Pancreatic Diseases and Diabetes

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Keypoints

- Pancreatic disease is a rare cause of diabetes.
- Acute pancreatitis is associated with transient hyperglycemia which rarely persists.
- Chronic pancreatitis secondary to any cause can lead to permanent diabetes which is typically difficult to control; imaging studies reveal dilated ducts and pancreatic calculi.
- Tropical calcific pancreatitis is a disease of unknown etiology found in low and middle income countries associated with large pancreatic calculi and diabetes (fibrocalculus pancreatic diabetes).
- Hereditary hemochromatosis is an inherited disorder that produces diabetes secondary to iron deposition in the pancreatic islets and subsequent islet cell damage.
- Pancreatic carcinoma may complicate type 2 diabetes, diabetes secondary to chronic pancreatitis and, most commonly, with fibrocalculus pancreatic diabetes. It is important to suspect malignancy in any patient who complains of back pain, jaundice or weight loss in spite of good glycemic control.
- Pancreatic surgery can lead to diabetes that is insulin-requiring and often difficult to control.
- Cystic fibrosis is a relatively common genetic disorder affecting the lung, pancreas and other organs. Up to 75% of adults with cystic fibrosis have some degree of glucose intolerance.

Introduction

Pancreatic disease is a rare cause of diabetes, accounting for less than 0.5% of all cases of diabetes. A number of disease processes affecting the pancreas can lead to diabetes; some of these are listed in Table 18.1.

Most of these conditions damage the exocrine as well as endocrine components of the pancreas. The exocrine parenchyma and islet tissue lie in intimate contact with each other and are functionally related. This may explain why parenchymal disease can readily impair β-cell function [1].

Acute pancreatitis

Acute pancreatitis varies considerably in its impact on the gland and its metabolism. Pathologic findings vary from mild edema to hemorrhagic necrosis, and the clinical presentation spans a wide spectrum from mild to fulminating or fatal illness.

The most common causes of acute pancreatitis are alcoholism and gallstone disease. Table 18.2 sets out the causes of acute pancreatitis. Classically, the disease presents with sudden onset of epigastric pain, associated with nausea and vomiting, aggravated by food and partially relieved by sitting up and leaning forward. Physical examination reveals low grade fever, tachycardia and hypotension. Jaundice may also be found infrequently. Cullen sign (periumbilical discoloration) and Grey Turner sign (flank discoloration) indicate severe necrotizing pancreatitis.

Commonly found metabolic abnormalities include hyperglycemia, hypocalcemia, hyperlipidemia, hypoalbuminemia and coagulation disorders [2]. Serum levels of amylase and lipase are elevated, but these are neither sensitive nor specific. Computed tomography (CT) or magnetic resonance imaging (MRI) shows edema of the pancreas. Loss of the normal enhancement on dynamic CT scanning indicates pancreatic necrosis.

Most patients with acute pancreatitis develop transient hyperglycemia, which mostly results from a rise in glucagon levels rather than from β-cell injury [3]. Hyperglycemia is usually mild and resolves within days to weeks without needing insulin treatment. Permanent diabetes is rare and occurs mostly in cases with fulminant disease and multiorgan failure, in whom the incidence approaches 25% [4]. Blood glucose levels exceeding 11.1 mmol/L (200 mg/dL) during the first 24 hours indicate a poor prognosis [5].

Non-specific elevations of serum amylase and lipase may also be found in diabetic ketoacidosis [6]. Acute pancreatitis, however,
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Tropical chronic pancreatitis is confined to tropical and subtropical regions of the world.

Pathologic features
The term chronic calcific pancreatitis accurately describes the pathologic changes in over 95% of cases of chronic pancreatitis in Western countries. The ductal and acinar lumina are filled with proteinaceous plugs which later calcify, forming small stones composed chiefly of calcium carbonate or calcite. Huge stones can occur but are more characteristic of tropical pancreatitis. The stones are found diffusely throughout the affected organ. Microscopically, there is atrophy of the ductal epithelium and stenosis of the ducts, associated with patchy fibrosis. There may also be foci of necrosis, with infiltration by lymphocytes, plasma cells and histiocytes [17]. Ultimately, the pancreas shrivels and develops an opaque capsule that may adhere to surrounding organs.

may affect up to 11% of patients with ketoacidosis, usually with mild or even no abdominal pain [5].

### Chronic pancreatitis

This condition is characterized by progressive and irreversible destruction of the exocrine pancreatic tissue, leading to exocrine pancreatic insufficiency and varying degrees of glucose intolerance which often require insulin. The causes of chronic pancreatitis vary according to the geographic location (Table 18.3).

Alcohol abuse accounts for most of the cases (>85%) in Western populations. Alcohol alters the composition of pancreatic secretions, leading to the formation of proteinaceous plugs that block the ducts and act as foci for calculi formation. Tropical pancreatitis is a distinct form of the disease that is not associated with excessive alcohol intake and is prevalent in the developing world [7].

Hereditary chronic pancreatitis is a rare entity, inherited in an autosomal dominant fashion. Mutations in a number of genes have been implicated including *PRSS1* (encoding cationic trypsinogen), *SPINK1* (serine protease inhibitor, Kazal type 1) and *CFTR* (cystic fibrosis transmembrane conductance regulator) [8–11].

Obstructive chronic pancreatitis is a rare condition that follows occlusion of pancreatic ducts by tumors, scarring, pseudocysts or congenital anomalies. Stones are not seen. Surgery or endoscopic dilatation may occasionally be curative.

Idiopathic pancreatitis, which accounts for 10–20% of all cases, affects two distinct age groups, one with onset at 15–25 years and the other at 55–65 years [12]. Cigarette smoking is a risk factor and mutations in specific genes have also been postulated [11,13,14].

### Epidemiology

Chronic pancreatitis is prevalent worldwide. In Western countries, the incidence is about 4 cases per year per 100000 popula-
As fibrosis progresses, the acini atrophy and eventually disappear, leaving clusters of islets surrounded by sclerosed parenchyma. Neoformation of islet cells from ductal tissue can occur (nesidioblastosis) (Figure 18.1). Immunohistochemistry studies reveal generalized decrease in the number of islets, accompanied by overall reduction in β-cell density and insulin immunoreactivity which correspond to disease duration and C-peptide levels (Figure 18.2; Table 18.4) \[18,19\].

### Table 18.4 Islet cell changes in chronic pancreatitis \[25\].

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Changes observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-cells</td>
<td>Decreased numbers (40% below controls)</td>
</tr>
<tr>
<td>α-cells</td>
<td>Increased numbers</td>
</tr>
<tr>
<td>β-cell:α-cell ratio</td>
<td>0.6–2.5 (controls 3.0–3.5)</td>
</tr>
<tr>
<td>PP cells</td>
<td>Increased numbers</td>
</tr>
<tr>
<td>δ (D) cells</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

As fibrosis progresses, the acini atrophy and eventually disappear, leaving clusters of islets surrounded by sclerosed parenchyma. Neoformation of islet cells from ductal tissue can occur (nesidioblastosis) (Figure 18.1). Immunohistochemistry studies reveal generalized decrease in the number of islets, accompanied by overall reduction in β-cell density and insulin immunoreactivity which correspond to disease duration and C-peptide levels (Figure 18.2; Table 18.4) \[18,19\].

### Clinical features and diagnosis

Abdominal pain is the predominant symptom and the usual reason for seeking medical care. The pain is usually steady, boring and agonizing and located in the epigastrium or left hypochondrium with radiation to the dorsal spine or the left shoulder. Bending forward or assuming the knee–chest position relieves the pain. The cause of the pain is unknown, but may relate to increased intrapancreatic or intraductal pressure, or to ischemia of the pancreas. It tends to remit and relapse and follows an unpredictable course. The development of end-stage pancreatic disease is associated with disappearance of the pain in many cases.

Exocrine pancreatic insufficiency may manifest with steatorrhea and features of fat-soluble vitamin deficiency. Steatorrhea may not be apparent on a low-fat diet. The combination of oily and greasy stools with diabetes should raise the suspicion of chronic pancreatitis.

### Investigations

Demonstration of pancreatic calculi on a plain X-ray of the abdomen is diagnostic (Figure 18.3). In cases where obvious calculi cannot be found, ultrasonography, CT scanning or endoscopic retrograde cholangiopancreatography (ERCP) will help to confirm the diagnosis. ERCP is considered the gold standard and usually reveals irregular dilatation of the pancreatic ducts with filling defects caused by stones (Figure 18.4). CT scanning shows patchy increases in parenchymal density and, ultimately, atrophy of the gland.
Figure 18.3 Pancreatic calculi, showing characteristic patterns in (a) alcoholic chronic pancreatitis, and (b) fibrocalculus pancreatic diabetes.

Figure 18.4 Investigations in chronic pancreatitis. (a) Endoscopic retrograde cholangiopancreatogram, showing dilatation and irregularity of the pancreatic ductal system in a patient with alcoholic chronic pancreatitis. Courtesy of Professor Jonathan Rhodes, Liverpool. (b) Ultrasound scan of the pancreas from a patient with fibrocalculus pancreatic diabetes, demonstrating highly echogenic parenchyma and duct walls (fibrosis), grossly dilated ducts and calculi. Courtesy of Dr. S. Suresh, Chennai, India.
Exocrine pancreatic function can be assessed by measuring the urinary excretion of compounds that are liberated in the gut by pancreatic enzyme action on orally ingested precursors such as NBT-PABA (para-aminobenzoic acid) or fluorescein dilaurate (pancreolauryl). Screening tests of pancreatic enzymes (fecal chymotrypsin, fecal elastase) are also used as they are simpler to perform but are less specific. Measurement of pancreatic output (via a tube placed in the duodenum) following ingestion of the Lundh test meal may also be helpful. Serum amylase is usually normal, except during acute attacks.

Diabetes in chronic pancreatitis
Abnormal glucose tolerance and diabetes complicate around 40–50% of cases of chronic pancreatitis. Unlike acute pancreatitis, the cause here is damage to the β-cells, owing to loss of trophic signals from the exocrine tissue [1,20]. The diabetes is of insidious onset and usually occurs several years after the onset of pain. The prevalence has been assessed at 60% after 20 years [21]. Half or more of patients require insulin for optimal glycemic control [22,23], but ketoacidosis is rare, even if insulin is withdrawn. Possible explanations include better preservation of β-cell function (compared with type 1 diabetes; T1DM) [24], reduced glucagon secretion and lower body stores of triglyceride, the major substrate for ketogenesis [24,25]. On account of the lower glucagon reserve, these patients are also prone to severe and prolonged hypoglycemia, and often diabetes is difficult to control with wide fluctuations of blood glucose levels.

Chronic diabetic complications
It was originally thought that patients with pancreatic diabetes were not at increased risk of microvascular complications. It has now been shown that retinopathy [26], nephropathy [27] and neuropathy [28] occur in these patients at frequencies similar to those with type 2 diabetes (T2DM). The risks of macrovascular complications, however, are relatively low. This may partly be explained by the low blood lipid levels that often accompany the malnutrition commonly seen in these patients [29].

Management of diabetes in chronic pancreatitis
Removal of obvious causes such as alcohol and hypertriglyceridemia will help to prevent progression of the damage to the gland.

Pain can be very difficult to manage. Measures include total abstinence from alcohol, dietary modification (small frequent meals with low fat content), analgesics and the somatostatin analogue, octreotide, which suppresses pancreatic exocrine secretion. In a subgroup of patients, massive doses of non-enteric-coated preparations of pancreatic enzymes have been shown to reduce pain. surgical interventions include sphencterotomy, internal drainage of pancreatic cysts, endoscopic removal of calculi (via ERCP), insertion of duct stents and denervation procedures. Total resection of the pancreas followed by whole pancreas or islet cell transplantation may be an option for intractable cases.

Malabsorption can be effectively treated with a low fat diet with pancreatic enzyme supplements (along with histamine H1 blocker or proton pump inhibitor to block gastric acid secretion) taken at meal times.

Diabetes can be managed along conventional lines, with a few caveats. High carbohydrate and protein intakes are encouraged along with fat restriction in order to prevent steatorrhea. Over 80% of patients require insulin; however, the required doses are typically low, around 30–40 units/day [22,23]. Diabetic control is often difficult to achieve, with frequent and severe hypoglycemia; reduced glucagon secretion may be responsible.

Tropical calcific pancreatitis
This is a distinct variety of chronic pancreatitis seen predominantly in low and middle income countries in the tropical and subtropical regions of the world [30,31]. This entity was first reported in 1959 by Zuidema [31] in patients from Indonesia. Later on, the disease was reported from several countries in Africa and Asia. The highest prevalence appears to be in Southern India, particularly in the states of Kerala and Tamil Nadu [32].

The disease usually starts in childhood with recurrent abdominal pain and during adolescence progresses to large pancreatic calculi and ductal dilatation (Figures 18.3 and 18.5). By adulthood, frank diabetes is found in more than 90% of patients [33]. Nevertheless, it remains a rare cause of diabetes, constituting less than 1% of all cases of diabetes even in regions where it is most prevalent [34]. A recent study in urban southern India reported a prevalence of 0.36% among subjects with self-reported diabetes and 0.019% among the general population [35].

The term tropical calcific pancreatitis is used to denote the prediabetic stage of the disease whereas the term fibrocalcious pancreatic diabetes (FCPD) is used to describe the clinical picture once diabetes has supervened (Figure 18.6).

The etiology of this condition remains unknown. Poor nutrition has been implicated as a possible factor; however, this may be the consequence rather than a cause of the pancreatopathy. The condition can also affect well-nourished individuals [36]. In the past, attention was also focused on the role of dietary toxins.
such as cyanogens (found in cassava), but this link has not been substantiated. Cases have been found to cluster in families, which may suggest a genetic etiology for the disease [37–40]. A number of studies have reported an association between the SPINK1 gene and tropical calcific pancreatitis [41–47]. A role has also been suggested for oxidant stress and free radical-mediated injury but this has not been proven conclusively [48].

Salient differences between alcoholic chronic pancreatitis and tropical calcific pancreatitis are summarized in the Table 18.5. The classic clinical triad of tropical calcific pancreatitis consists of abdominal pain, steatorrhea and eventually diabetes. The disease often progresses steadily from euglycemia through impaired glucose tolerance to frank diabetes. Most patients require insulin but are generally not prone to ketosis; some can be managed with oral antidiabetic agents (Figure 18.7). Studies have shown that the risk of developing pancreatic carcinoma in tropical calcific pancreatitis is 100-fold greater than in those without the disease and is much higher than in other forms of chronic pancreatitis [49]. Pancreatic malignancy should be suspected in individuals with tropical calcific pancreatitis if they complain of intractable pain or significant weight loss even after attaining good glycemic control.

Management of tropical calcific pancreatitis and FCPD is similar to that outlined for chronic pancreatitis.

### Hereditary hemochromatosis

This condition, also called idiopathic or primary hemochromatosis, is the most common autosomal recessive genetic disorder in Caucasians, with a prevalence of 4–5 per 1000 [50,51]. The classic triad of diabetes, cirrhosis and bronzed hyperpigmenta-

### Table 18.5 Differences between tropical calcific pancreatitis and alcoholic chronic pancreatitis.

<table>
<thead>
<tr>
<th></th>
<th>Tropical calcific pancreatitis</th>
<th>Alcoholic chronic pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>70:30</td>
<td>90:10</td>
</tr>
<tr>
<td>Peak age at onset (years)</td>
<td>20–30</td>
<td>30–50</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>Poor &gt; affluent</td>
<td>All groups</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Pancreatic morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of calculi</td>
<td>&gt;90%</td>
<td>50–60%</td>
</tr>
<tr>
<td>Features of calculi</td>
<td>Large; in large ducts</td>
<td>Small, speckled; in small ducts</td>
</tr>
<tr>
<td>Ductal dilatation</td>
<td>Usually marked</td>
<td>Usually moderate</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Heavy</td>
<td>Variable</td>
</tr>
<tr>
<td>Risk of pancreatic cancer</td>
<td>Markedly increased</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>&gt;90%</td>
<td>50%</td>
</tr>
<tr>
<td>Time course</td>
<td>Faster evolution</td>
<td>Slower evolution</td>
</tr>
</tbody>
</table>

Figure 18.6 Natural history of tropical calcific pancreatitis and fibrocalculous pancreatic diabetes.

Figure 18.7 The spectrum of diabetes in fibrocalculous pancreatic diabetes. Data from Mohan et al. [29].
Clinical features
The classic clinical features are hepatic cirrhosis, diabetes and skin hyperpigmentation (“bronzed diabetes”) (Figure 18.9). Hepatic fibrosis and cirrhosis usually only develop after age 40 years, unless other factors such as alcoholism are present. Portal hypertension, hepatic failure and hepatocellular carcinoma (in 15% of cases) are late sequelae [55]. Bronzing of the skin, which occurs in 70% of cases but may be less evident in darker-skinned races, is caused by both iron deposition in the subcutaneous tissue and increased melanin in the basal dermis. Hypopituitarism, hypogonadism, hypoparathyroidism and chondrocalcinosis with pseudogout are less common features.

Presenting symptoms include weakness, weight loss, diabetic symptoms, arthralgia, erectile dysfunction and skin pigmentation. Signs include hepatosplenomegaly, heart failure, skin pigmentation, testicular atrophy, arthropathy, hypogonadism and occasionally hypothyroidism. Many patients with hemochromatosis, however, are asymptomatic and may be detected during investigation for unrelated reasons.

Diabetes in primary hemochromatosis
The prevalence of diabetes depends on the severity of iron overload and presence of cirrhosis [56]. Up to 50% of patients have glucose intolerance and 25% have overt diabetes [57], although the disease is an extremely rare cause of diabetes in the general population. Both insulin resistance and β-cell failure contribute to the development of diabetes, and most patients eventually require insulin. These patients are prone to both microvascular and macrovascular complications [58], the risk of nephropathy being particularly high in those carrying the H63D mutation [59].
Investigations and diagnosis

The diagnosis should be suspected in any patient with diabetes, hepatomegaly or liver disease, skin pigmentation, arthritis and hypogonadism. A high index of suspicion is required to make an early diagnosis, because significant iron overload can exist with few or none of these clinical manifestations.

The total-body iron stores can be assessed using measurement of serum ferritin and percent saturation of transferrin. Serum ferritin is a useful screening test for relatives of affected individuals, but because ferritin is an acute phase reactant whose levels can be elevated in inflammatory states, abnormally high results should be confirmed by other tests (Table 18.6) [60]. Serum iron and percent saturation of transferrin are elevated early in the course of the disease, but lack specificity. A combined measurement of the percent transferrin saturation and serum ferritin levels provide a simple and reliable screening test for hemochromatosis. A positive test mandates genetic testing.

The role of liver biopsy in diagnosis and management of hemochromatosis has significantly diminished following the development of genetic testing for the C282Y mutation. The major role of liver biopsy at the present time is in excluding the presence of cirrhosis, which is a major risk factor in the development of hepatocellular carcinoma. Hepatic iron overload can also be detected using imaging techniques such as CT or MRI scanning.

All first-degree adult relatives of a patient with hemochromatosis should be tested for C282Y and H63D mutations, in an attempt to detect disease in the early precirrhotic phase at which stage treatment can prevent further progression.

Treatment

Treatment of hereditary hemochromatosis is by repeated venesection, which must be started as early as possible. Removal of excess iron by venesection prevents diabetes and cirrhosis and prolongs survival (Figure 18.10). Chelating agents such as desferrioxamine are not effective treatment and are reserved for patients who cannot undergo venesection.

Table 18.6 Diagnostic tests in hereditary hemochromatosis [60].

<table>
<thead>
<tr>
<th>Test</th>
<th>Hemochromatosis</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (µg/dL)</td>
<td>180–300</td>
<td>50–150</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>80–100</td>
<td>20–50</td>
</tr>
<tr>
<td>Total iron-binding capacity (µg/dL)</td>
<td>200–300</td>
<td>250–370</td>
</tr>
<tr>
<td>Serum ferritin (µg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>500–6000</td>
<td>20–300</td>
</tr>
<tr>
<td>Women</td>
<td>500–6000</td>
<td>15–250</td>
</tr>
<tr>
<td>Hepatic iron concentration (µg/g dry weight)</td>
<td>10000–30000</td>
<td>300–1800</td>
</tr>
</tbody>
</table>

Figure 18.9 Clinical features of hereditary hemochromatosis. The classic triad comprises diabetes, cirrhosis and hyperpigmentation of the skin ("bronzed diabetes").

Figure 18.10 Venesection treatment in hereditary hemochromatosis. When treatment is started before the onset of cirrhosis or diabetes, life expectancy is normalized. Adapted from Dymock et al. [58].
Part 4 Other Types of Diabetes

Picroxamine are more expensive, less safe and less effective than venesection. Diabetes may be improved by venesection, but usually requires insulin treatment. Management is often complicated by hypoglycemia caused by concomitant α-cell damage and glucagon deficiency. Hepatic transplantation for hereditary hemochromatosis were previously associated with a poor prognosis, but survival rates have improved of late. Diabetes tends to worsen after transplantation because of the use of immunosuppressant drugs [61].

Secondary hemochromatosis

Conditions such as thalassemia major, which require frequent blood transfusion, may lead to massive iron overload. Pancreatic damage and diabetes frequently result. The duration of disease and number of transfusions correlate well with the degree of glucose intolerance. It has been postulated that iron overload may induce autoimmune attack against the β-cells, thereby contributing to development of diabetes [62].

Pancreatic neoplasia

Adenocarcinoma of the pancreas is the fifth most common cause of cancer death and is increasing in its incidence [63]. It has a poor prognosis, with a 5-year survival rate of less than 3%

Although diabetes has long been associated with pancreatic adenocarcinoma, the nature and strength of the association remain controversial. A meta-analysis of 20 epidemiologic studies showed a twofold increased risk of pancreatic cancer among people with diabetes of more than 5 years duration [64], suggesting that diabetes is a risk factor for the neoplasm. Other studies, however, have concluded that the cancer preceded and caused the diabetes [65], a view supported by observations that diabetes may improve after resection of the tumor. Some studies have even suggested that diabetes protects against pancreatic cancer [66].

Tropical chronic pancreatitis is associated with a 100-fold increase in the risk of developing pancreatic carcinoma [50].

The diagnosis of pancreatic carcinoma must be suspected in any patient with T2DM who complains of unexplained weight loss (despite insulin therapy and apparently good control of diabetes), back pain or jaundice.

Pancreatic surgery and diabetes

Diabetes is a frequent complication of pancreatic resection performed for various indications. The incidence and severity of diabetes depends on the extent of resection of the distal segment, where the islets are most abundant. In one study, diabetes developed in 56% of cases following distal resection [67].

Diabetes is more likely to follow subtotal pancreatectomy than procedures such as lateral pancreaticojejunostomy and pancraeticoduodenectomy (Whipple procedure). Diabetes is obviously inevitable following total pancreatectomy.

Management of diabetes caused by pancreatic surgery

The diabetes is usually difficult to control, with wide excursions in blood glucose levels. Patients are exquisitely insulin-sensitive and prone to hypoglycemia as a result of the loss of glucagon function. Frequent small meals and multiple small doses of insulin can minimize these problems to an extent. Use of a subcutaneous insulin infusion pump may be beneficial in some cases. Patients with diabetes following pancreatectomy are ideal candidates for whole pancreas or islet cell transplantation.

Associated exocrine pancreatic insufficiency should also be addressed. Meals should be low in fat and high in carbohydrate and protein. Pancreatic enzyme therapy will help in controlling steatorrhea and stabilizing blood glucose [68].

Cystic fibrosis

Cystic fibrosis is a multisystem disease characterized by recurrent airway infection leading to bronchiectasis, pancreatic insufficiency, abnormal sweat gland function and urogenital dysfunction. It is an autosomal recessive disorder caused by mutations in the CFTR gene located on chromosome 7q22. This gene encodes a protein, cystic fibrosis transmembrane conductance regulator (CFTR), which regulates the chloride secretion across epithelial surfaces. Various mutations have been described of which deletion of the phenylalanine residue at position 508 (Δ508) is the most common [69,76]. The defect produces unusually viscous secretions which lead to pancreatic ductular obstruction, dilatation and pancreatic insufficiency. The incidence is 1 in 2500 live births in Caucasian populations, but the disease is much less common in Africans and Asians [70].

The most common clinical features are steatorrhea, failure to thrive and growth retardation, recurrent lung infections, hepatic biliary complications and symptoms of fat-soluble vitamin deficiency such as night blindness. The diagnosis is confirmed by the presence of an elevated sweat chloride concentration in excess of 60 mmol/L.

Diabetes in cystic fibrosis

The incidence of diabetes in children with cystic fibrosis is 2–3% (about 20 times higher than in the general population). The incidence rises steadily through adolescence, with up to 25% of patients in their twenties developing diabetes and a further 50% having glucose intolerance [71].

As the treatment of the lung disease in cystic fibrosis has improved, more and more patients are surviving into adulthood. This has led to an increase in the prevalence of diabetes in cystic fibrosis.

The major factor in the pathogenesis of diabetes is damage to the pancreatic β-cells secondary to exocrine pancreatic degeneration. Other postulated mechanisms include enhanced absorption of glucose [72] and autoimmune attack against the β-cell, which may explain why T1DM is more common in relatives of patients with cystic fibrosis [73]. The physiologic insulin resistance of
normal puberty may also contribute. Interestingly, diabetes develops more commonly in patients homozygous for Δ508 than in heterozygotes [74].

Diabetes is usually insidious in onset and characterized by a delayed, flattened and prolonged insulin secretory response to glucose [75]. Ketoadsisis is rare, although insulin treatment is usually required. As patients now survive longer [69], chronic microvascular complications are also frequently seen.

Management

Although some patients initially respond to sulfonylureas, most ultimately need insulin [76]. In addition to controlling diabetes, insulin also improves body weight and pulmonary and pancreatic function [71,77,78]. Starting from adolescence, all patients with cystic fibrosis should be regularly screened for diabetes using the oral glucose tolerance test or serial measurements of HbA1c [78].

Dietary modification in patients with cystic fibrosis who also have diabetes presents much the same difficulties as in patients with chronic pancreatitis. A diet rich in carbohydrates and protein but restricted in fat is recommended. Oral pancreatic enzyme therapy helps to improve nutrient digestion and absorption. Enteric-coated preparations of lipase can control steatorrhea. Fibrosing colonopathy is a concern in patients receiving higher strengths of lipase [79].

Conclusions

Although rare, diabetes secondary to pancreatic disease is potentially important. The underlying pancreatic disease may need treatment in its own right, while disorders with a genetic basis must be identified so that other family members can be screened. Diagnosis of pancreatic diabetes requires a high index of suspicion. Suggestive symptoms include features of pancreatic disease (steatorrhea, unexplained weight loss or back pain) and severe and brittle diabetes in the absence of a family history of diabetes.

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References

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62 Monge L, Pinach S, Caramellino L, Bertero MT, Dall’omo A, Carta Q. The possible role of autoimmunity in the pathogenesis of


