

Triglyceride-induced Pancreatitis: Diagnostic and Therapeutic Approach

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Abstract

Hypertriglyceride-induced pancreatitis is rarely associated with triglyceride levels less than 1000 mg/dl. However, triglyceride levels can drop rapidly with fasting that often accompanies acute pancreatitis. In addition, triglyceride levels can be elevated in the setting of acute pancreatitis as injury to the pancreas causes inadequate lipid metabolism leading to triglyceride elevation. Thus, the question arises whether high triglycerides induce acute pancreatitis or vice versa in patients presenting with elevated triglyceride levels. Also, the drop in triglyceride levels associated with fasting may result in failure to consider hypertriglyceridemia as the etiology for acute pancreatitis in a patient who presents with triglyceride levels below 1000 mg/dL. In this review, we discuss the relationship between hypertriglyceridemia and pancreatitis as well as causes of elevated triglyceride levels that must be considered in patients who present with both conditions. In addition, we present an evidence based algorithm that summarizes the approach to hypertriglyceridemia and pancreatitis in the setting of complex medical co-morbidities.

Introduction

Hypertriglyceride-induced pancreatitis is the third most common cause of pancreatitis after gallstones and alcohol [1,2]. It accounts for 1.3 to 3.8 percent of pancreatitis cases [1] and in one study, it was the identified etiology in 77.8% of severe acute pancreatitis in pregnancy with a mean triglyceride level at onset of 27.9 mmol/l [3]. Pancreatitis usually develops in patients with markedly elevated serum triglyceride levels (>1000 mg/dL) and/or lactescent serum specimens [1] which has been associated with increased mortality compared to other causes of pancreatitis [4]. Since measurement of serum triglyceride levels is often not considered at the time of admission in the setting of acute pancreatitis, failure to identify an obvious yet lethal cause may be missed easily because triglyceride levels rapidly drop during voluntary fasting [5]. There are no studies in the literature ascertaining how many of hypertriglyceride-induced pancreatitis cases are missed initially. The purpose of this review article is to elucidate an evidenced based algorithm to correctly identify these patients.

Demographics

In one large retrospective cohort study, patients who presented with hypertriglyceridemia-induced pancreatitis had a mean age of 54.2 ± 11.9 years. Three fourths of which are male and a great majority (78.9%) are Caucasians [6].

Clinical presentation

The initial presentation of Hypertriglyceridemia-induced pancreatitis is the same as that of pancreatitis of other causes (Table 1). It should be included as part of the differentials in any patient presenting with signs and symptoms of pancreatitis with a history of poorly controlled diabetes, hyperlipidemia or a family history of hyperlipidemia, hypothyroidism, alcoholism, and pregnancy [1,2,7,8]. The prevalence of diabetes among patients with hypertriglyceridemia is 41%, with an additional 11.6% having impaired glucose metabolism.

In addition, all patients with hypertriglyceridemia have at least one secondary factor contributing to their hypertriglyceridemia [6].

Severe clinical clues on physical examination may help physicians to suspect hypertriglyceridemia. Xanthomas are localized infiltrates of lipid-containing foam cells which may be found within the skin, tendons and subperiosteum in patients with hypertriglyceridemia. Xanthomas in the dorsum of hand and ankle (heterozygous familial hypercholesterolemia), planar xanthomas in the antecubital fossa (homozygous familial hypercholesterolemia), xanthomata on the palms, elbow and extensor surface of arms (type III hyperlipoproteinaemia) and eruptive xanthomata on the extensor surfaces of the forearm, lipemia retinalis, hepatosplenomegaly and milky plasma samples are all indicative of severe and chronic hypertriglyceridemia [9]. These classical findings however, have a very low incidence and are found in only less than 10% of cases. In addition, the triglyceride levels do not accurately predict whether patients would develop these signs, suggesting that factors other than

Table 1. Diagnosis of acute pancreatitis (2 out of 3) [15].

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| Abdominal pain characteristic of acute pancreatitis a |
| Serum amylase and/or lipase ≥ 3 times the upper limit of normal |
| characteristic findings of acute pancreatitis on CT scan b |

a – Unbearable epigastric pain radiating to the back in half of the cases, reaching max intensity in 30 minutes and persists for more than 24 hours without relief

b - Enlargement of the pancreas with diffuse edema, heterogeneity of pancreatic parenchyma, peripancreatic stranding, and peripancreatic fluid collections

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hypertriglyceridemia may contribute to their development [6].

Hypertriglyceridemia induced pancreatitis usually occurs when the serum triglyceride is more than 20 mM (1772 md/dl) acutely [6].

Serum amylase levels may appear falsely normal in patients with pancreatitis and serum triglyceride levels ranging from 500 to 6000 mg/100mL. This was first thought to be due to interference of light transmission in the colorimetric reaction caused by lactescent serum specimens [10]. However, Warshaw *et al.* suggested the presence of circulating amylase inhibitors in the serum and urine in patients with hypertriglyceride-induced pancreatitis [11]. True amylase levels can be determined after correcting the lactescent serum with serial dilutions with normal saline [10,11]. Interestingly, in one animal study, amylase levels were found to decrease by a factor of 4.33 in pancreases from hyperlipidemic acute necrotic pancreatitis compared with the normal-lipid acute necrotic pancreatitis group rats. It was suggested that the high-fat low-carbohydrate diet given to the hyperlipidemic rats may suppress the need for amylase and thus its mRNA expression in the pancreas [12].

Pathogenesis

There are a number of proposed mechanisms by which hypertriglyceridemia can cause pancreatitis. It may be secondary to rapid accumulation of chylomicrons in the pancreatic vasculature [13]. Chylomicrons are the largest lipid-transporting lipoprotein and can form a thrombus plug and obstruct the pancreatic circulation during rapid buildup causing ischemia and acidosis to the organ [13]. The acidic environment may cause premature activation of trypsinogen leading to autodigestion. Another hypothesis is that it may be secondary to the release of free fatty acids from triglycerides by pancreatic lipase [14]. These pro-inflammatory free fatty acids can induce free radical formation and damage to the pancreas or may in fact cause direct injury through chemical irritation together with lipoecithin [15]. Free fatty acids were found to cause edema and hemorrhage of canine pancreatic glands by Saharia *et al.* [14]. Hyperlipidemia induced pancreatitis in pregnancy is believed to be secondary to acute adipose infiltration and fat embolism of pancreatic vessels as a result of fat dissociation by human placental lactogen from the syncytiotrophoblasts and release of a substantial aggregate of free fatty acids [15].

Diagnostic approach

Patients with severe hypertriglyceridemia causing pancreatitis should be screened for the following:

1. Familial causes such as Type I, IV and V hyperlipidemia syndromes
2. Alcohol, Thyroid stimulating hormone (TSH), and Glucose levels
3. Medications that can cause hypertriglyceridemia such as steroids and valproic acid.

Familial hyperlipidemia syndromes

Type I and V causes severe hypertriglyceridemia enough to cause spontaneous pancreatitis while Type IV usually requires a secondary factor such as alcohol, diabetes mellitus, obesity or thyroid dysfunction to cause the disease [16].

Type I hyperlipoproteinemia is a rare genetic disorder of autosomal recessive trait. It can be classified further based on its defect: 1a – lipoprotein lipase deficiency, 1b – apoprotein II deficiency; and 1c –

presence of a lipoprotein lipase inhibitor. All defects cause an increase in circulating chylomicrons and subsequent hypertriglyceridemia. The resulting accumulation of triglycerides causes the patient's plasma to have a lactescent appearance. Patients with this disorder usually presents in childhood with eruptive and tuberous xanthomas and may have recurrent pancreatitis [16]. Familial lipoprotein lipase deficiency (1a) can be diagnosed by LPL enzyme assay. Management of the disorder includes maintaining a daily fat intake of 20g or less or 15% of total caloric intake. In addition, patients should avoid medications known to cause increased levels of triglycerides such as ethanol, estrogens, diuretics, and beta blockers [17]. In a 2009 study published in BMC Gastroenterology comparing twenty-four survivors of acute pancreatitis secondary to hypertriglyceridemia to a control of thirty one patients with severe hypertriglyceridemia who had not developed pancreatitis, five cases were found to have lipoprotein lipase deficiency [18]. There were no differences between the groups in terms of other risk factors for pancreatitis such as obesity, diabetes, or alcohol abuse outside of the acute phase. All of the patients found to have lipoprotein lipase (LPL) deficiency were thin and experienced their first episode of pancreatitis in childhood. The authors recommend measurement of lipoprotein lipase activity be reserved for patients who experienced their first episode of acute pancreatitis in childhood [18].

Type V hyperlipoproteinemia is characterized by an increase in both chylomicrons and very low density lipoprotein (VLDL). Patients with this disorder often have low low-density lipoprotein (LDL) levels as well. Such patients have been found to demonstrate particularly labile triglyceride levels with sharp increases when consuming alcohol and sharp decreases when eventually ceasing alcohol use [20]. These triglyceride fluctuations may delay the consideration of the lipid disorder as a possible factor contributing to acute pancreatitis. However, the disorder should be considered in all patients who have triglyceride levels greater than 1000 mg/dL at any point of time in their care. Type V hyperlipoproteinemia can be seen in patients with alcohol or diabetes induced hypertriglyceridemia. These factors simultaneously contribute to the development of pancreatitis. In these patients, the genetic disorder contributes to the overproduction of VLDL and chylomicrons, while alcohol or diabetes interferes with the clearance of triglycerides [9]. Estrogen therapy has also been found to induce pancreatitis in women with type V hyperlipoproteinemia [19].

Type IV hyperlipoproteinemia is an autosomal dominant condition characterized by an increased production of VLDL and generally require another factor such as diabetes or alcohol in order to induce pancreatitis [9,21]. Patients with this disorder typically have triglyceride levels below 1000 mg/dL. Therefore, this condition should generally be considered in the presence of contributing factors.

Secondary causes of hypertriglyceridemia

Non-insulin dependent diabetes mellitus is a well-known cause of hypertriglyceridemia and is the most common cause of hypertriglyceride-induced pancreatitis [1]. There are several mechanisms that may explain this phenomenon. One described thoroughly in literature that may play the largest role in hypertriglyceridemia in insulin resistant patients is the loss of the inhibitory effect of insulin on VLDL apolipoprotein B production by hepatocytes [22]. In addition, Lipoprotein lipase is regulated by insulin levels through gene expression, synthesis and secretion. All of these factors may be impaired in insulin-resistant patients [23]. While hypertriglyceridemia is the most common lipid abnormality in these patients, most well controlled diabetics have triglyceride levels that are within the normal range [24]. However,

abrupt elevations in serum triglyceride levels can occur and may result in pancreatitis [24].

Like triglyceride induced pancreatitis, patients with diabetic ketoacidosis (DKA) may also present with markedly elevated serum triglycerides and acute abdominal pain making it more difficult to differentiate the two entities [16,25]. Deficiency of insulin promotes lipolysis in adipose tissue followed by release of free fatty acids which will eventually be converted to very low density lipoproteins, which, coupled with the inhibition of lipoprotein lipase in peripheral tissues, results in hypertriglyceridemia [26]. Nair *et al.* evaluated the incidence of hypertriglyceridemia and occult pancreatitis in 100 patients with diabetic ketoacidosis. Their study showed that patients with DKA presenting with acute abdominal pain and hypertriglyceridemia (>500 mg/dl) may also have CT scan findings consistent for pancreatitis. DKA patients with pancreatitis had higher glucose levels with higher anion gap acidosis compared to the patients without pancreatitis. Serum triglyceride levels improved with resolution of ketosis but not with acidosis or anion gap [16]. The degree of hypertriglyceridemia however, did not correlate with the severity of ketoacidosis [25].

Alcohol, when taken with a meal high in saturated fat, can increase postprandial triglyceride level significantly. This is mainly because of alcohol's inhibitory effect on lipoprotein lipase, thereby decreasing the breakdown of chylomicrons and VLDL [26]. On the other hand, excessive alcohol intake can cause hypertriglyceridemia even in a fasting state because it promotes the synthesis of large VLDL particles in the liver. Furthermore, alcohol increases the synthesis of large VLDL particles in the liver, which is the main source of triglycerides in the hypertriglyceridemia associated with chronic excessive alcohol intake. In case of chronic consumption, lipoprotein lipase activity seems to adapt itself. [26]. In an animal study comparing the triglyceride levels after acute and chronic ingestion of alcohol, it was shown that the increase in triglyceride levels were less pronounced in rats subjected to chronic alcohol intake in a non-fasting state, confirming that chronic alcohol intake stimulates the production of extrahepatic lipoprotein lipase in response to the increased triglyceride concentration [12]. In some cases, acute alcohol intake may cause significantly elevated triglyceride levels with an increased risk of pancreatitis, especially patients with metabolic syndrome [26].

Medications such as estrogen, estradiol, glucocorticoids, thiazide diuretics, beta blockers, sertraline, protease inhibitors, valproate and related drugs, and isotretinoin can cause severe hypertriglyceridemia and the chylomicronemia syndrome in patients with inherited lipid metabolic syndromes (Table 2) [27]. These drugs reduce lipoprotein lipase and hepatic triglyceride lipase activity [28]. Oddly, fenofibrates, which decrease triglyceride levels, causes an increased risk of pancreatitis among patients with type 2 DM [29].

Table 2 shows a list of genetic and acquired cause of severe hypertriglyceridemia that maybe associated with pancreatitis. This was adopted from a scientific statement by the American Heart Association on triglycerides and cardiovascular disease [30].

Initial treatment

Initial treatment of hypertriglyceride-induced pancreatitis is no different from treating other causes of pancreatitis (bowel rest, aggressive intravenous hydration, pain control and anti-emetics). A recent study shows that goal-directed hemodynamic management guided by functional hemodynamic parameters such as stroke volume variation, compared to CVP-guided therapy, led to a significantly

Table 2. Causes of Sever Hypertriglyceridemia that maybe associated with pancreatitis [40].

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| Genetic |
| Lipoprotein Lipase Deficiency (Type 1a) |
| Apolipoprotein CII Deficiency (Type 1b) |
| Apolipoprotein AV deficiency |
| Glycosylphosphatidylinositol-anchored HDL binding protein-1 (GPIHBP1) Deficiency |
| Marinesco-Sjogren Syndrome |
| Chylomicron retention (Anderson) disease |
| Familial hypertriglyceridemia (Type IV) |
| Acquired Disorders of Metabolism* |
| Poorly controlled insulinopenic diabetes |
| Hypothyroidism |
| Pregnancy, especially in the 3rd trimester + |
| Drugs |
| a-interferon |
| Atypical antipsychotics |
| Table |
| Beta blockers such as atenolol † |
| Bile acid resins |
| L-Asparaginase |
| Estrogens (oral, not transcutaneous) |
| Protease inhibitors |
| Raloxifene Δ |
| Retinoic acid drugs |
| Sirolimus |
| Tamoxifen |
| Thiazides |
| Diet |
| Alcohol Excess, especially with ah high saturated-fat diet |
| Diseases |
| Autoimmune Chylomicronemia (antibodies to lipoprotein lipase; systemic lupus erythematosus |
| Chronic idiopathic urticarial |
| Renal Disease |

*These diseases are especially concerning in patients with preexisting hypertriglyceridemia, often on a genetic basis

+ Triglycerides increase with each trimester, usually becomes symptomatic in 3rd trimester especially in susceptible patients

† carvedilol preferred in DM patients with hypertriglyceridemia if beta blockers are indicated

Δ in women who experienced hypertriglyceridemia with estrogen therapy

improved survival, tissue oxygenation, and microcirculatory perfusion, as well as less histopathologic damage in porcine model of severe acute pancreatitis [31].

Target triglyceride level

Triglycerides should be decreased and maintained at <500mg/dL to prevent progression to pancreatic necrosis and organ failure [2].

Management strategies

As of now, there are no definite guidelines for treating hypertriglyceride-induced pancreatitis but previous case reports and series have shown success with intravenous insulin and/or heparin [32-36], and plasmapheresis [28]. There are still no randomized studies that compare the efficacy of the different treatment regimens used in the management of this disease. Insulin may be considered the first choice with or without heparin in patients with concomitant hyperglycemia, but appears to be slower in action compared with apheresis, which decreases serum triglycerides and decrease symptoms in a very short period of time [34].

Intravenous insulin ± heparin

Intravenous insulin and heparin administration should be considered in patients with concomitant hyperglycemia [32]. Insulin activate lipoprotein lipase which degrade chylomicrons into glycerol and free fatty acids resulting in rapid reduction of triglyceride levels [35,36]. Success has been reported using infusion of 5% dextrose with regular insulin (control serum glucose to <200mg/dL) together with 5000 units of intravenous heparin twice daily in decreasing serum triglyceride levels to <500 mg/dL and improve symptoms of pancreatitis within 4 days [28,32]. Subcutaneous regular insulin dosed at 0.1 unit/kg decreases triglyceride levels within 4 hours but the effect is not sustainable long term [37]. Intravenous insulin is more efficacious than subcutaneous insulin for treating hypertriglyceride-induced pancreatitis.

While insulin has been shown to be effective when used as monotherapy [37], intravenous heparin does not. Heparin stimulates the release of endothelial lipoprotein lipase and causing an initial rise of the circulating enzyme but is immediately followed by its degradation in the liver resulting in its further depletion and recurrence of hypertriglyceridemia [38]. That is why heparin is recommended only as an adjunct treatment to insulin. A single bolus of low molecular weight heparin (Dalteparin) was found to deplete lipoprotein lipase similarly to unfractionated heparin [39].

Apheresis

Apheresis is capable of rapidly lowering markedly elevated triglyceride levels, clear pancreatic enzymes, and provides symptom relief from pancreatitis within 2.5 hours [40,41]. Reports have shown a 41% (1,406 to 682 mg/dL) decrease in serum triglycerides after 1 session of apheresis alone [42]. Several studies have shown that apheresis can significantly decrease serum triglycerides and cause both clinical and laboratory improvement when conservative treatment with diet and pharmaceutical drugs fail. [28, 43-45]. All these studies also stress the importance of performing apheresis as soon as possible to maximize therapeutic benefit. Its limiting factor is, however, its availability and very high cost.

Prevention

Prevention of initial and recurrent pancreatitis from hypertriglyceridemia should be emphasized. Data from NHANES (National Health and Nutrition Examination Survey) show that the prevalence of patients with very high triglycerides levels (≥ 500 mg/dL [≥ 5.65 mmol/L]) are estimated to be to be 1.7% of the total study population or representing 3.4 million Americans [46]. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) has already stated that the initial aim of therapy for patients is to prevent acute pancreatitis through triglyceride lowering [47]. Such therapy includes very low fat diets ($\leq 15\%$ of calorie intake), weight reduction and physical activity, and usually a triglyceride-lowering drug such as fibrates or nicotinic acid [30]. However, drug treatment (with fenofibrates or niacin) of asymptomatic persons with high triglyceride levels, particularly those less than 22.6 mmol/L, is still not recommended because of lack of evidence for any considerable therapeutic benefit and subjects the patients to its adverse effects and high cost. [48]. Lastly, Pancreatic enzyme therapy has been shown to alleviate abdominal symptoms [49].

Risk factors for hypertriglyceridemia such as insulin resistance and alcoholism should be assessed in this setting as these are correctible

factors that can be treated to avoid future bouts of pancreatitis in patients with occult hereditary lipid metabolism disorders. In such patients, providers should evaluate a patient's diet for contributors to elevated triglyceride levels. Epidemiologic reports have shown the glycemic index of foods has a direct correlation to triglyceride levels [50]. In addition, interventional studies have demonstrated that substituting foods possessing high glycemic indexes for foods with lower glycemic indexes can reduce a patient's serum triglyceride level by as much as 15% to 25% [51].

Conclusion

In conclusion, we provide an evidence based algorithm to summarize the approach to the etiology of hypertriglyceride-induced pancreatitis.

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