Pancreatitis, pancreatic cancer, and diabetes

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We are so focused on insulin production that it is easy to forget the rest of the pancreas. The pancreas lies hidden behind the stomach at the back of the abdomen, adjacent to the duodenum, spleen, vena cava, aorta and other vessels, and the common bile duct. Pancreatic disorders may produce few or confusing symptoms. The pancreas is challenging to study, not only because of its anatomical position, but because it digests itself soon after removal from the body.

The islets produce insulin, glucagon, somatostatin, and pancreatic polypeptide. The alkaline digestive fluids produced by the exocrine acinar cells drain into the pancreatic duct. The main pancreatic digestive enzymes are trypsinogen, chymotrypsinogen, lipase, and amylase.

Pancreatic disease can cause diabetes, and is more frequent in people with diabetes than in those without.

Acute pancreatitis

Acute pancreatitis is a potentially life-threatening condition with an increasing English incidence of 22/100 000, and a case fatality of 6.7% by 60 days. It is linked to alcohol excess and social deprivation.1

Symptoms and signs include severe upper abdominal pain, nausea, vomiting, peritonitis, fever, and shock. Alcohol and gallstones are among multiple causes including drugs and chemicals. Incretin-based hypoglycaemic agents have been implicated (see below).

A meta-analysis found prediabetes or diabetes in 37% (95% CI 30–45%) of patients after a first episode of acute pancreatitis. Newly diagnosed DM developed in 15% of more developed countries where there is an age-standardised incidence of 8.2/100 000 aged 0–74 years.1 2 There are many other complications.

Chronic pancreatitis

Chronic pancreatitis usually follows recurrent acute pancreatitis but may be silent. Scarring impairs exocrine and endocrine function. Lack of pancreatic enzymes causes malabsorption with change in bowel habit (e.g. diarrhoea), pale, greasy, floating malodorous stools, weight loss, flatulence, bloating, abdominal discomfort and pain. Vitamin and mineral lack ensues. Pancreatic enzyme replacement therapy is vital in proven cases.

Alcohol, smoking, chemicals, and genetic factors (e.g. cystic fibrosis, haemochromatosis) are the main causes of chronic pancreatitis. Autoimmune pancreatitis is uncommon but treatable with steroids (patients may present with jaundice, less marked abdominal symptoms, and have positive autoantibodies).3

Fibrocalculous pancreatic diabetes (FCPD)

Found in tropical regions, particularly South India, FCPD is uncommon. Patients have chronic calcific pancreatitis with stones. Patients tend to be young and slim with a history of recurrent abdominal pain, and have both diabetes and malabsorption. Blood glucose control is difficult but ketosis is rare. Pancreatic cancer (CaP) may ensue. Incidence is unclear but Indian diabetes clinics report that the frequency is declining.4

Type 3 diabetes? No

The World Health Organisation (WHO) still classifies diabetes as type 1 and type 2, or gestational, and has not updated the classification for years.3 While there is much to learn about diabetes, other variants are well recognised, e.g. monogenic diabetes, and those secondary to pancreatic damage. See Diabetes UK5 and the American Diabetes Association (ADA).7

Hardt et al.8 classified diabetes thus: ‘type 1 diabetes: presence of autoantibodies, early onset, immediate insulin requirement; type 2 diabetes: absence of autoantibodies, no (or late) insulin requirement, insulin resistance; type 3 diabetes: absence of autoantibodies, and both exocrine pancreatic insufficiency and typical morphologic pathology.’ This is an oversimplification and in real life these categories may overlap.

Eight percent of the patients studied were labelled type 3c diabetes. Distribution of exocrine pancreas disease in this population included chronic pancreatitis (76%), haemochromatosis (8%), CaP (9%), cystic fibrosis (4%), and previous pancreatic surgery (3%).8 Faecal elastase screening suggests higher frequencies of pancreatic exocrine disease in diabetes. However, this methodology has been challenged by research using more detailed tests – low faecal elastase does not always mean malabsorption.9 Furthermore, people with diabetes may have malabsorption due to overgrowth of bacteria in the gut or small bowel disease (e.g. coeliac disease).

Confusingly, Alzheimer’s disease has also been called type 3 diabetes.10 Please do not use the term type 3 diabetes! It is time WHO produced up-to-date guidance. In the interim, I strongly suggest that the European Association for the Study of Diabetes and ADA produce a joint position statement on the classification of diabetes. Authoritative guidance is urgently needed.

Pancreatic cancer

Neuroendocrine tumours – insulinoma, glucagonoma and gastrinoma – are rare and may form part of a multiple endocrine neoplasia syndrome. The hormone produced in excess determines the symptoms.

Most CaPs arise in the cells relating to digestion – 85% are adenocarcinomas.11 Pancreatic adenocarcinoma is commoner in more developed countries where there is an age-standardised incidence of 8.2/100 000 aged 0–74 years.12

There may be few symptoms of CaP until it is extensive or has metastasised. Signs and symptoms depend on the site (about two-thirds occur in the head of the pancreas). Among Spanish CaP patients: ‘At presentation, the most frequent symptoms were asthenia (86%), anorexia (85%), weight-loss (85%), abdominal pain (79%), and choluria [dark bile-stained urine] (59%).’13 The abdominal pain may radiate to the back, be postural, or be poorly localised.
Common bile duct obstruction is most likely with tumours in the head of the pancreas producing jaundice, dark urine, and pale stools. Courvoisier’s sign – painless jaundice and a palpably enlarged gall-bladder – is rare.

Patients with CaP were compared with age-matched patients with other cancers, and non-cancer controls. Among CaP patients 68% had diabetes vs 19.6% lung, 10.4% breast, 14.8% prostate, 20.7% colorectal cancer and 23.5% non-cancer controls. Among CaP patients, 40% developed diabetes mellitus in the three years pre-diagnosis of CaP, as compared to 3.3–5.7% in the other groups.14

Pancreatic adenocarcinoma was diagnosed in 0.85% of US patients within three years of diagnosis of diabetes and aged ≥50 years. CaP patients were older than controls, and smoked.15 People with diabetes are more likely than non-diabetic controls to be diagnosed with CaP (RR 1.94 [1.66–2.27]), particularly within a year of diabetes diagnosis.16 Intense medical attention often reveals other diseases in newly-diagnosed diabetic patients.

Screening for CaP has been suggested for people within two years of new-onset diabetes aged ≥65 years old, with weight loss >2kg or BMI <25, and no family history of diabetes.17 But which screening test? The pancreas is a hidden organ, imaging is challenging and small tumours may be missed.18

Other risk factors for CaP include smoking, non-hereditary and chronic pancreatitis, obesity (and/or inactivity) and non-O blood group. About 5–10% of CaP patients are thought to have a genetic component.11 People with diabetes are also more likely to die from CaP than non-diabetics (hazard ratio [HR] 1.51 [1.24–1.83] after correcting for confounders).19 Metformin treatment may reduce the risk of CaP20 – more work is needed.

Is CaP causing the diabetes or vice versa – or is there an underlying problem causing both? Similar questions arise with pancreatitis.

Incretin-based drugs

A hot topic is whether incretin-based treatments (glucagon-like peptide 1 [GLP-1] agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) increase the risk of pancreatitis and/or CaP.

Among 972 384 patients on incretin-based medication for 1.3–2.8 years (maximum eight years) in an international retrospective observational study (follow-up 2 024 441 person years), 1221 had newly-diagnosed CaP (incidence 0.60/1000 person years). ‘Compared with sulfonylureas, incretin-based drugs were not associated with an increased risk of pancreatic cancer’ [HR 1.02 [0.84–1.23]].21

In 2014, ‘the FDA and the EMA have explored multi-streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs...Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal.’22

Recent meta-analyses of TECOS, SAVOR-TIMI 53 and EXAMINE presented at the World Diabetes Congress 2015 confirmed a small increased risk of pancreatitis with DPP-4 inhibitors (HR 1.578).23 Warn patients prescribed DPP-4 inhibitors or GLP-1 agonists of the risk of pancreatitis, and its symptoms.

Summary

People with pancreatitis often develop diabetes so check for this, e.g. annually. People with diabetes may develop overt exocrine pancreatic dysfunction. Seek this in patients with features of malabsorption; unusual weight loss; abdominal symptoms, e.g. pain; high risk of pancreatitis, e.g. alcohol excess; and those with unusual presentations. Such patients could also have CaP. Patients originating in India and other tropical countries may have FCPD.

Incretin-based drugs appear to increase the risk of pancreatitis but not CaP. Time will tell. There are other adverse effects, e.g. DPP-4 inhibitors may risk heart failure24 or joint pain.25

People with diabetes are more likely to have CaP than non-diabetic people. Be alert to the symptoms. Early diagnosis may be life-saving. Patients with CaP often have diabetes – keep checking.

Remember that the pancreas does more than one job!

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References