THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2024.65983
Med Bull Sisli Etfal Hosp 2024;58(3):389–394

Original Research

Evaluation of Oral Glucose Tolerance Test Results in Children with Cystic Fibrosis

Asli Bestas,[1] Edip Unal,[1] Amine Aktar Karakaya,[1] Nurcan Beyazit,[1] Suat Savas,[2] Velat Sen[3]

[1]Department of Pediatric Endocrinology, Dicle University Faculty of Medicine, Diyarbakir, Türkiye
[2]Department of Pediatrics, Dicle University Faculty of Medicine, Diyarbakir, Türkiye
[3]Department of Pediatric Pulmonology, Dicle University Faculty of Medicine, Diyarbakir, Türkiye

Abstract

Objectives: Current guidelines suggest that patients with cystic fibrosis (CF), who are over the age of 10, should be annually evaluated with oral glucose tolerance test (OGTT). In this study, it was aimed to evaluate the OGTT results in patients above the age of 10, who were followed up in our center with the diagnosis of CF.

Methods: In the study, 46 patients with CF at the age of 10 and above, who underwent OGTT were included. Data such as gender, age at diagnosis, anthropometric measurements, lung function (FEV1 %) and the OGTT results were obtained. In the analysis, the patient groups with normal glucose tolerance (NGT) and abnormal glucose tolerance(AGT) were compared.

Results: NGT was found in 37(80.4%) of the patients, and AGT was found in 9(19.5%) of the patients. The median fasting glucose levels of the patients in the NGT group and the mean glucose levels measured at 120 minutes in the OGTT were found to be lower compared to the patients in the AGT group(p<0.005). Although the mean body weight, height, VKİ-SDS, FEV1in the AGT group were found to be lower than the patients in the NGT group, the difference was not statistically significant (p>0.05).

Conclusion: We detected AGT in approximately 1 out of 5 patients with CF who were at the age of 10 and above. Almost half (44.4%) of the patients with AGT were found to have normal fasting blood glucose levels. Therefore, cystic fibrosis-related diabetes screening should be performed with OGTT instead of fasting blood glucose in patients with CF.

Keywords: Cystic fibrosis, cystic fibrosis-related diabetes, oral glucose tolerance test

Please cite this article as "Bestas A, Unal E, AktarKarakaya A, Beyazit N, Savas S, Sen V. Evaluation of Oral Glucose Tolerance Test Results in Children with Cystic Fibrosis. Med Bull Sisli Etfal Hosp 2024;58(3):389–394".

Cystic fibrosis (CF) is a multisystem autosomal recessive disease. It was first described by Andersen in 1938.[1] The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is located on the long arm of chromosome 7.[2] The frequency of cystic fibrosis differs between races. It has been reported that cystic fibrosis is more common in white people than in others. Its frequency in the white race has been reported as 1 in 2000-3500 live births.[3] Advances in the treatment of CF and increased care opportunities have led to prolongation of the life expectancy of patients. Along with the increased life expectancy of patients with CF, the frequency of complications related to the disease has also increased. Cystic fibrosis-related diabetes (CFRD) has a very important place among these complications.[4,5] It is the most common complication that occurs in patients with CF, after sinus disorders, asthma and reflux. Its frequency in adolescents has been reported to range between 12% and 20%.[6] Cystic fibrosis-re-

Address for correspondence: Aslı Bestas, MD. Department of Pediatric Endocrinology, Dicle University Faculty of Medicine, Diyarbakir, Türkiye
Phone: +90 412 248 80 01 **E-mail:** bestasasli@gmail.com

Submitted Date: February 09, 2024 **Revised Date:** March 25, 2024 **Accepted Date:** April 29, 2024 **Available Online Date:** September 30, 2024

lated diabetes usually has an insidious onset and a clinically silent course in the early stages. In most of the patients, the classic symptoms of diabetes such as polyuria and polydipsia are absent.[7] Cystic fibrosis-related diabetes should be diagnosed and treated at an early stage, as it causes reduction in lung functions, deterioration of nutritional parameters, microvascular complications and decreased life expectancy in patients with CF.[7,9] Current guidelines (ADA and ISPAD) recommend the oral glucose tolerance test (OGTT) as the gold standard in the screening of cystic fibrosis-related diabetes. These guidelines state that the patients with CF, who are above the age of 10, should be annually evaluated with the OGTT.[7,10] The patients diagnosed with CF, who are followed up in our center, are annually screened with the OGTT as recommended by the current guidelines. In this study, it was aimed to evaluate our OGTT screening results.

Methods

In the study, 46 patients with cystic fibrosis at the age of 10 and above, who underwent OGTT between 2012 and 2020 in the Department of Pediatric Endocrinology in Dicle University Faculty of Medicine, were included. Among the patients who were diagnosed with CF, those who had acute pulmonary exacerbation, those who were receiving systemic steroid treatment due to allergic bronchopulmonary aspergillosis and those with known diabetes, were excluded from the study.

Data such as gender, age at diagnosis, age at the time of participation in the study, anthropometric measurements (body weight, height, body mass index), pubertal assessment results, lung function (FEV1 %), fasting blood glucose levels, insulin levels and the OGTT results were obtained from the medical records of the patients.

The Harpenden Stadiometer (Holtain Ltd., Crymych, UK) was used to measure height, and an electronic scale with an accuracy of 0.1 kg was used to measure body weight. Body mass index (BMI) was calculated using the formula weight (kg)/[height (m)]^2. The height, weight and BMI standard deviation scores (SDS) were calculated using the web-based Child Metrics software[11] according to national data.[12] Systemic examinations were performed in all patients; puberty findings were evaluated according to the Tanner Scale.[13]

In the follow-up of 46 patients who were diagnosed with cystic fibrosis, the OGTT was performed. For the OGTT, 1.75 g/kg (maximum 75 grams) of glucose solution was given to the patients after eight hours of fasting, and the plasma glucose and insulin levels were measured at 0 and 120 minutes. The plasma glucose level was evaluated using an automated analyzer, and the insulin level was determined using the immunochemical method. The patients were classified according to the OGTT results, in compliance with the current guidelines.[1,10]

1. Normal glucose tolerance (NGT): Fasting plasma glucose <100 mg/dl and plasma glucose level measured at hour 2 of OGTT <140 mg/dl,
2. Impaired glucose tolerance (IGT): Fasting plasma glucose <126 mg/dl and plasma glucose measured at hour 2 of OGTT between 140-199 mg/dl,
3. Cystic fibrosis-related diabetes (CFRD): Fasting plasma glucose ≥126 mg/dl and plasma glucose measured at hour 2 of OGTT ≥200 mg/dl.

Patients with IGT and CFRD were classified as patients with abnormal glucose tolerance (AGT). Patient groups of normal and abnormal glucose tolerance were compared in the analysis.

Ethics Approval: The study was performed in accordance with the rules of Declaration of Helsinki and this study was initiated after the approval of the Dicle University Faculty of Medicine Ethics Committee (Number: 2021/111, Date: 04.02.2021).

Statistical Analysis

In the statistical evaluation of the data, the SPSS 20.0 Statistics (Armonk, New York: IBM Corp.) software package was used. Quantitative variables were expressed as mean±standard deviation (SD) or median (Interquartile Range); categorical variables were expressed as counts and percentages (%). The Shapiro-Wilk test was used to determine the normality of the data. Normally distributed data were compared using the Independent T-test; data that were not normally distributed were compared using a nonparametric test (the Mann-Whitney U test). The Chi-square test was used to examine categorical variables. In all tests, a p-value of <0.05 was considered statistically significant.

Results

Among the 46 patients with CF included in the study, 19 were female (41%) and 27 were male (59%). The median age at diagnosis of CF of the patients was 5.92 (1.4-9) years, while the median age at the time of participation in the study was 13.97 (11-16.4) years. 33 of the patients included in the study were in the pubertal period and 13 were in the prepubertal period. Anthropometric measurements, laboratory data and FEV1 levels of the patients are summarized in Table 1.

In the evaluation of the OGTT results of the patients, NGT was detected in 37 (80.4%), IGT was detected in 4 (8.6%) and CFRD was detected in 5 (10.8%) patients. When the patients were classified as NGT and AGT according to the OGTT results, it was observed that 37 (80.4%) had NGT and 9 (19.5%) had AGT. Anthropometric measurements, laboratory data and FEV1 values of the patient group with normal glucose tolerance and the patient group with AGT are summarized in Table 2.

Table 1. Clinical features of the patients with cystic fibrosis included in the study

	n=46
Age at Diagnosis, (years)	5.92 (1.4-9)
Age at the time of Participation in the Study, (years)	13.97 (11-16.4)
Gender	
Female, n (%)	19 (41)
Male, n (%)	27 (59)
BW-SDS	-1.60±1.25
Height-SDS	-1.21±1.05
BMI-SDS	-1.25±1.15
Hemoglobin A1c	5.6 (5.3-5.9)
Fasting insulin (mU/L)	7.37 (4.2-8.3)
Fasting glucose(mg/dL)	91.78±16.48
Glucose level at hour 2 of OGTT (mg/dL)	125.04 (89-138)
Insulin level at hour 2 of OGTT(mU/L)	14.8 (9.5-18.5)
FEV1 (%)	82.28±26.48

BW: Body Weight; BMI: Body Mass Index; SDS: Standard Deviation Score; OGTT: Oral Glucose Tolerance Test; data are given as mean±SD or median (Interquartile Range 25th–75th percentile).

Discussion

Cystic fibrosis is a common multisystem disease. In 85% of the cases, exocrine pancreatic insufficiency develops. Damage to the exocrine pancreatic tissue over the years leads to the loss of islet cells, which results in the development of CFRD.[14,15] Although the frequency of CFRD has been found to be 12-34% in general, these values vary depending on the age and ethnicity. It is estimated that CFRD develops in 5-6% of the patients with CF in the USA and Europe.[6,16] In our country, the frequency of CFRD has been reported as 3.4%.[17] In some centers, the OGTT is still not routinely performed in patients with CF and the diagnosis of CFRD is made according to fasting blood glucose levels. Therefore, the frequency of CFRD is estimated to be higher than it has been reported in the literature.[6,16,17] In the single-center prospective study conducted by Laang et al.[18], it was shown that the frequency of CFRD increased from 11% to 24% with routinely performed annual oral glucose tolerance tests. In another study with a high rate of annual OGTT screening, in which 527 patients with CF were evaluated, it was reported that the frequency of CFRD in the adolescent age group was 19%.[19] In a recent study conducted in Canada, 256 patients between the ages of 10 and 18 years were screened and the frequency of CFRD was found as 8.6%.[20] In the study of Haliloglu et al.[21], which was conducted in our country, 45 patients with CF between the ages of 5 and 18 years were evaluated with the OGTT and the frequency of CFRD was found as 11.1%.

In our study, 46 patients with CF between the ages of 10 and 18 were evaluated with the OGTT and the frequency of CFRD was found as 10.8% (5 patients). The frequency of CFRD found in our study was consistent with the literature.[20,21] In addition, IGT was present in 4 (8.6%) patients in our study. In 4 (44.4%) of the 9 patients with abnormal glucose tolerance, fasting blood glucose level was within the normal range. If the OGTT had not been routinely performed in the patients in our study, the diagnosis of one patient, who had normal fasting blood glucose but impaired glucose tolerance, and three patients, who had CFRD, would

Table 2. Comparison of the patients included in the study according to glucose tolerance classification

	Normal Glucose Tolerance (n=37)	Abnormal Glucose Tolerance (n=9)	p
Age at Diagnosis (years)	4.81 (1.16-8.76)	5.00 (3.84-11.5)	0.223[a]
Age at the time of Participation in the Study (years)	14.12 (10.25-16)	14.72 (13.31-17.21)	0.339[a]
Gender			
Female, n (%)	17 (45.9)	2 (22.2)	0.19[c]
Male, n (%)	20 (54.1)	7 (77.8)	
BW-SDS	-1.49±1.291	-2.04±0.985	0.241[b]
Height-SDS	-1.20± 1.068	-1.22±1.005	0.959[b]
BMI-SDS	-1.15± 1.186	-1.66±0.897	0.233[b]
Hemoglobin A1c	5.6 (5.25-5.80)	5.8 (5.45-6.65)	0.08 [a]
Fasting insulin (mU/L)	6.07 (4.76-8.95)	4.12 (3.30-7.59)	0.197[a]
Fasting glucose (mg/dL)	88 (79-99)	116 (91.5-117)	0.004[a]
Glucose level at hour 2 of OGTT (mg/dL)	103.22±21.30	214.78±51.92	0<001[b]
Insulin level at hour 2 of OGTT(mU/L)	15.60 (10.2-20.9)	11.50 (10.2-20.9)	0.170 [a]
FEV1 (%)	83.90±27.34	76.67±23.84	0.478[b]

[a]Mann-Whitney U test, [b]Independen t Samples t-test, [c]Chi-square test, data are given as mean±SD or median (Interquartile Range 25th–75th percentile); BW: Body Weight; BMI: Body Mass Index; SDS: Standard Deviation Score; OGTT: Oral Glucose Tolerance Test.

have been missed. Similar to our study, it was stated in previous studies that fasting blood glucose level alone did not have adequate sensitivity in detecting abnormal glucose tolerance in patients with cystic fibrosis.[22] In addition, it was reported that even in children under the age of 10, CFRD was detected with routine OGTT screening.[23] As in the above-mentioned studies, we recommend annual OGTT screening in order to detect abnormal glucose tolerance in patients with CF.Otherwise, only evaluating the fasting blood glucose levels will cause the diagnosis to be missed in almost half of the patients with abnormal glucose tolerance.

The symptoms of cystic fibrosis-related diabetes are usually indistinct and the disease progresses insidiously. It has been reported that increase in body weight and decrease in growth rate despite adequate nutritional support should be an indicator of CFRD development.[7] In a study, in which 25 patients with CF between the ages of 2 and 18 were included, patients with normal and abnormal glucose tolerance were compared; it was reported that the height, body weight and BMI SDS values were found to be significantly lower in the patients with AGT compared to the patients with NGT.[24] In a recent study conducted by Nguyen et al.[25], in which 281 patients with CF were evaluated with the OGTT, it was shown that the height and body weight SDS values were lower in patients diagnosed with CFRD than in patients with NGT. In the same study, it was stated that the weight SDS was less affected than the height SDS in patients with CFRD, and the height SDS value had begun to decrease in the first ten years of life, long before the first OGTT screening was performed. The authors of the study reported that growth retardation in patients with CF mayreflect early-stage glucose metabolism disorders.[25] In another study conducted by Jain et al.[22], it was reported that there was no significant difference between the patients with NGT and AGT in terms of anthropometric parameters. In our study, the anthropometric parameters of patients with NGT and AGT were compared. It was found that the body weight and height SDS values were lower in patients with NGT than the patients with AGT. However, the difference was not statistically significant. These findings were similar to the findings of the study of Jain et al.[22]

In patients with cystic fibrosis, the primary cause of death is pulmonary insufficiency. The known potential risk factors for pulmonary insufficiency are malnutrition, chronic Pseudomonas aeruginosa infection, pancreatic insufficiency and CFRD. In many previous studies, it has been reported that patients with AGT have worse pulmonary functions than patients with NGT.[26-29] In these studies, it has been shown that in patients with CF, increased glucose in airway epithelial cells helps the growth of pathogenic bacteria in the respiratory tract, blunts the immune response and makes the patients more susceptible to pulmonary infection.[30] In addition, studies have shown that the increase in blood glucose levels in patients with CF starts in the early stages of life.[31,32] In a study, high glucose levels were detected in patients with CF under the age of 10, which was found to be associated with a decrease in pulmonary functions.[32,33] In the study of Lanng et al.[31], in which 38 children and adults who developed CFRD were evaluated, a gradual decrease in pulmonary functions of the patients, starting about 4 years before the diagnosis of CFRD, was shown. In contrast to the above-mentioned studies, Jain et al.[22] reported in their study that there was no significant difference between the NGT and AGT groups in terms of pulmonary functions. In our study, pulmonary functions of patients with NGT and AGT were compared. It was shown that the FEV1 percentage was lower in patients with AGT than in patients with NGT. The difference between the groups was not significant. Our findings were consistent with the study of Jain et al.[22] Studies have shown that gender is a risk factor in the development of cystic fibrosis-related diabetes. Some studies have shown that the frequency of CFRD is higher in female patients[21,34,35], and some studies have suggested that life expectancy is shorter in female patients compared to male patients.[36,37] In patients with cystic fibrosis, the main cause of diabetes development is insulin deficiency due to the loss of pancreatic islet cells.[14,15] However, these studies reported that female patients with CF had higher insulin levels than male patients.[21,34,35] Although the reason for this is not exactly known, studies show that bacterial infections occur earlier and more frequently in women, and this may cause systemic inflammatory response, resulting in insulin resistance.[35] In addition, Battezzati et al.[38] have reported that increased insulin clearance contributes to the deterioration of glucose tolerance in adult female patients with CF. In our study, contrary to the literature, it has been shown that both the frequency of CFRD and the insulin levels are higher in male patients with CF than in female patients. This may be due to the small number of patients included in our study.

The limitation of this study is that it was designed retrospectively. OGTT results of all cases tested in the study covering the years 2012-2020 could not be obtained. The small number of patients and the lack of a power analysis when planning the study can be considered another limitation.

Conclusion

In conclusion, we detected abnormal glucose tolerance approximately in 1 out of 5 patients with cystic fibrosis who were at the age of 10 and above. Almost half (44.4%) of the patients with abnormal glucose tolerance were found to have normal fasting blood glucose level. Therefore, CFRD screening should be performed with OGTT instead of fasting blood glucose in patients with cystic fibrosis. Although the differences were not statistically significant, anthropometric measurements and pulmonary functions were found to be lower in patients with AGT than in patients with NGT. Therefore, detecting CFRD on time may provide better anthropometric measurements and pulmonary functions.

Disclosures

Patient Informed Consent: Since this study was designed retrospectively, patient consent was not obtained

Ethics Committee Approval: Dicle University Faculty of Medicine Ethics Committee (Number: 2021/111, Date: 04.02.2021).

Conflict of Interest: There is no conflict of interest between the authors

Financial Support (Funder's Name): No financial disclosure

Authorship Contributions: Concept – A.B., E.U.; Design – A.B., E.U., A.A.K.; Supervision – V.S., A.B., N.B.; Fundings –A.A.K., A.B., S.S.; Materials – A.A.K., N.B.; Data collection &/or processing – S.S., V.S., N.B., A.A.K.; Analysis and/or interpretation – S.S., V.S., N.B.; Literature search – A.B., E.U.; Writing – A.B., E.U.; Critical review - V.S., S.S., N.B.

Use of AI for Writing Assistance: None declared.

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