Abstract
Pancreatogenic diabetes is classified by the American Diabetes Association as a form of type 3 diabetes mellitus (T3cDM) secondary to acquired diseases of the exocrine pancreas. It is a clinically relevant condition, representing 5–10% of all diabetic cases in the Western population. It develops in about 50% of patients with chronic pancreatitis, in 80% of pancreatic cancer cases, in 70% of patients submitted to subtotal pancreatectomy and in over 7% of hemochromatosis cases. Patients typically develop symptoms associated with hyperglycemia, but they have a distinctly increased risk of hypoglycemia and glycemic instability. Hypoglycemic episodes associated with insulin or sulfonylurea therapy are more frequent and tend to be more severe and to last longer. Hypoglycemia is the consequence of impaired counterregulation and glucose recovery due to deficient glucagon secretion, blunted catecholamine response and subsequent impaired activation of hepatic glucose production. In terms of the therapeutic approach, maintenance of plasma glucose levels slightly above the normal range may be necessary to avoid frequent hypoglycemic reactions and to improve the quality of life.
Diabetes secondary to pancreatic disease was first described in 1788 by Sir Thomas Cawley, who reported the case of a man ‘aged 34 years, strong, healthy and corpulent’ who ‘was seized with diabetes’ and ‘gradually became emaciated and, despite treatment, eventually died’. At necropsy ‘the pancreas was full of calculi, which were firmly impacted in its substance. They were of various sizes, … their surface rough, like mulberry stones. The right extremity of the pancreas was very hard, and appeared to be scirrhous’.

More than 100 years later, in 1889, Minkowski demonstrated that experimental pancreatectomy in dogs caused diabetes, and in 1940 Schumacker estimated that at least 2% of all cases of acute pancreatitis were followed by overt clinical diabetes. In spite of the appreciation of the fact that acute pancreatitis was infrequently followed by overt diabetes, clinicians began to recognize chronic pancreatitis or relapsing acute pancreatitis as a common cause of glucose intolerance. Total pancreatectomy in humans was first performed in 1942. Extensive use of this procedure proved that more than 80–90% of the pancreas had to be removed before overt diabetes mellitus would ensue. An association between hemochromatosis and diabetes was recognized at the beginning of the century.

T3cDM is a clinically relevant condition prevalent among 5–10% of all diabetic subjects in the Western population [2], although its prevalence (fig. 1) and clinical importance have been underestimated and underappreciated until recently. Failure to correctly diagnose T3cDM leads to inappropriate medical therapy in these patients [3], due to concomitant conditions (maldigestion, malabsorption, etc.) affecting the patient’s nutritional status [4]. Moreover, the more common use of pancreatectomy and longer survival of patients with cystic fibrosis as well as, most importantly, the increasing prevalence of chronic pancreatitis suggest that T3cDM will require more attention by diabetologists and gastroenterologists.

**Epidemiology**

Data on the prevalence of diabetes secondary to pancreatic diseases remain scanty, but the frequency of this condition is likely to be higher than generally believed. According to an old study, pancreatogenic diabetes accounts for 0.5–1.7% of all the cases of

**Table 1. Diabetes mellitus secondary to diseases of the exocrine pancreas (T3cDM; American Diabetes Association classification 2013)**

1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

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diabetes mellitus. In a more recent report, the prevalence of secondary diabetes was estimated to be 9.2% in a cohort of 1,868 German diabetic patients for whom exocrine pancreatic insufficiency and pathologic imaging of the pancreas were documented [5]. In another cohort of 1,922 autoantibody-negative patients with exocrine and endocrine pancreas insufficiency and typical morphologic pancreatic alterations, only 8% were diagnosed with pancreatic diabetes, while 80% were defined as type 2 diabetes and 12% as type 1 diabetes. Actually, in this population, 76% had chronic pancreatitis, 8% by hemochromatosis, 9% had pancreatic cancer, 4% had cystic fibrosis and 3% had undergone previous pancreatectomy [3] (fig. 1).

According to the literature, diabetes develops in about 50% of patients with chronic pancreatitis with an incidence that increases over the time, being 0–22% at the onset of symptoms, and >80% 25 years after onset. By linear regression analysis, the annual rate of diabetes and insulin requirement can be calculated at 3.5 and 2%, respectively. The frequency of chronic pancreatitis is higher in populations with heavy alcohol consumption and in tropical countries, where the prevalence of diabetes secondary to fibrocalculous pancreatitis can be as high as 90% [2], accounting for up to 15–20% of all the diabetic population. In summary, the prevalence of diabetes due to pancreatitis is likely to be underestimated, the diagnosis of pancreatogenic diabetes is often missed and patients are commonly misclassified.

To induce deterioration in glucose metabolism, partial pancreatectomy in humans must be >50%, while total pancreatectomy is necessarily associated with diabetes. In healthy humans, hemipancreatectomy is followed by impaired glucose tolerance in 25% of patients, and usually no more than 20–25% of residual pancreas is required to ensure normal glucose homeostasis. The main causes of pancreatic surgical resection are: tumors, benign and malignant; pancreatic pseudocysts; and chronic and, very

Fig. 1. Distribution of causes of diabetes secondary to pancreatic diseases. From Cui and Andersen [27].
rarely, acute pancreatitis. Adenocarcinoma, the commonest tumor of the pancreas, is associated with very poor survival, and at diagnosis, for 75% of patients only palliative treatment is indicated. The prevalence of diabetes and impaired glucose tolerance in pancreatic cancer is as high as 80%. In 25–50% of the cases, diabetes is diagnosed up to 2 years prior to the cancer diagnosis. Diabetes is 14 times more likely to occur in patients with pancreatic cancer than in controls after adjustment for age, gender, BMI and family history of diabetes. Localization of the neoplastic process also has an impact on frequency: diabetes is more common in patients with carcinoma of the head than in those with carcinoma of the body and/or tail of the organ.

Pancreatic involvement in cystic fibrosis can result in impaired glucose tolerance and cystic fibrosis-related diabetes (CFRD). Recent figures show that overt hyperglycemia occurs in 4–10% of patients with cystic fibrosis, whereas impaired glucose tolerance is found in 8–75% [5]. These figures are likely to be underestimated because no systematic screening is commonly performed. With the increase in life expectancy brought about by improved medical therapy, the prevalence of diabetes mellitus has been shown to increase, occurring in up to 43% of patients aged >30 years. However, CFRD can occur at any age and no correlation exists between duration of the disease and severity of glucose intolerance.

Diabetes mellitus occurs in over 75% of patients with hemochromatosis [5]. Even though concomitant liver cirrhosis can affect glucose metabolism, this does not fully account for the diabetic condition. In contrast to chronic pancreatitis, in patients with hemochromatosis, diabetes is an early complication and, in some cases, can precede clinical recognition of the hemochromatosis. On average, diabetes mellitus is diagnosed approximately 1 year before hemochromatosis. It is rarely associated with obesity and affects males 10 times more frequently than females.

**Pancreatitis**

*Acute Pancreatitis*

Acute pancreatitis is an acute inflammatory process of the pancreas, with variable involvement of peripancreatic tissues and remote organ system failure. The diagnosis of acute pancreatitis is made if 2 out of 3 criteria are met: (1) severe abdominal epigastric pain, often radiating to the back; (2) serum lipase or amylase activity at least 3 times greater than the upper limit of normal; and (3) characteristic imaging findings of acute pancreatitis. Acute pancreatitis can be subdivided into 2 types: interstitial edematous and necrotizing pancreatitis.

The annual incidence of acute pancreatitis ranges from 13 to 45/100,000 persons. Gallstones and alcohol abuse are the leading causes of acute pancreatitis (more than 90% of cases worldwide). Drug reaction, hypertriglyceridermia, hypercalcemia due to hyperparathyroidism, infections, trauma, vascular diseases such as embolic and
autoimmune vasculitis, and circulatory shock are other, less frequent, causes of the disease [6]. A strong genetic component as well as environmental factors can also contribute to recurrent acute and chronic pancreatitis. Genetic variations in cationic trypsinogen, pancreatic secretory trypsin inhibitor 1 and cystic fibrosis transmembrane conductance regulator (CFTR) are among the strongest risk factors. These mutations are mainly found in sporadic pancreatitis, though they have been reported in alcohol-induced pancreatitis as well. The progression of pancreatitis is usually slow, and it takes long before a chronic form develops.

Back in 1896, Chiari proposed that autodigestion of the pancreas by premature activation of pancreatic enzymes was the mechanism of acute pancreatitis. Later it was realized that at least half of the acinar cells can be damaged independently of trypsinogen activation. So far, the exact pathogenesis of acute pancreatitis has not been clearly understood, although it is strongly influenced and/or mediated by systemic inflammatory response [6]. A systemic inflammatory response leading to fulminant pancreatic necrosis and multiorgan failure, with a mortality of 7–15%, can be observed in 20% of the patients. The systemic inflammatory response is supported and driven by activation of an inflammatory cascade mediated by cytokines, immunocytes and the complement system. Concomitantly, an antiinflammatory reaction, mediated by antiinflammatory cytokines and cytokine inhibitors, is activated. This antiinflammatory reaction may inhibit the immune response, rendering the host at risk of systemic infections. Interestingly, pancreatic beta cells express these intrinsic damage sensors, which have also been implicated in the pathogenesis of type 2 diabetes [6].

**Hormonal and Metabolic Abnormalities**

Hyperglycemia during acute pancreatitis is due to impaired insulin secretion, increased release of counterregulatory hormones and reduced peripheral glucose utilization. Marked hyperglycemia is associated with more severe pancreatitis and represents an adverse prognostic factor. Transient hyperglycemia and glycosuria are found in about 50% of patients with acute pancreatitis [5]. The incidence of glucose intolerance in acute pancreatitis ranges from 9 to 70%, and the degree of glucose intolerance is an indicator of the severity of pancreatitis. This wide range is accounted for by the definition of impaired glucose tolerance used in the different surveys, as well as by the cause of the acute inflammatory process. Alcohol, for example, is associated with more severe injury of pancreatic tissue, and alcoholic pancreatitis is complicated by a higher incidence of glucose intolerance. Hyperglycemia accompanying a bout of pancreatitis is the result of pancreatic damage and the concomitant stress condition. Both the severity and duration of the disturbance in carbohydrate metabolism are related to the extent of pancreatic tissue damage. Hyperglycemia and glycosuria usually subside within 3–6 weeks, but about 10% of patients continue to present with impaired glucose tolerance. Overt diabetes may persist after a first episode of acute pancreatitis in some patients, while in others it becomes manifest during the first years of follow-up. The incidence of diabetes after severe acute pancreatitis
can be as high as 60%, with higher incidence rates in cases of surgical pancreatic resection. Nevertheless, the etiology and frequency of abnormalities of glucose metabolism associated with acute pancreatitis still remain uncertain, and no predictive risk factors for the development and persistence of diabetes after acute pancreatitis have been identified.

In patients with acute pancreatitis, plasma insulin levels are lower than in healthy individuals with or without comparable degrees of stress [7]. Insulin secretion in response to glucose or glucagon is impaired, whereas alanine infusion results in a normal increase in plasma insulin levels. With amelioration of the acute process, normal insulin response is usually recovered. The plasma glucagon concentration is increased and tends to remain high for at least 1 week. The combination of hyperglucagonemia and hypoinsulinemia is sufficient to account for the development of ketoacidosis and the rare occurrence of diabetic coma [7].

Experimental studies have revealed increased basal levels of plasma pancreatic polypeptide (PP), suggesting a possible role of this peptide in the diagnosis of the disease. Nonetheless, in human studies plasma PP levels have been found within the normal values in the early phase of acute pancreatitis, and they fail to increase in response to hyperglycemia or secretin infusion. In a severely damaged pancreas, however, basal PP release may be low and could help in grading the severity of the disease.

Besides an elevation in plasma glucose levels, in a minority of patients with acute pancreatitis and no previous history of hyperlipidemia, the serum concentration of lipids may be elevated. A serum triglyceride level of >1,000–2,000 mg/dl in patients with type I, IV or V hyperlipidemia (Fredrickson classification) is a risk factor for acute pancreatitis. Plasma free fatty acid concentrations are elevated following acute pancreatitis as a consequence of impaired insulin secretion and concomitant increase in glucagon and cortisol secretion. Although the hormonal milieu that follows acute pancreatitis may favor the development of ketoacidosis, this is an unusual event, due to the persistence of residual endogenous insulin secretion sufficient to inhibit lipolysis and ketogenesis and due to deficient glucagon secretion.

Therapeutic Considerations
Acute pancreatitis is associated with significant hyperglycemia in 50% of patients, and occasionally ketosis or diabetic coma may develop. In the case of significant hyperglycemia, ketosis or coma, close monitoring of the plasma glucose concentration, electrolytes, ketones and other metabolic parameters is necessary, along with intravenous fluid and insulin infusion according to classic guidelines for the treatment of diabetic ketoacidosis. Hyperglycemia is considered the main obstacle to activation of a correct nutritional support, even in patients not affected by diabetes mellitus. Therefore, a correct insulin supply during artificial nutrition is needed, using parenteral or subcutaneous long-acting insulin analogues. It is recommended that patients with severe acute pancreatitis are managed by a multidisciplinary team in an intensive care unit. For patients with acute fulminant pancreatitis, conservative therapy rather than