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Review Article

Pancreatic Disorders and Diabetes Mellitus-A Review

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Abstract:

Diabetes mellitus is a common disease among patients with pancreatic cancer and chronic pancreatitis. Hyperinsulinemia and peripheral insulin resistance are the prevailing diabetic traits in pancreatic cancer, whereas reduced islet cell mass and impaired insulin secretion are typically observed in chronic pancreatitis. Whether or not a causal relationship exists between diabetes and pancreatic carcinoma is an intriguing but unanswered question. Diabetes often precedes pancreatic cancer and is thus regarded as a potential risk factor for malignancy. Conversely, pancreatic cancer may secrete diabetogenic factors. Given these findings, there is increasing interest in whether close monitoring of the glycaemic profile may aid early detection of pancreatic tumor lesions. Exocrine pancreatic insufficiency is frequently associated with diabetes, with high prevalence in both insulin-dependent and insulin-independent patients. The incidence of diabetes caused by exocrine pancreatic disease appears to be underestimated and may comprise 8% or more of the general diabetic patient population. Non-endocrine pancreatic disease can cause diabetes by multiple mechanisms. Genetic defects have been characterized, resulting in a syndrome of both exocrine and endocrine failure. Regulation of beta cell mass and physiological incretin secretion are directly dependent on normal exocrine function. Algorithms for diagnosis and therapy of diabetes should therefore address both endocrine and exocrine pancreatic function.

Key words: Pancreas, Disorders, Diabetes Mellitus.

Introduction:

The relationship between the pancreas and diabetes was established when Murkowski performed a pancreatectomy in the dog in 1889[1]. Early clinicians distinguished between pancreatic diabetes, due to obvious pancreatic disease, and the much more common form of diabetes in which the pancreas appeared normal. Only about 1-2% of human diabetes is considered to be due to overt pancreatic disease, but this may be an underestimate. Pancreas has a considerable reserve of islet beta cells and investigators need to excise 70-90% from healthy animals before they will develop diabetes[2]. Extensive pancreatic damage is therefore needed to cause human diabetes. Such damage occurs in severe cases of acute pancreatitis, in chronic pancreatitis, in pancreatic fibrosis (due, for example, to iron overload), or following surgical excision of the pancreas. Pancreatic carcinoma predisposes to diabetes by secreting circulating factors promoting insulin resistance as well as by pancreatic destruction. Pancreatic diabetes results in loss of both insulin and pancreatic glucagon, diabetic ketoacidosis is rare, and patients are sensitive to the action of insulin[3].

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Historical aspects:

Although some 19th century physicians had noted an association between diabetes and pancreatic disease, proof came when Oskar Murkowski removed the pancreas from a dog in 1889, although diabetes was an unexpected development! The role of the pancreatic islets emerged more slowly, in the absence of specific stains for islet cells and insulin, and early pathologists were baffled by the apparently normal appearance of the pancreas in most cases of diabetes.

The work of Frederick Allen showed that dogs did not develop diabetes until 80-90% of the pancreas had been removed, and that the development of diabetes could be avoided by use of a low-carbohydrate, low-energy diet. This was the origin of the starvation for children with diabetes.

Any form of extensive pancreatic damage may result in diabetes. These range from surgical excision of the pancreas (usually for a pancreatic tumor) to acute and chronic pancreatitis, tropical chronic pancreatitis (previously referred to as fibro-calculus pancreatic disease), pancreatic fibrosis, carcinoma of the pancreas, and inherited disorders affecting the pancreas such as cystic fibrosis.

A recent survey of 1868 people with diabetes found that 172 (7.2%) had identifiable pancreatic disease, including 135 with chronic pancreatitis (78.5%), 12 with hereditary haemochromatosis, 14 with pancreatic cancer and 7 with cystic fibrosis. The underlying diagnosis had been missed in half of these patients, and it seems likely that exocrine fibrosis. Exocrine pancreatic problems are under diagnosed in the diabetic clinic[1].

Acute pancreatitis:

Acute pancreatitis is a medical emergency resulting from inflammation of the pancreas. It presents with the cardinal features of acute upper abdominal pain radiating to the back, elevated levels of the pancreatic enzymes amylase and lipase and characteristic features on imaging.

The mechanism involves premature activation of enzyme precursors produced by the acinar cells triggering an inflammatory cascade. The common associated causes are gall stones and alcohol abuse. Acute pancreatitis is more common in people with diabetes than in non-diabetics. In some instances it may be a reflection of the underlying pancreatic disease that has caused the diabetes. Apart from, the acute pancreatitis appears to be more common in people with type 2 diabetes, possibly as a consequence of the associated obesity. It has been reported as a potential complication of the GLP-1 based therapies.

Acute pancreatitis is self-limiting in about 80% of cases, and resolves with conservative management. More severe cases are associated with profuse fluid loss into the peritoneal cavity, shock, and development of renal and pulmonary problems. Hemorrhage and necrosis may produce extensive loss of pancreatic tissue, and secondary infection may develop as the result of invasion by gut bacteria. The mortality of acute pancreatitis is about 4-5%.

Acute pancreatitis may sometimes occur as a manifestation of a chronic inflammatory process, or even pancreatic cancer, and may predispose to chronic pancreatitis. The pancreatic islets are relatively spared during acute pancreatitis, even when there is extensive damage to exocrine tissue, but acute hyperglycemia develops in >50% of cases and permanent diabetes in about 5%.

Chronic pancreatitis:

Chronic pancreatitis is due to persistent inflammation of the pancreas resulting in progressive loss of exocrine function, with secondary damage to the pancreatic islets. Chronic disabling pain is a common clinical feature, as is weight loss and (less frequently) jaundice. About 50% of those affected develop diabetes.

The commonest cause is alcohol abuse, defined as consumption of >60 g of alcohol per day, and this accounts for about 75% of cases, although only about 5% of those with alcoholic problems develop pancreatitis. Other known causes include tropical pancreatitis, cystic fibrosis, and genetic syndromes such as hereditary pancreatitis, which account for about 5% of cases. The remaining 20% of cases develop for reasons that are unknown.

Diagnosis is best made by contrast-enhanced computerized tomography (CT). Medical treatment includes avoidance of predisposing factors such as alcohol, oral ingestion of enzymes with food, control of diabetes and pain control. Pain may be intractable and result in narcotic addiction, and patients may require pancreatic resection to treat this complication.

Chronic pancreatitis predisposes to pancreatic carcinoma, which develops in about 40% of those with hereditary pancreatitis. The prognosis of chronic pancreatitis may be limited by other factors such as alcohol abuse, but is otherwise good.

Tropical Chronic pancreatitis:

Tropical chronic pancreatitis is a unique form of chronic pancreatitis seen only in developing countries, and can result in the condition of fibro calculus pancreatic diabetes (FCPD). It has clinical, radiological and pathological features that distinguish it from alcoholic and other form of chronic pancreatitis. It affects young adults, who present with abdominal pain due to pancreatic calculi. In contrast to alcoholic chronic pancreatitis, these stones are typically large and discrete. The condition progresses to progressive exocrine pancreatic failure resulting in malabsorption and diabetes.

The etiology of the condition is unknown, although it commonly develops against a background of poverty and malnutrition. Genetic mutations in the SPINK gene have been reported, and micronutrient deficiency and/or toxins are possible predisposing factors. Although rare, typical microvascular complications of diabetes may develop and the condition also carries a high risk of carcinoma of the pancreas. Diabetes develops up to a decade after the first symptoms of tropical chronic pancreatitis, typical in the 20-40 year age group. Patients may present with very high blood glucose levels, but diabetic ketoacidosis is rare. Most patients will require insulin for glucose control, and the long-term prognosis is good relative to other causes of chronic pancreatitis.

Carcinoma of the pancreas:

Ductal adenocarcinoma comprises about 90% of cases. The condition is clinically silent until the tumor has reached an advanced stage, when it presents with weight loss, pain, and/or jaundice. Late presentation largely explains its poor prognosis, with about 5% survival at 5 years. The condition is about twice as common in those with obesity or type 2 diabetes as in those without. Conversely, diabetes is present in up to 50% of those with carcinoma of the pancreas, and the diagnosis of diabetes often precedes the diagnosis of cancer. Tumor associated humoral factors conferring insulin resistance may be responsible. Progression to

pancreatic cancer has been shown to involve a cascade of gene mutations, of which KRAS is the most important. These occur in parallel with the development of progressive premalignant histological changes known as pancreatic intraepithelial neoplasia (PanIN) lesions. Early PanIN lesions are relatively common in the general population, and reflect the prevalence of other risk factors for pancreatic cancer. Since humoral markers are unavailable, pancreatic biopsy is impractical, and imaging techniques are expensive and carry the risk of false positives, possibilities for screening are currently limited.

Discussion:

From this brief review, it can be seen that abnormalities have been found in each of the stage in insulin-carbohydrate interaction enumerated in the introduction, and many of these have been suggested as fundamental in the pathogenesis of diabetes mellitus. Clearly no step can be considered in isolation, and in discussion the significance of pancreatic change in diabetes mellitus, abnormalities in other stage, and particularly in the control of cell mass and function must be considered. If the cell mass is reduced or if insulin is destroyed by excess insulinase, the feedback mechanism should restore normality. However, the ability of the feedback mechanism to cope with an abnormal situation is limited by the maximum secretary capacity of each cell, and by the potential growth of the cell mass.

In human juvenile diabetes, the fact that the cell mass, reduced at onset, continues to fall implies islet destruction. If we review briefly the various stages in the insulin carbohydrate cycle, the evidence for an abnormality in any other stage in juvenile patients remains suggesting an abnormal insulin structure in juvenile patients remains unconfirmed.

The clinical observation of relative insulin sensitivity in most juvenile diabetes suggests that there is no major abnormality in insulin transfer, antagonism, or in endorgan sensitivity. The finding of degranulated cells and low insulin content suggests that the islets are responding to hyperglycaemia, and that the feedback mechanism is functioning normally. The overall picture in juvenile diabetes is therefore one of maximal stimulation of a greatly reduced cell mass, with inadequate total insulin production. Several mechanisms may be responsible for the loss of cell in this condition. Gepts[4] found lymphocytic infiltration in and around the islets in fifteen of twenty-one cases of juvenile diabetes, in animals injected with homologous or heterologous insulin and freund's adjuvant[5-6] support the possibility that islet changes in juvenile diabetes may be due to an autoimmune disease. While circulating anti-islet antibodies have not as yet been demonstrated in juvenile diabetes, indirect supporting evidence is available. Landing et al[7] found antithyroid antibodies in 13% of a large series of juvenile diabetics, a significant figure in this age group despite the absence of sex matched controls, and Moore & Neilson[8] found abnormal complement fixation tests for both thyroid and gastric mucosa more commonly in a group of juvenile diabetics than in either adult onset diabetics or controls. While autoimmune destruction of the islet is a likely cause for some cases of diabetics, particularly those of juvenile onset, it is not proven, and other possible causes for the loss of B cells and islet inflammation in juvenile diabetics include viral infections and toxic agents.

The relationship between the pancreas and adult onset diabetics is perhaps more complicated, and certainly more confused. Many studies on adult onset diabetics, including those of islet histology and extractable insulin[9], unfortunately have not differentiated between obese and non- obese subject, more between those who could be treated by diet alone, sulphonylurea or insulin.

In contrast to juvenile diabetes, the cell mass in diabetes of adult onset is not greatly reduced. Insulin structure is normal as far as is known. Although most adult onset diabetics do not require insulin, the fact that they are relatively insulin insensitive suggests that there is an abnormality in insulin transfer, antagonism, breakdown or end organ responsiveness. It is difficult to establish a single etiology for idiopathic diabetes mellitus of adult onset as abnormalities are claimed for each of these stages.

The high level of circulating insulin in some adult onset diabetics suggests that there is no increased insulin breakdown. Besides no direct evidence reveals that exogenous insulin is transported in an abnormal way. Serum from untreated non-ketotic diabetes has not been shown to interfere with the action of added insulin, so it seems likely that in many obese diabetics some defect of end organ responsiveness is present.

There is evidence for a second abnormality in insulin carbohydrate interaction in adult onset diabetics. The presence of relatively normal cell mass and pancreatic insulin content despite hyperglycemia suggests that the feedback control of insulin release is not functioning normally, particularly as this situation can be rectified by the use of sulphonylureas. The situation in many cases of diabetes of adult onset can, therefore, be summarized as one in which a relatively normal pancreatic islet cell mass is responding inadequately to the hyperglycemia being caused in part end organ un-responsiveness to insulin.

The factors that may lead directly to the development of adult onset diabetes are many and because they include conditions in which an increased load is put on the pancreatic islets, the concept of exhaustion of the cell has been used. In other peripheral endocrine organs an increased work load is accompanied by an increase in gland size, and a grater functional capacity. In the adult human pancreas the size increase does not occur, and it may well be that an increased work load on the islet cell shortens its life, and in the absence of replacements, diminishes the islet mass. However, in the early stages of diabetes of adult onset, the islets are certainly not exhausted, as they contain adequate insulin and are capable of responding to the stimulus of to lbutamide. In our view the commonest precipitating factor leading to adult onset diabetes mellitus is the development of insulin resistance associated with obesity.

In this discussion we have not yet comment on the hereditary factor. Both diabetes of juvenile and adult onset type may occur in the same family and yet the abnormalities in insulin carbohydrate interaction are different in the two types. The most likely explanation is that there is an inherited liability to develop diabetes mellitus which is distinct from the factors which precipitate its onset and determine its type. Vallance-owen & Ashton[10] have found that 50% of relatives of diabetes are synalbumin positive, whereas 20% of controls are synalbumin positive. They find that all patients with idiopathic diabetes are synalbumin positive, whether of juvenile or adult onset type. The degree of synalbulmin antagonism may well be an expression of the inherited liability to develop diabetes mellitus. Vallance-owen's hypothesis that the synalbumin factor is the chain of insulin offers interesting possibilities. An excess of chain could imply an abnormality in manufacture or in breakdown of insulin, and could interfere with peripheral metabolism or with feedback.

Diabetes may occur secondarily to a variety of diseases which fall into two main groups, those affecting the pancreas directly, as in pancreatitis, haemochromatosis and pancreatic carcinoma and those indirectly as in Cushing's syndrome and acromegaly. There is no clear-cut correlation between the severity of these diseases and the development of diabetes, and the presence or absence of the inherited diabetic factor is likely to be an important variable. Coggeshall & Root[11] found a higher incidence of a family history of diabetes in acromegalics without diabetes.

Conclusion:

In conclusion we would like to stress once again that diabetes mellitus is a clinical syndrome not a pathogenetic entity. We prefer to use the term in the same sense as myxoedema, as a descriptive diagnosis, not implying a single pathogenesis. A clear parallel can be drawn between the various abnormalities which may lead to diabetes, and those leading to other endocrine disorders. Diabetes and Addison's disease may be due to surgical resection, or to destruction of the gland by infection, or an autoimmune process. Indeed, an autoimmune process may affect several endocrines simultaneously and diabetes occurs with surprising frequency among patients with autoimmune myxoedema and Addison's disease. The possibility that diabetes may be due to an abnormality in the production of insulin has its counterpart in myxoedema due to dyshormonogenesis, while end organ unresponsiveness has been described for parathormone as insulin. The two features which distinguish pancreatic cell hypofunction from thyroid, parathyroid and adrenal hypo-function are the limited capacity for growth of the adult human cells, and the presence of the inherited factor as a substrate with which any of the numerous other factors leading to diabetes may interact.

Integrated clinical, biochemical and pathological investigations offer the best hope of elucidating the two factors concerned in most cases of idiopathic diabetes mellitus, the inherited factor that predisposes towards diabetes, and the precipitating factor which leads to its final appearance.

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