GLUCOSE TOLERANCE STATUS IN INFANTS AND CHILDREN WITH CYSTIC FIBROSIS AND ITS RELATION TO PULMONARY EXACERBATIONS

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ABSTRACT:

Background*: Cystic fibrosis (CF) patients experience a notable increase in illness severity and death rates due to pulmonary exacerbations. Nevertheless, there is a scarcity of data regarding the parameters linked to the severity of exacerbations.*

Aim of the work: *In this study, our objective was to assess the influence of glucose tolerance on the frequency and severity of pulmonary exacerbations.*

Patients and Methods: *The study was a cross-sectional analysis of 25 patients with cystic fibrosis (CF) aged 1–17 years. The study took place at the pediatric pulmonology clinic in the Children's Hospital from July 1, 2021, to July 31, 2022. The oral glucose tolerance test (OGTT) was employed to ascertain the individual's glucose tolerance level. The patients were categorized based on their OGTT findings into two groups: CF patients with normal glucose tolerance and CF patients with abnormal glucose tolerance. The study documented the pulmonary exacerbations that occurred in the patients over the past year and examined how they were linked to their glucose tolerance status.*

Results: *Our research revealed that 7 (28%) of the patients included in the study exhibited impaired glucose tolerance. This condition was notably more prevalent among older children in comparison to newborns and young children with CF. Pseudomonas infection was identified in 71.4% of cystic fibrosis patients with poor glucose tolerance. Furthermore, a notable association was observed between the occurrence of pulmonary exacerbations and the blood glucose level (p = 0.011).*

Conclusions: *The present investigation revealed that impaired glucose tolerance is prevalent among the examined CF patients. Our findings indicate a strong correlation between impaired glucose tolerance and elevated rates of pseudomonas colonization, as well as an augmented likelihood of experiencing pulmonary exacerbations.*

Keywords: *Cystic fibrosis, children, exacerbations, glucose tolerance, infants*

INTRODUCTION:

Cystic fibrosis (CF) is a debilitating genetic disorder that is inherited in an autosomal recessive manner. On the long arm of chromosome 7[(1)], the cystic fibrosis transmembrane conductance regulator (CFTR) gene is where the mutations occur. Cystic fibrosis is characterized by pancreatic failure, which leads to exocrine dysfunction in 85% of patients and endocrine

dysfunction that ranges from impaired glucose tolerance (IGT) in 8–50% of CF patients to overt cystic fibrosis-related diabetes (CFRD) in 6–10% of patients. The prevalence of impaired glucose tolerance is high among children below the age of 10, with 40% of children aged 6 to 10 with cystic fibrosis being affected, especially those with severe mutations (class 1-3). Remarkably, approximately 5% of children aged five and below are affected by CFRD [(2)].

Individuals with cystic fibrosis who have impaired glucose tolerance (IGT) may not show any symptoms for extended periods. However, they may also exhibit clinical manifestations such as unexplained excessive urination or thirst, an inability to gain or sustain weight despite nutritional measures, deterioration in lung function, and a higher occurrence and seriousness of respiratory infections. Therefore, it is crucial to identify and treat glucose metabolism problems promptly and with a proactive approach in order to enhance life expectancy [(3)].

The significance of promptly identifying impaired glucose tolerance in CF is evident, as it is associated with clinical deterioration and heightened mortality. The conventional oral glucose tolerance test (OGTT) is considered the optimal method for identifying aberrant glucose tolerance in the pre-diabetic stage, and it remains the preferred test for diagnosing CFRD [(4)].

Cystic fibrosis (CF) exacerbations refer to episodes of abrupt worsening triggered by infection and marked by a rise in respiratory symptoms. These factors are associated with decreased quality of life and higher rates of death, hospitalization, and healthcare expenses. Moreover, pulmonary exacerbate-ions can be linked to both reduced glucose tolerance and lung function [(5)].

There is data suggesting that treatment can be beneficial for individuals with CF even prior to the development of CFRD. Initiating insulin therapy at an early stage enhances pulmonary function and reduces the incidence of acute respiratory infections [(6)]

AIM OF THE WORK:

our objective was to assess the influence of glucose tolerance on the frequency and severity of pulmonary exacerbations.

Study design:

This cross-sectional study was undertaken at the pediatric pulmonology clinic at the Children's Hospital from July 1, 2021, to July 31, 2022. The study sample was selected based on certain inclusion and exclusion criteria, making it convenient for the investigation.

Participants in the study:

The current investigation comprises a cohort of 25 pediatric patients diagnosed with cystic fibrosis. In order to be included, the patients needed to have a confirmed diagnosis of CF. They received this diagnosis either because their clinical symptoms were consistent with CF or because they had a family history of CF and evidence of abnormal CFTR function. This evidence could be shown through elevated sweat chloride tests on two different occasions or the identification of two CF-causing CFTR mutations [(7)]. The study included children between the ages of 1 and 17 who were diagnosed with cystic fibrosis. Patients with cystic fibrosis-related diabetes or other conditions that could influence their glucose tolerance were excluded from the study.

Every patient was extended an invitation to partake, and explicit agreement was acquired from both parents and children above the age of 8 before their inclusion in the study.

Data analysis refers to the process of examining and interpreting data in order to uncover patterns, trends, and insights.

All patients enrolled in this trial underwent a comprehensive medical assess-

ment, which included gathering demographic information, determining the age at which symptoms first appeared, assessing the duration of the condition, and evaluating symptoms related to impaired glucose tolerance, /or CFRD[8]. Measurements of clinical parameters and anthropometric characteristics were obtained, including weight (in kilograms), height (in centimeters), and body mass index (BMI). Subsequently, the data was documented based on Z scores.

The study documented data on the frequency and severity of pulmonary exacerbations, including the requirement for hospitalization, the length of hospital stay during exacerbations, sputum microbiology, and the kind and frequency of oral and intravenous antibiotics used in the last year. A pulmonary exacerbation was identified using Fuchs criteria specifically designed for patients with cystic fibrosis (CF). Pulmonary exacerbations (PEs) were then categorized as mild to severe based on the intensity of the respiratory symptoms and indications. Mild cystic fibrosis (CF) pulmonary exacerbations were defined as clinical events that were treated without hospitalization or as one-time events that did not develop into a clear lower respiratory tract condition. Moderate pulmonary embolisms (PEs) were defined as cases that needed to be hospitalized and antibiotics were given through an IV based on the patient's medical condition and microbiology of the sputum. Severe pulmonary embolism (PE) was characterized as those with oxygen saturation levels below 90% or necessitating admission to an intensive care unit (ICU)[9].

PATIENTS AND METHODS:

All CF patients included in the study performed an oral glucose tolerance test. The study participants were then categorized into two groups based on their glucose tolerance status: CF patients with normal glucose tolerance and CF patients with abnormal glucose tolerance. Demographic information and the frequency and severity of pulmonary exacerbations were compared in both groups of patients.

1. The oral glucose tolerance test was conducted on the Beckman Coulter Au 480 autoanalyzer using Beckman kits. The task was finished after abstaining from food overnight. The duration of fasting was decided based on the individual's weight. An oral dose of 1.75 grams per kilogram of glucose (with a maximum of 75 grams) was administered, and blood glucose levels were assessed at 0, 30, 60, 90, and 120 minutes. The test findings were interpreted as follows: A fasting blood glucose level below 100 mg/d (5.6 mmol/L) and a 120-minute blood glucose level below 140 mg/dl (7.8 mmol/L) are considered indicative of normal glucose tolerance. A fasting blood glucose level below 126 mg/dl (7 mmol/L) and a 120-minute blood glucose level between 140 mg/dl (7.8 mmol/L) and 200 mg/dl (11.1 mmol/L) are indicators of impaired glucose tolerance (IGT). CFRD is diagnosed when the fasting blood glucose level is 126 mg/dl (7 mmol/L) or higher, and/or the blood glucose level 120 minutes after a meal is 200 mg/dl (11.1 mmol/L) or higher[10]. Furthermore, the hemoglobin A1c level was assessed and interpreted as follows[11]: Normal values are 5.7%; levels between 5.7 and 6.4% indicate prediabetes, whereas values above 6.4% indicate diabetes.
2. Serum insulin assay was done using *Roche Diagnostics kit by Cobas e 411 analyzer. Serum insulin was measured at fasting, 30 mins, 60 mins, 90 mins and 120 mins. Insulin sensitivity index was calculated using QUICKI formula that comes from Quantitative Insulin Sensitivity Check Index which is a determination based on fasting insulin and

glucose levels obtained from blood sample. The two variables can be input in uU/mL (for insulin) and mg/dL or mmol/L (for glucose). The QUICKI formula is the inverse of the sum of the logarithms of fasting insulin and fasting glucose: QUICKI = 1 / (log (Fasting Insulin) + log (Fasting Glucose).

3. Serum C peptide was done using *Roche Diagnostics kit by Cobas e 411 analyzer. Serum C peptide was measured at fasting and 120 mins. *(*Roche Diagnostics Gmbh, Sandhofer Strasse 116, D-68305 Mannheim)*

4. Fecal elastase concentration was determined with a commercially available ELISA kit (Schebo-Tech, Wetten-berg, Germany) that uses two monoclonal antibodies against different specific epitopes of human pancreatic elastase. The intra- and inter assay variations were 5.8% and 7.7% respectively. Fecal elastase concentration ≥ 200 mcg/g indicates pancreatic sufficiency and <200 mcg/g defines pancreatic insufficiency which was categorized in to mild pancreatic insufficiency if fecal elastase from 100 – 200 mcg/g, moderate pancreatic insufficiency if fecal elastase from 50 – 100 mcg/g and severe pancreatic insufficiency if fecal elastase less than 50 mcg/g.

5. Sweat chloride test: It was performed using the Nanoduct system (Wescor Inc., Logan, Utah, USA) to confirm CF diagnosis. The results were considered normal if values were between 3 - 60 mmol/L (equivalent NaCl) and intermediate if values were between 61 - 80 mmol/L. CF was very likely if the results were equal to or above 80 mmol/L based on the user's manual. The minimum reading value was 3 mmol/L.

Microbiological analysis of respiratory secretions:

Ten sputum samples were taken through expectoration, accounting for 40% of the total. Another ten samples were obtained through sputum induction, also representing 40% of the total. The other five samples were acquired through bronchoalveolar lavage, making up 20% of the total. The specimens underwent processing for the cultivation of bacterial pathogens using established microbiological procedures. the specimens were inoculated on blood agar, chocolate agar, and MacConkey agar. These samples were cultivated at 37 °C in an aerobic chamber for 48 hours. Pathogens were identified and susceptibility testing was performed.

Pulmonary function tests:

Spirometry was utilized to conduct pulmonary function testing for children aged 5 years and older who were cooperative. The examination technique adhered to the guidelines set forth by the American Thoracic Society (ATS) regulations. The acquired variables include FVC (forced vital capacity) measured in liters and % expected, FEV1 (forced expiratory volume in one second) measured in liters and % predicted, and FEV1/FVC%. The forced expiratory flow between 25% and 75% of the expired volumes is referred to as FEF25–75. The findings were analyzed in accordance with the ATS Guidelines [(12)].

Scoring the severity of bronchiectasis:

The bronchiectasis severity index score (BSI) was employed to evaluate the severity of bronchiectasis in all subjects included in the study. The combination comprises clinical, radiological, and microbiological characteristics. This score encompassed nine distinct criteria. The aggregate score, which spans from 0 to 26 points, was computed by summing the values for each variable. Patients are categorized into three cohorts according to their total score: individuals with a low BSI score (0–4 points), those with an intermediate BSI score (5-8 points), and those with a high BSI score (9 points) [(13)].

Quantitative study of data using statistical methods:

The data were gathered, reviewed, categorized, and inputted into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were reported using measures of central tendency such as mean, standard deviations, and ranges for parametric data and median and inter-quartile range (IQR) for non-parametric data. In addition, numerical and percentage representations were used to portray qualitative characteristics. The chi-square test was employed to compare groups in terms of qualitative data. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent t-test while with non-parametric distribution were done by using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two parameters in the same group. A multiple linear regression analysis was conducted to determine the parameter that best predicts the total frequency of pulmonary exacerbations. P values below 0.05 were deemed statistically significant, whereas P values below 0.01 were regarded as extremely significant.

Ethical consideration:

The study protocol underwent a thorough evaluation and received permission from the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (reference number: FMASU M S 345/2019).

RESULTS:

A cross-sectional study was performed on a cohort of 25 individuals diagnosed with cystic fibrosis, ranging in age from 1 to 17 years. The population under study was divided into two subgroups based on the results of an oral glucose tolerance test: CF patients with normal glucose tolerance (n = 18) and CF patients with impaired glucose tolerance (n = 7).

Characteristics of the patient:

The patients under investigation consisted of 18 (72%) males and 7 (28%) females. There was a significant statistical difference between patients who had a normal glucose tolerance test (NGTT) and those who had an abnormal glucose tolerance test (AGTT) in terms of age and duration of disease. The median values for age and duration of disease were higher among patients with AGTT (10–16), 10 (8–16), and 4 (2–6) compared to patients with NGTT (4–6), respectively. The P values for these differences were 0.001 and 0.002, respectively. Furthermore, individuals with AGTT had a higher prevalence of dyspnea (71.4%) and constipation (71.4%) compared to patients with NGTT (27.8%, 16.7%) (P values = 0.045, 0.008), respectively. Furthermore, individuals with AGTT had a substantially higher bronchiectasis severity index score (12.43 ± 4.79) compared to patients with NGTT (8.22 ± 4.07) (P value = 0.037). The patient features and clinical data are outlined in Table (1).

Characteristics of pulmonary exacerbations:

Table (2) demonstrates a significant statistical distinction between patients with NGTT and AGTT in terms of sputum microbiology during exacerbations. Pseudomonas colonization was shown to be more common among patients with AGTT (71.4%) compared to those with NGTT (5.6%) (P value = 0.001).

Although there was no statistically significant difference in the frequency and severity of pulmonary exacerbations between patients with NGTT and AGTT, patients with AGTT had a higher average number of pulmonary exacerbations (6.71 ± 3.15) compared to patients with NGTT (4.50 ± 3.27). Additionally, patients with AGTT tended to have a higher number of moderate to severe pulmonary exacerbations (1.7 ± 0.86) compared to patients with NGTT (1.2 ± 1.8) (P values = 0.139, 0.231, 0.295).

Table 1: Demographic and anthropometric data among the studied patients:

Variables	Glucose tolerance test		Test value	P-value
	Normal glucose tolerance	Abnormal glucose tolerance		
	No. = 18	No. = 7		
Age (Years)				
Median (IQR)	4 (2 - 6)	10 (9 - 16)	-3.301‡	0.001***
Range	1 - 15	8 - 17		
Sex				
Male	14 (77.8%)	4 (57.1%)	1.064*	0.302
Female	4 (22.2%)	3 (42.9%)		
Paternal consanguinity (%)	11 (61.1%)	4 (57.1%)	0.033*	0.856
Family history of cystic fibrosis (%)	8 (44.4%)	3 (42.9%)	0.005*	0.943
Age of symptoms onset (months)				
Median (IQR)	2 (1 - 4)	3 (2 - 6)	-1.115‡	0.265
Range	1 - 7	2 - 30		
Duration of disease (years)				
Median (IQR)	4 (2 - 6)	10 (8 - 16)	-3.087‡	0.002***
Range	1 - 15	6 - 16		
Body mass index (kg/m2)				
Mean ± SD	16.39 ± 2.03	17.71 ± 3.25	-1.234•	0.230
Range	13 - 21	12 - 21		
Cough				
Productive cough	12 (66.7%)	7 (100.0%)	3.070*	0.080
Dry cough	6 (33.3%)	0 (0.0%)		
Dyspnea	5 (27.8%)	5 (71.4%)	4.001*	0.045**
Constipation	3(16.7%)	5 (71.4%)	6.946*	0.008***

P**: Significant; P ***: highly significant; *: Chi-square test; •: Independent t-test; ‡: Mann Whitney test

Table 2: Pulmonary exacerbations characteristics among the studied patients' groups

Variables	Glucose tolerance test		Test value ‡	P-value
	Normal glucose tolerance	Abnormal glucose tolerance		
	No. = 18	No. = 7		
Frequency of pulmonary exacerbations			1.533	0.139
Mean ±SD	4.50 ± 3.27	6.71 ± 3.15		
Range	0 – 11	3- 12		
Mild	38 (46.9%)	23 (48.9%)	0.049	0.824
Moderate	41 (50.6%)	22 (46.8%)	0.173	0.677
Severe	2 (2.5%)	2 (4.3%)	0.313	0.575
Severity of pulmonary exacerbations				
Mild				
Mean ±SD	2.11 ± 1.67	3.28 ±1.79	-1.479	0.139
Range	0 - 6	1 - 6		
Moderate				
Mean ±SD	2.28 ± 1.84	3.14 ± 1.22	-1.199	0.231
Range	0 - 6	2 - 5		
Severe				
Mean ±SD	0.11 ± 0.32	0.29 ±0.49	1.048	0.295
Range	0 - 1	0 - 1		
Duration of hospital stay (days)				
Median (IQR)	10 (7 - 15)	7 (3 - 10)	-1.131	0.258
Range	5 - 26	3 - 45		
pseudomonas colonization	1(5.6%)	5(71.4%)	11.990	0.001**
Use of intravenous antibiotics in the last year	14 (77.8%)	7 (100.0%)	1.852	0.174

P *: Significant; P **: highly significant; ‡: Mann Whitney test

Results of pulmonary function tests:

Table (3) demonstrates that there was no statistically significant disparity in lung function test outcomes between patients with NGTT and AGTT. Nevertheless, individuals with AGTT exhibit a higher occurrence of mild obstructive patterns (50.0%) compared to patients with NGTT (25.0%), but this disparity does not have statistical significance (P value = 0.635).

Table 3: Pulmonary function test results among the studied patients.

Pulmonary function test parameters	Glucose tolerance test		Test value•	P-value
	Normal glucose tolerance	Abnormal glucose tolerance		
	No. = 8	No. = 6		
Forced expiratory volume 1% of predicted				
Mean ± SD	76.33 ± 17.24	80.83 ± 14.25	-0.420	0.687
Range	61 - 95	66 - 103		
Forced vital capacity% of predicted				
Mean ± SD	92.00 ± 13.89	99.17 ± 9.54	-0.925	0.386
Range	76 - 101	90 - 117		
Forced expiratory volume 1 / Forced vital capacity				
Mean ± SD	82.33 ± 12.06	82.17 ± 11.53	0.020	0.984
Range	71 - 95	72 - 104		
Pulmonary function test results				
Normal	4(50.0%)	1 (16.7%)	0.321	0.571
Mild obstructive pattern	0 (0.0%)	2 (33.3%)	1.286	0.256
Moderate obstructive pattern	2 (25.0.%)	3 (50.0%)	0.225	0.635
Mixed obstructive and restrictive pattern	2 (25.0%)	0 (0.0%)	2.250	0.133

P *: Significant; P **: highly significant; •: Independent t-test

Statistical analysis of glucose tolerance test results and serum insulin levels among the studied patients' groups were shown on Table (4) which demonstrates that there was statistically significant difference in Oral glucose tolerance test levels at fasting, 30,60,90,120 minutes between patients with NGTT and AGTT. While levels of insulin show only significant difference at 90 min and c peptide results show only significant difference at 120 min.

Table 4: Statistical analysis of glucose tolerance test results and serum insulin levels among the studied patients' groups.

		Glucose tolerance test		Test value	P-value
		Normal glucose tolerance	Abnormal glucose tolerance		
		No. = 18	No. = 7		
Oral glucose tolerance test					
Fasting (mg/dl)	Mean ± SD	84.78 ± 11.25	101.71 ± 18.63	-2.802•	0.010**
	Range	65 – 118	84 – 131		
30 MIN (mg/dl)	Mean ± SD	126.50 ± 20.95	202.57 ± 29.74	-7.249•	0.000***
	Range	97 – 172	142 – 231		
60 MIN (mg/dl)	Mean ± SD	120.89 ± 30.34	244.00 ± 44.03	-8.024•	0.000***
	Range	89 – 196	206 – 306		
90 MIN (mg/dl)	Mean ± SD	102.06 ± 34.62	184.00 ± 108.39	-2.927•	0.008***
	Range	57 – 188	63 – 323		
120 MIN (mg/dl)	Mean ± SD	99.39 ± 22.72	156.86 ± 105.38	-2.253•	0.034**
	Range	66 – 144	55 – 289		
Interpretation	NGT	18 (100.0%)	0 (0.0%)	25.000*	0.000***
	IGT	0 (0.0%)	0 (0.0%)		
	INDET	0 (0.0%)	4 (57.1%)		
	CFRD FH-	0 (0.0%)	2 (28.6%)		

	CFRD FH+	0 (0.0%)	1 (14.3%)		
Serum Insulin (uIU/ml)					
Fasting (mIU/ml)	Median (IQR)	6 (4 – 7)	6 (1 – 13)	-0.154‡	0.878
	Range	0 – 14	0 – 15		
30 MIN (mIU/ml)	Median (IQR)	12 (5 – 20)	8 (6 – 28)	-0.030‡	0.976
	Range	1 – 35	6 – 60		
60 MIN (mIU/ml)	Median (IQR)	13 (6 – 22)	18 (8 – 92)	-1.334‡	0.182
	Range	1 – 63	7 – 98		
90 MIN (mIU/ml)	Median (IQR)	11 (6 – 15)	33 (24 – 40)	-2.886‡	0.004***
	Range	1 – 25	5 – 69		
120 MIN (mIU/ml)	Median (IQR)	7 (6 – 14)	14 (5 – 24)	-0.698‡	0.485
	Range	2 – 88	1 – 31		
Insulin sensitivity index	Mean ± SD	0.41 ± 0.08	0.41 ± 0.11	0.000•	1.000
	Range	0.33 – 0.61	0.31 – 0.59		
Serum C-peptide (ng/ml)					
Fasting (ng/ml)	Median (IQR)	1.05 (1 – 1.5)	1.6 (1.1 – 2)	-1.614‡	0.106
	Range	1 – 5.6	1.1 – 3.1		
120 MIN (ng/ml)	Median (IQR)	1.4 (1.2 – 2.6)	3.9 (1.8 – 7.5)	-2.308‡	0.021**
	Range	1.1 – 6.3	1.4 – 11.2		

P**: Significant; P ***: highly significant; *Chi-square test; •: Independent t-test; ‡: Mann Whitney test
NGT: normal glucose tolerance, IGT: impaired glucose tolerance, INDET: indeterminate glycaemia,
CFRD FH-: Cystic fibrosis related diabetes with negative fasting hyperglycemia.
CFRD FH+; Cystic fibrosis related diabetes with positive fasting hyperglycemia.

Table (5) showed Statistical analysis of sweat chloride test and fecal elastase results among the studied patients' groups that demonstrates that there was no statistically significant disparity in both tests outcomes between patients with NGTT and AGTT.

Factors that can be used to anticipate or forecast the occurrence of numerous episodes of worsening lung inflammation.

Table 5: Statistical analysis of sweat chloride test and fecal elastase results among the studied patients' groups.

		Glucose tolerance test		Test value	P-value	Sig.
		Normal glucose tolerance	Abnormal glucose tolerance			
		No. = 18	No. = 7			
Sweat chloride test (meq/L)	Mean ± SD	106.78 ± 26.91	120.57 ± 13.55	-1.282•	0.213	NS
	Range	30 – 153	99 – 136			
Sweat chloride test interpretation	(<60) negative	1 (5.6%)	0 (0.0%)	0.845*	0.655	NS
	(60 - 80) border line	1 (5.6%)	0 (0.0%)			
	(> 80) positive	16 (88.9%)	7 (100.0%)			
Fecal elastase (mcg/g)	(normal)more than 200	2 (11.1%)	0 (0.0%)	7.432*	0.059	NS
	(mild deficiency)100 – 200	3 (16.7%)	0 (0.0%)			
	(moderate deficiency)50- 100	10 (55.6%)	2 (28.6%)			
	(severe deficiency) less than 50	3 (16.7%)	5 (71.4%)			

P-value >0.05: non-significant; *: Chi-square test; •: Independent t-test

Significant positive correlations were observed between the total frequency of pulmonary exacerbations and age ($p = 0.014$), duration of disease ($p = 0.020$), number of hospital admissions in the last year ($p < 0.001$), 2 hours of serum glucose ($p = 0.011$), and bronchiectasis severity index ($p < 0.001$). Conversely, a negative correlation was found between frequent pulmonary exacerbations and oxygen saturation ($p = 0.006$). No significant statistical connections were seen between the frequency of pulmonary exacerbations and the other factors examined.

The aforementioned data is displayed in Table (6).

Table 6: Correlations between the frequency of pulmonary exacerbations in the last year and the other studied parameters.

Variables	Frequency of pulmonary exacerbations	
	r	p-value
Age (Years)	0.484	0.014*
Duration of disease (years)	0.461	0.020*
Number of hospital admissions in the last year	0.913	<0.001**
Duration of hospital stay (days)	0.564	0.010*
Oxygen saturation	-0.531	0.006**
Body mass index (kg/m2)	-0.034	0.870
Fasting serum glucose	-0.318	0.122
Serum glucose 30 minutes (mg/dl)	0.202	0.332
Serum glucose 60 minutes (mg/dl)	0.359	0.078
Serum glucose 90 minutes (mg/dl)	0.253	0.222
Serum glucose 120 minutes (mg/dl)	0.500	0.011*
Forced expiratory volume 1	-0.244	0.527
Forced vital capacity	-0.094	0.810
Forced expiratory volume 1 / forced vital capacity	0.000	1.000
Bronchiectasis severity index	0.661	<0.001**

P *: Significant; P **: highly significant

The results of a multivariate linear regression analysis indicate that the variable with the strongest association with the overall frequency of pulmonary exacerbations is a greater bronchiectasis severity index, with a statistically significant P value of 0.007, as presented in Table (7).

Table 7: Multiple linear regression analysis using total frequency of pulmonary exacerbations as a dependent variable to identify the most predictor parameter.

Total frequency of pulmonary exacerbations	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	S.E	Beta		
(Constant)	-37.783	9.880		-3.824	0.012
Bhallah score	1.484	0.395	1.933	3.758	0.013
Bronchiectasis Severity Score	0.986	0.228	1.438	4.334	0.007

t: independent t-test

DISCUSSION:

Individuals diagnosed with cystic fibrosis and pancreatic insufficiency exhibit a fear or aversion towards insulin and are susceptible to experiencing impaired glucose tolerance (IGT) and CF-related diabetes (CFRD). The existence of these concurrent medical conditions has been demonstrated to have a substantial effect on the occurrence of disease and death in CF[(14)]. The present study aimed to determine the correlation between glucose tolerance and the incidence rate of pulmonary exacerbations in infants and children diagnosed with cystic fibrosis.

The study found that AGTT was present in 28% of the CF patients examined. This was particularly noticeable in the older age group (10 years, with a range of 9–16 years) compared to the younger age group (4 years, with a range of 2–6 years) (p = 0.001).

Consistent with our research findings, Olesen et al. [(15)] documented that individuals with CF have a heightened susceptibility to CFRD as they age.

Granados et al. [16] also noted that CFRD becomes more common as individuals with CF get older, and it affects a considerable fraction of the CF population. Additionally, they found that lesser impairments in glucose tolerance are even more widespread.

In contrast to our findings, Prinz et al.[17] observed that 5.6% of CF patients aged 10 years had reported impairments in glucose tolerance. In addition, Yi et al. (10) found that 5% of their cystic fibrosis (CF) group, consisting of individuals between 6 months and 5 years old, developed cystic fibrosis-related diabetes (CFRD).

The observed results can be attributed to the gradual decline in pancreatic function as individuals age, leading to pancreatic insufficiency. This condition affects the endocrine function of the pancreas and the release of insulin, ultimately causing impaired glucose tolerance [18].

The findings of our study indicate that CF patients with AGTT experienced a considerably greater level of respiratory distress compared to those with NGTT.

The results of our study align with the findings of Ikäheimo et al., [19], indicating that dyspnea is more prevalent among CF patients with diabetes compared to those with normal glucose tolerance.

In a similar vein, Kocaaa et al.,[20] discovered that the CF group with defective glucose tolerance exhibited notably elevated levels of dyspnea, resting and exercise heart rate, and fatigue perception compared to the CF group with normal glucose tolerance.

The results could be because people with poor glucose tolerance are more likely to have bacteria colonize their respiratory system because their mucociliary clearance is worse and their ion transport is messed up. These infections elicit a profound inflammatory reaction in the pulmonary region. Moreover, persistent infection and recurrent inflammatory reactions can result in airway deterioration [21].

Constipation was observed to be more prevalent in individuals with AGTT (71.4%) compared to patients with NGTT (16.7%) in the present study. The results of our research align with those of a prior investigation [22], which observed a higher prevalence of constipation as a gastrointestinal symptom in individuals with a longer duration of diabetes or inadequate diabetes management.

It's possible that the results were caused by CFRD making gastrointestinal dysfunction worse. The thicker mucus discharges in the digestive tract could cause diseases that block or plug the intestines [23].

The present investigation revealed that patients with AGTT experienced a greater occurrence of pulmonary exacerbations (6.71 ± 3.15) compared to patients with NGTT (4.50 ± 3.27). However, this disparity did not reach statistical significance, potentially due to the limited sample size.

Moreover, according to Campbell et al.[5], CFRD leads to a rise in respiratory exacerbations, heightened infection with CF pathogens like pseudomonas aeruginosa, and a decline in lung function.

These results are similar to those of earlier studies by Lavie et al.[24] and Olszowiec-Chlebna et al.,[25], which showed that both CFRD and IGT are separate factors that make it more likely for CF pathogens to infect the lungs and make symptoms worse.

Contrary to our results, Mohan et al.[26] found that reduced glucose tolerance did not lead to a decrease in nutritional status or pulmonary function and did not make patients more likely to be hospitalized for pulmonary exacerbations.

The explanation for our findings lies in the fact that elevated blood glucose levels in patients undergoing AGTT may stimulate the proliferation of respiratory pathogens. This, in turn, results in heightened airway inflammation, deterioration of pulmonary function, and a rise in the occurrence and intensity of pulmonary exacerbations [27].

The present investigation revealed a notable disparity in pseudomonas colonization between AGTT patients and NGTT patients, with the former exhibiting much greater levels.

The results of our study align with the earlier studies conducted by Limoli et al.[27] and Reece et al.[28], which showed that both IGT and CFRD are associated with an elevated risk of pseudomonas Aeruginosa colonization. The results of Elidottir et al.[29] are in direct opposition to these findings. Elidottir et al. found that there were only a small number of CF patients who had chronic colonization of P. aeruginosa and other gram-negative bacteria. Additionally, there was no difference in the chronic bacterial colonization of these bacteria between the NGT and AGT groups.

It's possible that the higher percentage of pseudomonas colonization in CF patients with AGTT is because P. aeruginosa infections cause the airways to become more inflamed and last longer. This response is more common in these patients because the concentration of glucose in the airways increases when blood glucose levels surpass the threshold, which in turn affects the growth of respiratory pathogens [30].

The present investigation revealed that patients with NGTT and AGTT have comparable findings in lung function tests. These results align with the findings of Ziegler et al. [31], who observed no statistically significant disparity in lung function among children with NGT and AGT.

The results of Terliesner et al.[32], on the other hand, showed that pulmonary function was significantly lower in both pediatric and adult patients with prediabetes compared to those with normal glucose tolerance (NGT). In addition, Alicandro et al.[33] found that AGT is linked to a rapid deterioration in lung function in older children.

A possible explanation for our findings may be attributed to the absence of severe insulinopenia in our AGT patients as well as the limited sample size.

Our research showed that individuals with abnormal glucose tolerance (AGTT) who have cystic fibrosis (CF) were more likely to have a lower score indicating the severity of bronchiectasis compared to those with normal glucose tolerance (NGTT). This suggests a connection between aberrant glucose tolerance and the severity of bronchiectasis.

Our hypothesis posits that cystic fibrosis patients with AGTT have more severe bronchiectasis scores as a consequence of heightened bacterial colonization and a greater frequency of exacerbations, leading to accelerated radiological development.

Our investigation revealed notable positive associations between the overall occurrence of lung exacerbations and serum glucose levels. Contrary to our findings, Widger et al. [34] noted that the OGTT's assessment of glucose tolerance status does not change in relation to exacerbations.

One possible explanation for the direct correlations between the total frequency of pulmonary exacerbations in the previous year and serum glucose is the association between high blood sugar levels (hyperglycemia) and the increased occurrence of bacterial growth in the lungs (pulmonary colonization), as well as the severity of bronchiectasis leading to more frequent episodes of worsening lung symptoms (pulmonary exacerbations).

The results of our study highlight the detrimental effect of abnormal glucose tolerance (AGT) on the rising occurrence of pulmonary exacerbations. Additionally, it underscores the significance of doing glucose tolerance screening in children with cystic fibrosis (CF) who have frequent pulmonary exacerbations.

Study limitations:

The current study has various drawbacks. Initially, it was an observational

study with a limited number of CF patients, which may necessitate bigger cohort studies to validate its findings. Furthermore, the age range imposes limitations on the pulmonary function assessment of all subjects examined.

Conclusions:

The present investigation revealed that impaired glucose tolerance is prevalent among the examined CF patients. Our findings indicate a strong correlation between impaired glucose tolerance and elevated rates of pseudomonas colonization, as well as an augmented likelihood of experiencing pulmonary exacerbations.

Data availability statement:

All data produced or examined during this investigation is encompassed within this published publication.

Author contribution statement:

My contributed to the study design and conducted revisions of the text. HA conducted the study design and authored the primary paper. RA and SH participated in the study investigations and edited the text, while AE was responsible for data gathering. The authors have conducted a thorough examination of the article and have given their official endorsement.

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The author affirms the absence of any conflicting interests.

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حالة تحمل الجلوكوز عند الرضع والأطفال المصابين بالتليف الكيسي وعلاقته بالتفاقم الرئوي

ماجدة يوسف الصيفي [1] و رنا عبد الله أحمد [1] و صفية حسن زكريا [2] و أحمد محمد [3] وهبة عبد الله علي [1]

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المقدمة: يعتبرالتفاقم الرئوي من الأمراض التي لها معدل كبير للمراضة والوفيات بين مرضى التليف الكيسي للرئة, ومع ذلك، هناك بيانات محدودة حول العوامل المرتبطة بخطورة التفاقم. هنا، نحن نهدف إلى تحديد تأثير تحمل الجلوكوز على وتيرة التفاقم الرئوي وشدته.

المرضى والطرق: هذه دراسة مقطعية أجريت على٢٥ مريضًا بالتليف الكيسي في الفئة العمرية من ١ إلى ١٧عامًا في عيادة أمراض الرئة للأطفال في مستشفى الأطفال في الفترة من الأول من يوليو ٢٠٢١ إلى نهاية يوليو ٢٠٢٣. حالة تحمل الجلوكوز تم تحديده باستخدام اختبار تحمل الجلوكوز عن طريق الفم. تم تصنيف المرضى وفقًا لنتائج الخاصة بهم إلى مرضى التليف الكيسي الذين لديهم تحمل طبيعي للجلوكوز ومرضى التليف الكيسي الذين لديهم تحمل غير طبيعي للجلوكوز. تم تسجيل التفاقم الرئوي خلال العام السابق بين المرضى الذين شملتهم الدراسة، وتحديد علاقتها بحالة تحمل الجلوكوز.

النتائج: أظهر تحليلنا أن٢٨ بالمائة من المرضى الذين شملتهم الدراسة لديهم ضعف في حالة تحمل الجلوكوز، وهو ما لوحظ بشكل ملحوظ بين الأطفال الأكبر سنا مقارنة بالرضع والأطفال الصغار المصابين بالتليف الكيسي. تم اكتشاف عدوى الزائفة البكتيرية في ٤.٧١ بالمائة من مرضى التليف الكيسي الذين يعانون من عدم تحمل الجلوكوز بشكل طبيعي. وعلاوة على ذلك، كان هناك ارتباط احصائي كبير بين وتيرة التفاقم الرئوي ومستوى السكر في الدم .

الاستنتاجات: أظهرت الدراسة الحالية أن تحمل الجلوكوز غير الطبيعي ليس من غير المألوف بين مرضى التليف الكيسي المدروسين. خلصت نتائجنا إلى أن تحمل الجلوكوز غير الطبيعي كان مرتبطًا بشكل كبير بارتفاع معدلاتعدوي الزائفة البكتيرية وزيادة خطر التفاقم الرئوي.