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Detailed Description About Pancreatic Insufficiency in Cystic Fibrosis with Treatment: A Review Article

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Abstract

Cystic Fibrosis (CF) is one of the most commonly inherited genetic disorders which will show either asymptomatic features or it prone to severe multiorgan failure and sometimes it may turn into neoplasm and finally death if untreated. CF may hit more than 2000 genes in the human being, but of those ΔF508 mutation in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein is the most common one. The leading cause of death in CF patients is due to the involvement of lung and pancreas (pancreatic insufficiency). Even though the primary organ involved in CF is lung, but pancreatic involvement also relates with some important clinical manifestations like diarrhea, steatorrhea, malabsorption, hypovitaminosis, Cystic Fibrosis Related Diabetes (CFRD), pancreatic adenocarcinoma etc., seen in these patients, which is helpful for the physicians to make proper diagnosis and treatment. So, this review article purely focuses on CF especially in relation with pancreatic abnormalities which will be discussed under genetics, pathophysiology (both exocrine and endocrine), cancer, diagnosis and finally treatment.

Keywords: *Cystic Fibrosis (CF), Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), pancreatic insufficiency, pancreatic adenocarcinoma, Cystic Fibrosis Related Diabetes (CFRD).*

Introduction

Cystic fibrosis (CF) is one of the most life-threatening diseases due to which several infants, adults as well as elderly are died. The life expectancy of patients with CF was only a few months in the 19th century, the main cause for these deaths because of meconium ileus and malnutrition due to pancreatic malabsorption, but from past few decades, the survival rate is gradually increased to more than 40 years in developed countries. Unfortunately, as the survival rate, the incidence of CF is also continuously increasing especially in the adult population. By 2025, the number of cases with CF has been predicted to increase up to 70% in developed European countries. Cystic fibrosis metabolic syndrome is the term used in the USA for describing those individuals who usually have mutations in residual function of the Cystic Fibrosis Related Diabetes (CFTR) protein.[1]

The term ‘cystic fibrosis’ is coined by Dr. Dorothy Andersen while performing the seminal report on an autopsy. Mutation in CFTR gene (the gene responsible for fluid secretions) may lead to loss of functions in multiorgan which typically include lungs, liver, pancreas, gastrointestinal tract and male reproductive system. However, the involvement of lung had the highest impact on morbidity and mortality in these patients, interestingly the involvement of pancreas is also higher, and it is one of the earliest organs to be affected in humans with CF. The primary goal of this article is to have a complete comprehensive review on CF in relation with pancreas. We mainly focus on the pancreas, because of its involvement will reduce quality of life in patients with CF which may end up with death. A study conducted on mouse model which had CF, and they found that significant involvement of gastrointestinal obstruction is common and without pancreatic or lung involvement.[2] Hence this article purely includes pancreatic involvement of CF in relation with human beings but no to any other species.

Cystic fibrosis is characterized by indigestion if it involves pancreas i.e. pancreatic insufficiency (PI), CF also involves other organs with their related clinical manifestations, but those are out of scope for this article. Some studies have shown that 1:2500 is an incidence in white population with CF and about 90% of the patients with cystic fibrosis express PI.[3] It is estimated to exist most

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commonly in whites and 1/2000 live births as an autosomal recessive inherited pattern. Although gastrointestinal (GI) manifestations are less common, it appears in 85%-90% of CF patients. “There was an undeviating relationship between congenital cystic fibrosis and bronchiectasis” which was reported by Fanconi et al. Table-1 is showing approximate frequency of incidence and complications in the pancreas with CF. [4]

Table 1. Percentage frequency of associated complication in pancreas with CF

Organ	Complications	Approximate frequency (%)
Pancreas	Total achylia	85%-90%
	Partial or normal function	15%-20%
	Pancreatitis	-
	Abnormal glucose tolerance	20%-30%
	Diabetes	1%-2%

Waters et al. proved that 63% of newborns who born with CF are already having PI and almost 30 % of newborns with CF will develop PI within the next 36 months.[5] A study by Adriana Haack et al. said that CF has less prevalence among Asians and Africans when compared with other ethnic groups such as Finland, Canada, United States, and Europe.[6]

Genetics

Cystic fibrosis is a common inherited Autosomal Recessive disorder which is caused by the defective mutations in the CFTR gene on chromosome 7q31.2 and it has a high incidence on European whites and Ashkenazi Jews.[7] CF is a multifactorial disorder, hence patients with CF manifest with multisystem defects.[8] Around 2068 CFTR mutations are currently listed in ‘CFTR mutation database’ however, mutations in the ΔF508 CFTR gene allele have noted to be the most common mutations in CF.[9] And all the 2068 mutations in CFTR gene do not cause CF alone but rather would cause other related pathologies like severe pancreatic disorders, sinusitis, lung disorders, etc. Therefore, gene analysis couldn’t be a gold standard for the diagnosis of CF. [10]

The human CFTR spans 250 kb and is separated into 27 exons, 1480 amino acid glycoprotein with a molecular weight of 170,000.[3] The normal function of the CFTR gene is the production of a transmembrane chloride ion channel protein which regulates the amount of secretions by chloride stimulation and inhibits sodium absorption. CFTR protein functions by hydrolysis using ATP thus, defect in the CFTR gene leads to lack of CFTR protein thereby there is an absence of hydrolysis. The consequences of this would cause elevated sweat chloride, mucociliary dysfunction in the lung, decreased pancreatic function, etc.,[9]

Mutations in the CFTR gene causing CF has a great impact on pancreas leading to both exocrine as well as endocrine pancreatic insufficiency and these patients have a great risk of developing pancreatitis.[11] Different mutations in the CFTR gene cause several defective CFTR functions leading to different types of diseases classifying it into mild, moderate and severe.[7] The factors pertinent to develop CFTR mutations are noted to be the size of the exon of CFTR gene, repeated mutations, ethnic variations in CFTR mutation carriers, lack of reliable data, and uncommon CFTR mutation. ΔF508 gene mutation is most frequently provokes CF, which arose at least 53,000 years ago.[12] The classical mutations involved in the CF patients are ΔF508 and T5 allele in intron 8 of the CFTR gene. In ΔF508, different phenotypes involved are ΔF508/R117H, ΔF508/A1087P, and ΔF508D1152H.[11] Molly B Sheridan et.al selected eleven CF patients who have undergone a mutation screening and identified to have two different types of deleterious mutations.[8] Consequences of the CFTR dysfunction have a great risk of developing phlegm retention, infection and inflammation in lungs.[13] But we found that there is no noted evidence of pancreatic infections in patients with CF.

Most of the mutations associated with CF are due to deletion of three nucleotides in exon 10 of phenylalanine at position 508 in homozygous patients are pancreatic insufficient, however, some of the patients with these types of mutations may have an intact of pancreatic functions.[3] Mutations in

CF have been classified into six different classes based on type of mutations, functional consequences, and chloride regulation along with its association in pancreatic function which are provided in Table-2. Among all these mutations, the identical mutations observed are non-sense or frameshift mutations where there is an insertion of base pair at the normal site of DNA sequence.[15]

Table 2. Classification of CFTR mutations and associated functional defects in pancreas

Class	Functional consequences	Associated with	Type of mutations	Examples
I	Absence of synthesis	Pancreatic Insufficiency	Nonsense or frameshift mutations	G542X, 394delTT and 1717-1G>A
II	Improper synthesis	Pancreatic Insufficiency	Missense, amino acid deletion	F508del and N1303K
III	Improper regulation	Pancreatic Insufficiency	Missense, change in amino acid sequence	G551D
IV	Abnormal conductance	Pancreatic Sufficiency	Missense, change in amino acid sequence	R117H and R347P
V	Defective production	Pancreatic Sufficiency	Abnormal splicing, missense	A455E, 3849+10kbC>T
V1	Increased degradation	Pancreatic Sufficiency	Missense, change in amino acid sequence	4326delTC, Gln1412X,4279insA

The frequency of F508del in CFTR mutations is the most common and accounts for about 90% worldwide while the other mutations like G551D, W1282X, G542X and N1303K have greater than 0.1% and rest else mutations have a prevalence of less than 0.1%.[14] Class I–III mutations (e.g. Gly542X, Phe508del, Gly551Asp) which are considered not only have less prevalence but also to have highest degree of degradation which can be diagnosed with a sweat chloride level ≥ 100 mmol/L.[1] The severity of the disease depends on the frequency and type of CFTR mutations (deletion, missense, frameshift, splicing and stop mutations) and the structural, functional changes in CFTR gene provided in Table-3.[3]

CFTR mutations yield a catastrophic effect on the entire pancreas leading to maldigestion, malabsorption due to lack of pancreatic enzymes for the digestion which results in an imbalance between anion/fluid. The mutations involved in pancreatic insufficiency are said to be mild, moderate and severe by using 'Novel pancreatic insufficiency prevalence score' among those, mild group of mutations are at great risk of developing pancreatitis. Mutations in CFTR, serine protease inhibitor Kazal type 1 (SPINK1), variant R75Q of CFTR would markedly increase the risk of pancreatitis.[17]

Table 3. List of different CFTR mutations and its association with pancreatic phenotypes

Association	Mutations					Phenotypes
	Missense	Deletion	Stop mutations	Splicing	Frameshift	
Cystic fibrosis (CF)	G85E	F508del	R1162X	2184delA	3120+1G>A	Pancreatic insufficient
	-	R553X	W1282X	621+1G>T	2789+5G>A	
	-	I507del	N1303K	1717−1G>A	3659delC	
	-	G551D	R560T	711+1G>T	-	
	-	-	-	1898+1G>A	-	
	A455E	-	-	-	3849+10kbC>T	Pancreatic sufficient
	R334W	-	-	-	-	
	R347P	-	-	-	-	

Involvement of CFTR and SPINK-1 mutations in pancreatic autodigestion

In normal pancreas there is an autoactivation of trypsinogen which gets converted to trypsin this mechanism is inhibited by SPINK-1 and therefore, this acts as a protective mechanism to inhibit autodigestion of pancreas but in case of pancreatitis associated with CF there is a mutation in SPINK-1 and CFTR which would lead to excessive conversion of trypsinogen to trypsin in pancreas itself.

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Increased trypsin would destroy the pancreatic epithelium and leading to autodigestion, which is associated with pancreatitis.[3]

As there is a greater rate of destruction to the pancreatic parenchyma due to CFTR mutations, there is a higher amount of incidence of acute/chronic pancreatitis in pancreatic sufficient (PS) patients than in pancreatic insufficient (PI) patients. In the case of Cystic Fibrosis Related Diabetes (CFRD), exocrine pancreatic insufficiency (EPI) is an important risk factor.[2] The incidence of mutations in the CFTR gene is increased with idiopathic recurrent-acute or chronic pancreatitis, which explained in several studies.[15] Some of the idiopathic chronic pancreatitis will include CFTR gene mutation, stated by some publications.[16]

Pathophysiology

Exocrine

"CF results in absence of bicarbonate transport system which leads to mucoviscidosis" according to the Quinton hypothesis.[7] Embryologically, the healthy exocrine pancreas will grow and develop during the third trimester of pregnancy.[18] Changes occur in pancreas of fetus with CF include, having low flow of secretions and high protein concentration starts in utero and continues even after delivery, due to which obstruction is even getting worse.[7]

Normal location of CFTR protein is present on apical membrane of small pancreatic ducts contains epithelial cells which makes alkaline fluid that contains chloride and bicarbonate into ducts and it also facilitates to flush secretions into the duodenum which is the ultimate goal to reach inactive enzymes and convert into its active form for digestion of food.[2] A recent study in 2018 states that the absence of functional CFTR protein on epithelial cells of the pancreas is one of the ways to accumulate Ca2+ within the cells, this build-up of calcium eventually impairs the mitochondrial function. CFTR is an important and key protein that play a wide role in understanding the pathophysiology of CF. So, it is better to know the molecular structure and mechanism by which this protein is working. CFTR protein made of two transmembrane domains, two cytoplasmic nucleotide-binding domains (NBD) and one regulatory (R) domain. The mechanism by which CFTR will work is shown in Figure-1.[19]

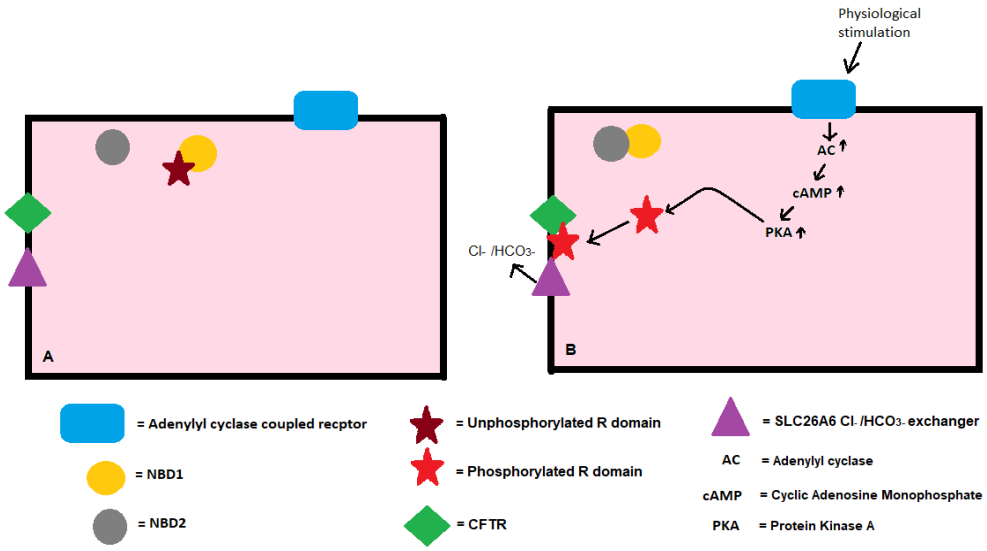

Figure 1. This figure shows normal mechanism by which CFTR protein will regulate secretions

The pancreatic ductal cell 'A' represents normal resting state of CFTR and other related protein under no physiological stimulus in which NBD1 domain is attached with unphosphorylated R domain, those are different domains of the same CFTR protein. When adenylyl cyclase (AC) couple receptors of ductal cell 'B' is activated by physiological stimulus will leads to increase in cyclic AMP and which activates the protein kinase A, the activated PKA will phosphorylate the R domain which is otherwise attached with NBD1as an unphosphorylated form, now the free form of R domain will

binds and activates both CFTR and other transporters (like SLC26A6 Cl-/HCO_3- exchanger) will leads to secretion of various anions like Cl-/HCO_3- into the ductal lumen of pancreas.

Normal pancreatic tissue produces and releases alkaline secretions, whereas mutated CFTR protein will not. This will cause high-salt and low volume secretions in the pancreatic duct lumen.[20] CFTR protein express on the epithelium of pancreas which transport anions (Cl^- and HCO_3-) and water into ducts. Sudden and complete failure or destruction of the exocrine cells in the pancreas may lead to indigestion and malnutrition.[17] Hence without flushing mechanism in pancreatic ducts due to a mutation in CFTR related gene, there is an accumulation of inactive or pro-enzymes within the pancreas. With progression, accumulation of these pancreatic secretions leads to inflammation due to epithelial injury and destruction. Inflammation is followed by fibrosis and fatty replacement or infiltrations as well as amyloid deposition, this amyloidosis is due to change in pH within the pancreas.[2] Normally increasing in pH towards alkaline is because of the secretion of anions within the ducts will which prevent the autoactivation of trypsinogen, but in CF this mechanism is impaired and due to decreased in pancreatic ductal pH may aids in autoactivation of trypsinogen followed by pancreatic autodigestion.[19] In one article they mention that co-release of H+ (protons) from acinar cells of the pancreas will acidify the pancreatic lumen eventually autoactivation of zymogens in wrong place results in tissue damage and inflammation.[15]

Patients with CF are classified into 6 groups according to their CFTR mutation in which someone are with pancreatic insufficient and others with pancreatic sufficient but the patients with PI involve loss of pulmonary functions than with PS patients.[2] PS patients are less severely affected than PI patients, but they have the risk of developing pancreatitis. Pancreatitis in PS patients is not because of damage to pancreatic acinar tissue, but because of decreased ductal flow. So, activation of trypsinogen within the pancreas may cause local inflammation by IL-1, TNF, and PAF. These formed cytokines are released from Kupffer cells of the liver into the systemic circulation which is responsible for the multisystem organ failure.[21] PI patients with CF may have a low or complete absence of exocrine pancreatic enzymes, lipase, phospholipases, colipase, proteases, and amylase, interestingly lingual lipase is increased, and salivary, brush-border enzyme amylase is normal or sometimes increased.[20]

Quality of life is decreased by most of the clinical manifestations and which may include abdominal pain and increased risk of acute pancreatitis in CF patients.[19] CF and CFTR-related disorder may involve exocrine insufficiency, pancreatitis, chronic sinopulmonary disease, intestinal disease, hepatobiliary disease and obstructive azoospermia in men.[15]

Due to decrease in secretions into the duodenum the pH of duodenum will decrease (pH <4) and becomes hyper acidic hence activity of the enzyme lipase especially on fatty meals (postprandial) is impaired, results in steatorrhea and fat malabsorption. In CF, duodenal epithelium is also damaged as like pancreatic epithelium, but not because of obstruction as usually happen in pancreas, but because of failure to neutralize chyme (which is secreted by duodenal epithelial cells) by pancreatic secretions due to absence of secretions from pancreatic ducts.[17] If trypsin levels drop to 10% below the normal limit in PI which may be related with steatorrhea and azotorrhea. Salivary isoamylase is increased in serum as well as in saliva, similarly serum pancreatic isoamylase will reduce in CF and PI patients.[4]

It is important to differentiate PI with PS patients because of different diagnosis and treatment. For example, PI patients with maldigestion are having steatorrhea and those patients require pancreatic enzyme therapy (PET) for lifelong, similarly, PET is not required for PS patients and they don't manifest steatorrhea as well. Another major clinically important difference is pancreatitis which is developed only in PS patients but not in PI, but they are few exceptions. PI patients report gassiness 1.6 times more when compared with PS patients. Pancreatic exocrine insufficiency (PEI) may be associated with flatulence, diarrhea. Normally fatty food will enter the GI and stimulate the release of cholecystokinin, which stimulates the pancreatic secretions which are required for lipid breakdown and aid for absorption. Luckily minute (only 5%-10% of what they release) quantity of the pancreatic juices are enough for proper digestion and hence clinically significant malabsorption and severe manifestations come into the picture until around 95% of pancreatic parenchyma will lose its function or destroyed.[20]

Body mass index (BMI) is also decreased in PI patients with cystic fibrosis due to malabsorption.[19] Chronic deficiency of nutrients significantly causes permanent stunting of stature,

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and especially vitamin E deficiency may cause cognitive impairment. [21] 10% of the patients with CF will also present with low bone mineral density (BMD) leads to poor bone health. Reason for this is because of improper absorption of vitamins D, vitamin K and calcium. Long term cystic fibrosis related diabetes (CFRD) may lead to peripheral insulin resistance which causes a reduction in BMD.[22] In these studies, they also mentioned that CF plays a crucial role in acute pancreatitis, alcohol-induced acute pancreatitis, and chronic pancreatitis.[19]

Endocrine

A person whose pancreas is affected in cystic fibrosis is said to have pancreatic insufficiency, pancreas produces insulin (a hormone which regulates blood sugar level in the blood) but when pancreas was unable to produce enough insulin, an individual with cystic fibrosis tends to develop CFRD, short stature, bone disease, and male hypogonadism.[23] Nesidioblastosis is a dysregulation of the function of pancreatic β-cells due to unknown etiology may lead to persistent hyperinsulinemic hypoglycemia. In patients with CF nesidioblastosis is seen but without hypoglycemia.[4] Cystic fibrosis undergoes two mutations which results in no CFTR function; these people after one year in their life might develop exocrine pancreatic insufficiency (PI) and then they are also are at greater risk of developing endocrine complications. CFRD can be classified into type 1 and 2 diabetes mellitus, with elevated blood glucose level (hyperglycemia) between both.[23]

Approximately around 50% of older patients with CF have recorded episodes of hyperglycemia. In this condition of hyperglycemia, CF is associated with diabetes mellitus leads to symptoms of nocturia, polyuria, dehydration, and weight loss.[29] In type 1 diabetes, the partial/complete destruction of insulin making β-cells in the pancreatic islets results in hyperglycemia, whereas in type 2 diabetes is resulted by a combination of reduced sensitivity to insulin and insufficient production of insulin.[23] In Type 2 diabetes mellitus, obesity which is usually seen is now witnessed in CF and may place an additional burden on the endocrine pancreas.[25] Normal insulin sensitivity is seen in CFRD but have a decreased and abnormal production of insulin. When CFRD is compared to Type 1A diabetes, in Type 1A, production of insulin declines rapidly with sudden and symptomatic onset But in CFRD gradually insulin production decreases and diabetes can become asymptomatic. With strong correlation of CFRD patients with exocrine pancreatic insufficiency shows that pre-existing exocrine pancreas could cause CFRD, at first was thought to be mainly responsible for reduction in endocrine pancreatic mass. Pancreatic islets look to be safe on autopsy studies, but the number and mass of islet cells are reduced in CF patients regardless if CFRD is present or not.[23]

A recent study shows that hyperglycemia rises the risk of deaths in patients with CFRD. In among individuals with cystic fibrosis and diabetes, those with HbA1c Levels above the clinically defined target of 6.5% are more likely die soon, when equated to those with lower values.[24] CFRD is an increasingly common and life-threatening comorbidity of CF, affecting approximately 35% of adults with CF but, the underlying causes of CFRD are not clearly known.[27] The decreased in islet cell mass and β cell dysfunction are the two major mechanisms which are thought to play a role in the development of CFRD.[2] These mechanisms are often accompanied with glucose responsiveness abnormalities and insulin secretory defects.[26] Delayed and diminished insulin and C-peptide (product of proteolytic processing of pro-insulin) secretion represents the Oral Glucose Tolerance Test (OGTT) in CF patients even in the absence of CFRD.[25] Even before the occurrence of clear diabetes, children with CF show impaired glucose tolerance on testing.[2]

Loss of CFTR function in human islets has been reported to impair insulin secretion and supplement glucagon secretion which suggests that loss of CFTR function in islet endocrine cells leads to CFRD via coupling of intrinsic disruption of β and α cell stimulus-secretion. This study shows that the CFTR does not essentially regulate α or β cell function and the cause of CFRD is largely dependent on islet loss and intra-islet inflammation in the setting of a complex and progressive multiorgan disease.[27] The condition of PI is persistently seen with the increase in diabetes risk. A recent finding in the article suggested patients with CF can preserve with pancreatic exocrine function to maintain normal ß-cell secretory capacity compared to an impairment seen in patients with pancreatic insufficiency. A recent finding in the article suggested patients with CF can preserve with pancreatic exocrine function to maintain normal ß-cell secretory capacity compared to an impairment

seen in patients with PI. CFRD is associated with deteriorating in nutritional status, lowering in pulmonary function, and increased mortality, which seems to be occurring before the early identification and treatment of it. Prior identification of patients with pancreatic insufficient CF (PI-CF), CFRD is at high-risk and which is highly essential in developing therapeutic measures pointed at preserving β-cell function.[28]

In patients with cystic fibrosis associated with diabetes mellitus (CFDM), an immunohistochemical staining studies of pancreatic tissue showed to be increased in number of somatostatin secreting delta cells. This finding is surprising as it proposes that the 'scarring process' damaging the endocrine pancreas in cystic fibrosis is not affecting all cell types in equal proportion. In patients with CFDM, there was no noteworthy change in C-peptide concentrations in response to arginine stimulation. There might be a possibility that local somatostatin excess might be producing the paracrine inhibition of insulin secretion.[29]

A study showed an increase in chromogranin A-positive hormone-negative (CPHN) endocrine cells happens in the pancreas of individuals with CF, as potential sign of regeneration of cells. In addition to this glucose intolerance is reported in 50% to 70% of adult individuals whose endocrine component of pancreas is affected and diabetes affecting 40% of adults aged 30 years old. A recent study shows an increased inflammatory mediator (which includes IL6, IL1B, CXCL10, TNF-alpha, and IFN-gamma) in the human CF islet reveals that islet loss and inflammation is caused by CFRD. β-cell trans-differentiation in humans with chronic pancreatitis was represented to be involved by Islet-derived chemokine CXCL10 and its receptor CXCR3 interaction. An increase in pancreatic nonhormone-expressing endocrine cells is seen in the setting of both Type 1 Diabetes and Type 2 Diabetes. Abundance of CPHN cells in chronic pancreatitis, suggests the damage in the exocrine pancreas which might also lead to morphological changes in the endocrine pancreas.[30]

Cancer

Individuals with CF may have an improved risk for malignancy, predominant in digestive tract cancers and leukemia. In a research study, total risk for cancer in individuals with CF equated with normal population, it resulted in both being the same. In a study conducted on CF patients reveals 13 types of digestive tract cancer, A detailed pie chart in Figure-2 is provided below for better understanding.[31]

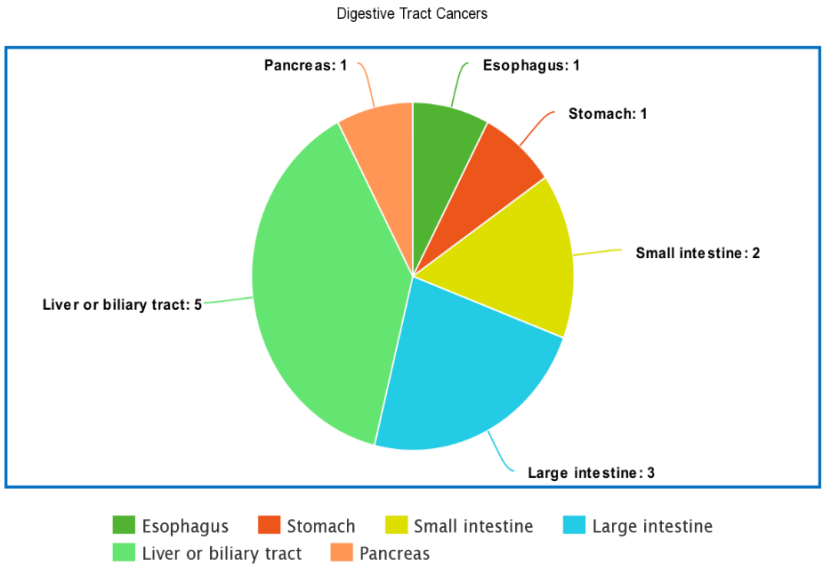

Figure 2. Graphical representation of different digestive tract cancers involved in CF

In CF, radiation-induced cancer is occurring more frequently in females than males, because in females are at higher risk for getting radiation-induced breast cancer and thyroid cancer. Patients will start living into the age at which cancer rates begin to increase considerably and will also undergo more annual CT scans.[32] The Standardized Mortality Ratio in women was witnessed to be more than twice high as in men.[34]

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Mutations in the CFTR genes can be seen an increased risk of evolving pancreatic cancer which is developed by patients with CF and it is an early onset form of chronic pancreatitis. A recent study analysis yielded a positive coupling of pancreatic cancer risk by CFTR carrier status. CFTR gene is associated with a slow rise in the danger of pancreatic cancer, whereas no association was found in between SPINK1 gene mutation to that of pancreatic cancer. Mutations in the CFTR gene lead to chronic pancreatitis, and the established inflammation increases the risk of neoplastic transformation. Moreover, patients with CFTR gene mutations and consequent EPI may develop a shortage in vitamin E and selenium, which were antioxidants and are presumed to offer protection from cancer.[33]

In some cases, presence of a single mutant CFTR allele may have an increase in exposure for pancreatic cancer by a procedure which is independent of chronic pancreatitis or inflammation. Increase in specific risk of pancreatic cancer in smoking is witnessed in individuals with hereditary pancreatitis, and lowers the age of diagnosis by 20 years.[35] Most patients with CF have received large quantities of antibiotics, pancreatic supplements and vitamin preparations which does not cause cancer at all.[34]

Diagnosis

If patients diagnosed with CF pancreatitis and CFTR-related pancreatitis, they may have recurrent-acute or chronic pancreatitis due to CFTR dysfunction. Widely accepted and clinical used diagnostic procedure over 50 years, for CF is sweat chloride test. This test procedure involves administration of pilocarpine through transdermal route to stimulate secretions from a sweat gland, followed by collection and measurement onto a filter paper or a Macroduct coil. The European Cystic Fibrosis Society (ECFS) provide some reference ranges for this sweat chloride test may include; normal ≤ 29 mmol/L, intermediate 30-60 mmol/L, and abnormal > 60 mmol/L, these values are for all ages. Similarly, several studies claimed that patients being diagnosed with CF which is either PS or PI, who have sweat chloride values < 60mmol/L. Some other miscellaneous diagnostic studies include transepithelial nasal potential difference (NPD) test, Intestinal ion channel measurement (ICM) and pancreatic function test which includes 72-hour fecal fat balance test as well as fecal elastase-1.[15]

Fecal elastase test is an excellent indicator of PI patients which having 98%-100% and specificity of 93%-100%, this test is not interrupted even though the patient is under pancreatic enzyme supplements. Children more than 8 years old who have PI is diagnosed with serum trypsinogen.[21] To know the difference between these (PS and PI) patient's, we must perform the secretin-pancreozymin stimulation test, which is more accurately estimate the pancreatic function, but it is invasive, expensive, and time-consuming procedure. 72-hour fecal fat collection is another most commonly performed test, but this test doesn't differentiate other GI-related malabsorption and PET need to be discontinued during the test period. A test with sensitivity of 99%-100% for PI indication and specificity of 93%-100% to distinguishing PI from PS of patients with CF is namely the stool elastase test. [20]

Fatty infiltrations and atrophy are the end-stage pancreatic disease in CF. So, to differentiate pancreatic from non-pancreatic CF patients, radiological studies place a key role. Ultrasonography provides information regarding pancreatic hyperechogencity in exocrine insufficient patients. Acoustic-Radiation-Force-Impulse (ARFI) is an imaging technique used to compare fatty vs fibrotic pancreas, it reveals that in defected pancreas i.e. PI, the pancreas is softer due to fat which is the dominating feature rather fibrosis. Another technique called the Dixon-MRI, which separates water and fat signal in parenchymal fat and water of abdominal organs in our studies which is a pancreas. Some other methods include Diffusion-weighted imaging (DWI) and Apparent diffusion-coefficient (ADC).[36]

If a neonate with CF, there is a release of some proteins (e.g. immune reactive trypsinogen (IRT)) from the pancreas into the blood, it is used as a screening test for newborns if CF is suspected.[17] IRT levels in newborns with CF are the clinical biomarkers to check exocrine pancreatic disease progression, these levels are declined with worsening of the condition.[18] A meconium screening test is the least common due to its false-negative results hence, alternatively sweat test is performed in infants to screen for CF.[2].

Criteria for diagnosis using sweat chloride test

The sweat chloride is said to be the gold standard for the diagnosis of CF and rules include:

1. Sweat chloride ≥ 60 mmol/L in sweat chloride test is confirmatory until the age of 6 weeks.
2. ≥ 2 CFTR mutations (provided in Table-3).
3. Sweat chloride value ≤ 29 mmol/L can rule out CF.
4. The sweat chloride test should be repeated at age of 2 to 6 months.
5. Patients with age of 6 months with a Sweat chloride value of ≥ 40 mmol/L considered to be abnormal range.
6. Sweat chloride value of ≤ 39 mmol/L after age 6 months could be excluded for the diagnosis of CF.

Genotyping, CT scan, pulmonary function tests cannot be confirmatory to diagnose CF, but a positive respiratory tract infection could be suspicious for CF. Identification of genotype has become more challenging even if the genotype was identified as there are a huge number of mutations noted till today and unfortunately many mutations of CFTR are unknown.[10]

Treatment

Pancreatic insufficiency is one of the major complications in CF with clinical manifestations of malabsorption, steatorrhea and poor growth therefore, the main goal of the treatment is to improve the nutritional status and to decrease the symptoms. The most commonly used treatment includes supplementation with pancreatic enzymes (lipase and proteases) and fat-soluble vitamins (A, D, E and K). To decrease the auto-destruction of pancreatic epithelium, the management includes H2 blockers and proton pump inhibitors which would help to decrease the acidic nature, increase the alkaline media and prevent steatorrhea. In case of endocrine pancreatic manifestations there is a drastic development of diabetes due to insulin deficiency therefore the treatment includes supplementation of insulin, high fat diet, oral hypoglycemic agents.[7]

The average life span of patients with CF has increased in the last few years, which is because of early diagnosis and improved treatment in early stages of the disease, but inadequately treated patients may have high energy stool losses which result in energy imbalance and malnutrition. Especially fat-soluble vitamins like A, D, E, and K are lost through feces without absorption in GI leads to a condition called hypovitaminosis, hence we must provide each patient with supplemental fat-soluble vitamins, those data are provided in Table-4.[6]

Table 4. Recommended dosage of fat-soluble vitamins for the CF patients

Vitamins	Dosage	Dosage
A	400-10000 UI (~2240 μg)	Daily
D	400-1800 UI (~18 μg)	Daily
E	50 mg (1 year)	Daily
	100 mg (1-10 years)	
	180mg (adolescents and adults)	
K	0.3-0.5 mg	Daily

Growth failure and chronic malnutrition are the consequences of newborns with CF, which can be prevented with good nutritional management such as pancreatic enzyme replacement therapy (PERT).[37] Some articles state that around 85% of patients with CF require PERT for the entire life.[5] To prevent malnutrition in PEI, proper nutritional management is required. PERT is recommended to the patients who have severe steatorrhea and malabsorption.[37] The main moto of this enzyme replacement during or just before meals to boost up the physiological exocrine response of the pancreas which is not functioning properly in CF patients, which shows positive improvement in gaining body weight and to decrease malabsorption. Several formulations such as non-enteric coated powders, enteric-coated tablets, enteric-coated microspheres and enteric-coated micro tablets were used for pancreatic enzyme supplement. Recommended dosage of lipase to take is 25,000 to 40,000 U/meal. Some new preparations contain porcine which is a pork extract and it is a pancreatin protected and pH sensitive microsphere but because of some ethical issues this drug is used only

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under certain circumstances. Still research is ongoing to discover the new methods for manufacturing of certain type of bacterial or fungal-derived lipases as an enzyme supplementation in PI.[38]

In general, CF patient less than 4 years of age should provide PERT with 1000 lipase units/kg bodyweight/meal. Similarly, those with greater than 4 years of age can be given at a dose of 500 lipase units/kg bodyweight/meal. Some studies shown that fat absorption in CF patients is improved with delayed-release formulations than conventional. US FDA recently approved a new formulation of pancrelipase delayed-release capsule (CREON®) and they demonstrate efficacy and safety of this drug which works effectively in children with CF under 7 years of age. This delayed-release capsule contains enteric-coated pancrelipase spheres of 0.7-1.6 mm in diameter which can be given as a dose of 6000-, 12 000- or 24 000-lipase unit capsules. [39] Enzyme supplementations are given around 500 to 4000 U lipase per gram of fat ingested per day to decrease the symptoms of steatorrhea if it is not controlled then the dosage will be raised to 2500 U lipase per kilogram per meal, doses greater than this levels would cause fibrosing colonopathy which is a known complication of higher enzyme supplementation therefore the patients are reevaluated to reduce the dosage of supplementation. However, in some patients the symptoms may not be resolved so other therapeutics may be considered which include powered preparations like Viokase; Axcan Scandipharm or other alternative brands of microencapsulated products. In CFRD goal of therapy includes controlling severe hyperglycemia and avoiding hypoglycemia by treating with long acting insulin.[41]

Hypercaloric diet is necessary for all CF patients because of their malabsorption. So, such diet should contain 30%-40% of fats, 20% of proteins and 40%-45% of carbohydrates. Maintenance of HbA1c levels below 7% is important for CF patients and which can be achieved by insulin therapy with recommended dose in between 0.5 - 0.8 u.i./kgb/day which is available as basal or bolus insulin.[41] CF patients who are born with PI are at a great risk of having a destruction of pancreas and liver therefore the best treatment is to have a pancreatic and liver transplantations which would help to have better prognosis. Another treatment option will be stem cell transplant of pancreatic mass which would help in the regeneration of pancreatic acini and ducts.[17]

As mentioned earlier CF is caused by the mutation in CFTR gene leading to abnormal CFTR protein in order to modify this abnormal function CFTR modulators which include CFTR protein correctors and potentiators are given as treatment. [42] Continuous glucose monitoring (CGM) test is even though not approved as a diagnostic tool, it can be used to check early glucose abnormalities for diabetes. Ivacaftor is a drug used to correct the insulin secretions which is otherwise defect in CF patients with G551D mutation. But the incidence of mutation in G551D gene in CF patients is quite uncommon (only 5% cases worldwide). Another combinational drug lumacaftor-ivacaftor can be used to modify CFTR gene for individuals with homozygous mutation in F508. Orkambi® is a brand name for that combination in which lumacaftor will modify CFTR intracellular processing, similarly CFTR channel activity will be improved by ivacaftor. But therapy for G551D mutated patients had better improvement in insulin secretions as compared to that of combinational drug for F508del related CF patients. So, population with F508del defect is difficult to correct.[41] An approval of CFTR modulators is made in homozygous F508del-CFTR that includes lumacaftor-ivacaftor, tezacaftor-ivacaftor which are CFTR correctors and potentiators. VX-659 or VX-445 a next generation drugs which can be given as a triple combination with tezacaftor and ivacaftor, those are used in phase 2 clinical trials.[42]

A study did by “Gavin” have provided that, children suffering from CF with EPI were given with pancrelipase (pancreatin) a delayed-release capsules which are associated with improvement in coefficient of Fat absorption (CFA), Coefficient of Nitrogen absorption (CNA), EPI symptoms when compared with placebo. Moreover, Pancrelipase delayed-release capsules known to have well tolerance.[43] Patients of CF with EPI are noted to have malabsorption in order to prevent this exogenous pancreatic enzyme supplementation to improve digestion is provided. This includes a microencapsulated TheraCLEC-Total (TCT), formulations which include bacterial lipase and fungal protease and amylase. TCT is noted to have less side effects and enrolled to help for digestion. TCT is developed with microbial-derived and crosslinked crystalline lipase, protease, and amylase which are well tolerated. TCT provides increased efficacy of fat and nitrogen absorption.[44]

Alpha dornase a recombinant human deoxyribonuclease I, in records of Health Ministry guarantees access for pancreatic enzymes in patients with PI. Diarrhea in CF may related with pathogenicity there by increase in infections so, to prevent such a complications patients are provided with probiotics at a dose of 100 g of food product containing 109 colony forming units (cfu) and insulin and/or oligofructose at 5 to 20 g which change intestinal microbiota in favor of patient is seen. Anti-inflammatory effect is also seen by providing fish oils (contain omega-3 fatty acids, docosahexanoic acid and eicosapentanoic acid) for the CF patients. N-acetylcysteine, polyethylene glycol or hypertonic contrast are given either orally using probes or through enemas (while keeping the patient hydrated) in case of partial or complete bowel obstruction respectively. An essential amino acid namely taurine, which will improve digestion of fat during its micellar phase in patients with CF who suffers from steatorrhea.[45] Pain management with non-narcotic analgesics and hydration to the patients with CF is important, but it might lead to complication such as distal intestinal obstruction syndrome (DIOS) due to severe constipation. It is good to discontinue excessive alcohol ingestion of CF and PS patients.[21]

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