Chronic pancreatitis (CP) is a chronic progressive inflammatory disease of the pancreas. The predominant cause of CP is considered to be alcohol abuse in countries such as USA, UK, Germany, Brazil, and Japan while it is idiopathic in countries such as India and China. Idiopathic CP that is prevalent in India is also known as tropical calcific pancreatitis (TCP). The term, TCP, is used to refer to a special type of CP with large pancreatic calculi that affects very young malnourished individuals who often develop diabetes and have an aggressive course of the disease. Initially described from Indonesia, it has been reported from many other tropical countries including India, Nigeria, Uganda, West Indies, Kenya, Sri Lanka, Medgasker and Zaire. The largest series has however, been described from South India by Geeverghese. Subsequently, there have been many reports of its occurrence in other parts of India (particularly Karnataka, Tamil Nadu, Orissa, Maharashtra and Delhi). However, recent observations, both clinical and genetic, have cast doubt about the terminology and description of TCP as discussed subsequently.

**EPIDEMIOLOGY**

The estimated prevalence of chronic pancreatitis is around 10-15/100,000 population in several western industrialized countries and 45.4/100,000 population in Japan. A community based survey in southern India showed a high prevalence of chronic pancreatitis in that community at 1:793 (36/28567; ~126/100,000 population), whereas the prevalence of calcific pancreatitis alone was 1:1020 (28/28567; ~98/100,000 population).

**REPORTED CHARACTERISTICS OF TCP**

The following features in a patient were considered to be characteristic of TCP:

i. Young age of onset
ii. Malnourished patient
iii. Residence in tropics
iv. No discernible cause of CP
v. Main pancreatic ductal dilatation with large pancreatic calculi
vi. Diabetes which is supposedly insulin requiring but ketosis resistant

**ETIOLOGY OF TCP- OLDER CONCEPTS**

The etiology of tropical pancreatitis is not known and is still considered idiopathic. It has been largely attributed to 2 important nutritional factors i.e. protein calorie malnutrition and consumption of cassava. Thus, it was also known as nutritional pancreatitis.

1. Malnutrition:

Protein calorie malnutrition has long been suspected as a likely cause for TCP because of the fact that the disease occurs predominantly in tropical countries where malnutrition is common and because of the reports from some of them including India, Uganda and Nigeria reveal that 80-90% of the subjects with calcific pancreatic come from poor socio-economic strata. Chronic protein undernutrition leads to structural as well as functional alterations in the pancreas.

2. Cassava Consumption:

The toxic hypothesis has been centered on consumption of cassava, a tuber root, which has cyanogenic glycoside and is used liberally in southern India where TCP is endemic. The putative toxin in cassava are cyanogenic glycosiudes mainly linamarin and lotaustralin. Cyanide is detoxified by the enzyme rhodanese by forming thiocyanate, which is excreted in the urine. This detoxification requires sulphur donors provided by dietary sulphur amino acids predominantly methionine. Other nutritional factors might also be important in the detoxification process such as protein, riboflavin, and vitamin B12 influencing hydrolysis of cyanogenic glycosides and their toxicity. It was believed that consumption of cassava coupled with dietary deficiencies leads to development of TCP.

**CURRENT UNDERSTANDING OF CHRONIC PANCREATITIS IN INDIA**

The understanding about chronic pancreatitis in India has lagged behind and unfortunately there has been no systemic effort to examine the various types, characteristics, and natural course
of CP especially with emerging role of mutations and changing socioeconomic and environmental influences. Of late however, significant amount of new data have accumulated through the efforts of several groups in different centers in India. The new studies have led to a better understanding of the disease.

A multicentre database has been prospectively maintained for the past 3 years and a study has been published based on this database. In a recent study, we have also evaluated 411 patients with chronic pancreatitis prospectively over the past 5 years. The data emerging from these studies have shown a vastly different picture of chronic pancreatitis in India.

**DIFFERENCES BETWEEN REPORTED CHARACTERISTICS OF TCP AND THE NEWER FINDINGS**

**Age:** In the AIIMS study, the mean age at onset of disease was 29.83±12.44 years and 318 (77.4%) were males. We found that the idiopathic CP affects both younger and older patients. This is later than that reported in earlier studies on TCP i.e. in childhood and adolescence (5). A report from Kerala, from where cases of later than that reported in earlier studies on TCP i.e. in childhood and adolescence (5). A report from Kerala, from where cases of later than that reported in earlier studies on TCP i.e. in childhood and adolescence (5). A report from Kerala, from where cases of later than that reported in earlier studies on TCP i.e. in childhood and adolescence. However, severe malnutrition is not associated with chronic pancreatitis but with pancreatic atrophy and insufficiency in patients with idiopathic CP (TCP) as 30.6 years (16).

**Nutritional status:** Malnutrition has been implicated in the pathogenesis of TCP. However, severe malnutrition is not associated with chronic pancreatitis but with pancreatic atrophy and insufficiency in patients with idiopathic CP (TCP) as 30.6 years (16).

**Residence in tropics:** Although the initial reports showed that patients with TCP are from tropical countries. However, reports of patients with similar phenotype have emerged from other non-tropical countries such as China. Furthermore, TCP has not been reported from other tropical countries. Brazil is a large tropical country with a population of multi-ethnicity. But the reports from Brazil showed that alcohol is the predominant cause of CP, and genetic mutations in CFTR and SPINK1 genes were present in patients with CP.

**Morphology of pancreas:** It is generally considered that patients with TCP have large duct disease with dilatation of main pancreatic duct and large ductal calculi. However, with the increasing awareness of the disease and better diagnostic modalities, less advanced forms of CP are being diagnosed. Most patients who present with recurrent acute pancreatitis without evidence of chronic pancreatitis in the beginning actually represent the early phase of CP. In a study we found that about 50% of patients with recurrent acute pancreatitis developed chronic pancreatitis during follow up. Such progression support the necrosis-fibrosis hypothesis in the development of chronic pancreatitis. Thus, the type of ductal involvement and presence or absence of calculi depend on the stage of the disease.

**Diabetes:** Diabetes has been reported earlier in up to 90% of patients with TCP. However, it was seen only in about 1/3rd of patients in the AIIMS study and 40.5% in the multicentre study. Contrary to the previous reports that majority of patients required insulin, it could be controlled in about 50% of patients without insulin suggesting that some endocrine functional reserve remained intact in them. Some experts have tried to make a distinction between painful chronic calcific pancreatitis with diabetes, the so-called Fibrocalculous diabetes (FCPD) and TCP with diabetes. However, most experts consider them as same disease, the difference being only in the clinical presentation – FCPD with diabetes and TCP with pain. Genetic mutations in the SPINK1 gene have also been found to be similar in FCPD and TCP with diabetes again suggesting that these are not 2 different diseases.

**Etiopathogenesis:** An old concept was that the majority of patients have TCP in India. In the AIIMS study, the cause of CP was alcohol in 157 (38.2%), idiopathic in 242 (58.9%), hereditary in 10 (2.4%) and others in 2 patients. Cassava consumption has been linked etiologically to TCP. This theory has also not found wide acceptance because of the following reasons: (i) we did not find cassava consumption as a risk factor in a case-control study; (ii) there was no difference in cassava consumption between patients with TCP and those without; (iii) patients with the so-called TCP from northern India do not consume cassava, and (iv) long-term cassava consumption did not produce diabetes or pancreatitis in a rat model.

**Recent concepts:** Two important concepts have emerged as being important in the pathogenesis of idiopathic CP (TCP). These include oxidative stress and genetic mutations.

1. **Oxidative stress:** Oxidative stress (OS) has been implicated in the pathophysiology of CP. Xenobiotics are detoxified in the body through phase I and phase II pathways chiefly in the liver. Increased exposure to xenobiotics such as alcohol, nicotine, petrochemical fumes may overwhelm the capacity of phase I and phase II detoxification pathways and result in oxidative stress. The pancreatic acinar cells are also exposed to oxidative stress. OS can cause cell damage either directly by cell membrane destruction, depleting the cells of antioxidants, toxicity from free radical peroxidation products or through altering signaling pathways, including redox regulation of genes. Free radical peroxidation products may act as second messengers and block exocytosis in the pancreatic acinar cells leading to increased autophagy and cinopahy thus diverting the pancreatic enzymes into interstitium, causing degranulation of mast cells and resulting in inflammation mediated by chemotaxis and pain. A few reports have shown an increased oxidative stress in patients with alcoholic and idiopathic
chronic pancreatitis. In a recent study, we showed that patients with chronic pancreatitis had increased oxidative stress and reduced antioxidant capacity.

2. Genetic mutation: The landmark discovery by Whitcomb et al. of a mutation in the gene for cationic trypsinogen on the long arm of chromosome 7 (7q35) in patients with hereditary pancreatitis verified the long held belief that a genetic defect underlies hereditary pancreatitis. A lot of interest has recently been generated in the possibility that there may be a genetic basis for TCP because of the following similarities between TCP and hereditary pancreatitis: (i) both diseases affect young individuals; (ii) calcification is very common in both; and (iii) there is an increased risk of pancreatic cancer in both. Moreover, Indians born in Kerala but residing outside India continue to have an increased prevalence of TCP. An association of HLA DQ (A*0201-B*03003) has been shown with TCP and diabetes (FCPD). However, one study from Bangladesh failed to show any mutation of the cationic trypsinogen gene among 13 patients with TCP. Another study did not find cationic trypsinogen gene mutation in 46 patients with FCPD.

Two groups demonstrated that the expected frequency of CFTR gene mutation was much higher among patients with idiopathic chronic pancreatitis i.e. 2.5 and 11.5 times the expected frequency seen in the general population. Affected patients with chronic pancreatitis were shown to have single gene CFTR mutations and/or 5T allele in intron 8 which resulted in a reduced activity of CFTR. In patients with typical cystic fibrosis, there are severe mutations affecting both alleles; the result is pancreatic insufficiency caused by atrophy of the pancreas. On the other hand, a mutation affecting only one allele may result in diseases such as chronic pancreatitis while retaining ‘pancreatic sufficiency’

More recently, a mutation in the pancreatic secretory trypsin inhibitor (PSTI, also known as serine protease Inhibitor Kajal type 1 or SPINK1) (N34S, chromosome 5) was found in 23% of patients with idiopathic pancreatitis versus 2% in the general population. A similar mutation has been reported in Japanese patients with idiopathic pancreatitis. SPINK1 inhibits trypsin within the pancreas but accounts for inactivation of only ~20% of all activated trypsin. It is therefore unlikely that the SPINK1 mutation alone will cause pancreatitis, but it might be a disease modifier lowering the threshold for pancreatitis. SPINK1 mutation has been found in 32-44% of patients with TCP from India.

In the AIIMS study we have found that 42% of patients with SPINK1 mutation and another 9% had CFTR gene mutation and 41% had CFTR gene polymorphisms suggesting a strong genetic predisposition in patients with idiopathic CP.

Natural course of CP: Previous studies had shown a rapid progression of the disease with early death in patients with so-called TCP. However, not all patients present with advanced CP but with recurrent acute pancreatitis as we have also shown earlier. In the AIIMS study, most patients had good response to treatment and a near normal life expectancy. This could be attributed to be improved nutritional status, multimodality therapy, and better health care delivery.

Diagnosis: The diagnosis of CP is based on a combination of clinical evaluation and imaging studies. In advanced disease, a plain film of the abdomen or a contrast enhanced computerized tomography (CECT) may show the pancreatic calcification and establish the diagnosis. In early cases, demonstration of ductal changes through endoscopic retrograde cholangio-pancreatography (ERCP) or magnetic resonance cholangio-pancreatography (MRCP) will establish the diagnosis. Pancreatic function tests are indeed the most sensitive test to detect earliest changes in the exocrine pancreas but they may be abnormal in any cause of pancreatic insufficiency e.g. cystic fibrosis and not necessarily in chronic pancreatitis. Endoscopic ultrasonography has been touted as the most sensitive method of detecting earliest changes of pancreatitis in the parenchyma and can diagnose early chronic pancreatitis in an appropriate clinical setting. The gold standard for diagnosis is histopathology but that is rarely obtained unless the patient undergoes a pancreatic resection. Intraductal protein plugs with or without calcification and periductal fibrosis with little inflammatory infiltration are characteristic features of CP.

Management: Medical treatment of CP is aimed at relieving pain and steatorrhea and controlling diabetes.

Pain Relief: For pain relief initially non-opioid and later opioid analgesics are used. Another approach has been to use pancreatic enzymes (proteases) based on the understanding that delivering these enzymes in the duodenum could result in suppression of cholecystokinin (CCK) and hence a decrease in pancreatic exocrine secretion. Their role in relieving pain is however, questionable. The results of a meta-analysis of 6 randomised controlled trials showed no benefit of enzyme therapy in relieving pain. However, non-enteric coated pancreatic enzyme supplementation may relieve pain in patients with small pancreatic duct disease, idiopathic pancreatitis and in female patients. The Asia-Pacific consensus report on chronic pancreatitis also suggested pancreatic enzymes and non-opioid analgesics as the initial therapy for pain relief in patients with chronic pancreatitis.

Use of antioxidants has also been suggested recently for pain relief in chronic pancreatitis. We have also shown that anti-oxidant supplementation relieved pain in chronic pancreatitis.

Surgery is required predominantly for intractable pain in about a third of patients. Its results are good only in patients with dilated ductal system which is the case in the majority of TCP patients. The most common operation performed is lateral pancreateojunostomy (modified Puestow’s operation). In one of the AIIMS studies, relief of pain was obtained in 90% of patients at 3 months after the surgery and this relief was long lasting in 82% of patients at 5 years. The results of surgical drainage are
less gratifying in chronic pancreatitis in the western world, as the predominant etiology there is alcohol abuse and the behaviour of alcoholic chronic pancreatitis may be different from that of TCP. In occasional patients with pancreatitis restricted to one portion of the gland or in those patients with normal size ducts or in those having recurrent pain following lateral pancreateojunostomy, pancreatic resection has been performed with fairly good results, but often with unavoidable exocrine and endocrine deficiencies or relapse. 

**Endoscopic therapy:** Similar to surgery, the dilated pancreatic ductal system can be decompressed by endoscopic sphincterotomy and pancreatic ductal stone clearance by a combination of basketing and extracorporeal shock wave lithotripsy (ESWL). Various endoscopic series have reported 50-70% success for clearing the main pancreatic duct and 60-80% long term pain relief with complications of <10%. We have also found good results of endotherapy in ~60% of patients with tropical pancreatitis. A recent randomized controlled trial comparing endoscopic and surgical treatment modalities showed surgery to be better than endotherapy. However, a trial of endoscopic therapy before subjecting the patient to surgery may still be warranted as the initial results of endoscopic therapy are encouraging and the patients prefer less invasive procedures.

**Chronic Pancreatitis—Past versus Present Understanding:** The popularly held believes about idiopathic CP (TCP) in India includes (i) it affects young patients often in their childhood and adolescence, (ii) patients are malnourished with a body mass index (BMI) as low as <18.5, (iii) cassava might be causally associated, (iv) most patients are diabetic at presentation, and (v) the natural course is aggressive with patients dying in the prime of their lives. Generally referred to as tropical calcific pancreatitis (TCP), the idiopathic CP in India is thus usually considered different and discussed in isolation. In contrast, the recent data suggest the following— (i) idiopathic CP affects both younger and older patients, and their profile of CP is almost similar (ii) the phenotype of Indian patients with idiopathic CP is somewhat similar to that reported from other countries, (iii) most patients with idiopathic CP are not malnourished and cassava is not an etiology, (iv) SPINK1 and/or CFTR mutations are present in up to 66% of patients, (v) diabetes is present in only 1/3rd of patients, and (vi) the prognosis of idiopathic CP is good both in regards to the pain relief and survival. In the AllMS study, only 5.8% of the patients could satisfy the standard criteria of tropical pancreatitis. Similarly, in the multicentre study from India, tropical pancreatitis constituted only 3% of patients with CP. 

**Need for a change in terminology:** The recent understanding about genetic susceptibility in patients with chronic pancreatitis puts a big question mark about the term ‘tropical pancreatitis’ which has a geographical rather than etiological connotation. The word ‘tropical’ refers to a particular geographical location with tropical climatic conditions. The term ‘tropical’ is not justified because of many reasons: (i) the word ‘tropical’ usually refers to diseases that are of infectious etiology e.g. ‘Tropical myositis’, ‘Tropical sprue’, ‘Tropical splenomegaly syndrome’ etc. as has also been defined by WHO “Tropical diseases encompass all diseases that occur solely, or principally, in the tropics. In practice, the term is often taken to refer to infectious diseases that thrive in hot, humid conditions, such as malaria, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, Chagas disease, African trypanosomiasis, and dengue” (htTCP://www.who.int/topics/tropical_diseases/en/). On the other hand, data have established that genetic mutations play an important role in the pathogenesis of idiopathic chronic pancreatitis. (ii) The climatic conditions have remained the same for the past 30-40 years so is the genetic make up of the population. It follows therefore, that both the climatic factors and genetic predisposition have remained unchanged in India over the years. Yet, there has been a change in the phenotype of chronic pancreatitis. (iii) The term ‘tropical’ makes the disease esoteric, confines it to a geographical location and makes the data non-generalizable.

We believe that given the phenotypic similarities between idiopathic CP in different parts of India and in other countries, strong genetic predisposition in more than half of patients, and the absence of any evidence of climatic influence, the term ‘tropical calcific pancreatitis’ is inappropriate and does not conform to the present day understanding of the pathogenesis of idiopathic chronic pancreatitis. Till a consensus evolves over a better term, we may continue to use the term non-alcoholic idiopathic chronic pancreatitis.

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