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A Look Inside the Pancreas: The "Endocrine-Exocrine Cross-talk"

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Abstract

Though the pancreas has traditionally been considered a combination of two separate organ systems, both the exocrine and endocrine portions are structurally and functionally interrelated. Disease processes diffusely involving the pancreas can give rise to both endocrine and exocrine dysfunctions and pancreatic diseases account for less than 0.5% of all cases of diabetes. Chronic pancreatitis and fibrocalculous pancreatic diabetes are the two most common diseases of the exocrine pancreas which can give rise to beta cell dysfunction and diabetes. On the contrary, prominent changes in the structure and functions of the exocrine pancreas have been identified in a significant number of the commonly encountered forms of diabetes, where exocrine insufficiency is unexpected otherwise. A number of hypotheses have been put forward by different workers at different time frames to explain the mechanisms of exocrine pancreatic insufficiency in patients with primary pancreatic endocrine dysfunction. Though the frequency of exocrine insufficiency seems quite high in the literature, paucity of data exists on the beneficial effect of enzyme supplementation in diabetes patients with/without exocrine abnormality.

Keywords: Endocrine-exocrine cross-talk; Exocrine pancreatic insufficiency; Insulo-acinar axis; Enteropancreatic reflexe; Fecal elastase

Introduction

Diabetes, the largest non-communicable disease, currently affects more than 382 million people aged between 20-79 years across the globe [1] and type 2 diabetes undoubtedly is the major underlying subtype. Pancreatic disease is a rare cause of diabetes, accounting for less than 0.5% of all cases of diabetes [2]. Any disease process that diffusely injures the pancreas like pancreatitis [acute/chronic], trauma, infection, pancreatic surgery and pancreatic carcinoma can give rise to both endocrine and exocrine dysfunction. With the exception of pancreatic malignancies, damage to the pancreas must be extensive for diabetes to occur. The other known causes of pancreatic diabetes are Fibrocalculous Pancreatic Diabetes [FCPD], cystic fibrosis and haemochromatosis. On the other hand, prominent changes in the structure and functions of the exocrine pancreas have been identified in a sizable number of the commoner forms of diabetes, who are usually not expected to have exocrine insufficiency [3]. Studies have shown changes in the size of zymogen granules, loss of acinar cells, acinar fibrosis and pancreatic atrophy in both Type 1 and Type 2 diabetes [4-6]. Exocrine Pancreatic Insufficiency [EPI] has also been documented in some forms of Maturity Onset Diabetes in Young [MODY], namely MODY 3, MODY-5, MODY-8.

In this review we shall discuss the underlying mechanism of this "endocrine-exocrine cross-talk" within the pancreas and its practical and therapeutic implications.

Anatomy and Physiology of Relevance

Although pancreas has traditionally been considered as two separate organ systems, both the exocrine and endocrine portions are interrelated. Within the pancreas the exocrine parenchyma and endocrine islet tissue lie in intimate contact with each other and are anatomically and physiologically interconnected. This is partly due to the fact that pancreatic islets are not surrounded by any capsule/membrane and acinar tissue of the pancreas lies in close contact with these islets. The capillary plexuses arising of major feeding arteries supply the islets and acini separately. But the outflow of blood from the islets drains into acinar capillary network. So, the exocrine pancreas receives at least a part of its blood flow coming through the nearby islets which forms the so called "insulo-acinar axis"; as a result acinar cells are exposed to high concentration of islet hormones. Such intra-pancreatic portal system suggests a possible influence of endocrine islets upon the exocrine pancreas.

The acinar cells of the pancreas secrete enzymes as zymogen granules and this secretion is viscid & slightly acidic with a sluggish flow. There are no muscles in the duct wall of the pancreas and so there are no peristaltic movements. The ductular epithelial cells produce thin, watery, alkaline fluid in a "jet" like flow, which dilutes the viscid fluid and allows its easy flow into the main duct. The pancreatic fluid also contains a protein named Lithostathine S, which keeps the calcium of the pancreatic juice in a soluble state. These physiological processes inhibit stone formation within the pancreatic ducts in normal condition.

Endocrine Insufficiency in Diseases of the Exocrine Pancreas: Mechanisms

Chronic Pancreatitis [CP] and FCPD are the two most common diseases of the exocrine pancreas which can give rise to beta cell dysfunction and diabetes.

In CP, pancreatic tissue pressure has been found to be elevated in all the regions of pancreas and there is tissue hypoxia due to alteration in the pancreatic microcirculation. These abnormalities supposedly activate Pancreatic Stellate Cells [PSC], help them to proliferate and stimulate type 1 collagen secretion resulting in pancreatic fibrosis [7]. This contributes to gradual and progressive endocrine dysfunction. Interestingly enough, high glucose concentrations also stimulate PSC activation via PKC-p38 MAP kinase pathway and may aggravate

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pancreatic fibrosis and thus produces a vicious cycle [8] (Figure 1). Ultrasonography reveals dilated Main Pancreatic Duct [MPD] with pancreatic atrophy and parenchymal calcification at times.

The primary insult in FCPD is on the epithelial cells of the ducts and interlobular ductules of the pancreas resulting in impaired watery alkaline secretions and failed flushing system. As a result there is stagnation of the secreted enzymes from the acini and increased pressure within the acini and ductules. There is subsequent pressure atrophy and death of the acinar cells with local fibrosis. The resultant reduction in acinar mass causes exocrine insufficiency. Damage to the ductular epithelium also gives rise to inadequate secretion of soluble Lithostathine S and its conversion to more lithogenic Lithostathine H2. The viscid intra-ductal secretion with high intra-luminal pressure and intra-ductal calculi produce metaplastic changes in the ductular epithelium which ultimately result in decreased beta cell neogenesis from the ductal progenitor cells. The fibrosis of the acinar cells and surrounding parenchyma produces hindrance to intra-pancreatic insulin circulation and its access to the blood vessels. Damage to the endocrine tissue together with impaired beta cell neogenesis and decreased insulin delivery to the draining microvessels are perhaps the underlying cause of diabetes (Figure 2) [9]. Multiple large calculi can be seen along the dilated MPD in both X-ray (Figure 3) and ultrasound abdomen. In one of our series of 157 patients with onset of diabetes before 30 yrs of age, the prevalence of FCPD was 12.7% [Unpublished].

Exocrine Insufficiency in Diseases of the Endocrine Pancreas: Mechanisms

Exocrine abnormality has been described in different forms of "non-pancreatic" diabetes, the incidence being around 50% and 35% in "insulin dependent" and "non-insulin dependent" diabetes respectively using both direct [secretin-pancreozymin test] and indirect [fecal elastase 1 concentrations] tests of pancreatic function [10]. Fecal elastase concentration was shown to be inversely correlated with diabetes duration and HbA1c-levels and positively correlated with C-peptide levels in a mixed cohort of diabetic population [11]. Moreover, in Type 2 diabetes, serum amylase and trypsin levels were found to be low compared to healthy controls and those were inversely related to fasting plasma glucose. A recently published study has also shown the inverse relationship between HbA1c and fecal pancreatic elastase in Type 2 diabetes [12]. However, there are studies which have come out with divergent conclusions as far as EPI is concerned. For an example, Miroslav Vujasinovic and colleagues found that only 5.4% of their 150 diabetic patients [Type 1, insulin treated Type 2, non-insulin treated type 2] had low fecal elastase-1 concentration indicative of exocrine insufficiency [13].

A number of hypotheses have been put forward by different workers at different times to explain the mechanisms of EPI in patients with pancreatic endocrine dysfunction.

Insulin has been considered a trophic factor for the nearby exocrine tissue as evidenced by different in-vivo and in-vitro studies [14]. Acinar cells located closed to the portal vessels arising from the nearby islets are comparatively bigger and produce more enzymes than those located at a distance. It has also been seen that patients without any residual beta cell functions display more obvious histopathological changes in the exocrine pancreas than those with some existing insulin secretion. Insulin also increases the enzyme output from cultivated islets in in-vitro experiments. For example, insulin regulates amylase gene transcription [15]. So, not surprisingly a good correlation has been observed between residual beta cell function and fecal elastase 1 concentration. But what remains unexplained, is the occurrence of acinar cell dysfunction in only 50% patients of Type 1 and in some c-peptide positive Type 2 diabetics.

Altered secretion or action of other islet hormones [glucagon, somatostatin, pancreatic polypeptide] have been put forward as another explanation [16]. Elevated glucagon levels, which is found in both forms of diabetes has been suggested to contribute to exocrine damage and dysfunction. Somatostatin is a relevant negative regulator of intestinal function including the exocrine pancreas and elevated levels, as described in streptozotocin-induced diabetes, have been shown to reduce exocrine function as well. However, studies involving these hormones have been performed in animal models only and the secretory patterns of these islet hormones are known to differ in Type 1 and type 2 diabetes.

Autoimmune destruction of both the components of pancreas was another issue of interest. Many small studies from Japan have shown presence of antibodies directed against different exocrine antigens in Type 1 diabetic patients. For example in different study populations involving type 1 diabetics, antibody against pancreatic cytokeratin was found in 39%, antibody against Bile Salt Dependent Lipase [BSDL] in 73.5% and antibodies against lactoferrin or carbonic anhydrase in 77% of all the patients [17,18].

The other suggested pathogenetic mechanisms are hyperglycaemic injury to the pancreas, abnormal secretion of Cholecystokinin [CCK], acinar cell insensitivity to CCK, diabetic focal microangiopathy followed by pancreatic fibrosis and atrophy, simultaneous damage of exocrine and endocrine tissues by viral infections and genetic changes affecting both the compartments. Larger and colleagues looked into the clinical correlates of exocrine pancreatic failure in both type 1 and type 2 diabetes. In their cohort, the association of EPI with BMI and vascular disease suggested a role of pancreatic arteriopathy in exocrine dysfunction in Type 2 diabetes [19]. The loss of continuous interstitial matrix connection between the endocrine and exocrine pancreas by fibrosis may result in a dysfunctional insulino-acinar axis due to defective cellular paracrine communication in both prediabetes and diabetes [20].

Another plausible explanation of the EPI in diabetes seems to be the result of diabetic neuropathy, autonomic neuropathy to be more specific [21]. It's a well-known fact that regulation of enzyme synthesis and secretion depends on local neurons and their signals. The enteropancreatic reflexes, which mediate upto 50% of pancreatic response following a meal, are impaired in autonomic neuropathy.

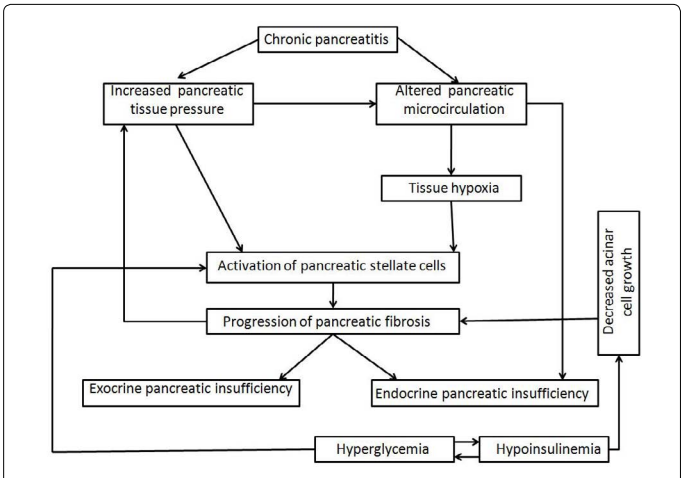

Figure 1: Mechanisms of diabetes in CP.

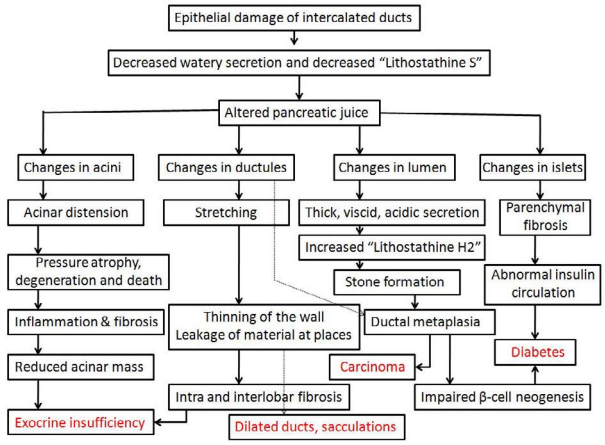

Figure 2: Pathogenesis of FCPD.

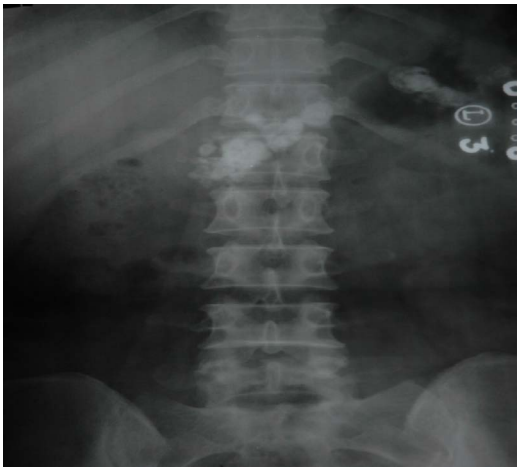

Figure 3: Straight X-ray abdomen showing large calculi along MPD in FCPD.

This can potentially culminate in EPI. Moreover, gastric emptying and delivery of nutrients to the proximal small intestine is delayed in presence of intestinal autonomic neuropathy. As a result, there is reduced stimulus to CCK secretion and subsequent impaired exocrine pancreatic secretion. This is supported by the fact that significant increase in exocrine insufficiency occurs with the course of diabetes.

In a recently published meta-analysis of prospective, observational studies involving 2891 patients, that used fecal elastase-1 estimation to determine exocrine insufficiency one in every three diabetics were found to be suffering from exocrine dysfunction [22]. Despite most of these published evidences showing a high frequency of exocrine abnormality, we still believe signs/symptoms of exocrine insufficiency is a rare manifestation in the so called "garden variety" of type 2 diabetes. In day to day practice, very few diabetic patients develop overt exocrine disease possibly because of the large functional reserve of the exocrine pancreas.

Clinical Consequences of Exocrine Pancreatic Insufficiency in Diabetes

Exocrine insufficiency in diabetes is not only a subclinical disease, but it can give rise to deficiency of macronutrients, steatorrhoea and consequent qualitative malnutrition of fat soluble vitamins. This abnormality might also explain the commonly encountered vague abdominal symptoms in patients with diabetes. Steatorrhea is not uncommon in patients with diabetes and exocrine insufficiency [23]. Studies have also pointed out towards the association between clinical symptoms of exocrine insufficiency [stool consistency, meteorism/flatulence] and the degree of steatorrhoea. However, in our unpublished observation only 25% of FCPD patients had abdominal pain and 5% had steatorrhoea at presentation. This may be explained by low dietary fat intake in our patients. There may also be a selection bias; patients with steatorrhoea and/or pain abdomen initially consult gastroenterologists rather than endocrinologists.

Vitamin D is known to play an important role in the regulation/function of the innate and adaptive immunity and vitamin D deficiency might be involved in the pathogenesis of type 1 diabetes. Vitamin D deficiency has also been linked to obesity, insulin resistance and Type 2 diabetes. A significant correlation between reduced fecal elastase 1 levels and low vitamin D levels has also been demonstrated [24] and this may be another explanation of diabetes in exocrine insufficiency.

Interestingly enough, the incretin axis might also be altered in patients with steatorrhoea [25] as the secretion of incretins depends on the presence of end products of digestion inside the intestinal lumen. The abnormal incretin response could then give rise to abnormal glucose homeostasis.

Therapeutic Implications

Considering the correlation of abdominal symptoms with steatorrhoea and a probable role of maldigestion and incretin defects, a number of trials with pancreatic enzymes were conducted in diabetic patients with varying outcomes. There was significant reduction in 24 hours fecal fat excretion with enzyme replacement compared to placebo in most of those studies.

If we look at those studies on enzyme replacement therapy on glycemic control, the outcomes are different. In a study by O´Keefe, high-dose pancreatic mini-microspheres improved, but did not normalize fat absorption, which they hypothesized, was the residual influence of diabetes and malnutrition on intestinal absorptive functions.
They did not observe any positive effect on HbA1c and also noticed overall less stable glycaemic control in chronic pancreatitis. Another interesting observation was that changing treatment from active enzyme supplementation to placebo [and vice versa] resulted in major problems with glucose control; blood glucose levels became abnormal in 28 of 29 patients, one patient required hospitalization for symptomatic hypoglycaemia during placebo treatment, and one developed diabetic ketoacidosis after recommencing active enzyme supplementation. They came up with the suggestion that enzyme initiation and initial adjustment should be carefully supervised in-hospital [26]. In another small study, enzyme replacement did not result in any positive effect on HbA1c but more stable control was observed over the entire day on pancreatic supplementation [27]. However, in an Indian study involving patients of FCPD, pancreatic enzyme supplementation over a 6 month period significantly reduced post-prandial glucose and HbA1c, improved nutrition and overall quality of life [28]. The positive effect of enzyme supplementation on blood glucose can be explained by the reversal of incretin defects observed in these patients as shown by Ebert and his colleagues [25].

Summarizing the findings of these studies there is no general recommendation so far for routine enzyme supplementation in diabetics. Treatment is justified if steatorrhea and relevant abdominal symptoms are present. More studies are required on the impact of pancreatic enzymes on glucose metabolism and qualitative malnutrition.

Conclusions

The "exocrine-endocrine cross-talk" within the pancreas has a strong anatomical and physiological basis. A number of hypotheses have been put forward by different workers to explain EPI in islet dysfunction, probably underscoring the fact that the exact pathogenetic mechanism is yet to be crystallized. Although the evidences suggest that exocrine dysfunction is common in diabetes, clinical experience is somewhat discordant. EPI can be diagnosed by fecal elastase-1 concentration, which is non-invasive and easy to perform. Paucity of data exists on the beneficial effect of enzyme supplementation in diabetes patients with/without exocrine abnormality. Unless more studies involving large population are available, it is premature to recommend testing for EPI as a part of routine diagnostic work-up in diabetes.

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