Review Article

Metabolic pancreatitis: Etiopathogenesis and management

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ABSTRACT

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.

Key words: Hypercalcemia, hypertriglyceridemia, metabolic etiologies, pancreatitis

INTRODUCTION

Acute pancreatitis is an inflammatory condition of pancreas. The suddenness of its onset, the limitless agony that accompanies it and the mortality attended upon render it one of the most formidable catastrophes. The increased incidence of pancreatitis, coupled with new treatment options, poses a challenge for primary care physicians. Over the last 20 years, the incidence of acute pancreatitis increased 10-folds.[1] Depending on its severity, it can have severe complications and high mortality despite treatment. While mild cases are often successfully treated with conservative measures, such as nothing by mouth and aggressive intravenous fluid rehydration, severe cases require intensive medical management and occasional surgical intervention to deal with complications of the disease process. Mortality

secondary to pancreatitis ranges from 2% to 9%.[2] 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.[3] 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.

HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia increases the risk of acute pancreatitis, accounting for a minor but a significant proportion of patients (2%-7%).[4] The tendency for pancreatitis markedly increases when triglyceride level crosses 1000 mg/dL, a level at which chylomicrons are present.[5] The capacity of the pancreas to produce an exocrine lipase might explain the specificity of pancreatic involvement with extreme hypertriglyceridemia. Table 1 mentions various causes of hypertriglyceridemia. While the familial causes often present with serum triglyceride levels of 500-1000 mg/dL, they are often aggravated by secondary factors, which should carefully be sought after.[6]

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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 erythematosis
  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

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 xanthomata or lipemia retinalis.

Treatment of acute episodes of pancreatitis includes hemodynamic stabilization, cessation of all oral intake, placement of a nasogastric tube and control of metabolic disturbances. Restricted energy intake is associated with a brisk decrease in plasma triglyceride levels. Nonpharmacologic treatment includes weight reduction, dietary modification, and exercise. Dietary modification should decrease weight, overall energy intake, and intakes of fat and refined carbohydrates (i.e., foods with a high glycemic index).[10] Alcohol consumption should be restricted. Recommended fat intake is restricted to 10%-15% of total energy intake (about 15-20 g/day), with reductions in all types of fat.[11]

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.[12] 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.[12] 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.[13] 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.[16] 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)
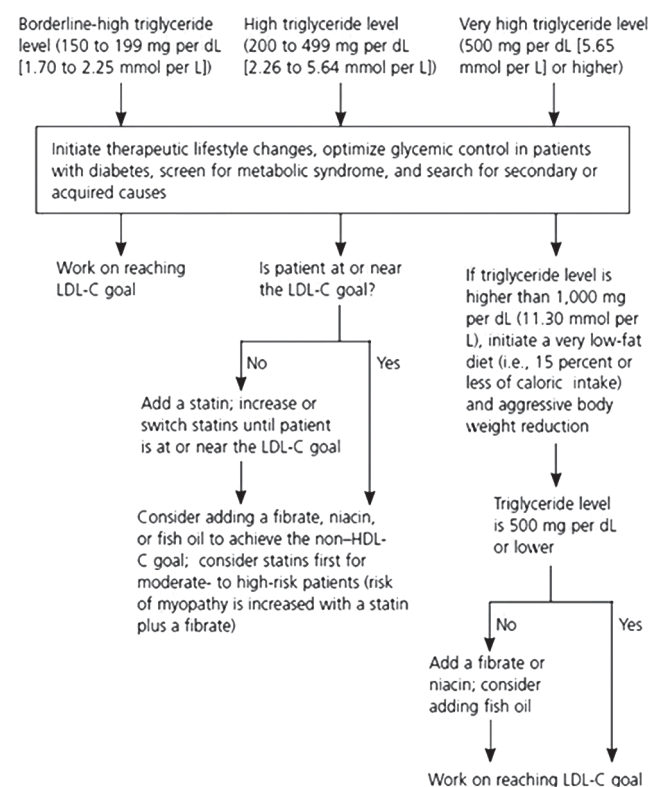
and -γ (similar to thiazolidinediones) and hold theoretic advantages for treatment of type 2 diabetes and metabolic syndrome. However, an analysis of phase 2 and 3 trials found significant associations between muraglitazar and death, myocardial infarction, and stroke.[18] Heparin and insulin, by virtue 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

Borderline-high triglyceride level (150 to 199 mg per dL [1.70 to 2.25 mmol per L])

High triglyceride level (200 to 499 mg per dL [2.26 to 5.64 mmol per L])

Very high triglyceride level (500 mg per dL [5.65 mmol per L] or higher)

Initiate therapeutic lifestyle changes, optimize glycemic control in patients with diabetes, screen for metabolic syndrome, and search for secondary or acquired causes

Work on reaching LDL-C goal

Is patient at or near the LDL-C goal?

If triglyceride level is higher than 1,000 mg per dL (11.30 mmol per L), initiate a very low-fat diet (i.e., 15 percent or less of caloric intake) and aggressive body weight reduction

No   Yes

Add a statin; increase or switch statins until patient is at or near the LDL-C goal

Consider adding a fibrate, niacin, or fish oil to achieve the non–HDL-C goal; consider statins first for moderate- to high-risk patients (risk of myopathy is increased with a statin plus a fibrate)

Triglyceride level is 500 mg per dL or lower

No   Yes

Add a fibrate or niacin; consider adding fish oil

Work on reaching LDL-C goal

NOTE: *In patients who have achieved the LDL-C goal, the secondary target of treatment should be achieving the non–HDL-C goal (i.e., 30 mg per dL [0.78 mmol per L] higher than the LDL-C goal.)*

Figure 1: Algorithm for management of hypertriglyceridemia. (Adapted from Am Fam Physician 2007;75:1365-71)

because of unexplained pancreatic disease.[51] Another series from South India has reported that 12% of patients with PHPT had pancreatic disease.[38] The sex distribution showed a male preponderance with the male:female ratio being almost 2:1.[35,38] 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.[47,52] The presentation of pancreatic disease in PHPT into 4 important classes:[38] (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.[53] Pathologic changes of early acute pancreatitis with hypercalcemia have been observed in several animal species.[54,55] It was shown that hypercalcemia induced a secretory block and accumulation of digestive zymogens within the pancreatic acinar cells.[56]

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.[57] 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.[38]

2. Hypercalcemia leads to the formation of pancreatic calculi and by modifying pancreatic secretion, may lead to protein plug formation.[58] The resultant ductal obstruction can lead to subsequent attacks of acute or chronic pancreatitis.[32]

3. Factors other than calcium, such as genetic risk factors, may predispose patients with PHPT to acute pancreatitis.[59]

   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.[9,60] The accompanying acidosis, dehydration, and transient hypertriglyceridemia too are implicated in pancreatic injury.[61] Other hypotheses include the following:

a. Deficiency of insulin, which serves as a trophic factor for pancreatic exocrine tissue[62] 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.[63]

b. A persisting elevation of glucagon and somatostatin levels in diabetes can contribute to exocrine damage and dysfunction.[64,65]

c. Autoimmune damage of pancreatic exocrine tissue in type 1 diabetes mellitus.[66] 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 protoporphyria,[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 hypertriglyceridemia 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.

REFERENCES

1. Kingsnorth A, O'Reilly D. Acute pancreatitis. Br Med J 2006;332:107-6.
2. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198-210.
3. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: Etiology and common pathogenesis. World J Gastroenterol 2009;15:1427-30.
4. Yoon YK, Ji JH, Mun BS. Hypertriglyceridemia-induced pancreatitis. Korean J Gastroenterol 2008;51:309-13.
5. Dominguez-Munoz JE, Malfertheiner P, Ditschuneit HH, Blanco-Chavez J, Uhl W, Buchler M, *et al.* Hyperlipidemia in acute pancreatitis. Relationship with etiology, onset, and severity of the disease. Int J Pancreatol 1991;10:261-7.
6. Kota SK, Kota SK, Jammula S, Krishna SV, Modi KD. Hypertriglyceridemia-induced recurrent acute pancreatitis: A case-based review. Indian J Endocrinol Metab 2012;16:141-3.
7. Kimura W, Mossner J. Role of hypertriglyceridemia in the pathogenesis of experimental acute pancreatitis in rats. Int J Pancreatol 1996;20:177-84.
8. Weber CK, Adler G. From Acinar Cell Damage to Systemic Inflammatory Response: Current Concepts in Pancreatitis. Pancreatology 2001;1:356-62.
9. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: Incidence and correlation with biochemical abnormalities. Am J Gastroenterol 2000;95:3123-8.
10. Jenkins DJ, Kendall CW, Augustin LS, Franceschi S, Hamidi M, Marchie A, *et al.* Glycemic index: Overview of implications in health and disease. Am J Clin Nutr 2002;76:266S-73.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
12. Barter PJ, Rye KA. Cardioprotective properties of fibrates: which fibrate, which patients, what mechanism? Circulation 2006;113:1553-5.
13. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, *et al.* Diabetes, plasma insulin, and cardiovascular disease: Subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med 2002;162:2597-604.
14. Carlson LA. Nicotinic acid: The broad-spectrum lipid drug. A 50th anniversary review. J Intern Med 2005;258:94-114.
15. Sood A, Arora R. Mechanisms of flushing due to niacin and abolition of these effects. J Clin Hypertens (Greenwich) 2009;11:685-9.
16. Carlson LA. Niaspan, the prolonged release preparation of nicotinic acid (niacin), the broad-spectrum lipid drug. Int J Clin Pract 2004;58:706-13.
17. Covington MB. Omega-3-Fatty Acids. Am Fam Physician 2004;70:133-40.
18. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005;294:2581-6.
19. Monga A, Arora A, Makkar RP, Gupta AK. Hypertriglyceridemia-induced acute pancreatitis--treatment with heparin and insulin. Indian J Gastroenterol 2003;22:102-3.
20. Ross CJ, Liu G, Kuivenhoven JA, Twisk J, Rip J, van Dop W, *et al.* Complete rescue of lipoprotein lipase–deficient mice by somatic gene transfer of the naturally occurring LPL S447X beneficial mutation. Arterioscler Thromb Vasc Biol 2005;25:2143-50.
21. Baggio G, Manzato E, Gabelli C, Fellin R, Martini S, Enzi GB, *et al.* Apolipoprotein C-II deficiency syndrome. Clinical features, lipoprotein characterization, lipase activity, and correction of hypertriglyceridemia after apolipoprotein C-II administration in two affected patients. J Clin Invest 1986;77:520-7.

22. Ho KM, Yeo J. Plasmapheresis in the management of pancreatitis related to hypertriglyceridaemia. Anaesth Intensive Care 1999;27:117.

23. Piolot A. Nadler F, Cavallero E, Coquard JL, Jacotot B. Prevention of recurrent acute pancreatitis in patients with severe hypertriglyceridemia: Value of regular plasmapheresis. Pancreas 1996;13:96-9.

24. Etemad B, Whitcomb DC. Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682-707.

25. Fernández-del Castillo C, Harringer W, Warshaw AL, Vlahakes GJ, Koski G, Zaslavsky AM, et al. Risk factors for pancreatic cellular injury after cardiopulmonary bypass. N Engl J Med 1991;325:382-7.

26. Tadeo Ruiz G, Ais Conde G, Vázquez Santos P, Manzanares JJ. Pancreatitis caused by hypercalcemia of malignant origin. Rev Esp Enferm Dig 1996;88:640-2.

27. Waele BD, Smitz J, Willems G. Recurrent pancreatitis secondary to hypercalcemia following vitamin D poisoning. Pancreas 1989;4:378-80.

28. Gaur S. Sarcoidosis manifested as hypercalcemic pancreatitis. South Med J 2001;94:939-40.

29. Davies M, Klimiuk PS, Adams PH, Lumb GA, Large DM, Anderson DC. Familial hypocalciuric hypercalcemia and acute pancreatitis. Br Med J (Clin Res Ed) 1981;282:1023-5.

30. Stemp LI. Pancreatic injury after cardiopulmonary bypass. N Engl J Med 1992;326:572-4.

31. Koppelberg T, Bartsch D, Printz H, Hasse C, Rothmund M. Pancreatitis in primary hyperparathyroidism (pHPT) is a complication of advanced pHPT. Dtsch Med Wochenschr 1994;119:719-24.

32. Cope O, Culver PJ, Mixter CG Jr, Nardi GL. Pancreatitis, a diagnostic clue to hyperparathyroidism. Ann Surg 1957;145:857-63.

33. Michalopoulos A, Papadopoulos V, Apostolidis S, Paramythiotis D, Zatagias A, Harlaftis N, Severe acute pancreatitis as a first symptom of primary hyperparathyroidism: A rare case report. Endocrinologist 2007;17:278-81.

34. Sitges-Serra A, Alonso M, de Lecea C, Gores PF, Sutherland DE. Pancreatitis and hyperparathyroidism. Br J Surg 1988;75:158-60.

35. Carnaille B, Oudar C, Pattou F, Combemale F, Rocha J, Proye C. Pancreatitis and primary hyperparathyroidism: Forty cases. Aust N Z J Surg 1998;68:117-9.

36. Bess MA, Edis AJ, van Heerden JA. Hyperparathyroidism and pancreatitis. Chance or a causal association?. JAMA 1980;243:246-7.

37. Vestergaard P, Mosekilde L. Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. BMJ 2003;327:530-4.

38. Jacob JJ, John M, Thomas N, Chacko A, Cherian R, Selvan B, et al. Does hyperparathyroidism cause pancreatitis? A South Indian experience and a review of published work. ANZ J Surg 2006;76:740-4.

39. van Lanschot JJ, Bruining HA. Primary hyperparathyroidism and pancreatitis. Neth J Surg 1984;36:38-41.

40. Ronni-Sivula H. The state of health of patients previously operated on for primary hyperparathyroidism compared with randomized controls. Ann Chir Gynaecol 1985;74:60-5.

41. Smith FB, Cooke RT. Acute fatal hyperparathyroidism. Lancet 1940;2:650-1.

42. Mixter CG Jr, Keynes WM, Cope O. Further experience with pancreatitis as a diagnostic clue to hyperparathyroidism. N Engl J Med 1962;266:265-72.

43. Dubost C, Jehanno C, Poirier A, Duranteau A. Is there a risk of acute pancreatitis after parathyroidism? Nouv Presse Med 1980;9:3281.

44. London NJ, Lloyd DM, Pearson H, Neoptlemos JP, Bell PR. Pancreatitis after parathyroidectomy. Br J Surg 1986;73:766-7.

45. Reeve TS, Delbridge LW. Pancreatitis following parathyroid surgery. Ann Surg 1982;195:158-62.

46. Shearer MG, Imrie CW. Parathyroid hormone levels, hyperparathyroidism and acute pancreatitis. Br J Surg 1986;73:282-4.

47. Prinz RA, Aranha GV. The association of primary hyperparathyroidism and pancreatitis. Am Surg 1985;51:325-9.

48. Bismar HA, El-Bakry AA. Primary hyperparathyroidism. Saudi Med J 2003;24:1214-8.

49. Younes NA, Al-Trawneh IS, Albesoul NM, Hamdan BR, Sroujieh AS. Clinical spectrum of primary hyperparathyroidism. Saudi Med J 2003;24:179-83.

50. Muthukrishnan J, Jha S, Modi KD, Jha R, Kumar J, Verma A, et al. Symptomatic primary hyperparathyroidism: A retrospective analysis of fifty one cases from a single centre. J Assoc Physicians India 2008;56:503-7.

51. Agarwal A, George RK, Gupta SK, Mishra SK. Pancreatitis in patients with primary hyperparathyroidism. Indian J Gastroenterol 2003;22:224-5.

52. Carey MC, Fitzgerald O. Hyperparathyroidism associated with chronic pancratitis in a family. Gut 1968;9:700-3.

53. Mithofer K, Fernandez-del Castillo C, Frick TW, Lewandrowski KB, Rattner DW, Warshaw AL. Acute hypercalcemia causes acute pancreatitis and ectopic trypsinogen activation in the rat. Gastroenterology 1995;109:239-46.

54. Frick TW, Hailemariam S, Heitz PU, Largiader F, Goodale RL. Acute hypercalcaemia induces acinar cell necrosis and intraductal precipitates in the pancreas of cat and guinea pig. Gastroenterology 1990;98:1675-81.

55. Frick TW, Wiegand D, Bimmler D, Fernandez-del Castillo C, Rattner DW, Warshaw AL. A rat model to study hypercalcemia induced pancreatitis. Int J Pancreatol 1994;15:91-6.

56. Frick TW, Mithofer K, Fernandez-del Castillo C, Rattner DW, Warshaw AL. Hypercalcemia causes acute pancreatitis by pancreatic secretory block, intracellular zymogen accumulation and acinar cell injury. Am J Surg 1995;169:167-72.

57. Haverback BJ, Dyce D, Bundy H, Edmondson HA. Trypsin, trypsinogen, and trypsin inhibitor in human pancreatic juice: Mechanism for pancreatitis associated with hyperparathyroidism. Am J Med 1960;29:424-33.

58. Noel-Jorand MC, Verine HJ, Sarles H. Dose-dependent and long-lasting effects of repeated intravenous injections of calcium on canine secretin-stimulated pancreatic juice secretion. Eur J Clin Invest 1981;11:25-31.

59. Felderbauer P, Karakas E, Fendrich V, Bulut K, Horn T, Lebert R, et al. Pancreatitis risk in primary hyperparathyroidism: Relation to mutations in the SPINK1 trypsin inhibitor (N34S) and the cystic fibrosis gene. Am J Gastroenterol 2008;103:368-74.

60. Kota SK, Jammula S, Kota SK, Meher LK, Modi KD. Acute pancreatitis in association with diabetic ketoacidosis in a newly diagnosed Type 1 diabetes mellitus patient; Case based review. Int J Clin Cases Investig 2012;4:54-60.

61. Fulop M, Eder H. Severe hypertriglyceridemia in diabetic ketosis. Am J Med Sci 1990;300:361-5.

62. Korc M, Owerbach D, Quinto C, Rutter WJ. Pancreatic islet-acinar cell interaction: Amylase messenger RNA levels are determined by insulin. Science 1981;213:351-3.

63. Löhr M, Klöppel G. Residual insulin positivity and pancreatic atrophy in relation to duration of chronic type 1 (insulin dependent) diabetes mellitus and microangiopathy. Diabetologia 1987;30:757–62.

64. Dyck WP, Rudick J, Hoexter B, Janowitz HD. Influence of glucagon on pancreatic exocrine secretion. Gastroenterology 1969;56:531-7.

65. Gyr K, Beglinger C, Kohler E, Trautzl U, Keller U, Bloom SR. Circulating somatostatin Physiological regulator of pancreatic function?. J Clin Invest 1987;79:1595-600.

66. Panicot L, Mas E, Thivolet C, Lombardo D. Circulating antibodies

against an exocrine pancreatic enzyme in type 1 diabetes. Diabetes 1999;48:2316-23.

67. Taniguchi T, Okazaki K, Okamoto M, Seko S, Tanaka J, Uchida K, *et al.* High prevalence of autoantibodies against carbonic anhydrase II and lactoferrin in type 1 diabetes: concept of autoimmune exocrinopathy and endocrinopathy of the pancreas. Pancreas 2003;27:26-30.

68. Ewald N, Raspe A, Kaufmann C, Bretzel RG, Kloer HU, Hardt PD. Determinants of exocrine pancreatic function as measured by fecal elastase-1 concentrations (FEC) in patients with diabetes mellitus. Eur J Med Res 2009;14:118-22.

69. El Newihi H, Dooley CP, Saad C, Staples J, Zeidler A, Valenzuela JE. Impaired exocrine pancreatic function in diabetics with diarrhea and peripheral neuropathy. Dig Dis Sci 1988;33:705-10.

70. Shen FC, Hsieh CH, Huang CR, Lui CC, Tai WC, Chuang YC. Acute intermittent porphyria presenting as acute pancreatitis and posterior reversible encephalopathy syndrome. Acta Neurol Taiwan 2008;17:177-83.

71. Komatsu K, Shimosegawa T, Uchi M, Maruhama Y, Toyota T. Erythropoietic protoporphyria with severe liver dysfunction and acute pancreatitis. J Gastroenterol 2000;35:391-5.

72. Weizman Z, Picard E, Barki Y, Moses S. Wilson's disease associated with pancreatitis. J Pediatr Gastroenterol Nutr 1988;7:931-3.

73. Ohtani T, Soyano M, Kito H, Sugiyama K, Iwamura H. Acute hemorrhagic pancreatitis in a patient with glycogen storage disease type 1. J Jpn Pediatr Soc 1985;89:1838-44.

74. Kikuchi M, Hasegawa K, Handa I, Watabe M, Narisawa K, Tada K. Chronic pancreatitis in a child with glycogen storage disease type 1. Eur J Pediatr 1991;150:852-3.

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