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REVIEW

Rather safe than sorry – the role of general practitioners in preventing pancreatitis

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Introduction

Pancreatitis is a complex disease that varies in severity and course and involves autodigestion of the pancreas. The pancreatic tissue injury resulting from pancreatic enzymes leads to functional abnormalities in the gland. As a result, long-term sequelae may affect other organ systems in the form of metabolic disorders and exocrine pancreatic insufficiency (EPI).

Incidence and aetiology

Considering pancreatic disease, acute pancreatitis may be considered the most common, while pancreatic cancer is the most lethal. The global pooled incidence of acute and chronic pancreatitis has been reported as 34 and 10 cases per 100 000 of the general population per year, respectively. While cases of acute pancreatitis are more or less equally distributed among men and women, twice as many men go on to develop chronic pancreatitis compared to their female counterparts.[1] Progression from acute to chronic pancreatitis is considered a disease continuum with 20% of acute pancreatitis patients developing recurrent pancreatitis and a third of those ultimately developing chronic pancreatitis.[2] Such progression may be associated with irreversible tissue damage, deterioration in function and serve as a risk for developing pancreatic carcinoma.[3] As a result, the majority of patients suffering from acute and recurrent pancreatitis develop post-pancreatitis diabetes.[2]

Gallstones (cholelithiasis) and alcohol have been identified as the two main aetiologies of acute pancreatitis and account for 55–70% of all cases, depending on the demographic region. Endoscopic retrograde cholangiopancreatography (ERCP) may induce post-procedure pancreatitis in 2–12% of patients due to biliary sphincter balloon dilation, difficult cannulation, sphincter of Oddi manometry and pancreatic sphincterotomy.[4] However, rectally administered indomethacin is a safe and effective prophylactic measure in at-risk patients.[5] Other important aetiologies of acute pancreatitis include hypertriglyceridaemia, medication use, autoimmune disorders and genetic predisposition while approximately 20% of cases are classified as idiopathic.[6]

In South Africa, previous studies have noted an exceptionally high proportion (70%) of acute pancreatitis to be attributable to alcohol abuse, while 20% may be attributed to biliary complications.[7,8] The global prevalence of cholelithiasis varies significantly, being higher in Western countries, the elderly and female patients. In South Africa, a time-dependent increase has been noted in the number of cholecystectomies performed and may be attributed to urbanisation and the high incidence of obesity.[9]

Pathophysiology and risk factors

Bile acids, alcohol and other compounds involved in precipitating acute pancreatitis act as acinar cell toxins. These toxins and factors like ductal obstruction may produce an inflammatory response related to knock-on cellular effects in the pancreatic tissue that include aberrant calcium signalling, mitochondrial dysfunction, premature trypsinogen activation within the acinar cells and impaired autophagy.[3]

The most significant risk factors for recurrent acute pancreatitis and chronic pancreatitis include idiopathy, active alcohol intake and smoking.[3] The risk of developing acute pancreatitis due to alcohol abuse is dependent on the dose and duration of such abuse and only around 10% of patients who consume excessive quantities of alcohol continue to develop chronic pancreatitis.[10]

Hypertriglyceridaemia results from irregular lipoprotein metabolism or may occur secondary to uncontrolled diabetes mellitus, alcohol abuse, or medication use. Accumulating triglycerides are dependent on pancreatic lipase for metabolism to free fatty acids, resulting in lipotoxicity and subsequent inflammation in pancreatic tissue.[11,12]

Drug treatment may potentially serve as a risk factor for or contribute to the pathophysiology of pancreatitis. While several drugs and drug classes have been implicated, angiotensin-converting enzyme (ACE) inhibitors, oral oestrogen and hormone replacement therapy, diuretics, valproic acid and antiretroviral drugs serve as examples.[12,13] The mechanisms by which drugs contribute to pathology may include pancreatic duct constriction, localised angioedema, toxicity, and hypersensitivity reactions as well as metabolic effects involving lipid metabolism. Although treatment of hyperglycaemia and hyperlipidaemia are crucial in preventing acute pancreatitis or recurrence thereof, it should be noted that some statins and hypoglycaemic agents

have also been associated with an increased risk of developing acute pancreatitis.[13]

Pancreatitis may be more prevalent in HIV-positive patients. Aside from aetiological factors that are common in HIV-negative individuals, antiretroviral drug treatment, opportunistic infections and malignancy may contribute to pancreatic pathology in patients infected with and/or treated for HIV.[14]

Symptoms and diagnostic criteria

The foundation for diagnosis of acute pancreatitis is a combination of clinical features and the presence of elevated plasma concentrations of pancreatic enzymes (Table I). Differential diagnosis should include other causes of epigastric abdominal pain, e.g. peptic ulcer disease, choledocholithiasis, cholecystitis, perforated viscus, acute mesenteric ischaemia and intestinal obstruction.

Management

No disease-specific pharmacotherapy is available for the treatment of acute pancreatitis. However, early fluid administration in the form of Ringer's lactate is associated with a significant reduction in systemic inflammatory response syndrome (SIRS), potentially binding to unsaturated fatty acids to inhibit their toxic effects.[3] Additionally, analgesic support is of importance and may include parenteral paracetamol, nonsteroidal anti-inflammatories, and opioids. Importantly, patient-specific considerations should apply, e.g. contraindication of NSRIs in acute kidney injury.[17] Trials investigating the prophylactic use of antibiotics in acute pancreatitis have not been able to indicate a clear benefit and, therefore, guidelines recommend against its use.[3]

While additional details regarding in-patient treatment and investigations and procedures are beyond the scope of this review, it should be highlighted that identification of the precipitating aetiology, if possible, is a key step in treating it and preventing recurrence. Furthermore, patient factors depending, counselling related to alcohol use and/or smoking and medication reconciliation may also contribute to improving patient outcomes and preventing recurrence. Referral of patients

Table I: Diagnostic criteria, signs, and symptoms of acute pancreatitis[15-18]

Clinical features, history, and examinations	Comment
Diagnosis is based on two of the following three features	
Abdominal pain	Acute onset often radiating to the back
Elevated serum lipase	3 x the upper limit of normal; amylase also suitable
Characteristic findings via abdominal imaging	Ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI)
History, additional examinations, and other observations	
Alcohol abuse	> 50 g of alcohol per day
Hyperlipidaemia	Triglycerides > 10 mmol/L
History of gallbladder disease	See text for detail
History of acute pancreatitis	Indicative of recurrent and/or chronic pancreatitis
Recent history of ERCP	See text for detail
Medication use	See text for detail
Family history	May indicate genetic predisposition
Physical examination	Positive Grey-Turner, Cullen signs (haemorrhagic pancreatitis)
SIRS	Tachycardia; hypo-/hyperthermia; leucocytosis/-penia; tachypnoea
Impaired mental status	Usually in severe cases; Glasgow coma scale (GCS) < 15

Table II: Products available for the management of hypertriglyceridaemia

Drug choice	Trade name	Comment
Fibrates		
Bezafibrate *Initially 200 mg daily, increase to 200 mg 2–3 x daily after meals; controlled release (CR) 400 mg once daily*	200 mg: Bezalip® tablets 400 mg: Sandoz Bezafibrate® tablets 400 mg CR tablets: Bezalip® Retard; Bezachole SR®; Dyna-Bezafibrate SR®	May induce dermatological effects and arrhythmia; gastrointestinal side effects are usually self-limiting. May increase anticoagulant effects with warfarin; caution advised in patients with gallstones. Fenofibrate may cause haemolysis in G6PD deficiency. Gemfibrozil may cause headache, blurred vision, and transient leukopenia. Contraindicated in pregnancy.
Fenofibrate *200 mg with the main meal*	Lipanthyl® capsules 200 mg Pravafen® capsules (pravastatin sodium 40 mg and fenofibrate 160 mg)	
Gemfibrozil *Initially 300 mg twice daily, increase to 600 mg twice daily, 30 minutes before morning and evening meals*	Lopid® tablets 600 mg	
Nicotinic acid derivatives		
Acipimox *500–750 mg daily in divided doses*	Olbetam® capsules 250 mg	May induce cutaneous flushing, pruritus, urticaria, heartburn, nausea, dyspepsia. Take caution in porphyria. Contraindicated in severely impaired kidney function, active peptic ulcer disease and pregnancy.

Table III: Products available for the management of exocrine pancreatic insufficiency[18,23]

Drug choice	Trade name	Comment
Pancreatin	Creon® 10 000 capsules containing lipase 10 000 units*, protease 600 units*, amylase 8 000 units* (pancreatin 150 mg)	1 capsule with all meals (25 000 units) and snacks (10 000 units). Swallowed whole with liquid, or opened and the pellets washed down, or sprinkled on soft food and swallowed without chewing. Take half the dose at the start of the meal and the remainder during or directly after.
	Creon® 25 000 capsules containing lipase 25 000 units*, protease 1 000 units*, amylase 18 000 units* (pancreatin 300 mg)	

*Fédération International Pharmaceutique/European Pharmacopoeia (PhEUR)

to a dietician and endocrinologist may also aid the management of triglyceride levels and diabetes.

A 2014 population-based cohort study in the United Kingdom found that 92% of patients who died within three months of their first pancreatitis diagnosis had visited a general practitioner within two months preceding the diagnosis.[19] This highlights the potential for early identification of at-risk patients and that lifestyle and therapeutic interventions may assist in improving patient outcomes.

Treatment of hypertriglyceridaemia is necessary in patients with serum triglyceride levels above 10 mmol/L.[18] Indeed, even mild to moderate measurements under fasting conditions may exacerbate acute pancreatitis in the event of diagnosis.[3] In this regard, decreasing the consumption of simple carbohydrates and fats may be beneficial and therapeutic interventions are often necessary.[12]

While case reports indicate a role for statins in drug-induced acute pancreatitis, a 2012 meta-analysis of large, randomised trials indicated that statins decrease the risk for acute pancreatitis in the general population.[20] However, considering that HMG-CoA reductase inhibitors, i.e. statins, demonstrate weak triglyceride-lowering effects, they may be combined with first-line therapy, fibrates, to achieve synergistic lipid-lowering effects if so required (Table II). However, beware of the increased risk of myopathy, especially with older fibrates, e.g. gemfibrozil. The fibrates regulate gene expression via peroxisome proliferator-activated receptor alpha (PPAR-α) and may decrease serum triglyceride concentrations by up to 40%.[18]

Nicotinic acid, or niacin, inhibits hormone-sensitive lipase via the cAMP pathway to decrease plasma fatty acid concentrations and may be used as a second-line agent. Although it is often associated with gastrointestinal side effects and facial flushing, it is inexpensive and efficient.[11,18] Acipimox, a nicotinic acid analogue, acts on the same mechanism, albeit with a more favourable side-effect profile and no significant detrimental effects on glucose metabolism.[21] Omega-3 fatty acids may be used in combination with other agents as they can hinder lipoprotein production at doses exceeding 3 g per day.[11,18]

Despite earlier belief, acute pancreatitis is not considered self-limiting and patients often suffer a variety of sequelae after recovery from an acute episode.[2] Failure to address the underlying aetiology may lead to recurrent or chronic pancreatitis. As a result, chronic pancreatitis is often associated with limited exocrine and endocrine pancreatic function and depends on symptomatic treatment, insulin, and pancreatic enzyme replacement therapy (PERT) (Table III).[22]

Patients' response to PERT depends on their degree of residual pancreatic function as well as the composition and size of their meals. While total lipase replacement is not necessary to prevent steatorrhoea, increased dosing may be required in the case of persistent weight loss, or should stool consistency not improve adequately and/or fat or oily droplets be visible in the stool.[23] Considering that pancreatic enzymes are deactivated by gastric acid, the addition of a histamine 2 (H_2) receptor blocker or proton pump inhibitor (PPI) may be considered to increase enzyme bioavailability in cases of poor response.[18,23]

Conclusion

Acute pancreatitis is often associated with lifestyle factors, including alcohol abuse, cigarette smoking and poor diet. These and other precipitating factors may contribute to the presence of hypertriglyceridaemia which presents a modifiable risk factor. General practitioners have a vital role in early identification of at-risk individuals, mediating early diagnosis of pancreatitis and to potentially improve patient outcomes.

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