterone is known to reduce frequency and strength of gallbladder contractions, which can lead to biliary stasis and sludge formation [78]. Estrogen has a similar effect, decreasing gallbladder contractions as well as increasing the circulating cholesterol levels, resulting in an increased risk of gallstone formation [80]. At baseline, endogenous ovarian hormones cause fluctuations in the circulating levels of serum lipids and apolipoproteins [82,83]. However, in pregnancy, there is a significant upregulation in the production of lipids and TGs to support fetal development and supply maternal energy to support fetal growth [82,84,85]. In one study examining concentrations of lipoprotein lipids in pregnant versus non-pregnant females, there was a 3.6-fold increase in TGs, a 49% increase in LDL, and a 23% increase in HDL in pregnant females compared to non-pregnant females [85]. This upregulation predisposes pregnant women to clinically relevant DL and has been shown to trigger AP in some rare cases [13,86–88]. Alcohol consumption has also been linked to pancreatitis in pregnancy, and heavy consumption has been associated with the development of DL [78,89].

Pancreatitis in pregnancy is associated with a significant morbidity and mortality risk for both mothers and fetuses, with previous studies showing a mortality rate of 37% and 11–37%, respectively [90]. Most of the risk to neonates is due to increased chances of preterm labor in the setting of maternal pancreatitis [90]. However, this has drastically improved due to the improvement in maternal screenings and imaging studies, as well as better neonatal care, with newer studies reporting an incidence of maternal mortality <1% and perinatal mortality from 0 to 18% [90,91].

COVID-19-related DL has also been described in the literature and has been linked to several different mechanisms including medications, acute liver failure, enzyme deficiency, and secondary hemophagocytic lymphohystiocytosis (HLH) syndrome [16,92–94]. As previously discussed, LPL is a key enzyme in the breakdown and metabolism of lipids and is responsible for catalyzing the hydrolysis of TGs circulating in the blood (carried by lipoproteins such as very low-density lipoprotein and CM) into fatty acids [22,95]. Defects in this enzyme results in impaired lipid metabolism, which manifests as FCS and aberrant lipid deposition [22,96]. The patient described in one study presented with mild COVID-19 symptoms that resolved with only supportive care. However, two weeks later, she presented with nausea and food aversion, and laboratory studies revealed significant elevations in TG levels [16]. She was found to have LPL deficiency after all other causes of acute HTG were ruled out, and it was theorized that an excess production of autoantibodies following the patient's recent COVID-19 infection was responsible for this transient drop in the LPL activity [16]. This patient did not develop clinical signs of AP. Interestingly, another case report described the development of severe HTG in a COVID-19 patient treated with the drug tocilizumab (TCZ), which is a recombinant monoclonal antibody against interleukin-6 used as a treatment option in severe hospitalized COVID-19 cases [92]. In this case, one of the two patients that developed HTG with TCZ treatment for COVID-19 did develop AP, although the authors did not mention how this episode of AP was treated [92]. In a third study, 5 of 48 patients in a one-month span during the height of the COVID-19 pandemic were found to have substantially elevated TG levels requiring intervention to prevent AP [93]. The direct relationship between COVID-19 and dyslipidemia leading to pancreatitis is still poorly understood and warrants further investigation.

It is well documented in many excellent reviews that numerous medications have been linked to the development of pancreatitis, through a variety of unique mechanisms [97–99]. This review focuses specifically on those medications that result in significant alterations in HTG, resulting in DL-associated pancreatitis. As previously mentioned, TCZ was associated with clinically significant HTG which resulted in an episode of AP [92]. During its development, TCZ resulted in a small percentage of patients experiencing increases in

total cholesterol and LDL, but TG elevations were not observed or included in the side effect profile of the drug [100]. Selective estrogen receptor modifiers such as tamoxifen and clomiphene, as well as estrogen replacement therapies, have also been indicated in the development of HTG, with resulting DL-associated pancreatitis [12,101–106]. These effects are mediated through the mechanisms previously discussed concerning estrogen effects on circulating cholesterol and lipid levels. Psychiatric medications have also been associated with HTG and resulted in episodes of pancreatitis in several cases [106,107]. Specifically, atypical antipsychotics (which function through the modulation of serotonin, dopamine, norepinephrine, and histamine) [108] have been linked to HTG-induced pancreatitis [107]. A few other medications, including hydrochlorothiazide, mirtazapine, and all-trans-retinoic acid, have also been implicated less frequently in cases of HTG-induced pancreatitis [106,109–111]. Clinicians should remain vigilant for DL-associated pancreatitis when prescribing medications with side effect profiles that include DL.

8. Treatment and Prevention Strategies

Treatment of AP is a complex and multifactorial process, including supportive care, medications, and occasionally surgical intervention, and is outside the scope of this review. Instead, we focus in this section on the treatment and prevention options for HTG (in the context of AP), in both the outpatient and inpatient settings (Table 1).

HTG has been linked to several etiologies, including modifiable factors such as diet and amount of exercise, as well as heritable and genetic conditions such as familial dysbetalipoproteinemia and FCS [112,113]. Since no FDA-approved TG-lowering medications are effective in FCS, the main therapy in FCS is a very low-fat diet which would reduce TG packaged into CMs. Furthermore, medium-chain triglycerides (MCTs) are not packaged into CMs, and they are often used in patients with FCS to augment caloric intake [114]. It has been shown in a recent trial that in patients with FCS, Olezarsen may represent a new therapy to reduce plasma TG levels by reducing the hepatic synthesis of APOC3 [115]. BMI is a well-known modifiable risk factor associated with HTG; therefore, a healthy balanced diet and proper amounts of weekly exercise are highly encouraged to maintain normal TG levels [112,116–118]. In the setting of moderate TG elevations <500 mg/dL, dietary considerations should include decreasing carbohydrates, substituting polyunsaturated and/or monounsaturated fats for saturated fats, and avoiding excess intake of refined carbohydrates like table sugar, honey, and agave nectar [112,119]. Additionally, water should be substituted for sweetened beverages and sodas, which are high in artificial sweeteners and fructose [120]. With TG elevations >500 mg/dL, dietary modification requires the transition to a very low-fat diet (VLFD), which limits fat intake to 20–30 g per day and has been shown to lead to an improvement in TG levels [112,121]. These changes should be performed concomitantly with consistent exercise regimes to assist in weight loss [113].

Table 1. Treatment and prevention options for hypertriglyceridemia in both outpatient and inpatient settings.

Treatment	Setting	Drug Class	Mechanism of Action	Effect in HTG	Side Effects
Lifestyle/diet modification	Outpatient	N/A	N/A	Lowers TGs	N/A
Fenofibrate	Outpatient	Fibric acid derivative	Binds to PPAR in the liver, decreases APOC3 production, increasing LPL activity	Promotes CM and VLDL clearance	Nausea, headache, constipation, back/joint pain, cough, flu-like symptoms
Atorvastatin	Outpatient	Statin	Inhibits activity of HMG-CoA reductase enzyme	Mild decrease in TG synthesis, primary function is to lower LDL cholesterol and decrease overall risk of pancreatitis	Myalgia, myopathy, liver dysfunction
Omega-3 fatty acids	Outpatient	Antilipemic agent	Reduced synthesis and secretion of VLDL; upregulation of LPL	Decreased TG production and increased LPL activity to promote increased metabolism	Nausea, gastrointestinal discomfort, diarrhea, heartburn, headache
Volanesorsen	Outpatient	Antisense oligonucleotide	Selective inhibitor of *APOC3* mRNA	Promotes TG clearance by blocking APOC3 activity	Thrombocytopenia
Vupanorsen	Outpatient	Antisense oligonucleotide	Selective inhibitor of *ANGPTL3* mRNA, increases LPL and EL activity	Accelerated lipolysis and TG metabolism	Injection site erythema/pruritus, myalgia, malaise
Evinacumab	Outpatient	Monoclonal antibody	Inhibits activity of ANGPTL3—increases LPL and EL activity	Accelerated lipolysis and TG metabolism	Urinary tract infections, injection site erythema, arthralgia, myalgia, nausea, abdominal pain, fatigue
Plasmapharesis	Inpatient	N/A	Extracorporeal exchange of plasma, typically for fresh frozen plasma	Rapid TG clearance, useful in urgent/emergent situations	Hypotension, gastrointestinal bleed, allergic reaction
Insulin	Inpatient	Glucose-lowering agent	Activation of insulin receptor, which facilitates glycogen/lipid/protein synthesis, DNA synthesis, and cell growth/differentiation	Activates LP and increases TG hydrolysis and CM degradation	Hypoglycemia, local hypersensitivity, hypokalemia
Heparin	Inpatient	Anticoagulant	Inactivation of thrombin	Releases of stored LPL from endothelial cells, increasing TG catabolism	Bleeding events, thrombocytopenia, injection site erythema

Abbreviations: ANGPTL3—angiopoietin-like protein 3; APOC3—apolipoprotein C3; CM—chylomicron; EL—endothelial lipase; HMG-CoA—hydroxymethylglutaryl-coenzyme A; LPL—lipoprotein lipase; N/A—not applicable; PPARs—peroxisome proliferator-activated receptors; TGs—triglycerides; VLDL—very low density lipoproteins.

Medical therapy can be utilized either as a preventative strategy to lower baseline TG levels, or as a treatment after an episode of DL-associated pancreatitis with the same goal of lowering TG levels [112,122,123]. Most frequently used are fibric acid derivatives, such as fenofibrate or gemfibrozil, which function by activating transcription factors for nuclear peroxisome proliferator-activated α-receptors (PPAR-α), leading to downstream hepatic apoC-III production and increased LPL-mediated lipid metabolism [112,124,125]. Statins may also be used in combination with fenofibrate (but not gemfibrozil), which functions through the inhibition of the enzyme HMG Co-A reductase and results in decreased cholesterol synthesis and increased LDL receptor expression [112,122,126–128]. Omega-3 fatty acids have also been shown to help with lowering serum TGs, through the decreasing production of very low-density lipoproteins (VLDLs) in the liver and increasing VLDL clearance from circulation [112,129–132]. Investigational drugs have also been examined for beneficial effect in DL-associated pancreatitis, such as the antisense oligonucleotides Volanesorsen (which blocks apoC-III synthesis by targeting *APOC3* mRNA) and Vupanorsen (which targets the angiopoietin-like protein 3 (ANGPTL3) mRNA) or the monoclonal antibody Evinacumab (targets ANGPTL3) [112,133–139]. Long-term data on these investigation therapies are lacking, and it is an area of ongoing discovery [122].

In the setting of an acute episode of pancreatitis due to HTG, the two well-described treatment options are plasmapheresis or insulin and heparin infusions [122,123,140,141]. Plasmapheresis (PEX), or the process of extracorporeal removal of pathogens and targeted substances from the plasma before return to the body [142], is shown to significantly decrease TG levels in the setting of acute DL-related pancreatitis [122,123,143–146]. PEX facilitates rapid clearance of TGs from the blood stream, with a much faster onset of action compared to conventional medical therapies [147–149]. Plasma is usually exchanged for fresh frozen plasma. Complications occurring during PEX are typically related to bleeding issues, such as gastrointestinal bleeds or hypotension and are generally due to the use of additional anticoagulant therapies like heparin or citrate, which are necessary during PEX to prevent line clotting [150–152]. Alternatively, if HTG is more moderate than severe, or if PEX is not available at a particular institution, then intravenous infusions of insulin and heparin have been well documented as treatment options to lower TG levels [122,123,153–157]. Insulin works in this setting by activating LPL activity, which increases the rate of TG hydrolysis into fatty acids and CM degradation to decrease serum TG levels [122,158,159]. Importantly, dextrose must be given during insulin therapy to prevent life-threatening hypoglycemia [159,160]. Heparin is often used in combination with insulin, as numerous studies have shown these therapies provide greater TG-lowering effects when given together rather than separately [122,161–164]. Heparin acts on endothelial cells, causing the release of stored LPL which will then function to break down TGs [122]. Patients receiving heparin therapy must be monitored for potential bleeding events [164].

Finally, metabolic, and bariatric surgery has been described as a valid prevention strategy for DL-associated health complications. Multiple studies have shown long-term benefits (>5 years) including lower serum LDL, HDL, and TG levels in patients after various gastric bypass procedures [165–168]. One study examined the impact of metabolic surgery on the recurrence of pancreatitis in a patient with familial LPL deficiency and multiple episodes of DL-associated AP and found that at 2 years postop, gastric bypass surgery decreased the patient's TGs significantly and he had not had any further episodes of AP [167]. Metabolic and bariatric surgery should be considered for obese patients with DL, both for metabolic benefits as well as risk reduction for future pancreatitis episodes.

9. Key Perspectives

Robust evidence exists correlating elevated HTG levels to the occurrence of AP. Despite the caveat of some studies utilizing different TG cut-off levels to signify the degree of HTG severity, the consensus suggests that patients with an abnormal TG level >1000 mg/dL are at high risk of having AP. Other elements of DL, such as decreased HDL-C, are significantly linked with the development of AP. In addition to DL being an etiology of AP, its arguably

greater impact is in worsening the severity of AP and increasing the risk for ARP in the future. These recurrent bouts of inflammation and pancreatic injury likely contribute to the development of CP and pancreatic cancer. Despite an abundance of research in the field of DL-associated pancreatitis, there seems to be a paucity of research investigating the association of DL with CP and pancreatic cancer. Therefore, more prospective mechanistic and clinical studies of these associations are warranted. Additionally, this review shed light on unique clinical presentations of DL which were likely overlooked due to their rarity. However, these may increase in clinical relevance as the prevalence of chronic conditions affecting lipid metabolism continue to grow. Finally, our review presented an overview of current therapies for the management of HTG. While these have been shown to be effective tools for clinicians in the acute setting, the greatest emphasis should be placed on the management of the co-morbid conditions (primary or secondary) which cause DL, via both lifestyle modification and medication.

10. Conclusions

The amelioration of DL should be a focus of the long-term clinical management of any patient with AP as this will decrease the severity and incidence of future episodes. The connection between DL and pancreatitis is strong. Expanding our understanding of these diseases and disseminating our current knowledge is vital in mitigating its impact on morbidity and mortality.

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