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Review Paper

A Comprehensive Review of Cystic Fibrosis: Mechanisms, Clinical Features, and Treatment

Nikhil Gajare*, Saad Mulla, Mayuri Pednekar, Pooja Pednekar, Omkar Rawool, Nagesh Virkar

Vijayrao Naik college of pharmacy, shirval , Kankavli - 416602, Maharashtra, India

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ABSTRACT

A life-limiting autosomal recessive condition called cystic fibrosis (CF) is brought on by mutations in the CFTR gene, which impair ion transport between epithelial cells. Thick, viscous mucus from this malfunction affects several organ systems, especially the gastrointestinal and respiratory systems. The most prevalent mutation, ΔF508, increases the severity of the condition by interfering with the folding and function of the CFTR protein. Impaired chloride secretion, increased sodium reabsorption, and dryness of airway surfaces are all part of the pathophysiology of cystic fibrosis (CF), which encourages mucus buildup, persistent infection, and inflammation. Persistent respiratory infections, bronchiectasis, pancreatic insufficiency, malabsorption, and growth failure are the clinical manifestations of cystic fibrosis. Pseudomonas aeruginosa and other opportunistic bacteria are important in the development of illness. Diagnosis relies on sweat chloride testing, newborn screening, and genetic analysis for CFTR mutations. Despite the lack of a cure, improvements in treatment, such as CFTR modulators, antimicrobial therapy, and airway clearance methods, have greatly enhanced patient outcomes and quality of life. Early diagnosis and comprehensive treatment have significantly improved the quality of life and survival of patients with CF. In order to address the fundamental flaw and enhance long-term results, ongoing research is investigating new therapy strategies.

INTRODUCTION

Cystic fibrosis (CF), is a single gene-disease with autosomal recessive inheritance, is caused by mutation (chemical change) in the CF gene apartly named the CFTR (Cystic fibrosis transmembrane conductance regulator) protein.[1] Mutations in CFTR disrupt chloride secretion, sodium reabsorption, and water transport, leading to mucus hyper-concentration and decreased

***Corresponding Author:** Nikhil Gajare
Address: *Vijayrao Naik college of pharmacy, shirval , Kankavli - 416602, Maharashtra, India*
Email ✉: gajare.nikhilvncop@gmail.com
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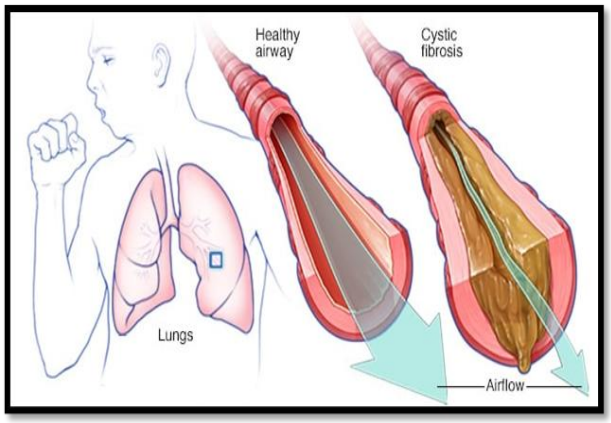
mucociliary clearance. [1] This disease was marked by malabsorption of fats and proteins, steatorrhea, stunted growth, and pulmonary infection. The injury to the pancreas and the failure to secrete enzymes into the gastrointestinal tract accounted for the nutritional failure, which was believed to result in the patient's susceptibility to lung infection, which was usually the terminal event. The thick, sticky mucus in the ducts of the mucus glands in the body accounted for the second name "mucoviscidosis".[2] Cystic fibrosis is caused by pathogenic mutation in a single large gene located on human chromosome 7 that encodes the cystic fibrosis membrane conductance regulator protein.

MECHANISM OF CYSTIC FIBROSIS: The classification of CFTR mutations is now most often divided into seven groups from class I through VII as described by Kris De Boeck and Margarida Amaral.[3] A single mutation could be assigned to many classes.



The ΔF508 mutation, for instance, is a deletion mutation, which causes misfolding of the CFTR protein, followed by subsequent proteasome-mediated degradation, and results in improper chloride channel function. Additionally, this mutation also causes a deficiency in the translation of CFTR; thus, the ΔF508 mutation can at least be assigned to three classes, and may be assigned to classes II and III [4].

CFTR mutation: Class1: It is mutation caused by little or no production of CFTR protein. Class 1 mutations cause absence of functional CFTR protein due to defective mRNA production or rapid degradation of abnormal protein [5]

Class 2: mutations produce misfolded CFTR protein**,** which is degraded in the cell (ERAD), preventing it from reaching the cell membrane. [6]

Class 3: mutations cause defective CFTR channel gating (channel does not open properly) mutations produce a normal CFTR protein that reaches the membrane but fails to open properly, causing cystic fibrosis. [7]

Class 4: mutations produce CFTR protein that reaches the membrane but conducts ions poorly, causing mild cystic fibrosis. [8]

Class 5: mutations reduce CFTR quantity due to splicing or promoter defects, producing mild cystic fibrosis symptoms. [9]

Class 6: mutations produce unstable CFTR at the plasma membrane, leading to reduced function and variable disease severity. [10]

All mutations result in decreased chloride secretion and, consequently, increased sodium resorption into the cellular space. The increased sodium reabsorption leads to increased water resorption and manifests as thicker mucus secretions on epithelial linings and more viscous secretions from exocrine tissues. Thickened mucus secretions in nearly every affected organ system result in mucous plugging with obstruction pathologies. [11][12] The most commonly affected organs include the sinuses, lungs, pancreas, biliary and hepatic systems, intestines, and sweat glands.

CLINICAL FEATURES OF CYSTIC FIBROSIS: CF is caused by dysfunctional transport of chloride and/or other ions(such as sodium and bicarbonate) that leads to generation of thick, vis-cous secretions (eg. mucus) in the lungs, pancreas, liver, intestine, and reproductive tract and increased salt content in sweat gland

secretions. Ultimately, progressive lung disease is the main cause of CF complications and patient mortality. 8 The course of disease varies greatly and can begin from a few months after birth to decades after birth, with many patients exhibiting mild or atypical symptoms. Therefore, clinicians should take care to avoid excluding CF as a possible diagnosis in cases where patients exhibit only a few typical CF signs and symptoms.[13]

1. **Respiratory tract involvement**: Cystic Fibrosis primarily affects the lungs, causing a persistent productive cough and obstructive airway disease. Early features include hyperinflation of lungs and reduced pulmonary function. Recurrent infections lead to chronic inflammation and damage to bronchial walls. This damage results in loss of airway support and development of bronchiectasis. Patients experience exacerbations with cough, dyspnea, tachypnea, and increased sputum. Chronic infections are commonly caused by Pseudomonas aeruginosa and Staphylococcus aureus. Other microbes and fungi may also colonize the airways over time. Neutrophil activity increases mucus viscosity by releasing DNA and proteins. Thick mucus causes airway obstruction, promoting infection and inflammation in a vicious cycle. Progressive lung damage leads to respiratory failure, which is the major cause of death in CF patients.
2. **Sinus disease:** Sinus disease occurs when secretion viscosity increases, obstructing the sinus ostia. Sinus infections can trigger lower respiratory exacerbations in some patients, although organisms found in sinuses do not always match those recovered from lungs. These coexisting processes include ciliary dysfunction, increased inflammatory mediators, and increased pathogenic bacterial colonization, including *Pseudomonas aeruginosa*. The result of this syndrome is impaired sinus secretion clearance. Subsequently, chronic sinusitis occurs, and secondary structural damage may occur. the single CFTR mutation rate for a group of chronic rhinosinusitis cases was significantly higher than the corresponding rate for the general population (7% versus 2%).[14]
3. **Digestive system diseases:** Approximately two-thirds of CF patients exhibit CF insufficiency of the exocrine pancreas from birth, with an additional 20% to 25% developing this condition during the first several years of life, and most exhibiting signs of fat malabsorption by one year of age.[12] CF associated pancreatic disease tends to be progressive; many patients with apparently normal or marginal pancreatic function at birth develop overt evidence of pancreatic insufficiency in childhood or adulthood.[11] Overall, approximately 85% of individuals with CF eventually develop clinically significant pancreatic insufficiency.[12] Common symptoms and signs of pancreatic insufficiency include steatorrhea, characterized by frequent, bulky, foul-smelling stools that may be oily, as well as failure to thrive or poor weight gain resulting from malabsorption of fat and protein. Infants with severe untreated pancreatic insufficiency occasionally present with edema, hypo-proteinemia, electrolyte loss, and anemia due to malabsorption of macro- and micronutrients. Some patients also may present with symptoms caused by deficiencies of the fat-soluble vitamins A, D, E, and K. Vitamin K deficiency can present as a coagulopathy and vitamin D deficiency as rickets. Continued defective ductular and acinar pancreatic secretion functions lead to progressive pancreatic damage that can trigger acute or recurrent pancreatitis. Moreover, patients with exocrine pancreatic insufficiency often develop dysfunction of the endocrine

pancreas, leading to glucose intolerance and CF-related diabetes. With regard to other CF-associated digestive system disorders, 10% to 20% of newborns with CF present with meconium ileus characterized by obstruction of the bowel by meconium, which is a risk factor for poor CF prognosis. Rectal prolapse, which previously was rarely detected in children with CF, has been detected frequently in recent years and appears to be associated with constipation and/or malnutrition. Focal biliary cirrhosis caused by inspissated bile is present in many patients and may cause elevated serum alkaline phosphatase and lobular hepatomegaly. A minority of CF patients develop periportal fibrosis, cirrhosis, symptomatic portal hypertension, and variceal bleeding that are associated with progressive liver disease.[12]

SIGN AND SYMPTOMS:

- Frequent lung infections
- Loose or oily poop (stool).
- Trouble breathing.
- Frequent sinus infections
- A nagging cough.
- Slow growth.
- Failure to thrive inability to gain weight despite having a good appetite and taking in enough calories.
- A cough that won't go away and brings up thick mucus.
- A squeaking sound when breathing called wheezing.
- Limited ability to do physical activity before tiring.
- Repeated lung infections.
- Irritated and swollen nasal passages or a stuffy nose

TREATMENT: There is no cure for cystic fibrosis, but treatment can ease symptoms, lessen complications and improve quality of life. Close monitoring and early, aggressive intervention is recommended to slow the worsening of CF over time. This can lead to a longer life.

1. **Airway clearance techniques:** Airway clearance techniques help loosen lung mucus so it can be coughed out. Removing mucus improves breathing and lowers the chance of infections. Pharmacotherapies have targeted airway bronchodilation, mucolytic, sympathomimetic, anticholinergic, and anti-inflammatory categories.[15] Most pharmacological studies focused on airway clearance are inconclusive. A recent Cochrane review of mucolytic agents in chronic obstructive lung disease suggests this agent class may be of benefit. Airway Clearance Therapy is a group of techniques used to remove thick, sticky mucus from the lungs. It is a key part of managing respiratory diseases, especially cystic fibrosis. [14]
2. **Medication:** The most common airway pathogen in patients with CF is Pseudomonas aeruginosa. Because chronic colonization of the airways with this bacterium is associated with a more rapid decline in lung function (5), aerosolized antibiotics have been advocated both for eradication of initial infection and for suppression of the chronic infection.

A. Antibiotics: It prevent or treat lung infections and improve lung function. Your healthcare provider may prescribe oral, inhaled, or intravenous (IV) antibiotics.

B. Anti-inflammatory medicines**:** such as ibuprofen or corticosteroids, reduce inflammation. Inflammation causes many of the changes in cystic fibrosis, such as lung disease. Ibuprofen is especially helpful for children, but side effects can include kidney and stomach problems. Corticosteroids can cause bone thinning and increase blood sugar and blood pressure.

C. Bronchodilator: It relax and open airways. These treatments are taken by inhaling them.
D. Mucus thinner: make it easier to clear the mucus from your airways. These treatments are taken by inhaling them.

3. **CFTR Modulator:** CFTR modulators make faulty CFTR proteins work better. They help with lung function and can help prevent lung problems or other complications. The CFTR mRNA translates into a 1,480-amino acid protein. Soon after co- and post-translational folding, and core glycosylation in the endoplasmic reticulum (ER), CFTR protein traffics to the Golgi complex, where it is fully glycosylated.[16] The CFTR protein regulates the proper flow of water and chloride in and out of cells lining the lungs and other organs. In people with CF, mutations in the CFTR gene result in either a defective protein being produced or no protein at all. This leads to the buildup of thick, sticky mucus, which can lead to infections in the lungs and damage to the pancreas. It can also lead to problems in other parts of the body.[17] There are five CFTR modulators for people with certain CFTR mutations:
   - Alyftrek (vanzacaftor/tezacaftor/deutivacaftor)
   - Trikafta (elexacaftor/tezacaftor/ivacaftor)
   - Symdeko (tezacaftor/ivacaftor)
   - Orkambi (lumacaftor/ivacaftor)
   - Kalydeco (ivacaftor)

DIAGNOSIS OF CYSTIC FIBROSIS: The significant advances in the diagnosis and treatment of CF over the past decade have increased our understanding of the disease, making this an opportune time to reexamine the criteria for a diagnosis of CF.[18][20]

1. Sweat Chloride Test: A sweat test measures the amount of chloride in your sweat. Chloride is a type of electrolyte. Electrolytes are electrically charged minerals that help control the amounts of fluids and the balance of acids and bases (pH balance) in your body. Chloride and sodium form the salt found in your sweat. Normally, chloride moves in and out of your cells through a protein called the cystic fibrosis membrane conductance regulator (CFTR). This protein can be found in the organs that make sweat and mucus, such as your lungs, sweat glands, and intestines. Mucus is the slippery substance that protects the linings of your airways, digestive tract, and other organs and tissues.[19]

2. New born screening: Newborn screening (NBS) for cystic fibrosis is done in the first few days after birth. By diagnosing CF early, CF health care providers can start medicines for CF as early as possible and help you learn ways to keep your child as healthy as possible.[18][20] This can help delay or prevent serious, lifelong health problems related to CF. Research shows that children who receive CF care early in life have better nutrition and are healthier than those who are diagnosed later. Cystic fibrosis can affect people of every race and ethnicity, and all children should undergo newborn screening as well as follow-up sweat testing at a CF Foundation-accredited care centre after a positive newborn screen.[21][22] Results from newborn screening for CF can take longer than one week after a blood sample is collected. Ask your baby's primary health care provider when you can expect results.[23] When high IRT levels are detected in the blood, the results of the newborn screening are said to be positive. A positive newborn screening result tells you that your baby might have CF. Some babies that have a positive NBS test for CF do not have CF. This is called a false-positive. Some babies with a negative NBS test for CF do have CF. This is called a false-negative. So, anyone, at any age, who has symptoms of CF should have a sweat test to see if they have CF. [24][2]

3. Genetic testing: Genetic changes, often called mutations, in the CFTR gene cause CF. The CFTR gene gives your cells instructions on how to make CFTR protein. CFTR protein regulates the movement of chloride into and out of your cells and is involved in mucus production. In people with CF, the CFTR protein doesn't work properly.[25][26] The result is thicker, stickier mucus. Genetic testing works by identifying mutations in the CFTR gene that cause CF. There are currently more than 2,000 trusted source known CFTR gene mutations that can lead to CF.[28] Genetic testing uses a sample of blood, saliva, or cells rubbed from the inside of your cheek. Prenatal genetic tests may use a sample of placenta or amniotic fluid. Once collected, genetic testing samples are sent to a lab for analysis.[31][27]The *CFTR* gene encodes a protein that regulates the flow of chloride ions through membranes.[30] Mutations in *CFTR* alter protein function, which in turn causes the symptoms of CF in afflicted patients. Because different mutations alter protein function in different ways and to different degrees, there are wide variations in the severity of the clinical syndrome. To date, scientists have found >1500 mutations in the *CFTR* gene. ΔF508, a deletion of three nucleotides in DNA, causes the protein to lack the amino acid phenylalanine (F) at position 508. This one mutation accounts for 70% of CF chromosomes worldwide and 90% of CF patients in the United States. Individuals homozygous for ΔF508 (~50% of patients) have the most severe form of CF. [29][32]

CONCLUSION

Cystic fibrosis is a multicomplex Mutations in the CFTR gene cause cystic fibrosis, a complicated, multisystem genetic condition that causes thick, viscous secretions and poor ion transport. These anomalies mostly impact the digestive and respiratory systems, leading to dietary deficits, pancreatic insufficiency, recurrent infections, and chronic lung illness. The accuracy of diagnosis and treatment strategies have been greatly enhanced by developments in our knowledge of the genetic causes of cystic fibrosis (CF), especially the categorization of CFTR mutations. Early detection, which can be achieved through genetic analysis, sweat chloride testing, and newborn screening, is essential for starting treatment on time and stopping the progression of the illness. Comprehensive treatment approaches, including as airway clearance procedures, antibiotic therapy, anti-inflammatory drugs, and CFTR modulators, have significantly improved patient outcomes, quality of life, and life expectancy even though there is presently no cure. Future treatments that are more potent and possibly curative could result from ongoing research into gene-targeted medicines and personalized medicine. To improve long-term prognosis and lessen the burden of cystic fibrosis, a multidisciplinary approach, early intervention, and continuous therapy breakthroughs are crucial.

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