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REVIEW

Hypertriglyceridemia-Related Pancreatitis In Patients With Type 2 Diabetes: Links And Risks

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Abstract: Disturbances in glucose and lipid homeostasis are cardinal features of the metabolic syndrome that affect millions of people worldwide. These conditions have multi-organ impact, and while cardiovascular effects are usually the core for studies and preventive measures, other systems may also be affected, including the pancreas. Acute pancreatitis related to severe hypertriglyceridemia is an under-recognized condition that could lead to significant morbidity and mortality. Therefore, when suspected, prompt diagnosis and treatment should be initiated to cover the various aspects of this disorder. Though commonly known to be associated with excess of alcohol use, hypertriglyceridemia-related pancreatitis is particularly observed in diabetics, especially when uncontrolled. Here, we portray the possible mechanisms and clinical features that link type 2 diabetes, hypertriglyceridemia and pancreatitis, and discuss their health-related outcomes and the current and novel treatment options for this unique disease.

Keywords: hypertriglyceridemia, acute pancreatitis, type 2 diabetes, cardiovascular disease, metabolic syndrome

Introduction

The prevalence of metabolic syndrome is high, affecting 20–30% of the general population in developed countries. About a third of the adult population in the United States is estimated to answer the diagnostic criteria for the metabolic syndrome,[1] a cluster of cardiometabolic risk factors including abdominal obesity, elevated blood pressure, high fasting plasma glucose levels and typical dyslipidemia characterized by increased triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol. It is therefore not surprising that the metabolic syndrome and each of its features predispose to the development of diabetes and cardiovascular disease. Furthermore, the incidence of other systemic disorders with adverse consequences increases as well. In this review, we will draw a line between three interrelated conditions: type 2 diabetes mellitus, severe hypertriglyceridemia (HTG) and acute pancreatitis. Collectively, HTG-related pancreatitis in diabetics is often underdiagnosed, although it may result in serious condition and systemic complications, warranting early identification and intervention.

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Acute Pancreatitis: An Overview

Acute pancreatitis is the most common pancreatic disease worldwide,[2] occurring in 40/100,000 of the western population,[3] and casting a significant burden over the health-care system as estimated by a cost of $2.6 billion.[4,5] While death rates from

acute pancreatitis decreased in recent years to less than 2% of the admissions, its incidence is increasing,[6,7] making pancreatitis one of the most common causes for gastrointestinal hospitalizations.[8] The clinical course of acute pancreatitis can range from mild and self-limiting to severe forms with necrosis of the pancreatic parenchyma and subsequent organ failure and death. Generally, the course of pancreatitis can be divided into acute and late phases: The first days and up to two weeks constitute the acute phase, in which the risk for systemic inflammatory response syndrome (SIRS) and resultant organ failure is increased. This is followed by a late phase, which is characterized by local pancreatic complications, which may develop because of necrosis.[9] Hitherto, the treatment of acute pancreatitis is based on supportive care, with no disease-specific treatments available. The causes for acute pancreatitis are heterogeneous: gallstones (40% of the cases), alcohol (30% of the cases), drugs, genetics (mutations and polymorphisms such as PRSS1, SPINK1, CFTR, chymotrypsin C, claudin-2 and calcium-sensing receptor), autoimmune conditions (Less than 5% of the cases), iatrogenic [up to 10% undergoing endoscopic retrograde cholangiopancreatography (ERCP)], infections (less than 1% of the cases) such as mumps, Epstein–Barr virus, cytomegalovirus and ascaris, as well as severe HTG which is thought to be the third most common contributing etiology for acute pancreatitis, observed in up to 7% of the cases. HTG poses a significant risk for the development of acute pancreatitis. A large study that assessed the effect of statin use on acute pancreatitis using data from 4 million subjects demonstrated a 12.5-fold greater risk of acute pancreatitis among subjects with severe HTG (defined as serum triglycerides >1000 mg/dL) compared to subjects without HTG.[10]

Despite the variety in etiologies, the diagnosis of acute pancreatitis is uniform and is based on at least two out of three diagnostic criteria:[9] 1) Abdominal pain; 2) Elevated Amylase or Lipase serum levels (defined as at least three times the upper limit of the normal range) and 3) Radiographic findings of acute pancreatitis.

Hypertriglyceridemia In Clinical Practice

Prevalence And Risk Factors

HTG is defined as elevated fasting plasma triglycerides above 150 mg/dL.[11] The prevalence of HTG in western societies approaches 25% to 30% and is correlated with features of the metabolic syndrome.[12] The rate of severe HTG is significantly lower, reported as 1.7% when a cutoff of >500 mg/dL is used,[13] and 0.1–0.4% with HTG >1000 mg/dL in different populations.[14–17] Varying triglyceride cutoffs were suggested over the years by professional groups for defining "severe HTG". The Endocrine Society clinical practice guidelines proposed defining fasting triglyceride levels between 1000 and 1999 mg/dL as severe HTG and above 2000 mg/dL as very severe HTG, aiming to emphasize the significant increase in the risk for acute pancreatitis associated with these levels.[18]

HTG observed in patients with type 2 diabetes is commonly mild to moderate. However, the severity of HTG is closely related to the concurrent dysregulation of metabolic measures, particularly hyperglycemia, insulin resistance, central obesity, hepatosteatosis and sedentary lifestyle. Many additional factors may significantly increase triglyceride levels when uncontrolled, including alcohol intake and hypothyroidism, as well as secondary factors such as pregnancy, renal failure and various medications (Table 1). In addition, the tendency of HTG to worsen during metabolic derangements is influenced by the genetic susceptibility of each patient. Accordingly, severe HTG is often induced by a combination of primary genetic predisposition and dysregulation of secondary metabolic causes or alcoholism.

Genes

In the past, HTG was classified according to the Fredrickson classification of hyperlipoproteinemia phenotypes, based on the electrophoretic patterns of lipoprotein fractions.[19] In the genomic era, with the understanding that the genetic basis for HTG is complex, the clinical utility of this classification became less significant. Mild-to-moderate HTG is usually polygenic, whereas severe HTG, especially in young patients, is more likely to be due to monogenic causes and is associated with substantially increased fasting concentrations of chylomicrons[20] (Table 1); both are worsened when combined with secondary factors. Accordingly, hypertriglyceridemic states often result from the interaction of cumulated multiple susceptibility genes and environmental stressors. In most families, HTG is not a dominantly inherited trait. Moreover, carriers of the same mutation may show a wide range of triglyceride concentrations and severity of HTG phenotypes.[21] Therefore, genetic testing is not indicated in most cases and performed mainly in children and adolescents with severe chylomicronemia syndromes. Possible causative mutations are in genes that regulate catabolism of triglyceride-rich lipoproteins, such as in cases of lipoprotein lipase (LPL)

Table 1 Etiologies Of Hypertriglyceridemia

Hypertriglyceridemia	
Primary	**Secondary**
Familial hyperchylomicronemia (type 1) Lipoprotein lipase (LPL) deficiency or mutations in genes regulating the catabolism of triglyceride-rich-lipoproteins (APOC2, APOA5, GPIHBP1, LMF1, GPD1)	Obesity Diabetes mellitus (especially when undiagnosed or uncontrolled) Metabolic syndrome components may have genetic susceptibility
Familial combined hyperlipidemia (type 2b; multygenic)	Hypothyroidism
Familial dysbetalipoproteinemia (type 3; APO-E mutations)	Excessive alcohol intake
Familial hypertriglyceridemia (type 4) Mixed Hypertriglyceridemia (type 5; multigenic)	High glycemic index or saturated fat diet, with excessive energy intake
Rare genetic diseases: familial partial lipodystrophy	Drugs (Thiazides, non-selective beta-blockers, estrogens, tamoxifen, bile-acids resins, corticosteroids, protease inhibitors, cyclosporine, retinoids, anti-epileptics, antipsychotics, etc.)
	Pregnancy
	Cushing's syndrome
	Autoimmune conditions
	Advanced renal disease/nephrotic syndrome
	Advanced liver disease

deficiency or dysregulation of its cofactors (APOC2, APOA5, LMF1, GPIHBP1 and GPD1).[22]

Association With Cardiovascular Disease

Mild-to-moderate HTG is considered a common risk factor for atherosclerotic cardiovascular disease (ASCVD), reflecting increased levels of triglyceride-rich lipoproteins, evolving into remnant particles that contain high concentration of cholesterol which may contribute to atherosclerotic plaque development.[23,24] Moreover, the hydrolysis of the triglyceride-rich lipoprotein particles at the endothelial surface is suggested to generate local inflammation, further contributing to the macrophage foam cell formation and the atherosclerotic process.[24] However, in conditions of severe HTG, the saturation of lipoprotein lipase may prevent efficient hydrolysis of large particles such as chylomicrons and very-low-density lipoproteins (VLDL), and therefore the triglyceride-rich lipoproteins may be too large to cross the endothelial barrier and could not enter the intima and cause atherosclerosis, thus suggesting that cholesterol in very large lipoproteins may be less atherogenic than cholesterol in smaller lipoproteins.[25] Accordingly, lifetime severe HTG due to genetic causes is not always accompanied by atherosclerotic cardiovascular disease.[26]

Hypertriglyceridemia-Related Pancreatitis

Impact Of Hypertriglyceridemia Severity

HTG is considered responsible for 1–7% of all cases of pancreatitis.[27] Systematic review of 34 studies found that the overall incidence of HTG-associated acute pancreatitis may even reach 9%, indicating that it is the third most common acute pancreatitis etiology after gallstones and alcohol.[28] Elevated triglyceride levels in serum are associated with increased risk for acute pancreatitis, which is particularly observed in severe HTG. Triglyceride levels above 500 mg/dL or 1000 mg/dL are common thresholds for initiating lipid-modifying agents for reducing the risk of developing pancreatitis, though it is thought that values triggering acute pancreatitis often exceed 2000–3000 mg/dL.[29,30] The risk may depend on the type and characteristics of the circulating triglyceride-rich lipoproteins, with the greater risk associated with higher circulating levels of chylomicrons. The rate of acute pancreatitis in patients with severe HTG may reach 15–20%,[31] and in a recent study from an integrated health-care system it was shown that for each 100 mg/dL unit of increase in the triglyceride levels above 1000 mg/dL, there was a 3% increase in

risk of developing pancreatitis.[32] Nevertheless, although a gradual stepwise increase in the risk of acute pancreatitis is clearly observed in patients with severe (1000–2000 mg/dL), very-severe (2000–3000 mg/dL) and extreme (>3000 mg/dL) hypertriglyceridemia,[17] a large retrospective epidemiological study has shown that even mild-to-moderate HTG, from values of 177 mg/dL and above, was associated with a consecutive increase in the risk of acute pancreatitis.[33] It is possible that the risk of developing pancreatitis is not uniform in its relation with HTG, and that HTG might be both a cause and an effect of other metabolic factors associated with pancreatitis including diabetes, obesity and alcohol use, that when uncontrolled, acute pancreatitis may be triggered. It is also possible that when a patient arrives to medical care with acute pancreatitis and abdominal pain, he is already in a prolonged fasting state so that the triglyceride levels associated with the onset of pancreatitis have diminished. Detection of lactescent serum, physical examination findings such as eruptive xanthomas or lipemia retinalis, and features of the metabolic syndrome should raise suspicion for underlying HTG in patients presenting with pancreatitis.[34]

Pathogenesis And Mechanistic Considerations

The pathogenetic theories for acute pancreatitis are multiple, as many causes of acute pancreatitis have been discovered, and therefore whether there is a common pathogenic pathway that triggers various forms of acute pancreatitis is controversial.[35] The exact mechanism involved in HTG-induced pancreatitis is not completely clear. HTG in animals with defect in LPL activity was shown to be associated with pancreatitis and histological evidence of hemorrhage and necrosis of the pancreas leading to lobular destruction.[36,37] Fatty acid-induced toxicity was also shown to be associated with mitochondrial damage in hypertriglyceridemic animal pancreas.[37,38] The large diameter of triglyceride-rich lipoproteins especially chylomicrons may impair the circulatory flow in the pancreatic capillary beds resulting in ischemia that may harm the acinar structure. Enzymatic degradation of triglyceride-rich lipoproteins generates proinflammatory free fatty acids that can lead to further damage of pancreatic acinar cells and microvasculature.[27] The inflammatory process may cause necrosis, edema and pancreatic inflammation, which may lead to a systemic inflammatory response. Interestingly, low-grade inflammation was suggested as the mediating factor between mild-to-moderate HTG and higher risk of acute pancreatitis.[39] Dysregulation of key enzymes involved in triglyceride metabolism may also be associated with HTG-induced pancreatitis; for example, mutations in the LPL gene causing significant reduction in LPL activity may lead to pregnancy-induced chylomicronemia and pancreatitis.[40] HTG-related pancreatitis has also been reported in rare disorders such as glycogen storage disease and lipodystrophies.[41,42]

Morbidity And Health-Related Outcomes

The rate of inpatient hospitalizations for acute pancreatitis significantly increased in the preceding decade.[43] This may be associated with the rising prevalence of metabolic syndrome and diabetes, which were also shown to be associated with increasing severity and mortality from acute pancreatitis.[44,45] Retrospective studies show a positive correlation between HTG and acute pancreatitis complications.[46] In a meta-analysis of observational studies, triglyceride-related pancreatitis was associated with worse prognosis compared to non-triglyceride-related pancreatitis, including increased risk for renal failure, respiratory failure, shock, SIRS and Acute Physiology and Chronic Health Evaluation (APACHE-II) scores.[47] Increased triglyceride levels were also shown to be associated with the development of multiple or persistent organ failure among patients hospitalized with acute pancreatitis, regardless of etiology.[48,49] In addition, a progressive increase in the incidence of pancreatic necrosis, newly diagnosed diabetes mellitus, longer hospital stays and mortality were observed with the increase in HTG on admission for acute pancreatitis.[50] Accordingly, health-care-related costs were also demonstrated to be higher in severe hypertriglyceridemic patients who developed acute pancreatitis, due to more outpatient and emergency department visits, hospitalizations and longer length of stays during the hospital visits.[51]

Recurrent Pancreatitis

The overall risk of recurrent attacks after the sentinel episode of pancreatitis may reach 20% and varies according to etiology.[52] Recurrence is more often evident with alcoholic etiology and when surgical treatment of biliary pancreatitis is delayed.[53–55] The severity of the first-time acute pancreatitis episode was also shown to predict recurrent episodes.[56] The literature data regarding the recurrence rate of pancreatitis in the setting of severe HTG are conflicting, and range from zero to about third of the patients with pancreatitis, possibly due to varying control

of secondary factors and the extent of successful reduction in serum triglycerides with medical treatment.[57–59] Patients who continue to have elevated triglyceride levels are at an increased risk of recurrent pancreatitis as compared to patients that achieve normalization of their triglyceride levels.[60] In our previous analysis of a cohort of 171 patients with HTG-related pancreatitis, 16% suffered from recurrent pancreatitis during a mean follow-up of 7 years; extreme HTG with peak triglyceride levels exceeding 3000 mg/dL as well as inability to hold triglyceride levels under 500 mg/dL were strong and independent predictors of recurrent pancreatitis.[58] These laboratory values and alcohol abuse were also associated with a stepwise increase in the number of recurrent episodes of pancreatitis during long-term follow-up.

Type 2 Diabetes, Dyslipidemia And Pancreatitis

Diabetic Dyslipidemia

Dyslipidemia is common in people with type 2 diabetes. Insulin resistance is associated with overproduction and reduced catabolism of large triglyceride-rich lipoproteins; this contributes to HTG that is often observed in subjects with diabetes.[61] Insulin resistance also leads to decreased LPL activity in adipose tissue and muscle. Moreover, the activity of cholesteryl ester transfer protein (CETP) contributes to an enrichment of cholesterol in VLDL and remnant particles. This promotes the exchange between VLDL triglycerides and cholesteryl esters from low-density lipoproteins (LDL) and HDL, leading to cholesterol-depleted HDL and LDL particles; as their triglyceride content is hydrolyzed by hepatic lipase, the cholesterol-depleted LDL particles become smaller and denser.[62] Small, dense LDL particles are thought to be more atherogenic than larger, buoyant LDL particles.[63] They are less cleared by the LDL receptors, tend to be retained in the arterial wall and are more likely to undergo modifications such as oxidation and glycation, thus promoting the generation of foam cells, an initial phase of atherosclerosis. Accordingly, LDL particle number (LDL-P) is increased and is thought to be a better prognostic marker for atherosclerotic cardiovascular disease than LDL cholesterol (LDL-C), particularly when a discordance between LDL-P and LDL-C exist, as commonly seen in patients with metabolic syndrome and diabetes.[64,65] Patients with metabolic syndrome and diabetes often have a typical lipid profile, and the triad consisting of elevated serum concentrations of triglycerides, a high prevalence of small dense LDL particles and a low concentration of HDL-C with increased catabolism is often named as "diabetic dyslipidemia".[66] Furthermore, the dysregulation of hepatic lipid homeostasis, particularly lipolysis with increased availability of fatty acids from the adipose tissue and hepatic de-novo lipogenesis, leads to lipid accumulation in hepatocytes resulting in non-alcoholic fatty liver disease, commonly seen in subjects with type 2 diabetes.[67] The advances in the understanding of the pathophysiology of diabetic dyslipidemia are summarized in recent reviews.[61,67] Yet, the pathophysiologic basis of diabetic dyslipidemia is still not completely understood and requires further research.

Type 2 Diabetes And Acute Pancreatitis

Large cohort studies have reported that subjects with type 2 diabetes from Western populations have higher risk for developing acute pancreatitis compared to those without diabetes.[68,69] This was further demonstrated in an Asian population-based cohort study, in which patients with diabetes had a 2-fold greater incidence of acute pancreatitis versus non-diabetics.[70] The etiology of acute pancreatitis is commonly multifactorial; when severe HTG is present, diabetes and alcohol abuse are often the dominant contributing factors observed, though interplay of other factors may be seen. Diabetes is the most common secondary factor encountered in patients with HTG-related pancreatitis, and triglyceride levels are higher in patients with undiagnosed or poorly controlled diabetes, thereby increasing the risk of pancreatitis.[34] In our cohort of patients with severe HTG-related acute pancreatitis in the setting of the general population, type 2 diabetes was evident in 62%, increasing to 79% in those with extreme HTG.[58] Moreover, severe HTG was particularly associated with insulin-treated diabetes, which probably reflected advanced or uncontrolled diabetes as the main metabolic driver for HTG-related pancreatitis. Studies have also reported the association between the use of anti-diabetic drugs and reduction in the risk of acute pancreatitis,[70–72] with attaining lower triglyceride levels shown to be associated with lower rates of pancreatitis.[58,73]

The intertwined contributing factors and close interactions between severe HTG, type 2 diabetes and acute pancreatitis are illustrated in Figure 1.

Chronic Pancreatitis And Diabetes

Chronic pancreatitis is diagnosed according to criteria that include: (a) recurrent bouts of abdominal pain with increase in the level of serum pancreatic enzymes, (b)

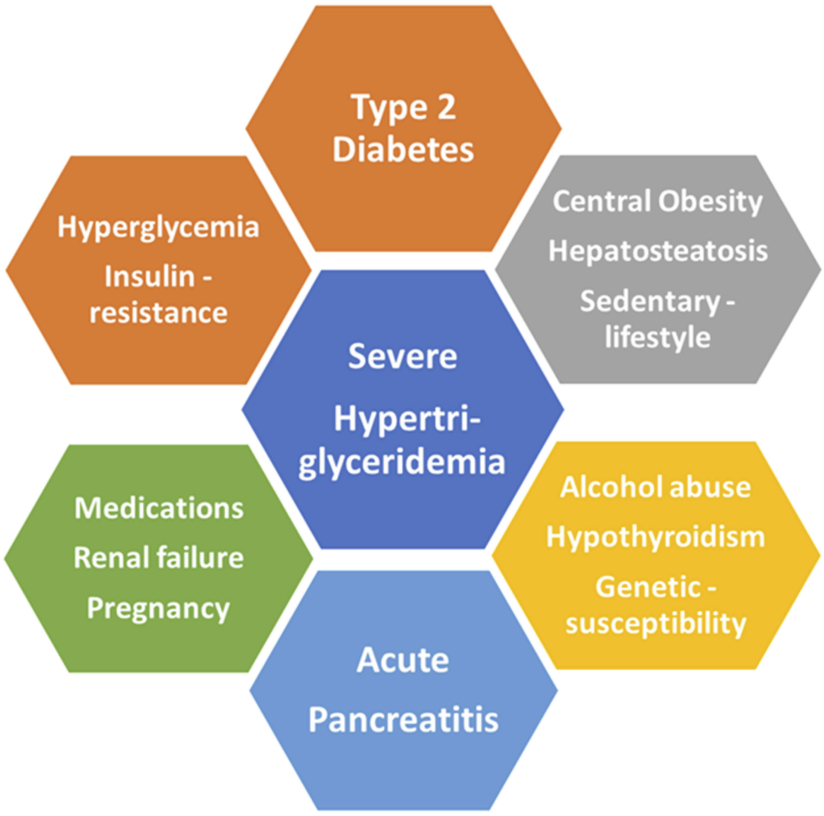

Figure 1 Intertwined factors contributing to hypertriglyceridemia-related pancreatitis in type 2 diabetes.

radiological findings of strictures and dilatation in pancreatic ducts and/or pancreatic calcifications and (c) histological proof.[74] Chronic pancreatitis is characterized by ongoing inflammation of the pancreas that results in progressive loss of the endocrine and exocrine functions of the pancreas owing to atrophy and/or replacement with fibrotic tissue.[75] The inflammatory process can be due to array of different disorders, including genetic predisposition, chronic obstructive causes (pancreatic tumors and variations in pancreatic ductal anatomy), metabolic disorders such as hypercalcemia (as in primary hyperparathyroidism) and HTG, or autoimmune disorders. However, the most prevalent cause of chronic pancreatitis remains chronic alcohol abuse. These disorders may result in similar functional consequences that include recurrent abdominal pain and maldigestion due to exocrine insufficiency. In addition, progressive fibrotic destruction of the pancreatic parenchyma leads to reduced beta cell mass and reduced insulin secretion, which may result in the development of diabetes mellitus secondary to endocrine insufficiency, commonly referred to as pancreatogenic diabetes or type 3c diabetes mellitus. Exocrine insufficiency, calcifications and pancreas surgery were shown to be contributing factors to the development of diabetes in the setting of chronic pancreatitis, in addition to traditional risk factors such as obesity and family history.[76] Episodes of hypoglycemia are common in patients with pancreatogenic diabetes and are associated with increased mortality.[77]

Management Of Pancreatitis In The Setting Of Hypertriglyceridemia

General Considerations

1. Fluid resuscitation: Volume depletion and third-space loss can worsen the course of acute pancreatitis and increase mortality. Some retrospective studies demonstrated a reduction in morbidity and mortality when aggressive fluid administration in the first 24 hrs of treatment was implemented,[78,79] though a recent review published by the American Gastroenterological Association Institute concluded that the current evidence is insufficient to favor intensive fluid resuscitation.[80]
2. Antibiotic therapy: Recent studies[81,82] and meta-analyses[83,84] have shown that routine prophylactic

use of antibiotics does not result in clinical benefit. However, the considerable methodological heterogeneity between clinical trials assessing the routine prophylactic use of antibiotics in acute pancreatitis and their somewhat contradicting results may suggest that sub-groups of patients with acute pancreatitis, such as those who develop persistent organ failure and those with extensive necrosis, may in fact benefit from early administration of antibiotics.

3. Nutrition: Recent clinical trials have shown that early oral or enteral feeding is not associated with significant adverse events and may in fact decrease pain and subsequent use of opioids and may even be associated with a decrease in length of hospitalization.[85–88] Dietary modifications are tailored to disease severity. In mild acute pancreatitis, a regular diet may be continued while severe pancreatitis mandates enteral nutrition.

Treatment Of Hypertriglyceridemia

The cornerstone of treatment of HTG is lifestyle modification. Interventions to reduce triglyceride levels include reduction in excessive body weight and in consumption and intake of mono- and disaccharides, total amount of dietary carbohydrates, as well as saturated fat in the acute phase of severe HTG and/or pancreatitis. Abstinence from alcohol is also important.

Patients should permanently adhere to their diet – otherwise, their triglyceride levels will increase despite the intake of drugs. In addition, medium-chain triglycerides (MCT) are an option to treat patients with severe HTG, aiming to prevent postprandial chylomicronemia. In patients on a low-fat diet, supplemental MCTs provide additional calories without increasing circulating triglycerides. Unlike long-chain fatty acids, which are incorporated into chylomicrons and enter the lymphatic circulation, MCT fatty acids bind to albumin and transported via the portal vein to the liver where they are oxidized to ketones and are not significantly incorporated into lipids synthesized in the liver. As MCTs may potentially lead to ketosis, care should be used in diabetic patients or hospitalized patients with ketosis or acidosis.

Increased habitual physical activity and utilization of n-3 polyunsaturated fatty acid supplements are also recommended. Routine initial pharmacological treatment is based on fibrate therapy, in conjunction with dietary modifications and the addition of statins when cardiovascular risk is increased. In severe cases, drug combinations may be required. Ezetimibe inhibits the absorption of cholesterol in the intestine, targeting the NPC1L1 intestinal cholesterol transporter. It is usually used as an add on therapy to statins in the management of hyperlipidemia, though it may also be a useful adjunct therapy in patients with HTG. The addition of ezetimibe to fenofibrate resulted in a greater decrease in LDL-C levels and increase in HDL-C levels than either drug alone or resulted in a shift of LDL particles from small dense particles to more large buoyant particles.[89,90]

Although severe HTG significantly improves with combined lifestyle and pharmacotherapy, in patients with long duration of diabetes it is typically not possible to totally normalize triglyceride levels. In addition, due to the pharmacodynamics of most therapies to lower HTG, monitoring of serum creatinine concentrations, creatinine phosphokinase (CPK), liver enzymes and muscle symptoms is advocated when drug combinations are used.

Fibrates

Fibrates, derivatives of fibric acid, are the mainstay of HTG treatment, reducing triglyceride levels by 25–40%.[91] Fenofibrate, bezafibrate and clofibrate are the commonly used fibrates. Gemfibrozil is less used today due to the increased risk for renal impairment, rhabdomyolysis and interaction with statins. Fibrates act by modulating peroxisome proliferator-activated receptor alpha function in the liver, resulting in reduced hepatic secretion of VLDL and increased lipolysis of plasma triglycerides.[92] Thereby, fibrates can also lower dense LDL particles and even increase HDL-C levels. Generally, treatment with fibrates is well-tolerated, though rare reports of hepatitis, myositis, renal failure and rhabdomyolysis have been documented, especially when combined with statins.[91] Despite the promising mechanism of treatment and effect of lipoprotein particle levels, the effectiveness of fibrates on lowering cardiovascular morbidity and mortality is less than optimal, and its use for secondary prevention remains debated. Evidence-based analyses concluded that there is moderate-quality level of evidence for a potential positive effect of fibrates in secondary prevention of non-fatal stroke, myocardial infarction and vascular death.[93,94]

Pemafibrate is a novel selective peroxisome proliferator-activated receptor-α modulator (SPPARMα) with a suggested favorable benefit–risk balance than older fibrates, including superior effects of on triglyceride reduction and HDL-C elevation, and less adverse effects on liver and kidney function, with fewer drug interactions,

and a large-scale trial (PROMINENT) evaluating the impact of pemafibrate on cardiovascular outcomes in type 2 diabetes patients with dyslipidemia is currently in progress.[95]

Omega-3 Fatty Acids (Fish Oils)

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids reduce hepatic VLDL production,[96] which results in reduction in triglyceride transporting lipoproteins and in lower serum triglyceride concentrations of about 20–35%, depending on the severity of HTG.[97] Moreover, EPA may have beneficial effects on plaque formation and progression, endothelial function, and foam-cells formation.[98] Currently, two forms of purified EPA are available for clinical use: Icosapentate (icosapent; Epadel) which is available in Japan only and icosapent ethyl (Vascepa) which is approved for use in the United States for severe HTG. The effects of these EPA only regimens on cardiovascular outcomes were further explored in several clinical trials (JELIS and REDUCE-IT).[99,100] Briefly, these studies demonstrated that adding EPA to statins resulted in reduction in triglyceride levels and improvement in various cardiovascular outcomes, though it is debated whether the reduction in cardiovascular outcomes is secondary to the effect on triglyceride-rich lipoproteins. We refer the readers to a recently published review which summarizes the main results of these trials.[101]

Niacin

Nicotinic acid (Niacin), a broad-spectrum lipid-regulating agent, affects cholesterol metabolism, yielding reduction in total cholesterol, triglycerides, LDL-C and lipoprotein (a) levels, as well as an increase in HDL-C levels.[102] It has also been suggested that Niacin might even induce a non-lipid-mediated atheroprotective effect.[103] As niacin has failed to reduce cardiovascular events when added to statins in large randomized clinical trials, its use in clinical practice has lessened in recent years.[104,105]

The Effect Of Glucose Lowering Agents On Triglycerides

Apart from its effect on glucose homeostasis, insulin activates LPL, an enzyme that promotes chylomicron degradation into glycerol and free fatty acids. Insulin has also been shown to increase messenger-RNA levels of LPL in animal-derived adipocytes in vitro.[106] Interestingly, insulin monotherapy was described as an effective and overall safe treatment in the setting of HTG acute pancreatitis.[107,108] The use of insulin is often needed in diabetic patients with hypertriglyceridemic-associated pancreatitis, as its effect is often faster than that of oral medications aimed to reduce HTG.

Additional Therapies For Severe Hypertriglyceridemia

Plasma exchange: plasmapheresis may be effective in rapid removal of triglycerides from the serum of patients with severe HTG pancreatitis. Triglycerides may be decreased by 60–80% after 2 sessions of apheresis. However, most data come from case reports or small series, and the clinical benefit in improving outcomes in acute pancreatitis is less conclusive.[109,110] In addition, apheresis is expensive and is not without risks for complications such as bacteremia, vein thrombosis and bleeding, and therefore apheresis treatment should be highly individualized.

Heparin infusion: In addition to its anticoagulation effect, heparin also stimulates the release of LPL, which is attached to endothelial cells, and therefore contributes to the reduction in triglyceride levels in serum. However, it was reported that long-term infusion of heparin may deplete LPL leading to reduction of chylomicron catabolism and rebound increase in triglyceride levels.[111] Therefore, it is suggested that due to concern of rebound hypertriglyceridemia and risk of hemorrhage into the pancreas during acute attack of pancreatitis, the continuous infusion of heparin should preferably be avoided.

Lomitapide: Lomitapide is a microsomal triglyceride transfer protein (MTTP) inhibitor that is currently approved for the treatment of homozygous familial hypercholesterolemia. As it reduces triglycerides in addition to all apo-B containing lipoproteins it may also be useful in the management of patients with severe genetic HTG and recurrent acute pancreatitis who are refractory to traditional treatment. However, long-term hepatic safety may be a concern and direct clinical trial evidence is lacking for this indication.[112]

Novel Therapies For Hypertriglyceridemia

Gene replacement therapy: Gene therapy is an emerging new player in the field of dyslipidemias and cardiovascular diseases. Gene replacement therapy was developed for LPL-deficiency, an autosomal recessive condition caused by a homozygotic null mutation of the LPL gene. This unique rare disorder cannot be treated by enzyme replacement therapy due to the short half-life of the LPL protein. This has set the path for the development of gene therapy,

based on the LPL^{s447x} gene named Glybera.[113] While data regarding efficacy and safety of treatment were promising, though limited, its marketing has been halted because of its high price-tag.[114]

Antisense oligonucleotides (ASO): ASO are a class of RNA-based therapeutic agents, which bind selectively to mRNA encoding specific proteins. By binding to mRNA, ASO facilitate degradation through the ubiquitous ribonuclease RNase H1, which results in lower production of specific proteins.[115] Currently, ASO therapies are being developed for targeting ApoC3, a modulator of triglyceride metabolism through inhibition of LPL activity. Initial results from clinical trials with antisense-mediated inhibition of hepatic *APOC3* mRNA (drug name: volanesorsen) provide promise for these therapies in reducing triglyceride levels and increasing insulin sensitivity and HDL-C levels.[116]

Monoclonal antibodies: Angiopoietin-like protein 3 (ANGPLT3) antibodies: ANGPLT3 is a protein which is synthesized in the liver and inhibits LPL activity, resulting in reduction in triglyceride hydrolysis. REGN1500 (Evinacumab) and IONIS-ANGPTL3-LRx are fully human monoclonal antibodies which bind to ANGPLT3 and by doing so activate LPL. A reduction in triglyceride levels was recorded in animal models and in a phase 1 study.[117] Currently, there are several clinical trials assessing the effects of ANGPLT3 modulating drugs.

The various medications highlighted earlier, such as fibrates and fish-oils, do not have an immediate effect. Therefore, in cases of severe HTG-related pancreatitis, prompt and broad treatment should be initiated in the acute phase in addition to the lipid-lowering drugs, including fasting, intravenous fluids, insulin therapy, and consideration of the use of plasmapheresis in severe cases.

Summary

Pancreatitis in the setting of diabetes and severe HTG is a unique and often underdiagnosed disease with significant morbidity and increased risk for mortality. When suspected, prompt diagnosis and treatment should be initiated to cover all three aspects of this condition, by providing supportive therapy, lowering glucose levels, and subsequently reducing triglycerides with the aid of lifestyle modifications and pharmaceutical agents. Currently, novel therapeutics aimed to provide greater effect on triglyceride levels are being developed and may prove effective in reducing both ASCVD and the rate of acute pancreatitis.

Disclosure

The authors report no conflicts of interest in this work.

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