Tropical calcific pancreatitis

An overview

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Abstract: Tropical calcific pancreatitis is a nonalcoholic type of chronic pancreatitis affecting the children and young adults characterized clinically by recurrent abdominal pain in childhood, diabetes in adolescent and death in early childhood. Although the exact etiology is not known, malnutrition and chronic cassava toxicity either singly or in combination are presumed to be the prime factor in pancreatic injury unopposed by detoxification of free radical. Moreover micronutrients deficiency, oxidant stress and antioxidant deficiency might play substantial role. Diabetes secondary to tropical calcific pancreatitis is a distinctive and frequent problem, being named by W.H.O. study group as 'fibrocalculous pancreatic diabetes (FCPD) and classified as one of the variant of the so-called malnutrition related diabetes mellitus (MRDM).

Key words: Tropical calcific pancreatitis (TCP), malnutrition, cassava, diabetes, abdominal pain.

Introduction

"An emaciated adult male, with protuberant upper abdomen, bilateral parotid gland enlargement, skin infections lying in a hospital bed of a tropical country with a diabetic chart in front of the bed". Yes this is the sad story of the patient of tropical calcific pancreatitis (TCP), which is not a global, but a real problem of the tropics. TCP may be defined as a non alcoholic type chronic pancreatitis affecting children and young adults of the low-income group, characterized clinically by recurrent abdominal pain in childhood, diabetes in adolescent and death in early adulthood. This disease entity has been
described in literature as TCP, Fibrocalculous pancreatic diabetes (FCPD), Nutritional pancreatitis, Juvenile tropical pancreatitis syndrome. We submitted this overview of TCP because Japanese physicians seem to be unfamiliar with this disease entity, while they are increasingly addressing it in the classification of chronic pancreatitis.

**Epidemiology**

Having been first described by Zuidema in Jakarta\(^1\), Indonesia 35 years back, cases have been reported in several countries including Bangladesh, Brazil, India, Indonesia, Jamaica, Nigeria, Sri Lanka, Thailand, Uganda, Zaire, Zambia\(^2\). But the single largest series of cases to date is from the south western state of Kerala, India. Geevarghese\(^3\) observed this disease in endemic proportion in two major medical college hospitals in the state. To date more than 1000 cases have been carefully studied by Geevarghese\(^4\). The majority of his patients were between 16 and 30 years of age. The male to female ratio was 1.6 to 1. Studies from Bangladesh\(^5\) showed that most of the cases were from lower socioeconomic classes, and were below 24 years old with a BMI of 13-18.

**Etiopathogenesis**

Although the etiology of TCP is not clearly determined, epidemiologic, clinical and experimental data strongly suggest malnutrition as a possible prime etiologic agent. TCP is virtually prevalent in poorer countries where the diet is poor, nutrition substandard and per capita income low. Some of the signs of TCP such as hair and skin changes, cyanotic lips, bilateral parotid gland enlargement and pancreatic fibrosis were also seen in classic Kwashiorkor\(^1\). Structural and functional changes in the pancreas in primary protein deficiency also support malnutrition as a possible etiological candidate but recent observations have indicated that TCP is not a consequence of Kwashiorkor. Among 50 patients of Kwashiorkor in Miraj, India no one had pancreatic calcification on X-ray films of the abdomen\(^6\). On detailed dietary enquiry conducted by a study group in India, TCP patients and controls have not shown any difference in their protein (53 grams/day) or calorie intake, and fat intake in both the groups were equally low (27 grams/day)\(^7\). A potential toxic effect of Cassava (Manihot Esculenta) through its content of cyanogenic glycosides (Linamarin and Linamarase) is cited as a possible etiologic factor based on epidemiologic data\(^7,9,10\). It is seen that TCP is prevalent in those areas, where people eat Cassava as their staple diet such as Kerala, Nigeria, Indonesia, Uganda, Malawi, Thailand. Cassava root contains 65 mgs of toxic glycosides/100 gms. Hydrocyanic acid is liberated when the glycosides react with HCL in the stomach, which is alleged to cause pancreatic injury. The enzyme rhodanase acts on hydrocyanic acid to produce Thiocyanate in the presence of adequate amounts of methionine and cystine which are deficient in protein malnutrition. Experimental evidence in support of Cassava as a cause of TCP was obtained from: rats fed with a diet containing 22.8 gms of cassava for 18 months, pancreatic changes consisting of dilated ductules, papillary infoldings, eosinophilic materials in ductular lumina and round cell infiltration, as is seen in TCP. Epidemiologic studies, however, have shown conflicting data such as why not all people who consume Cassava do not develop the disease and why
the disease also occur in individuals with no history of Cassava consumption. But these exceptions do not rule out the possibility as in any chronic diseases the suggested etiologic factor cannot be demonstrated in 100% of cases. Cyanogens impair a number of enzymes including superoxide dismutase, an important scavenger of free radicals which proposed to cause cell injury\(^{14}\). On the other hand Malnutrition such as deficiencies of methionine, zinc, copper, and selenium interferes with cyanogens detoxification\(^{19}\). Cassava containing cyanogens along with malnutrition creates an ideal setting for free radical injury by promoting the generation of free radicals and by decreasing the ability to scavenge them.

From above discussions it may be presumed that TCP is a multifactorial disease. Malnutrition and Cyanogen toxicity may lead to free radical injury but there might be other etiologic factors such as genetic, familial and immunological factor for which no conclusive data are yet available\(^{17, 18}\). Braganza suggested that nonalcoholic pancreatitis in the UK is a result of (a) heightened but unmitigated oxidative detoxification reactions in the pancreas and liver, coupled with (b) exposure to xenobiotics biotransforming cytochrome P-450 and (c) a relative deficiency of antioxidants\(^{17}\). She has now extended the hypothesis to include TCP\(^{20}\). In preliminary studies she found evidence of increased exposure to xenobiotics, specially polycyclic aromatic hydrocarbons (cigarette and firewood smoke and vehicular fumes) in patients of TCP compared to controls\(^{21}\). This was associated with elevated theophylline clearance (a marker for heightened P-450 activity), but the detoxifying mechanism (measured as urinary D-glucaric acid) was not activated. These interesting observations need to be substantiated and extended before we attach an etiological role to these factors.

**Pathology**

The pathology of the pancreas as noted by many observers is remarkably similar. The pathology of TCP has been observed from surgically resected specimens, biopsy specimens obtained at surgery, and autopsy specimens. The pancreas is firm, fibrous, gritty to touch. Its consistency varies in different regions of the pancreas. Heterogenous areas showing early fibrosis, advanced fibrosis, cystic dilation of the glands and advanced stages of calculi formation can be seen in the same pancreas. The pancreatic duct may be eccentrically placed as a result of destruction of the pancreas. Pancreatic calculi of different size and shape are distributed throughout the duct system\(^{22}\). Pancreas in advanced TCP is of two types, either fibrotic pancreas or adipose pancreas\(^{23}\). The fibrotic variety is more common. Fibrotic shrunken pancreas in adults may be hardly bigger than an adult little finger. The adipose pancreas is yellowish and appears as the same size as or even bigger than the normal pancreas and very soft. This result from a near total replacement of pancreas with fat. Only surviving islets and a few lobules of exocrine pancreas may be seen. Microscopically dilatation of the ducts, pancreatic lithiasis, chronic inflammatory cell infiltration, fibrosis and atrophy of the parenchyma are seen. Pancreatic ducts in TCP show varying degree of dilation, hypertrophy and atrophy. To a large extent these changes are influenced by the presence or absence of calculi in the ductal system. The duct of Wirsung is often dilated...
and may contain calculi or protein plugs with enmeshed desquamated epithelial cells, erythrocytes or leucocytes. In segments containing calculi, the epithelium is atrophic or desquamated. In the absence of calculi, the duct of Wirsung may show epithelial proliferation with formation of papillary process.

Occasionally squamous metaplasia may be seen but is a rare change. The proliferative changes are more common in smaller ducts and ductules. The ductules proliferate with formation of solid buds of epithelium or may canalize to form new ductules. Some of these may differentiate into new islets (nesidioblastosis). Protein plugs are not frequent.

Characteristically the inflammatory component in TCP is not prominent, except in advanced cases. Most of the cellular infiltrates are composed of lymphocytes and plasma cells which show periductal distributions. Interstitial inflammation is not marked and acute inflammatory cells have not been observed in any cases. Perineural inflammatory reaction is noted in some. The periductal inflammatory component is seen mostly around the duct of Wirsung and large ducts containing calculi. It is difficult to exclude the role of incarcerated calculi in the reaction. The clinicopathological evidence does not suggest that TCP is an inflammatory disease but is indicative of a degenerative disease.

The pancreas in TCP may show a spectrum of changes which may be local, focal or diffuse. The earliest change observed in exocrine pancreas is simple atrophy, this changes may be seen in widely scattered pancreatic lobules. The earliest change detectable under the light microscope is loss of bipolar staining of acinar cells which is due to loss of zymogen granules. The cells appear shrunken, thus distorting acinar form.

The most remarkable finding is the absence of any necrosis, calcification or inflammatory reaction in the parenchyma in the early phase. Gradually fibrosis starts and classically leads to "cirrhosis of pancreas". The exocrine pancreas may show almost total disappearance with replacement fibrosis. The atrophy and fibrosis may be so advanced as to make it difficult to identify the structure as a pancreas. The only surviving structures are the islets which may show hypertrophy and atrophy and the scattered ducts. Several hypertrophic nerves and ganglia may be seen with surviving islets in close proximity. The visible islets of Langerhans appear intact and untouched. There is no insulitis. Hypertrophy as well as atrophy are seen. Nesidioblastosis (is a multifocal ductulo-insular proliferation involving all the cellular components of the islets) is a well described feature.

Immunoperoxidase staining has shown normal insulin and glucagon content in the cells. The islets are probably destroyed due to surrounding fibrosis (strangulation) and possibly also by disruption of vasculature. The latter could affect transport of hormones into the circulation and derange fuel mediated modulation of islet function. There are no studies of the islet number in TCP but extensive loss of pancreatic mass suggest that the total number must be severely diminished with progression of the disease.

**Pancreatic calculi**

Patients with tropical pancreatitis have intraductal stones. Parenchymal calcification (intra acinar or interstitial) is not seen. Multiple stones of varying size, some as small as sand particles and others as big as
3 cm in diameter and weighing up to 20 g, are distributed throughout the main pancreatic ducts and wedged in the ductules. The calculi have an unusually knobby and irregular surface, some are staghorn shaped and a few are smooth and rounded. They are hard in consistency and greyish white in colour. Solitary calculi are occasionally seen near the ampulla of Vater. The larger stones are usually located in the head of the pancreas.

Morphological and elemental analysis of pancreatic stones in TCP patients was done by many investigators. Pitchumoni et al showed that the nidus of PC is comprised of a very fine network of fibers. Elemental analysis shows the presence of iron, chromium, nickel. Surprisingly calcium is found to be totally absent. The composition of the outer layers of Pancreatic stones (shell) is found to be totally different when compared to the nidus. Calcium is found to be abundant and Ni is found to be totally absent. In addition to calcium, other elements such as Fe, Cr, K, Cl, P, Si, Al, Mg, and Na are also detected. These observations are interesting in view of similar studies on stones from alcoholic pancreatitis suggesting that the thermodynamics of stone formation in the pancreas, irrespective of etiological factors, i.e. chronic alcoholism, malnutrition, or idiopathic, are the same.

In patients who had no radiologically demonstrable calculi in antemortem X-rays of the abdomen, postmortem examination of the pancreas showed multiple tiny radio-opaque material which was shown to consist of intraductal calculi.

‘TCP without calculi’ (non calcific TCP) has been described. Balakrishnan compared characteristics of patients with and without calculi. In general patients without calculi have a less severe exocrine problem. It is possible that the rates of calcification are different in different patients. The role of pancreatic stone protein (PSP) is yet to be investigated in TCP. Nagalomith described two autopsies with pathological changes restricted to the tail of the pancreas. He called them ‘localized and arrested’. The head and the body of the pancreas were reportedly normal.

**Clinical features**

The clinical picture of a well established case of TCP with diabetes mellitus and pancreatic calculi is characteristic enough to make on the spot diagnosis of the diseases. The presenting complaints of most patients are abdominal pain and the effects of diabetes mellitus.

**Abdominal pain**

Abdominal pain often denotes the onset of tropical pancreatitis. In children however, abdominal pain is often ignored or attributed to parasitic infestations which are quite common in developing nations. Nearly 95% of patients have a long standing past history of abdominal pain. Recurrent attacks of abdominal pain lasting for hours to days are aggravated by eating food. Characteristically the pain is located in the epigastrium, umbilical region or hypochondrium. Patients assume the typical pancreatic posture, sitting up in the bed, leaning forward with the palm of the hand pressing on the sites of abdominal pain. The pain is severe, occurs more frequently in the early stage and gets milder and less intense and frequent as the disease progresses.
Pancreatic diabetes

Most of the patients with TCP seek initial medical attention for diabetes mellitus which becomes clinically apparent a few years after the pancreatitis. A pain-free period of 1 or 2 years and an apparent transient improvement in the clinical picture prior to the onset of diabetes is not unusual. The simultaneous onset of diabetes and abdominal pain is seldom seen. The age of onset of diabetes was below 30 years in 72% of the 325 cases studied by Geervarghese and Pitchumoni.

Metabolic peculiarities of pancreatic diabetes

1. Ketosis resistance: In TCP patients (despite severe hyperglycemia) ketosis is very rare. The majority do not become ketogenic despite stopping insulin treatment for long periods even when requiring large doses for glycaemic control. According to a study carried by Yajnik et al. of 70 patients over 7 years, no patients developed ketosis except one. A number of his patients stopped insulin for months (for lack of money) and became severely hyperglycaemic (plasma glucose > 40 mmol/L) but never ketogenic even when suffering severe systemic infections. There are a number of hypothesis to explain this metabolic peculiarity:
   1) Residual beta cell function, adequate to prevent ketosis.
   2) Concomitant destruction of alpha cells and thus loss of glucagon, a major ketogenic hormone.
   3) Subcutaneous fat loss and therefore, reduced supply of NEFA - the fuel for ketogenesis.
   4) Resistance to subcutaneous adipose tissue lipolysis by adrenaline.
   5) Carnitine deficiency affecting transfer of NEFA across the mitochondrial membrane.

2. Insulin resistance: True insulin resistance, defined as a daily requirement of above 200 units of insulin in the absence of infection or ketosis, occur in pancreatic diabetes. Zuidema has pointed out that diabetes in some of his patients with pancreatic calcification was difficult to control with usual doses of insulin. This experience is shared by others. It is surprising since the insulin requirement after total pancreatectomy is only about 40 units. The nature of insulin resistance in pancreatic diabetes is poorly studied, but is attributed to insulin antibodies.

Considering all these, diabetes in TCP is certainly a distinctive problem which led the W.H.O study group to rename it as a distinctive disease entity as fibrocalculous pancreatic diabetes (FCPD) and classified it as one of the two subgroups of the so-called malnutrition-related diabetes mellitus (MRDM), the other group being protein deficient pancreatic diabetes (PDPD). FCPD as subgroup of MRDM implies malnutrition as an important diagnostic criteria of FCPD. But confusion arose when some patients of TCP or FCPD do not show any evidence of malnutrition and rarely FCPD may be associated with obesity. To overcome this confusion Mohan et al proposed a set of diagnostic criteria for FCPD which are the most comprehensive to date (Table 1). On the other hand PDPD is a homogenous form of diabetes with all its peculiarities in the malnourished patients of young age without pancreatic calcification and pancreatic fibrosis.
Table 1. Diagnostic Criteria for fibrocalculous pancreatic diabetes (FCPD)

1. Occurrence in a tropical country.
3. Evidence of chronic pancreatitis: pancreatic calculi on X-ray or at least three of the following:
   (a) abnormal pancreatic morphology by sonography, CT scan or ERCP;
   (b) chronic abdominal pain since childhood;
   (c) steatorrhoea;
   (d) abnormal pancreatic function test;
4. Absence of other causes of chronic pancreatitis, i.e. alcoholism, hepatobiliary disease or primary hyperparathyroidism e.t.c.

Features like clinical malnutrition, young age at onset, absence of ketosis are useful adjuncts but not diagnostically essential.

Investigations

Ultrasonography and CT scan: Mohan and his colleagues reported the findings on sonography of the pancreas in FCPD\(^6\). The pancreas appears hyperechoic with irregular margins and irregularly dilated ducts and shows stones in the lumen. CT scanning has allowed a closer look at pancreatic morphology during life. In the early stages pancreatic mass is preserved and swelling of parenchyma is evident. In more advanced stages the pancreas shows varying degrees of atrophy; in extreme cases little pancreatic parenchyma is visible, its place being taken by a bag of stones and duct appears irregularly dilated with stones in the lumen. In some cases fat infiltration is prominent.

Exocrine pancreatic function

The diagnosis of TCP seldom depends on demonstration of biochemical abnormality. However the measurements of specific pancreatic enzymes (serum immunoreactive trypsin, pancreatic isoamylase, lipase and stool chymotrypsin) have led to a better understanding of exocrine pancreatic damage in TCP. Serum immunoreactive trypsin measurements showed a spectrum of exocrine pancreatic involvement\(^7,8\). In early cases (normal glucose tolerance and IGT) serum immunoreactive trypsin was subnormal in only a few subjects, while in some it was markedly elevated suggesting active pancreatitis; the exocrine reserve appears relatively well preserved. In advanced cases (FCPD) serum immunoreactive trypsin was subnormal in most cases and severely diminished in over two-thirds. Stool chymotrypsin measurements showed similar results\(^9,10\), as did serum pancreatic isoamylase\(^9,10\).

Pancreatic secretory studies performed on duodenal aspirates have confirmed a marked decrease in lipase activity in the large majority of patients\(^11\). In one study using secretin-pancreozymin stimulation of the pancreas, a marked decrease in volume and enzyme output with preservation of bicarbonate concentration, was noted\(^12\).

In another study from the same institution performed on a larger number of patients, a decrease in enzyme and volume was noted but in addition the bicarbonate output was also suppressed in nearly 50% of the patients\(^12\). In
a study from Uganda, those with pancreatic lithiasis gave consistently abnormal pancreatic secretory responses: the total volume response, bicarbonate output and maximal bicarbonate concentration were significantly lower than those in the control group. None showed a normal bicarbonate output\(^4\). Such discrepancies in results in secretin-pancreozym tests may be attributed to different stages of the disease (ductular proliferation or destruction) or to the lack of specificity of the test itself.

**Endocrine pancreatic function**

Yajnik et al\(^6\) measured beta cell function in TCP patients with different degrees of glucose tolerance. Plasma C-peptide concentrations were normal in those with normal glucose tolerance or IGT, whereas diabetic subjects as a group showed diminished concentrations. In the diabetic group (FCPD) plasma C-peptide concentrations were widely scattered: in \(<75\%\) they were severely diminished, indistinguishable from type I diabetic patients.

Interestingly none of these FCPD patients had presented with ketosis, suggesting that some other mechanisms in addition to beta cell function are involved in their ‘ketosis-resistance’. There was an inverse correlation between peak plasma C-peptide concentration during the glucose tolerance test and Hba1c concentration, suggesting that beta cell function was an important determinant of regulation of blood glucose in TCP. Even more significantly, C-peptide and serum immunoreactive trypsin concentrations were directly correlated\(^6\). Thus a direct relationship between exocrine and endocrine measurements has been described in TCP for the first time. A follow-up study showed that clinical improvement after anti-diabetic treatment was associated with improved betacell function\(^6\).

Information on alpha cell function in FCPD is sparse. The nature of islet destruction (secondary to exocrine pancreatitis and therefore involving the whole islet rather than specific cells) would suggest that insulinopenia be accompanied by glucagon deficiency. Proneness of these patients to hypoglycaemia and their resistance to ketosis have both been empirically ascribed to glucagon deficiency. Mohan V et al\(^4\) reported plasma glucagon concentrations in FCPD patients with substantial residual beta cell function. In this group, fasting plasma glucagon concentration was well preserved but the expected paradoxical rise after oral glucose was absent. Yajnik et al\(^6\) observed normal plasma glucagon concentrations even in those with severe insulinopenia, and the paradoxical rise after oral glucose was also present. It appears that alpha cell are more resistant to damage than beta cell or are able to compensate better: alternatively the islets damage in FCPD could be more selective for beta cells than hitherto believed.

**Exocrine endocrine correlation**

Pancreatic exocrine-endocrine interactions have been recognized for many years. Thus endocrine deficiency (IGT and diabetes mellitus) is common in subjects with chronic pancreatitis, and endocrine loss parallels exocrine loss\(^4\). On the other hand, exocrine pancreatic deficiency has been demonstrated in IDDM and NIDDM subjects without any history of exocrine pancreatic disease. Exocrine pancreatopathy of ‘primary’ diabetes mellitus is thought to arise from the loss of local trophic effects of insulin on adjacent
Subjects with TCP showed the most severe exocrine deficiency and there was a gradient of exocrine-endocrine loss in that group. Those with relatively better exocrine preservation showed a normal or impaired glucose tolerance, and the group with the most severe exocrine loss showed diabetes mellitus (FCPD).

Is TCP pre-malignant?

Four surgically resected specimens from 27 patients operated on in one institution had malignancy. Two siblings with TCP and pancreatic cancer were reported by Philip GT. Biopsy of the pancreatic mass at surgery was not diagnostic in those cases and histological proof of metastatic cancer of the pancreas was obtained only on follow-up. Does malignancy in TCP develop because of chronic irritation caused by the calculi or because of some genetic predisposition or other factors are responsible? The answer is not known, but requires further evaluation.

Management

Management of many TCP patients is influenced by their poor socioeconomic status and lack of education. Social and religious belief often contradict medical principles and interfere with the treatment.

Treatment of pancreatic diabetes.

In TCP patients, diabetes commonly develops in the second or third decade of life, although it was also diagnosed at 9 years of age in some patients. General principles of dietary management are the same as for other types of diabetes except for some additional considerations. Extra calorie and protein intake is necessary for tissue building, and fats are restricted even more due to the exocrine pancreatic deficiency. Intake of food at regular intervals is stressed to avoid hyperglycaemia.

Requirement and choice of anti-diabetic drugs are determined by residual beta cell function. More than 80% require insulin for satisfactory control of hyperglycaemia and to ensure weight gain. Up to 20% patients may respond to oral hypoglycemic agents (sulfonylureas), sometimes for many years after diagnosis. Higher doses of insulin initially required in the more severely hyperglycaemic, usually settle down to, 1.5Ukg-1day-1 within a few weeks.

Treatment of exocrine problem

Patients with severe degrees of pain respond only to injections of pethidine hydrochloride. Surgery is performed for severe and recurrent pain. The best procedure is exploration of the pancreatic ducts, removal of the stones by a scoop, and longitudinal anastomosis of the split surface of the pancreas to jejunum as suggested by Puestow and Gillesby. In some of these cases the relief of pain, even with surgery is temporary.

In TCP, frank steatorrhoea is rarely reported, possibly due to low dietary fat intake. Oral pancreatic enzymes are useful in the treatment of steatorrhoea and also in those who fail to gain weight despite good control of blood glucose concentration and adequate dietary intake. The cost is the major restraint on their use.

Summary

Recently tropical calcific pancreatitis (TCP) has gained much attention. Both the exocrine and endocrine abnormalities are well explored. As the socioeconomic condition of
TCP-prevailing countries improves, although a little bit, the disease profile and the morbidity and mortality of the disease are also changing. Now the patients are not dying in their 2nd or 3rd decade of life probably due to earlier detection, improvement in hospital care and overall management facilities. But the overall disease frequency is not decreasing in a parallel way. The still unresolved problem is its etiopathogenesis. When first described, malnutrition was thought of as the sole etiology, but nowadays significant number of the patients are not malnourished. Moreover it is also detected even in obese and business executives. Cassava consumption is decreasing significantly. Unchanged are its geographical segregation, occurrence in strict non-alcoholics and early onset of the disease. No environmental factor have been yet identified. But increased oxidant stress with simultaneous decreased antioxidant states following exposure to xenobiotics (smoking, firewood smoke) in the pathogenesis of this disease has created a new 2 insight. We are hopefully looking forward.

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熱帯地方の貧困層の小児や若千成人にみられる非アルコール性の慢性膵炎で、小児期に反復する腹痛で発症し、10〜20歳で膵性糖尿病になり、20〜30歳で死亡する類似の病像を示す症例をTropical calcific pancreatitis（熱帯性石灰化慢性膵炎）という。高率に膵石を伴う。成因は乳幼児期からの熱量、蛋白質、micronutrients（亜鉛、銅、セレン）の摂取不足に加えて食事中シアノ産生物質や環境中oxidantsなど複合因子によると推測されている。病理像は世界各国にみられる慢性膵炎典型例に類似する。最近は、生活環境や医療事情の改善により、全身栄養障害の減少や生存期間の延長など病像が変貌しつつある。糖尿病を重視する立場からはFibrocalculous pancreatic diabetesと呼ばれ、同一地域にみられるProtein-deficient pancreatic diabetesを合わせてMalnutrition-related diabetes mellitus（MRDM）と総称し、糖尿病の一亜型に分類されている。