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Novel Tool For Early Detection of Cystic Fibrosis

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ABSTRACT

Cystic fibrosis (CF) is a hereditary disorder characterized by the accumulation of thick, sticky mucus in various organs, primarily affecting the lungs and digestive system. Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a protein involved in ion transport across cell membranes. The defective CFTR protein leads to impaired chloride ion transport, resulting in the production of thick mucus that obstructs airways and hampers the normal function of various organs such as the lungs, pancreas, liver and intestine, significantly impacting the quality of life. Diagnosis is usually through a combination of clinical evaluation, family history assessment, sweat chloride testing, genetic testing, and imaging studies. Airway clearing procedures, bronchodilators, antibiotics for infections, enzyme replacement therapy for pancreatic insufficiency, and nutritional supplementation are among the treatment options. Novel medicines that target the underlying genetic abnormality, such as CFTR modulators, have shown encouraging results in improving lung function and overall health in recent years.

Keywords: cystic fibrosis, digital clubbing

1. INTRODUCTION TO CYSTIC FIBROSIS

Cystic fibrosis is one of the most common autosomal recessive disorders, characterized by the accumulation of thick mucus secretions that lead to the blockage of airways and secondary infections. The organs most commonly affected due to cystic fibrosis are the lungs and pancreas. Chronic lung disease caused by recurrent infection eventually leads to the formation of fibroids in lungs, causing permanent lung damage and even leading to secondary cardiac failure, with the only option for long-term survival being a successful heart-lung transplant.

In 85% of patients with cystic fibrosis, pancreatic function is impaired due to the blockage of pancreatic ducts, impairing fat digestion and leading to malabsorption of nutrients. This can be amended by consuming oral supplements of pancreatic enzymes.

Other problems commonly encountered are nasal polyps, rectal prolapse, cirrhosis and diabetes mellitus. Approximately 10% of newborns or children with cystic fibrosis also present with an obstruction of the small bowel in the form of meconium ileus. Almost all males with cystic fibrosis have a congenital bilateral absence of the vas deferens (CBAVD), leading to infertility. Other complications can include chronic pancreatitis, diffuse bronchiectasis and bronchopulmonary allergic aspergillus.

Clinical manifestations of cystic fibrosis can vary widely, but common symptoms include persistent cough, wheezing, recurrent lung infections, finger clubbing, poor weight gain, and malabsorption. Cystic fibrosis can also affect other systems, such as the liver, sinuses, sweat glands, and reproductive organs.

Cystic fibrosis is by far the most serious autosomal recessive disorder in children of Western European descent due to a variety of proposed reasons such as multiple cystic fibrosis loci, a high mutation rate, meiotic drive and heterozygote advantage, seen in the resistance to chloride-secreting bacterially-induced diarrhea, the most likely explanation.

The incidence of cystic fibrosis varies among different populations and ethnicities. According to the Cystic Fibrosis Foundation, in the United States, approximately 1 in every 3,700 newborn children has CF. Globally, cystic fibrosis affects an estimated 70,000 to 100,000 individuals.

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is coded for by the CFTR gene on chromosome 7q31 and spans a genomic region of an estimated 250 kb and contains 27 exons. The CFTR protein functions as a chloride channel, playing a crucial role in ion transport across cell membranes.

The first mutation identified of the CFTR gene was a deletion of three adjacent base pairs on the 508th codon, resulting in the loss of a phenylalanine residue, accounting for 70% of the mutation to CFTR on average. This mutation is also known as ΔF508, preventing the CFTR protein form reaching the epithelial cell membrane. There are over 1300 single gene-mutations that can also result in cystic fibrosis. The defective CFTR protein leads to impaired chloride ion transport, resulting in altered ion and fluid balance in the affected organs.

There are 6 classes of cystic fibrosis, categorized on the basis of the presence of the CFTR protein, the presence of structural and/or functional defects of the protein.

1. Class I CF is when there is a complete absence of the CFTR protein. It is usually detected in newborn children through a positive sweat test. The sweat chloride ions are over 60 millimoles per litre.

2. Class II is the abnormal misfolding of the CFTR protein. It is a processing defect that results in the chloride ions being unable to leave the cell. It also results in a positive sweat test.

3. Class III is when the protein is in normal amounts, but its activation is not there, therefore there is defective regulation of the protein making it non-functional.

4. Class IV is when there are lesser numbers of proteins and the ions cannot move across, conductance is hampered and is non-functional.

5. Class V is when there is a reduced abundance of the protein.

6. Class VI is when the regulation of ion channels is altered.

Early diagnosis of cystic fibrosis is crucial because it allows for prompt intervention and management, which can significantly improve outcomes. Early treatment and ongoing care can help prevent or manage complications, improve lung function, and enhance the quality of life for individuals with CF. Additionally, early diagnosis enables genetic counselling for affected individuals and their families, allowing them to make informed decisions about family planning and prenatal testing.

The sweat test is a commonly used diagnostic test for CF. It measures the amount of chloride ions in sweat, as individuals with cystic fibrosis tend to have elevated levels of chloride due to the dysfunctional CFTR protein. The sweat test is non-invasive and involves collecting a small amount of sweat on the skin and measuring the chloride concentration. Elevated chloride levels provide strong evidence for a cystic fibrosis diagnosis, especially when accompanied by clinical symptoms and genetic testing.

Cystic fibrosis is typically diagnosed in infancy or early childhood. Newborn screening programs have been implemented in many countries, including the United States, to identify cystic fibrosis in the earliest stages of life, although diagnosis requires a combination of clinical evaluation, family history assessment, sweat chloride testing, genetic testing, and imaging studies. However, cystic fibrosis can also be diagnosed in adolescence or adulthood if symptoms are milder or atypical. The severity of cystic fibrosis symptoms can vary widely among affected individuals, even among those with the same mutations.

The diagnosis of cystic fibrosis can sometimes be missed or delayed, especially in individuals with atypical or milder forms of the disease. The National Institutes of Health estimates that about 10% of individuals with cystic fibrosis have atypical or non-classic presentations, which can make diagnosis more challenging. Furthermore, cystic fibrosis may be mistaken for other respiratory conditions, leading to misdiagnosis.

Treatment strategies for cystic fibrosis aim to alleviate symptoms, prevent complications, and improve overall quality of life. They include airway clearance techniques, bronchodilators, antibiotics for infections, pancreatic enzyme replacement therapy, and nutritional supplementation. In recent years, the development of CFTR modulator therapies, such as ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor combinations, has shown remarkable success in targeting specific mutations and improving lung function.

While there is currently no cure for cystic fibrosis, advancements in research and treatment have significantly improved the prognosis and life expectancy for individuals with CF. Ongoing research continues to explore new therapeutic approaches and aims to enhance the understanding of the underlying mechanisms of the disease.

One of the symptoms that I will be exploring further in this research paper is digital clubbing. Digital clubbing is a symptom frequently associated with hypoxia of the fingers, i.e. low oxygen in the blood in the tarsals and metatarsals. This could be seen as an indicator of poor pulmonary function and in cystic fibrosis, indicates a pulmonary blockage, reducing oxygen in the blood.

2. REVIEW OF LITERATURE

A. Finger clubbing in cystic fibrosis

The paper titled "Finger clubbing in cystic fibrosis" by T.J. Pitts-Tucker, M.G. Miller, and J.M. Littlewood explores the phenomenon of finger clubbing in individuals with cystic fibrosis (CF). Finger clubbing refers to the enlargement of the fingertips and thickening of the nail beds [1]. The authors examine the prevalence and significance of finger clubbing in CF patients.

The study finds that finger clubbing is relatively common in CF, with approximately 30% to 40% of patients exhibiting this characteristic [1]. The article discusses various theories regarding the underlying causes of finger clubbing in CF, including inflammation, hypoxia, and genetic factors.

In this study, it was present in 73 patients of the sample of 105, nearly 70% of the sample [1]. Its presence has been associated with poorer prognosis and increased morbidity in CF, including a higher risk of pulmonary exacerbations, decline in lung function, and reduced survival rates. Thus, identifying and understanding the underlying mechanisms of finger clubbing in CF are crucial for optimizing patient care.

The exact pathophysiology of finger clubbing in CF remains unclear. Several hypotheses have been proposed, including inflammation, hypoxia, abnormal growth factor signalling, and genetic factors. Chronic inflammation and recurrent infections in the lungs of CF patients may contribute to the development of finger clubbing through the release of cytokines and growth factors. Additionally, hypoxia-induced vascular changes and abnormalities in the platelet-derived growth factor pathway may also play a role [1].

The presence of finger clubbing in CF patients can aid in the diagnosis and monitoring of the disease. However, it is important to note that finger clubbing is not specific to CF and can be observed in various other conditions, such as pulmonary fibrosis, bronchiectasis, and lung cancer. Therefore, its presence should be interpreted in conjunction with other clinical features and diagnostic tests to differentiate CF-related clubbing from other causes.

According to medical textbook (P. J Mehta), digital clubbing can have causes that relate to various organ systems. Clubbing can have pulmonary causes, cardiac causes, alimentary causes, hormonal causes, as well as other miscellaneous causes.

Currently, there are no specific treatments for finger clubbing in CF. The primary focus remains on managing the underlying CF-related complications, such as pulmonary infections and airway inflammation. Aggressive airway clearance techniques, antibiotic therapy, and anti-inflammatory agents are commonly employed in CF management [1].

Finger clubbing is a clinically significant manifestation in cystic fibrosis. While its exact etiology remains elusive, finger clubbing has been associated with worse outcomes in CF patients. Early recognition and appropriate

management of finger clubbing can contribute to improved patient care and outcomes. Further research is needed to unravel the underlying mechanisms and develop targeted interventions for finger clubbing in CF.

B. Correlation Between Digital Clubbing and Pulmonary Function in Cystic Fibrosis

Digital clubbing, characterized by the bulbous enlargement of the fingertips and nail changes, is a clinical manifestation frequently observed in cystic fibrosis (CF) patients. This literature review aims to provide an overview of the existing research on the correlation between digital clubbing and pulmonary function in CF, highlighting its clinical significance, potential underlying mechanisms, diagnostic implications, and impact on disease management.

The medical textbook by P. J Mehta defines clubbing as the enlargement of the soft part of the end of the nails (the terminal phalanges) in both the horizontal and vertical clubbing of nails. The swelling of the terminal phalanges occurs due to the swelling of the terminal phalanges occur due to swelling (interstitial edema) and dilation of the arterioles and capillaries in the body.

Digital clubbing is considered a significant clinical marker in CF, with a reported prevalence ranging from 15% to 40% among CF patients. It has been associated with more advanced lung disease, decreased pulmonary function, and poorer prognosis. The presence of digital clubbing is often indicative of underlying chronic respiratory inflammation, recurrent infections, and hypoxia, highlighting the importance of understanding its correlation with pulmonary function.

The exact mechanisms linking digital clubbing and pulmonary function in CF are not fully understood [9]. However, several hypotheses have been proposed. Chronic inflammation and infection in the lungs may trigger a cascade of inflammatory mediators, growth factors, and vascular changes, leading to the development of digital clubbing. Hypoxia-induced alterations in the platelet-derived growth factor (PDGF) pathway and abnormalities in bone remodelling have also been suggested as potential contributing factors.

Multiple studies have examined the relationship between digital clubbing and pulmonary function in CF. Findings have indicated a correlation between the presence and severity of digital clubbing and decreased lung function parameters such as forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) [9]. CF patients with digital clubbing tend to have more severe airflow obstruction, reduced gas exchange, and increased respiratory symptoms compared to those without clubbing [9].

Digital clubbing can serve as a useful clinical marker to assess disease severity and monitor disease progression in CF. It may help clinicians identify CF patients at higher risk of pulmonary complications and aid in treatment planning. However, it is important to note that digital clubbing is not specific to CF and can be observed in other conditions such as bronchiectasis and lung cancer. Therefore, its presence should be interpreted in conjunction with other clinical features and diagnostic tests to differentiate CF-related clubbing from other causes.

The presence of digital clubbing in CF patients often signifies more advanced lung disease and may require more aggressive treatment strategies. Aggressive airway clearance techniques, prompt management of respiratory infections, and optimization of CFTR modulator therapies are essential in mitigating disease progression. In severe cases, lung transplantation may be considered.

Digital clubbing is a clinically significant manifestation in cystic fibrosis and is associated with decreased pulmonary function and more severe lung disease. Understanding the correlation between digital clubbing and pulmonary function can aid in disease assessment, treatment planning, and monitoring of CF patients. Further research is warranted to elucidate the underlying mechanisms and explore potential interventions to prevent or mitigate the development of digital clubbing and its impact on pulmonary function in CF.

The correlation of clubbing with age is a notable aspect to consider in understanding its implications. Typically, babies and children diagnosed with cystic fibrosis do not exhibit clubbing unless their lung function faces significant limitations. However, as individuals transition into their teenage years and adulthood, those with CF tend to experience clubbing more frequently, particularly during exacerbations or as their lung function progressively deteriorates. This correlation between clubbing and age highlights its potential role as an indicator of disease

severity and progression. Furthermore, assessing the presence of clubbing could also serve as a valuable tool in evaluating the effectiveness of treatment regimens, providing insights into the overall management of cystic fibrosis.

Table 1: CORRELATION WITH CHLORIDE IONS [10]

Result	Age <6 months (mEq/L Cl^-)	Age >6 months (mEq/L Cl^-)
Positive	≥60	≥60
Intermediate	30–59	40–59
Normal (CF unlikely)	<30	<40

(De Boeck et al. 2006; Farrell et al. 2008; Borowitz et al. 2009)

In summary, the determination of cystic fibrosis presence hinges on the concentration level: a reading surpassing 60 indicates a positive confirmation, reinforcing the diagnosis. This aligns with a genetic classification of class 1. Meanwhile, concentration levels ranging from 40 to 59 signify an intermediate range, potentially falling within genetic classifications of class 2, class 3, or class 4. This phase is marked by heightened susceptibility to pulmonary complications. Notably, within this range, clubbing manifestations spanning from grade 2 to grade 5 can be identified, offering a visible marker of disease progression and severity.

C. Correlation of Sweat Chloride Concentration with Classes of the Cystic Fibrosis Transmembrane Conductance Regulator Gene Mutations

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Sweat chloride concentration is a key diagnostic parameter for CF, as elevated levels indicate impaired chloride transport due to CFTR dysfunction. This literature review aims to explore the correlation between sweat chloride concentration and different classes of CFTR gene mutations, highlighting its diagnostic implications, genotype-phenotype relationships, and potential limitations.

Measurement of sweat chloride concentration using the pilocarpine iontophoresis test has been widely adopted as a diagnostic tool for CF. Elevated sweat chloride levels (>60 mmol/L) are typically indicative of CF. However, it has been observed that sweat chloride concentrations can vary within the CF population, with some patients having intermediate or borderline levels. Understanding the correlation between sweat chloride concentration and CFTR gene mutations can help improve the accuracy of CF diagnosis, particularly in cases with atypical clinical presentations.

The CFTR gene mutations are categorized into different classes based on their impact on CFTR protein function. Class I and II mutations lead to defective CFTR protein production or trafficking, resulting in severe CF phenotypes. Patients with these mutations often exhibit high sweat chloride concentrations. In contrast, class III mutations, known as gating mutations, impair chloride channel regulation but do not entirely abolish CFTR function. These individuals typically have lower sweat chloride concentrations, which may overlap with the normal range. Classes IV and V mutations affect CFTR protein conductance and abundance, respectively, and can result in variable sweat chloride levels. Finally, class VI mutations affect CFTR protein stability and may contribute to intermediate sweat chloride concentrations.

While the correlation between sweat chloride concentration and CFTR gene mutations is valuable for CF diagnosis and genotype-phenotype relationships, it is important to acknowledge its limitations. Some individuals with CF may have atypical clinical presentations and normal sweat chloride levels, known as "sweat chloride borderline" cases. Additionally, factors such as age, hydration status, concurrent medications, and assay variability can influence sweat chloride measurements, introducing potential sources of variability and false-positive or false-negative results.

Sweat chloride concentration remains an essential diagnostic tool for CF, particularly in combination with genetic testing. Advances in CFTR functional assays and next-generation sequencing have expanded our understanding of the correlation between specific CFTR gene mutations and sweat chloride levels. This knowledge has facilitated the development of CFTR modulator therapies targeting specific mutation classes. Further research is needed to refine diagnostic algorithms, investigate the impact of rare CFTR variants on sweat chloride concentration, and explore potential modifiers that may influence the genotype-phenotype correlation.

The correlation between sweat chloride concentration and CFTR gene mutations plays a crucial role in the diagnosis and management of CF. Understanding the relationship between specific mutation classes and sweat chloride levels aids in accurate diagnosis, genotype-phenotype predictions, and treatment selection. Ongoing research efforts aim to improve the diagnostic utility of sweat chloride testing, address limitations, and advance personalized therapeutic interventions for individuals with CF.

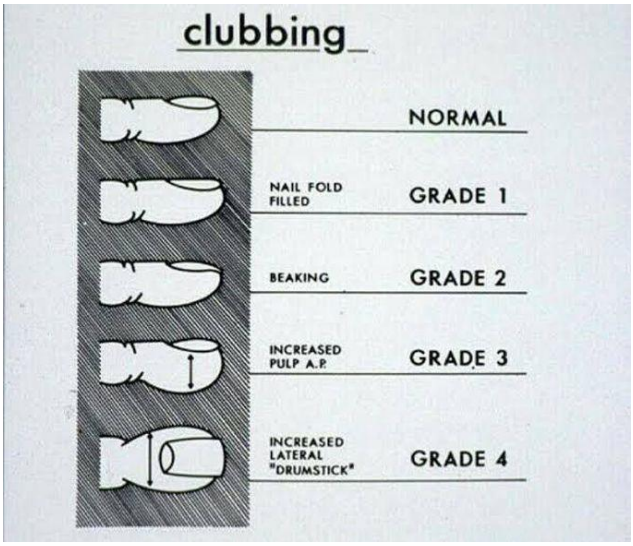

Figure 1. THE 4 GRADES OF DIGITAL CLUBBING [11]

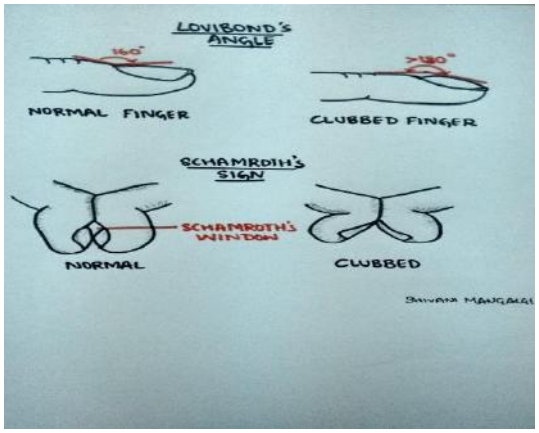

Figure 2. LOVIBOND'S ANGLE AND THE SCHAMROTH'S SIGN [12]

Figure I shows the various grades of clubbing and the symptoms commonly associated with it. Figure II shows the two common methods used to test for digital clubbing, Lovibond's angle and the Schamroth's window test.

Table 2: SYMPTOMS OF DIGITAL CLUBBING AS A POSSIBLE PREDICTOR FOR THE CLASS OF CYSTIC FIBROSIS

Grade of Digital Clubbing	Symptoms of Digital Clubbing	Possible Class of Cystic Fibrosis
1	Fluctuation and softening of nail-beds	6
2	Obliteration of the onychodermal angle (>160º)	5
3	Accentuated convexity of nail	3,4
4	Clubbed appearance of the fingertip	2
5	Development of a shiny or glossy change in nail and adjacent skin with longitudinal striations	1

3. DIAGNOSTIC APPLICATION

A. Rationale behind creation of application

An application was created with the purpose of helping us in the diagnosis of cystic fibrosis by using digital clubbing, a common symptom, as a benchmark. The application uses images from patients in order to calculate the angle between their fingers, based on the Lovibond angle, which indicates the grade of clubbing.

So, if clubbing is present which is evident through a digital device, and if the patient is not responding to the regular line of treatment for 3 to 4 months for bronchial asthma, sinusitis, then the physician can straightaway send the patient for investigations of cystic fibrosis. This angle can then be correlated to the class of cystic fibrosis if the patient has a history of it.

The proposed application enables direct measurement and grading of clubbing angle by physicians. For confirmed cystic fibrosis cases, it aids treatment assessment through bi-monthly angle measurements, reflecting treatment effectiveness. Reversibility is indicated by an angle shift from obtuse to acute (<180 degrees).

The tool facilitates periodic nail image capture, angle measurement, and treatment effectiveness grading in follow-ups. In new cases, detected clubbing helps determine severity (grade 3 or 4). Positive family history prompts referrals for clinical tests like chloride ion or sweat tests.

While the application presents a promising avenue for diagnosing cystic fibrosis through digital clubbing assessment, it is important to acknowledge its limitations. One notable constraint arises from the limited research available to definitively establish a precise correlation between the Lovibond angles, used to determine the grade of digital clubbing, and the severity or progression of the condition. This lack of extensive empirical evidence may potentially impact the application's accuracy in grading clubbing severity solely based on these angles. Further comprehensive research is needed to solidify this relationship and enhance the application's reliability in clinical settings.

In light of the current scarcity of well-established correlations between Lovibond angles and clubbing grades, caution is advised when interpreting the application's results. Until more robust scientific evidence is gathered, a nuanced understanding of its limitations is essential for accurate diagnosis and informed clinical decision-making.

4. MOTIVATION AND NOVELTY

Cystic fibrosis is a complex genetic disorder that affects many individuals worldwide. It primarily impacts the respiratory and digestive systems, causing difficulties in breathing and digestion. One intriguing symptom often associated with CF is digital clubbing, a condition characterized by the abnormal enlargement and rounding of fingertips. While previous research has explored the relationship between CF and digital clubbing, the underlying mechanisms remain largely unknown. By delving into this fascinating topic, I aim to shed light on the association between CF and digital clubbing. The study not only aims to deepen our understanding of the disease but also holds the potential for earlier detection and improved management of cystic fibrosis.

This research endeavour represents a novel approach to unravelling the intricate connections between cystic fibrosis and digital clubbing. By focusing on the interplay between these factors, the study aims to contribute new insights into the underlying mechanisms of CF-related complications. While previous investigations have primarily examined each aspect in isolation, my research takes a comprehensive and integrated approach. Furthermore, we will explore the potential diagnostic value of digital clubbing along with the sweat chloride test, with the hope of developing non-invasive methods for early detection and monitoring of CF-related complications. By addressing these research gaps, we aspire to pave the way for improved clinical management and enhanced quality of life for individuals living with cystic fibrosis.

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