

Diabetes Mellitus and the Exocrine Pancreas

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Diabetes and carbohydrate intolerance can occur in pancreatitis. Although one-half of patients with acute pancreatitis will have some evidence of glucose intolerance during their acute illness, few will require insulin administration on either a short- or long-term basis. The diabetes seen in acute pancreatitis is likely due to a combination of factors, including alerted insulin secretion, increased glucagon release, and decreased glucose utilization by the liver and peripheral tissue. Chronic pancreatitis is often associated with diabetes mellitus, with the incidence as high as 70 percent when pancreatic calcification is present. These patients tend to be very sensitive to the effects of insulin and hypoglycemia. This is probably secondary to concurrent hepatic disease, malnutrition, and a relative decrease in glucagon reserves. The diabetes seen in chronic pancreatitis is associated with decreased insulin production. Finally, although the endocrine pancreas may influence the exocrine gland through a portal system, primary diabetes mellitus probably does not result in clinically significant alterations in pancreatic exocrine function.

Diabetes mellitus and glucose intolerance are recognized complications of acute and chronic pancreatitis [1]. Multiple factors including widespread alterations in neurohumoral function and islet destruction are likely of importance in the genesis of the diabetes mellitus that develops in this setting. This review will examine some of those factors and attempt to relate them to the natural history of these disease states.

DIABETES MELLITUS AND ACUTE PANCREATITIS

Clinical Presentation

Although 30 percent of patients with severe acute pancreatitis will demonstrate glycosuria and 50 percent an elevated blood sugar level [2], the diabetes in this setting is usually self-limiting and resolves in parallel to the pancreatitis [3]. Occasionally, patients with acute pancreatitis do develop diabetic ketoacidosis and require insulin therapy [2]. These patients appear to be susceptible to hypoglycemia, so insulin should be administered cautiously [2]. A small percentage (1-2 percent) of patients will remain diabetic after a single attack of pancreatitis [4].

Pathogenesis

The diabetes mellitus seen with acute pancreatitis is probably multifactorial and includes pancreatic islet destruction and a "hyperglycemic" hormonal milieu.

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Since the endocrine and exocrine pancreas reside in the same anatomic domain, it is not surprising that factors that result in widespread cellular and vascular damage [5] should result in injury to both portions of the organ. A decrease in islet function appears to be present in acute pancreatitis, although some controversy still exists.

Johansen and Ornholt [4] identified decreased insulin secretion in acute pancreatitis. In contrast, Donowitz et al. [6] find an increase in basal and alanine-stimulated insulin levels in patients with initial acute attacks of pancreatitis. In the latter study, insulin levels from patients with recurrent acute attacks of pancreatitis did not differ from control subjects. Recently, Seligson et al. [7] examined patients with pancreatitis and demonstrated a decrease in the response of C-peptide secretion to oral glucose. Although the differences in these studies may be related to the method used to study insulin secretion, the patient population and the timing of the study, in some patients with acute pancreatitis decreased insulin secretion appears to be a factor in the development of diabetes.

Glucagon reserves in the pancreas appear to surpass those of insulin. Early investigation demonstrated that the diabetes resulting from pancreatic resection was more easily controlled if the entire pancreas was removed [8]. Yasugi et al. [9] demonstrated that, following pancreatic resection, glucagon secretion can be preserved at a point at which insulin secretion diminishes. Donowitz et al. [6] demonstrated a dramatic increase in basal and alanine-stimulated plasma glucagon levels during the initial attacks of pancreatitis. Therefore, although diabetes and diabetic ketoacidosis may occur in the absence of hyperglucagonemia [10], it appears to be of importance in the development of the diabetic state in acute pancreatitis.

Elevations in blood glucose levels can arise from several primary pathogenic sources as recently outlined by DeFronzo et al. [11]. These include a decrease in insulin release, a decrease in the hepatic uptake of glucose, and an alteration in the peripheral utilization of glucose. Having commented on insulin secretion in acute pancreatitis, I would like to focus on glucose utilization. Acute pancreatitis is often characterized by hypovolemia and shock; a setting recognized to be associated with increased adrenergic secretion. Epinephrine, produced as part of the "stress" response, has been shown to inhibit insulin secretion *in vivo* [12]. Recently, Deibert and DeFronzo [13] have shown, in man under euglycemic conditions, that epinephrine also acts to block the effect of insulin on hepatic glucose metabolism and peripheral glucose uptake. Thus, an additional factor in the development of the diabetes seen in acute pancreatitis may be decreased glucose utilization.

DIABETES MELLITUS AND CHRONIC PANCREATITIS

Clinical Presentation

Diabetes mellitus is a well-recognized complication of chronic pancreatitis. Overt diabetes or glucose intolerance can precede the onset of pancreatic calcification in chronic pancreatitis and was observed in 30 percent and 20 percent of patients, respectively, in one series [2]. When pancreatic calcifications are present, that group observed overt diabetes in 70 percent of patients, and an additional 20 percent demonstrated glucose intolerance. Diabetes often precedes steatorrhea in chronic pancreatitis. This finding is not unexpected since the apparent pancreatic exocrine reserve is threefold greater than the endocrine reserve as measured in experimental pancreatic resection [9].

Several features of the diabetes mellitus associated with pancreatitis are worthy of

consideration. These patients appear to be very sensitive to insulin and readily experience hypoglycemia [14]. Linde et al. [15] noted hypoglycemic episodes in 14 of 18 insulin-treated patients and, in three, it was believed to be the cause of death.

There are several factors which likely contribute to this insulin sensitivity. First, these patients often abuse ethanol and hepatic gluconeogenesis may be directly inhibited [16]. Second, these patients frequently have a poor caloric intake. Third, some [15], though not all [6], patients with chronic pancreatitis have been reported to have low plasma glucagon levels. Since glucagon appears to be important in the maintenance of blood glucose levels at least in part through the stimulation of hepatic glucose production, it is probably important in the development of hypoglycemia. Furthermore, patients with chronic liver disease, a condition often associated with chronic pancreatitis, appear to be glucagon-resistant relative to hepatic glucose production [17]. This tends to place them in a precarious situation relative to the development of hypoglycemia in that they are both underproducing (chronic pancreatitis) and resistant to (chronic liver disease) glucagon.

A potential benefit of the decreased glucagon levels in chronic pancreatitis is that it may prevent prolonged episodes of hyperglycemia. In addition, glucagon apparently accelerates ketonemia [10], presumably by reducing the liver's ability to convert free fatty acids to ketoacids and thus may be an important factor in the apparently low incidence of diabetic ketoacidosis in chronic pancreatitis.

The vascular complications seen with the diabetes mellitus associated with chronic pancreatitis are said to occur infrequently. This statement is based, in large part, on the observations of Sevel et al. [18] relative to the development of diabetic retinopathy in chronic pancreatitis (incidence of retinopathy 7.4 percent in chronic pancreatitis). Although this study is intriguing, further investigation is needed to determine if the natural history of vascular disease in this form of diabetes mellitus differs from that seen in other diabetics.

Pathogenesis

The diabetes seen in chronic pancreatitis is multifactorial and likely includes decreased insulin release [19] and a relative preservation of glucagon over insulin reserves [9]. This decreased insulin secretion is probably secondary to progressive islet destruction through recurrent bouts of pancreatitis, or a direct toxic effect of alcohol on islet cells similar to that shown for the exocrine pancreas [20]. The relevance of the observation that patients with chronic pancreatitis have altered basal and meal-stimulated levels of a number of gastrointestinal hormones to the diabetic state is unknown [21].

THE EFFECTS OF DIABETES ON EXOCRINE PANCREATIC FUNCTION

How can the endocrine pancreas influence the exocrine portion of the organ? The endocrine pancreas is connected to the exocrine pancreas through a portal system. This potentially allows high concentrations of islet peptides to reach pancreatic acinar cells [22].

Insulin has been demonstrated to specifically bind to pancreatic acinar cells [23] and to stimulate protein phosphorylation in that tissue [24]. In addition, protein synthesis by pancreatic acini is diminished in diabetic mice [23–25]. *In vivo* experiments in diabetic mice demonstrate that amylase secretion in response to cholecystokinin is diminished, although the mechanism is unclear [26]. Whether these alterations in the exocrine pancreatic function in diabetes are secondary to a

decrease in insulin secretion or other factors such as decreased cholinergic input secondary to an autonomic neuropathy is unclear.

Alterations in exocrine pancreatic function have been studied exclusively in juvenile-onset diabetes. Although a decrease in amylase secretion is generally described [27], a diminished secretion of proteases has also been noted [28]. In spite of the fact that these studies suggest a degree of pancreatic exocrine dysfunction in some patients with primary diabetes, it appears unlikely that it is enough of a change to result in malabsorption.

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