INTRODUCTION

Acute pancreatitis is a medical emergency. Alcohol and gallstones are the most common etiologies accounting for 60%-75% cases. Other important causes include postendoscopic retrograde cholangiopancreatography procedure, abdominal trauma, drug toxicity, various infections, autoimmune, ischemia, and hereditary causes. In about 15% of cases the cause remains unknown (idiopathic pancreatitis). Metabolic conditions giving rise to pancreatitis are less common, accounting for 5%-10% cases. The causes include hypertriglyceridemia, hypercalcemia, diabetes mellitus, porphyria, and Wilson’s disease. The episodes of pancreatitis tend to be more severe. In cases of metabolic pancreatitis, over and above the standard routine management of pancreatitis, careful management of the underlying metabolic abnormalities is of paramount importance. If not treated properly, it leads to recurrent life-threatening bouts of acute pancreatitis. We hereby review the pathogenesis and management of various causes of metabolic pancreatitis.

HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia increases the risk of acute pancreatitis, accounting for a minor but a significant proportion of patients (2%-7%).[4] There are many causes of acute pancreatitis, which can be easily identified in 75%-85% of patients. Gallstones and alcohol are the most common causes contributing to 38% and 36% of cases, respectively.[5] Metabolic causes, although less common, constitute an important and treatable component of its etiologic actors. They include hypertriglyceridemia, hypercalcemia, porphyria, diabetes mellitus, and rarely Wilson’s disease. The current article focuses on these rare causes, pathogenesis, and specific management of the underlying metabolic diseases.

Key words: Hypercalcemia, hypertriglyceridemia, metabolic etiologies, pancreatitis
Chylomicrons are triglyceride-rich lipoprotein particles. These are large enough to occlude the pancreatic capillaries leading to ischemia and subsequent acinar structural alteration and release of pancreatic lipase. Enhanced lipolysis leads to increased concentration of cytotoxic free fatty acids in the circulation. This results in vascular endothelial cell damage, sludging of red cells and pancreatic ischemic injury.[7] Once a cellular injury pattern has been initiated, cellular membrane trafficking becomes chaotic, with the following deleterious effects: (1) lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin; (2) intracellular trypsin triggers the entire zymogen activation cascade; and (3) secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells. Activated neutrophils then exacerbate the problem by releasing superoxide (the respiratory burst) or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local (and, in severe cases, systemic) inflammatory responses. The early mediators defined to date are tumor necrosis factor-alpha, IL-1, interleukin-6, and interleukin-8, platelet activating factor (PAF).[8]

These mediators of inflammation cause an increased pancreatic vascular permeability, leading to hemorrhage, edema, and eventually pancreatic necrosis. As the mediators are excreted into the circulation, systemic complications can arise, such as bacteremia due to gut flora translocation, acute respiratory distress syndrome, pleural effusions, gastrointestinal hemorrhage, and renal failure. The systemic inflammatory response syndrome can also develop, leading to the development of systemic shock. Eventually, the mediators of inflammation can become so overwhelming to the body that hemodynamic instability and death ensue.

Noticeably, normoamylasemia is possible in about 50% of patients with hypertriglyceridemia-induced pancreatitis. The mechanism is believed to be the interference with in vitro determination of the actual amylase level by disturbance of the calorimetric methods. Serial dilutions of the sample could reduce interference of light transmission by hyperlipidemia serum.[9] Associated clinical clues include eruptive xanthomatous or lipemia retinialis.

Table 1: Causes of hypertriglyceridemia

| Familial causes of hypertriglyceridemia (Friedrickson classification) |
|------------------|------------------|
| Type 1 (Familial chylomicronemia),     | |
| Type 2B (familial combined hyperlipoproteinemia),     | |
| Type 4 (Familial hypertriglyceridemia),     | |
| Type 5 (primary mixed hyperlipidemia),     | |
| Secondary causes |
| Obesity |
| Metabolic syndrome |
| A diet with a positive energy-intake balance and a high fat or high glycemic index content |
| Insufficient physical activity |
| Alcohol consumption |
| Diabetes mellitus, particularly type 2 |
| Renal disease, especially uremia or glomerulonephritis |
| Hypothyroidism* |
| Pregnancy: physiologic triglyceride concentrations double during the third trimester |
| An autoimmune disorder, such as a paraproteinemia or systemic lupus erythematosus |
| Any of several types of medications, including |
| Corticosteroids |
| Estrogens, especially those taken orally |
| Tamoxifen |
| Antihypertensives: e.g., noncardioselective β-blockers, thiazides |
| Isotretinoin |
| Bile-acid-binding resins |
| Cyclophosphamide |
| Antiretroviral regimens, especially for HIV infections |

Psychotropic medications: phenothiazines, second generation antipsychotics

In general, monotherapy with a pharmacologic agent should be attempted first, together with dietary adjustments. Combination treatment may be required for refractory severe hypertriglyceridemia. Fibric acid derivatives, such as gemfibrozil, bezafibrate, and fenofibrate, are a mainstay of hypertriglyceridemia treatment.[10] These fibrates can reduce plasma triglyceride levels by up to 50% and raise plasma high-density lipoprotein cholesterol (HDL-C) concentrations as much as 20% with simultaneous reduction of small dense low-density lipoprotein (LDL) particles.[11] The mechanism of action of fibrates includes modulation of the activity of peroxisome proliferator-activated receptor-α in the liver, with reduced hepatic secretion of very low-density lipoprotein (VLDL) and increased lipolysis of plasma triglycerides.[12] Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Newer statins used at higher doses can markedly reduce levels of triglycerides. They are not a first-line therapy when triglyceride levels exceed 500 mg/dL. However, statins can reduce triglyceride levels by 20%-40%.[11] The daily consumption of 2-4 g of niacin (nicotinic acid) can
lower plasma triglyceride levels by up to 45%, raise plasma HDL-C by up to 25%, and reduce plasma LDL-cholesterol by up to 20%.[14] However, niacin frequently causes light-headedness, cutaneous flushing, or pruritus. These adverse effects can be minimized by starting therapy at low doses then gradually increasing the daily dose; concomitant use of acetylsalicylic acid and laropiprant, DP1 receptor antagonist (that mediates prostaglandin D2-induced vasodilatation and flushing);[15] or use of longer-acting preparations.[14] Less common adverse effects include elevations of liver enzymes, increased levels of uric acid, gastrointestinal distress, and worsened glucose tolerance. Omega-3 fatty acids lower plasma triglyceride levels, particularly in persons with hypertriglyceridemia, by inhibiting the synthesis of VLDL cholesterol and triglycerides in the liver. A review of human studies concluded that approximately 4 g per day of omega-3 fatty acids reduced serum triglyceride concentrations by 25%-30%, increased serum LDL-cholesterol levels by 5%-10%, and increased HDL-C levels by 1%-3%.[17] Figure 1 depicts the algorithm for treatment of hypertriglyceridemia.

Glitazar drugs are dual agonists of peroxisome proliferator-activated receptor-α (similar to fibrates) and -γ (similar to thiazolidinediones) and hold theoretic advantages for treatment of type 2 diabetes and metabolic syndrome. However, an analysis of phase 2 and 3 trials found significant associations between muraglitazar and death, myocardial infarction, and stroke.[18] Heparin and insulin, by virtue of their endothelial lipoprotein lipase-activating property, can be of help.[19] Lipoprotein lipase (LPL) gene therapy/purified apo CII can be initiated in cases of hyperlipoproteinemia type 1 caused by LPL deficiency.[20,21] Extracorporeal elimination of lipoproteins by plasmapheresis is useful in rapidly lowering elevated serum triglycerides. This method has been employed with success in patients with acute pancreatitis and in pregnant women with hypertriglyceridemia-induced pancreatitis.[22,23]

**HYPERCALCEMIA**

Hypercalcemia can lead to acute pancreatitis.[24] Causes include hyperparathyroidism, malignancy (often in the setting of bony metastases or multiple myeloma), vitamin D toxicity, sarcoidosis, familial hypocalciuric hypercalcemia, and total parenteral nutrition and infusions of perioperative high-dose calcium during cardiopulmonary bypass.[25-30] Traditionally, acute pancreatitis has been considered a complication of primary hyperparathyroidism (PHPT).[31,32] If muscular/myopathic, urologic, or nervous system symptoms coexist with acute pancreatitis, patients should be evaluated for hyperparathyroidism.[33] The prevalence of acute pancreatitis in PHPT has been estimated to be between 1.5% and 13%.[31,34-40] The initial description of the association was described as early as 1940 when Smith and Cooke described a patient who succumbed to acute pancreatitis correlated to hyperparathyroidism.[41] In 1962 Mixter et al. reported 62 cases of pancreatitis occurring in association with PHPT after reviewing the published work.[42] Subsequent reports have focused on the development of pancreatitis in patients who are operated on for hyperparathyroidism.[43-45] However, while some studies have found an increased incidence of pancreatitis in patients with PHPT, others have not.[37] One possible reason for this turn could be the changing profile of PHPT in the developed countries, where symptomatic disease remains uncommon and pancreatic disease with PHPT extremely rare. In addition, the occurrence of PHPT among patients with pancreatitis appears to be very infrequent.[46,47] Data from other developing countries show this association in approximately 2.5% of patients.[48,49] In the series of 51 cases of primary hyperparathyroidism by Muthukrushnan et al., 4 patients had pancreatic calcification with past history suggestive of acute pancreatitis.[50] One center from the North India has reported that in 6.8% of patients with PHPT, the disease was initially suspected.

![Figure 1: Algorithm for management of hypertriglyceridemia. (Adapted from Am Fam Physician 2007;75:1365-71)](image)
because of unexplained pancreatic disease. Another series from South India has reported that 12% of patients with PHPT had pancreatic disease. The sex distribution showed a male preponderance with the male:female ratio being almost 2:1. This is in contrast to the female preponderance we see in PHPT without associated pancreatic disease. The commonest manifestation of pancreatic disease with PHPT was the history of recurrent upper abdominal pain. The patient can either present with life-threatening acute pancreatitis or a painless chronic pancreatitis characterized by malabsorption and secondary diarrhea. The presentation of pancreatic disease in PHPT into 4 important classes: (a) PHPT presenting as acute pancreatitis, (b) PHPT presenting as acute recurrent pancreatitis with no evidence of chronic pancreatitis, (c) PHPT presenting as chronic pancreatitis with or without pancreatic calcification, and (d) PHPT complicated by acute pancreatitis in the postoperative period.

**Hypercalcemia as the mediator of pancreatic injury in PHPT**

In animal models acute pancreatitis has been induced, when a 2-fold increase in serum ionized calcium was obtained by either bolus injections or by continuous infusion of calcium. Pathologic changes of early acute pancreatitis with hypercalcemia have been observed in several animal species. It was shown that hypercalcemia induced a secretory block and accumulation of digestive zymogens within the pancreatic acinar cells.

The molecular mechanism of hypercalcemia-mediated pancreatic injury has still not been elucidated and remains a matter of conjecture. They are 3-fold:

1. Hypercalcemia from PHPT leads to de novo activation of zymogens, including trypsinogen to trypsin, resulting in acinar cell damage, autodigestion of the pancreas and subsequent pancreatitis. Various factors, including alcohol abuse, ductal hypertension, ischemia, hyperlipidemia, viral infections, and hypercalcemia, may trigger acute pancreatitis by increasing intracytoplasmic calcium levels. Hypercalcemia per se, in addition to being an independent risk for the precipitation of pancreatic cellular injury, could also augment pancreatic disease in patients with ongoing pancreatic injury because of other causes.

Hypercalcemia-induced cellular injury leads to the following deleterious effects: (1) lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin; (2) intracellular trypsin triggers the entire zymogen activation cascade; and (3) secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells. Activated neutrophils then exacerbate the problem by releasing superoxide or proteolytic enzymes. Finally, macrophages release cytokines, such as tumor necrosis factor-alpha, IL-1, interleukin-6, and interleukin-8, PAF, which further mediate local (and, in severe cases, systemic) inflammatory responses. These mediators of inflammation cause an increased pancreatic vascular permeability, leading to hemorrhage, edema, and eventually pancreatic necrosis.

Recurrent acute pancreatitis can progress to chronic pancreatitis, as described by the necrosis–fibrosis theory. The South Indian study has proposed that presence of hypercalcemia correlated to PHPT among patients susceptible to tropical chronic pancreatitis (TCP), a form of chronic calcific nonalcoholic pancreatitis may cause an unmasking of preclinical and subclinical diseases.

2. Hypercalcemia leads to the formation of pancreatic calculi and by modifying pancreatic secretion, may lead to protein plug formation. The resultant ductal obstruction can lead to subsequent attacks of acute or chronic pancreatitis.

3. Factors other than calcium, such as genetic risk factors, may predispose patients with PHPT to acute pancreatitis.

Treatment of underlying cause of hypercalcemia and appropriate surgical measures are needed to manage the hyperparathyroidism-induced pancreatitis.

**Other causes**

They include diabetes mellitus, porphyria, Wilson’s disease, and glycogen storage disorders.

Both type 1 and type 2 diabetes mellitus can present with pancreatic involvement. The acute hyperglycemic states of diabetic ketoacidosis and hyperglycemic hyperosmolar coma are the most common offending factors leading to inflammation and injury. The accompanying acidosis, dehydration, and transient hypertriglyceridemia too are implicated in pancreatic injury. Other hypotheses include the following:

a. Deficiency of insulin, which serves as a trophic factor for pancreatic exocrine tissue leads to pancreatic exocrine insufficiency. This hypothesis was supported by the fact that patients without any beta-cell function display more obvious morphologic changes than those with some residual insulin secretion.

b. A persisting elevation of glucagon and somatostatin levels in diabetes can contribute to exocrine damage and dysfunction.

c. Autoimmune damage of pancreatic exocrine tissue in type 1 diabetes mellitus. In a study, antibodies against lactoferrin or carbonic anhydrase (both directed against
exocrine targets) were present in 77% of patients classified as type 1 diabetes mellitus.[67]

d. Diabetic autonomic neuropathy leading to deranged pancreatic secretion and subsequent pancreatic exocrine insufficiency.[68] A study by Ewald et al. demonstrated that diabetes duration was inversely correlated with fecal elastase 1 concentrations (FEC) and there was also a correlation between C-peptide levels and FEC.[68]

Interruption of the enteropancreatic reflexes by an autonomic neuropathy might impair 50% exocrine pancreatic response to a meal.[69]

Porphyria, particularly acute intermittent porphyria[70] and erythropoietic protoporphyrina,[71] occasionally present with pancreatic involvement. The reported pancreatic diseases associated with porphyria include acute pancreatitis, chronic pancreatitis, chronic pancreatitis with cystadenocarcinoma, and transient macroamylasemia. Spastic contraction of sphincter of Oddi resulting from autonomic neuropathy in porphyria leads to pancreatitis.[70] Fasting and diminishing calorie intake plays an aggressive role in pathogenesis of pancreatitis.

Infiltrative disorders, such as Wilson’s disease, lead to intracytoplasmic accumulation of copper.[72] Excessive concentration of these elements is toxic to various components of the cell leading to membrane disintegrity, increased permeability, and subsequent lysosomal degeneration. These changes in pancreas activate the pancreatic proteolytic enzymes, leading to autodigestion and inflammation.

Glycogen storage disorders specifically type 1 (Von Gierke’s disease) can lead to acute pancreatitis, hemorrhagic pancreatitis,[73] chronic pancreatitis,[74] and pancreatic pseudocyst formation. Excessive glycogen accumulation leading to pancreatic duct blockade and the accompanying hypertriglyceridermia are implicated in pathogenesis of pancreatitis.[74]

CONCLUSION

After gall stones and alcohol, metabolic factors contribute to a significant proportion of etiology of pancreatitis. Unless dealt with judiciously, they lead to recurrent episodes of pancreatitis and accompanying comorbidities. Prompt identification followed by appropriate treatment results in cure and prevention of untoward complications.

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