Exocrine-endocrine Interplay in Pancreatic Disease

R.M. Anjana

Ranjit Unnikrishnan

Madras Diabetes Research Foundation and
Dr. Mohan's Diabetes Specialities Centre
WHO Collaborating Centre for Noncommunicable Diseases
Prevention and Control and IDF Centre of Education
Chennai, Tamil Nadu

INTRODUCTION

The human pancreas has traditionally been considered as having structurally and functionally separate endocrine and exocrine components, the former represented by the islets of Langerhans and the latter by the acinar tissue and the corresponding ducts. Recently, it has become clear that the two components of the pancreas are intimately inter-related and do not function in isolation. Disease processes of the exocrine pancreas have been shown to affect endocrine function and vice-versa. This chapter will deal with the physiological basis of the complex endocrine-exocrine interplay occurring in the pancreas and their implications on pancreatic disease.

STRUCTURE OF PANCREAS

The human pancreas develops from the dorsal and ventral pancreatic buds, which are outgrowths of the foregut. Fusion of these two buds gives rise to the definitive pancreas. The exocrine

and endocrine tissues of the pancreas therefore share a common origin from the embryonic foregut (endoderm). The further differentiation of precursor cells into each component of the gland depends on exposure to various factors such as follistatin, fibroblast growth factor, and the notch receptor system (for exocrine tissue) and neurogenin, Isl-3, PAX-0, and PAX-6 (for endocrine tissue).[1]

Exocrine tissue comprises nearly 95% of the adult pancreas; the islets of Langerhans and connective tissue together constitute only 5%. There are nearly 1 million islets in the adult pancreas, each containing around 5000 cells. The four main cell types in the islets are the α-cells (secreting glucagon), β-cells (insulin), δ-cells (somatostatin), and pancreatic polypeptide (PP) cells. The four types of cells are present in the ratio 20:68:10:2. The β-cells are located at the center of each islet, whereas the other cell types are found at the periphery. More recently, a 5th type of cell termed as the epsilon cell has been described; the main secretory product of this cell is ghrelin.[2]

The exocrine pancreas consists of the acinar cells, ductules, and ducts. They are located in close proximity to the islets and are not physically separate from them. The acinar cells secrete more than 15 different enzymes involved in the digestion of carbohydrates, fat, and proteins.

The exocrine and endocrine components of the pancreas are linked by the pattern of their blood supply. Blood from the pancreatic intralobular arteries first supply the islet cells through a capillary glomerular network. The efferent vessels from these glomeruli coalesce and subsequently supply the exocrine tissue and ductal system. This pattern of blood flow implies that acinar cells are exposed to high concentrations of islet hormones and represents a means by which the endocrine pancreas can influence exocrine function. The exocrine and endocrine pancreas also share a common innervation.

In view of the intimate structural and functional relationship between the exocrine and endocrine components of the pancreas, it is not surprising that diseases of the endocrine

Table 1.
Inter-relationship between Exocrine and Endocrine Disorders of Pancreas

I. Effects of diabetes mellitus on exocrine pancreatic function
   A. Acute pancreatitis
   B. Exocrine pancreatic insufficiency
   C. Pancreatic cancer

II. Exocrine pancreatic disorders causing diabetes
   A. Chronic pancreatitis
      1. Alcoholic chronic pancreatitis
      2. Tropical chronic pancreatitis
   B. Pancreatic cancer
   C. Cystic fibrosis
   D. Pancreatic surgery

pancreas can affect exocrine function and vice-versa. Table 1 enlists some of these conditions.

EFFECT OF ENDOCRINE PANCREAS ON EXOCRINE FUNCTION

Insulin has been found to have widespread effects on pancreatic exocrine tissue.[3] Insulin receptors have been identified on the surface of acinar cells. In the short-term, insulin can potentiate the response of acinar tissue to various stimuli such as gut hormones and neurotransmitters, while in the long run, it can influence the biosynthesis of pancreatic enzymes. Administration of insulin to animals with experimental diabetes has been shown to improve exocrine pancreatic function.

In addition to its effects on carbohydrate metabolism, glucagon has been found to reduce the volume of pancreatic juice, as well as its protein, amylase and bicarbonate content.[4] Pancreatic polypeptide has also been shown to inhibit both basal and stimulated secretion of pancreatic juice.[5] Somatostatin also has an inhibitory effect on pancreatic exocrine function. The effect of ghrelin on exocrine function is unclear.[6]

EFFECT OF ENDOCRINE DISEASE ON EXOCRINE PANCREATIC FUNCTION

Diabetes Mellitus

Considering the effects of insulin on acinar cell function, it is not surprising that biochemical evidence of exocrine pancreatic insufficiency is not infrequent in diabetes, although clinical deficiency is rare. Mohan et al[7] studied exocrine pancreatic function using the fecal chymotrypsin assay in patients with fibrocalculous pancreatic diabetes (FCPD), type 1 diabetes, and type 2 diabetes. The prevalence of exocrine pancreatic insufficiency was found to be 87.5%, 23.5% and 4.5%, respectively. Exocrine pancreatic insufficiency can develop in diabetes as a result of acinar atrophy (lack of trophic action of insulin), pancreatic fibrosis secondary to vasculopathy, impaired neural regulation secondary to diabetic neuropathy, and autoimmune-mediated inflammation.

Although diabetes has not been traditionally considered as a risk factor for acute pancreatitis (AP), recent studies suggest that adults with type 2 diabetes run a higher risk of developing this condition than their peers without diabetes. The risk was increased 5.2-fold in individuals aged 18–44 years and 2.45-fold in those aged above 45 years.[8] Diabetic ketoacidosis (DKA) has also been recognized as a risk factor for AP.[9] The risk probably stems from the profoundly elevated triglyceride levels often found in these patients.

Recently there has been some concern over the risk of AP with certain anti-diabetic medications. A recent population-based cohort study[10] assessed the risk for AP in patients with diabetes mellitus (DM) and its relation to treatment. It was found that while sulfonylureas increased the risk of AP, use of insulin and metformin was protective. The most recently introduced class of antidiabetic agents which act on the incretin system have come under particular scrutiny because they act directly on the

pancreas, altering hormonal secretion. A population-based matched case-control study from the United States[11] compared 1,269 hospitalized cases with AP and 1,269 control subjects matched for age category, sex, enrollment pattern, and diabetes complications. It was shown that the use of the incretin-based therapies exenatide and sitagliptin was associated with increased odds for hospitalization with AP. It has been shown in animals that exposure to glucagon-like peptide 1 (GLP-1) leads to pancreatic ductal cell proliferation. It has further been postulated that this can lead to occlusion of ducts with consequent back pressure on acini and development of AP.[12]

Chronic pancreatitis also occurs more frequently in diabetes. However, on account of the relatively insidious nature of chronic pancreatitis, it is often difficult to conclude whether pancreatitis is the cause or an effect of diabetes. An endoscopic retrograde cholangiopancreatography (ERCP)-based study in 156 patients (18 with type 1 and 138 with type 2 diabetes) showed morphological changes suggestive of chronic pancreatitis in 76.7% of patients.[13]

Similarly, the relationship between diabetes and pancreatic cancer is bidirectional. Several epidemiological studies have revealed the increased risk of developing pancreatic cancer among patients with diabetes. Increased risk has been shown for patients with type 1 as well as type 2 diabetes.[14] The highest risk of pancreatic cancer is seen in patients with pancreatic diabetes (particularly FCPD),[15] which is not surprising, as chronic pancreatitis itself is a risk factor for pancreatic cancer. There are also concerns that the ductal proliferation and acinar to ductal metaplasia noted with the use of incretin-based therapies for diabetes may predispose long-term users of these agents to the development of pancreatic cancer, although more studies are needed before conclusions can be drawn.[12] The effect of exocrine pancreatic malignancy on the development of diabetes will be discussed in subsequent sections of this chapter.

EFFECT OF EXOCRINE PANCREAS ON ENDOCRINE FUNCTION

The acinar cells play a critical role in β-cell development and maintenance. Animal models of chronic pancreatitis show loss of islet cells in parallel to exocrine tissue loss.[16] Ligation of the pancreatic duct produces islet cell atrophy, in addition to loss of acinar cells.[17] While the exact mechanism by which exocrine pancreatic function affects islet function is not clear, the role of the pancreatic regenerating protein (Reg I) has received considerable attention.[18]

EFFECT OF EXOCRINE DISEASE ON ENDOCRINE PANCREATIC FUNCTION

Acute Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas, which often affects the surrounding tissues and even remote organs and systems. The main risk factors for AP are alcohol abuse, obesity, and gallstone disease. Diabetes has also been recently recognized as a risk factor (vide supra). While the manifestations of AP are often severe and life-threatening, it has usually only transient effects of endocrine pancreatic function. The most common endocrine manifestation noted is transient hyperglycemia, which is usually related to counter-regulatory hormone excess than to endocrine pancreatic damage. A single episode of AP does not usually increase the risk of diabetes in later life.

Chronic Pancreatitis

Chronic pancreatitis is a chronic inflammatory disease of the pancreas characterized by fibrosis and destruction of exocrine pancreatic tissue. Although the pathology initially affects the exocrine tissue, diabetes is common in advanced cases

of chronic pancreatitis. In fact, recurrent abdominal pain, steatorrhea and diabetes, form the classic triad of chronic pancreatitis.

Alcohol abuse is the most frequent cause of chronic pancreatitis in the Western countries. Alcoholic chronic pancreatitis (ACP) usually affects young or middle-aged males. The prevalence of diabetes in these cases varies from 60–70% (in patients who have pancreatic calculi) while it is only around 30% in noncalcific ACP.[19] Other factors like age, ethnicity, and family history of diabetes may also play a role in development of diabetes.

Tropical chronic pancreatitis (TCP) is a peculiar form of non-alcoholic chronic calcific pancreatitis found in tropical parts of Central Africa, Asia, and South America. Although most patients are lean and belong to the lower socioeconomic strata, the disease is not unknown among affluent sections of society, and many patients are not lean.[20] Patients usually come to medical attention during adolescence or early adulthood, although symptoms of exocrine pancreatic insufficiency (steatorrhea and recurrent abdominal pain) often start in childhood. Diabetes, termed FCPD occurs more commonly in TCP than ACP. The exact etiology of TCP and FCPD remain unknown, although dietary and genetic factors have been implicated.

Chronic pancreatitis leads to a reduction in the number of islet cells as well as their functional capacity. Excessive fibrosis occurring in chronic pancreatitis has been postulated to lead to chronic ischemia and atrophy of the islet cells. The role of insulin resistance in the development of diabetes following chronic pancreatitis is controversial.

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disorder affecting, among other organs, the gastrointestinal tract and lungs. The genetic defect, which is inherited in an autosomal recessive fashion, is a mutation in the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR), which regulates salt and water transport across cell membranes. It is considered to be the most common autosomal recessive inherited disorder among

Caucasians. In the pancreas, CF causes degeneration of exocrine tissue with consequent β-cell damage. The incidence of diabetes in children with CF is 2–3%, which increases to 25% in young adulthood.[10] The risk of developing diabetes has been shown to be related to the severity of the mutation in the CFTR gene; patients with less severe type IV mutations have a lower risk of developing diabetes (and less exocrine insufficiency) compared to those with more severe mutations.

Pancreatic Cancer

As mentioned earlier, the relationship between diabetes and pancreatic cancer is complex.[21] While diabetes can increase the risk of pancreatic cancer, more commonly, patients with pancreatic cancer may present with diabetes as one of the manifestations of the disease. Around 70% of patients with pancreatic cancer have either impaired glucose tolerance (IGT) or diabetes.[2] In many cases, diabetes remits or resolves after treatment of the malignancy. The exact mechanisms of development of diabetes in pancreatic cancer are not clear but may include increased peripheral insulin resistance and tumor-derived factors causing diabetes. The alteration of the islet cells in most of the patients seems to be the reason for impaired glucose metabolism, which can be either due to the direct effect of the carcinoma or the release of diabetogenic substance from the cancer cells. The suspect causing the alteration is a substance known as islet amyloid polypeptide (IAPP), which is normally released by the β-cells along with insulin. It has diabetogenic effect in vitro and in vivo.

Elevated plasma levels of IAPP are found in patients with pancreatic cancer. However, subsequent studies have failed to show increased levels of IAPP—expressing cells in the tumor-affected areas of patients with pancreatic cancer.[22]

Pancreatic Surgery

Surgical procedures on the pancreas often result in development of diabetes. The risk of diabetes after pancreatic surgery depends on the type of procedure employed, extent of the gland resected,

and the indication for which the surgery is performed. Surgical operations on the pancreas are usually divided into drainage and resection procedures, each of which have their specific indications.

Drainage procedures are simpler to perform than resection and there is no removal of any part of the gland. Drainage procedures include pancreaticojejunostomy and pancreaticogastrostomy. These operations are usually not associated with the postoperative development of diabetes.

On the other hand, resection procedures involve removal of part of the pancreas. Whether the patient develops diabetes after a resection procedure depends on the part and extent of the gland removed. Postoperative diabetes rates vary from 10% to 25% in Frey's longitudinal pancreaticojejunostomy combined with local pancreatic head excision and from 7.5% to 21% in Beger's duodenum-preserving pancreatic head resection.[23] In distal pancreatectomy, diabetes does not develop unless >60% of the gland is removed. Diabetes is obviously inevitable following total pancreatectomy.

Pancreatic Diabetes

Diabetes secondary to pancreatic diabetes is often brittle and difficult to control. The patient may present with extremely high blood glucose values, consequent to the low endogenous insulin reserve. However, ketoacidosis is uncommon; this has been attributed to the following factors.[24]

- Presence of residual insulin secretion, which, although insufficient to prevent hypoglycemia, are sufficient to suppress lipolysis and ketogenesis
- Abnormalities in counter-regulatory hormone (particularly glucagon) release, secondary to widespread pancreatic damage
- Lack of fat reserve to act as substrate for ketogenesis secondary to fat malabsorption and malnutrition

Although DKA is rare, patients with pancreatic diabetes do

develop microvascular complications at a rate similar to that of patients with type 2 diabetes. Studies by Mohan et al and other investigators have shown that patients with FCPD have the same risk of developing retinopathy, nephropathy, and neuropathy as do patients with type 2 diabetes.[25–27] However, the risk of macrovascular complications was found to be significantly lower.[28]

MANAGEMENT OF PANCREATIC DIABETES

The main aim of treating pancreatic diabetes is to control hyperglycemia and prevent complications, while at the same time avoiding malnutrition and life-threatening hypoglycemia, thereby ensuring a good quality of life. While all patients with diabetes should attempt to keep their blood glucose levels as close to the normal range as possible, this is often difficult in pancreatic diabetes because of the brittle nature of the disease. Therapeutic targets need to be individualized in each case.

Patients with pancreatic diabetes are advised to consume small frequent meals and avoid long gaps between them. The diet should be rich in protein and low in fat. The use of pancreatic enzyme supplements may ameliorate the symptoms of malabsorption to a certain extent.

Although a few patients with pancreatic diabetes may be able to control their hyperglycemia with diet or oral antidiabetic agents, the majority ultimately requires insulin. Multiple dose of insulin injections (MDI) with frequent monitoring of blood glucose levels will help patients achieve the best possible levels of control. Use of insulin analogs is likely to be associated with less hypoglycemia, and by extension, better glycemic control, but large studies in this patient population are lacking.

The use of continuous subcutaneous insulin infusion (CSII) pump represents an attractive therapeutic option in patients with pancreatic diabetes as it will help in the attainment of euglycemia with minimal risk of hypoglycemic episodes. It is

likely to be most useful in patients who have undergone subtotal or total pancreatectomy and who have no functional insulin reserve left.

Development of back pain and weight loss in a patient with pancreatic diabetes whose glycemic control is adequate should prompt a search for occult pancreatic malignancy.

CONCLUSION

Exocrine pancreatic insufficiency and DM are relatively common medical problems. However, the relationship between the two has only recently become evident. Clinicians should be alert to the presence of exocrine pancreatic insufficiency in patients with diabetes, as well as to the development of diabetes in patients with exocrine pancreatic disease. Diabetes secondary to pancreatic disease has certain peculiar features, which should be kept in mind while treating patients with this condition.

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