



HYPOGLYCEMIA AS A NEW CHALLENGE IN TREATMENT WITH MODULATORY THERAPY IN PATIENTS WITH CYSTIC FIBROSIS

HIPOGLIKEMIJA KAO NOVI IZAZOV U LIJEČENJU MODULATORNOM TERAPIJOM PACIJENATA SA CISTIČNOM FIBROZOM

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SAŽETAK Cilj: Otkriće takozvanih CFTR modulatora postavilo je novu prekretnicu u liječenju cistične fibroze (CF) kod pacijenata s mutacijama F508del. **Metode:** Uticaj modulatorne terapije na glikoregulaciju kod pacijenata s CF godinu dana prije i godinu dana nakon uvođenja terapije. **Rezultati:** 16 pacijenata liječeno je u Klinici za dječije bolesti u Banjoj Luci, kliničke, mikrobiološke karakteristike, kao i kontinuirano mjerenje glukoze postavljanjem glukometra praćene su tijekom 12 mjeseci terapije. **Zaključak:** Korištenje glukoznog senzora pokazalo se superiornijom metodom u poređenju sa OGTT-om u liječenju poremećaja glikoregulacije kod naših pacijenata.

Ključne riječi: cistična fibroza, modulatorna terapija, plućna funkcija, glikoregulacija, kontinuirano praćenje glukoze, hipoglikemija.

INTRODUCTION

Cystic fibrosis (CF) is a hereditary disease caused by a mutation of the gene that codes the synthesis of a protein called cystic fibrosis transmembrane conductance regulator or CFTR (Cystic Fibrosis Transmembrane Conductance Regulator). The most common genetic defect is the F508del mutation. Due to its structure and function, CFTR has an indisputable role in the active transport of electrolytes through the cell membrane of the epithelial cells of the glands located in the respiratory, digestive and reproductive systems (1). As a consequence of the changed CFTR protein, the normal balance of fluids and electrolytes is disturbed, a thick, viscous secretion is created, which as such leads to the closing of the outflow channels, with consequent tissue damage in the mentioned systems. Chronic lung disease is a predictor of CF patient survival. In addition to structural damage to the walls of the airways and

hypersecretion of mucus in the airways, the defense against infection is also impaired. Increased production and release of pro-inflammatory cytokines, interleukin 8 (IL8), IL1, IL6 and leukotriene B4 from the epithelial cells of the airways leads to the attraction of even more neutrophils into the airways and thus establishes a vicious circle that leads to lung destruction (2).

One of the main forms of neutrophils' fight against pathogens is phagocytosis, after which mechanisms are activated that can effectively destroy phagocytosed microorganisms. The creation of reactive oxygen species (ROS) is an important antimicrobial mechanism in neutrophils. Oxidative burst determines the possibility and strength of the activation of the first line of innate immunity through the intensity of glycogenolysis, the enhancement of oxidation processes and the measurement of the level of highly toxic reactive oxygen metabolites (hydrogen peroxide and peroxide anions)



which are released and destroy the ingested particles. Although ROS are intermediate products of the NADPH oxidase complex in healthy individuals, results regarding NADPH oxidase function and ROS generation in CF neutrophils are under investigation. Many of these show that oxidative burst-dependent antimicrobial mechanisms are impaired in CF neutrophils (3). In his study, R o b l e d a - A v i l l a et al. analyzed the influence of CFTR mutations, i.e. inhibition of CFTR function, on the production of ROS in neutrophils and it showed that blocking of CFTR channels in non-CF neutrophils has reduced hROS production when stimulated with lipopolysaccharide (LPS).

This lack of function could be explained by the spontaneous release of ROS due to the influence of CFTR on the myeloperoxidase activity of neutrophils and the respiratory burst (4). Cifani et al showed that the absence of CFTR is associated with defective pathogen killing, increased secretion of proinflammatory cytokines, and decreased production of reactive oxygen species (ROS)(5). Malhotra and others. showed in their study that ROS concentrations in the peripheral blood of patients were significantly increased during pulmonary exacerbations and decreased during treatment, indicating a clear association with the changing inflammatory/infectious status of patients with CF (6). Studies have also shown that certain microorganisms additionally weaken the protective functions of granulocytes the susceptibility to infection of the airways of patients with CF. A healthier lung in CF appears to be associated with neutrophil subpopulations with increased oxidative burst capacity and capacity for neutrophil apoptosis within the airways (7).

Impaired immunoregulation in CF leads to chronic airway colonization by *Ps. aeruginosa* and repeated exacerbations of lung disease, which causes a decrease in lung functions that further deteriorate due to malnutrition, the

development of diabetes mellitus, and non-compliance with adequate treatment measures.

The most common extrapulmonary complication in CF is CFRD (Cystic fibrosis-related diabetes CFRD), which has characteristics of type 1 and 2 diabetes. Cystic Fibrosis-Related Diabetes (CFRD) shares characteristics of both type 1 and type 2 diabetes mellitus, but it is a distinct form of diabetes with unique clinical and pathophysiological features. CFRD is characterized by insulin deficiency resulting from pancreatic β -cell dysfunction and loss, although, unlike type 1 diabetes, it is not autoimmune in origin. Pancreatic duct obstruction contributes to chronic pancreatitis, loss of islets of Langerhans, ductal fibrosis, and eventually leads to fatty degeneration of the pancreatic tissue, culminating in pancreatic insufficiency. Progressive exocrine dysfunction further damages nearby pancreatic islets, thereby impairing pancreatic hormone production (8).

The initial stage of hyperglycemia development in children with cystic fibrosis is primarily due to delayed insulin secretion during the first phase of insulin release, driven by a reduction in both β -cell mass and overall insulin secretion. Furthermore, mutations in the CFTR gene may diminish glucagon release from pancreatic α -cells, leading to an inadequate counterregulatory response to hypoglycemia. Hypoglycemia in cystic fibrosis may arise from delayed first-phase insulin secretion, glucagon deficiency, malnutrition, gastrointestinal disorders, liver disease, and incretin dysregulation (9).

Incretins, such as glucose-dependent insulinitropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), also play a critical role in CFRD by contributing to β -cell dysfunction. These hormones are secreted by the gut in response to carbohydrate intake. Individuals with cystic fibrosis may experience both spontaneous and iatrogenic hypoglycemia, which can occur in both fasting and postprandial states. Fasting hypoglycemia is



often associated with malnutrition and increased energy demands during inflammation or acute infections, while postprandial (reactive) hypoglycemia results from impaired first-phase insulin release following glucose intake, followed by prolonged and delayed second-phase insulin secretion(10). Additionally, the body's ineffective counterregulatory response to hypoglycemia may exacerbate the duration and severity of hypoglycemic episodes.

According to some authors, endocrine dysfunction of the pancreas in patients with cystic fibrosis is a consequence of exocrine dysfunction, because CFTR is detected in a small number of β -cells, but was detected in a large number of α -cells. Therefore, the destruction of the exocrine pancreas and the spilling of inflammatory contents into the endocrine part, the consequent inflammation, destruction and disorganization of the endocrine part lead to the appearance of CFRD (8).

Dysfunctional CFTR is associated with impaired insulin secretion and beta cell dysfunction, which is enhanced in the presence of oxidative stress. This explains that the reduction of lung functions in CFRD occurs due to hyperglycemia-patterned activation of the pro-inflammatory cascade by increasing oxidative stress, changing the viscosity of mucus, which contributes to the colonization of the airways by various pathogens (9). Glucose metabolism disorder is a significant predictor of pulmonary function impairment in patients with CF (10). Therefore, early detection and identification of glycemic abnormalities in patients with CF is of great importance for the survival of these patients.

Until 2019, treatment of CF patients was limited to symptomatic measures. However, the development of a new class of drugs, the so-called CFTR modulators, has set a new milestone in the treatment of CF for patients with F508del homozygous mutations or F508del heterozygous (11). Modulators work by helping the defective CFTR protein to

function more efficiently. Two active substances, Elexacaftor and Tezacaftor, function as correctors, i.e. they bind to the faulty CFTR protein, helping it to fold properly so that more of the protein can attach to the cell membrane, instead of being broken down. The substance Ivacaftor, which has the role of a potentiator, i.e. the CFTR protein binds and keeps the channel open so that more sodium and chloride ions are exchanged through it. By applying the triple therapeutic combination, more CFTR protein reaches the cell membrane, making the protein more active and functional (12).

It has been proven that the most significant effects of the application of modulatory therapy are the improvement of patients' lung function, reduction of chloride concentrations in sweat, improved body mass index, slowing down of disease progression, and reduced need for antibiotics (13-15). The use of modulatory therapy reduces chronic inflammation not only in the lungs but also in the pancreas, which can lead to improved glycoregulation in CF patients (16).

The specifics of the nutritional status of CF patients is that due to high energy consumption in the body and malabsorption, it is very difficult to maintain optimal weight, and a hypercaloric diet is required. It is recommended that CF patients over the age of 2 consume 110-200% more calories than their peers of the same sex. In addition, in patients with CFRD, the hypercaloric diet must be designed in such a way as to maintain the normal level of glycemia necessary for the proper functioning of the body (17-18). However, there are still not enough research that combine the impact of modulatory therapy on pulmonary functions, glycoregulation and nutritional status in patients with CF regardless of the presence of diabetes that used continuous glycemic monitoring as a tool for change detection.



THE AIM

The goal is to determine the impact of the application of modulatory therapy on lung function, nutritional status and glycoregulation in patients with CF in the Republic of Srpska, based on the results obtained from the ambulatory glucose profile obtained using a device for continuous glycemic monitoring.

The research was carried out retrospectively in the period from July 2022 to July 2023 at the Clinic for Children's Diseases in Banja Luka. Out of 25 patients diagnosed with CF in the Republic of Srpska, 16 subjects, aged 7 to 24, who met the criteria for the introduction of combined immunomodulatory therapy, were included in the study. The inclusion criterion for the introduction of combined modulatory therapy (ivacaftor/tezacaftor/elexacaftor) is the presence of at least one genetic mutation F508del. In 13 patients, modulatory therapy was applied in the dose regimen ivacaftor 75mg/ tezacaftor 50mg/ elexacaftor; 100mg, two tablets in the morning and Ivacaftor 150mg one tablet in the evening, while three patients had a dose of ivacaftor 37.5mg/ tezacaftor 25mg/ elexacaftor; 50mg two tablets in the morning and Ivacaftor 75mg one tablet in the evening administered orally, approximately 12 hours apart.

In all patients, we analyzed age, sex, nutritional status expressed through body mass index and body weight, lung function, type of genetic mutation, presence of chronic colonization by the most important pathogens and extrapulmonary complications of the disease (diabetes mellitus) before and after the introduction of combined modulatory therapy. Assessment of lung function included measurement of FVC (*Forced Vital Capacity*) and FEV1 (*Forced Expiratory Volume 1 Second*) expressed in percentages, using a spirometer (Jaeger GmbH, Germany) with a standardized procedure. Documented colonization meant microbiological confirmation of pathogens from sputum or

deep throat swab. Body mass index (BMI) at diagnosis was calculated as the quotient of body mass in kilograms and the square of body height in meters.

Endocrinological Evaluation of Cystic Fibrosis Patients

All cystic fibrosis patients aged 10 years and older undergo an annual Oral Glucose Tolerance Test (OGTT) using 75g of liquid glucose. A pathological OGTT result indicates the need for insulin therapy. Initially, insulin detemir at 1-3 IU is introduced, and later the patients introduce with multiple daily insulin injection if needed. In addition to the OGTT, other endocrinological parameters are monitored, not only in patients over 10 years old but also in younger patients. These parameters include HbA1c every three months and fasting glucose levels. The diagnosis of Cystic Fibrosis-Related Diabetes (CFRD) and the initiation of insulin therapy are based on OGTT results and other laboratory-assessed endocrinological markers. In our cohort, before starting modulator therapy, CFRD was diagnosed in four participants based on pathological OGTT results, and insulin therapy was introduced.

All participants underwent a comprehensive endocrinological evaluation before the introduction of the continuous glucose monitoring. This system utilizes the Guardian Sensor (Medtronic MiniMed) as an integral component, which requires calibration at least twice daily. Calibration was performed using Accu-Chek (Roche) glucometers, with all participants properly trained in their use for self-monitoring of blood glucose at home.

Participants also received education, not just on proper handling and use of the continuous glucose monitoring device, but guidelines for managing critical situations, such as hypoglycemic events (glucose levels below 3.9 mmol/L) and appropriate carbohydrate intake. One key recommendation was to confirm sensor glucose values with capillary measurements whenever possible.



Additionally, participants were advised to document any irregularities in sensor readings.

All patients had fasting blood glucose, HbA1c, and 13 subjects used a device for continuous glycemic monitoring for 14 days on two occasions, before and after initiation of modulatory therapy, in order to determine the ambulatory glucose profile, and based on this, glycoregulation was determined. The interpretation of results from AGP was carried out according to the recommendations of the Consensus from 2019, regardless of whether the respondent has been diagnosed with diabetes or not, that is, whether he is receiving any form of insulin or not (19). After the first AGP analysis, insulin was discontinued in one patient due to severe hypoglycemic episodes that were observed.

Statistical analysis was done in the SPSS program. Standard methods were used to describe the variables, i.e. categorical variables were described numerically and in percentages, and numerical trend measures were described by the mean value and standard deviation. The influence of the therapy was examined by t-test for paired samples for numerical variables, and non-

parametric tests (Wilcoxon test) for categorical ones. The group was divided depending on the use of insulin into two subgroups and variables from AGP were examined in both subgroups. Correlation with lung functions was performed using the Pearson correlation coefficient, and the graphs were made using the regression linear method of dependence between variables. A value of p below 0.05 was taken as statistical significance.

RESULTS

16 subjects suffering from cystic fibrosis took part in the study, of which 9 were male and 7 were female. In 75.0% of patients, the first symptoms of the disease appeared in the first year of life. The average current age of the respondents is 15.68 ± 5.46 years, with the youngest respondent being 7 and the oldest 24 years old. Genotyping analysis showed that 14 (87.5%) patients were homozygous for delta F508, while 2 (12.5%) were heterozygous for delta F508. The average BMI of the patients at the beginning of the study was 16.98 ± 2.36 kg/m². The basic demographic and clinical characteristics of the patients before the introduction of therapy are shown in Table 1.

Table 1. Socio-demographic, clinical and genetic characteristics of CF patients at baseline.

Variables	n	%
Sex		
Male	9	56.3
Female	7	43.8
Age, years (SV$\pm$SD)	15,68 $\pm$ 5.46	
Initial symptoms age		
Up to 30 days	4	25.0
From 30 days to 1 year	8	50.0
More than 1 year	4	25.0
Age of diagnosis		
Up to 3 months	3	18.8
Up to 3 months to 1 year	7	43.8
From 1 to years	2	12.5
From 3 to 6 years	2	12.5
Over 6 years	2	12.5
Weight, kg (SV$\pm$SD)	42.69 $\pm$ 17.20	



Hight, cm (SV±SD)	157.74±17.65	
BMI, kg/m² (SV±SD)	16.98±2.36	
Adequate for the age	6	37.5
Malnutrition	3	18.8
Border line	7	43.8
Initial symptoms of the disease		
Mekonial ileus	1	6.3
Sindrom of malnutrition	7	43.7
Recurrent bronchial obstructions	8	50.0
Gene mutation		
Homozygous delta F508	14	87.5
Heterozygous delta F508	2	12.5

Values are presented as mean±standard deviation for numerical variables; Categorical variables are presented as frequencies, that is, the number of individual cases with percentages of the total number of cases for each category.

We examined the effect of the modulatory therapy through the characteristics of the patients before and one year after the introduction of the therapy. We used statistical tests for paired samples, non-parametric for categorical, and t-test for numerical variables

. The results are shown in Table 2.

Table 2. Characteristics of subjects before they started the therapy and 12 months after taking therapy for numerical variables.

Variable	Before the therapy	After the therapy	t-test	P
FEV1	80.13±26.27	98.06±25.21	-4.42	0.001
FVC	80.63±21.99	98.00±20.10	-4.51	<0.001
Chlorides in sweat	95.91±22.95	41.33±21.38	4.97	0.001
Body weight	42.69±17.20	51.03±12.68	-3.22	0.006
Body height	157.74±17.65	162.87±15.07	-4.20	0.001
BMI	16.98±2.36	18.94±2.50	-5.91	<0.001
Fasting blood glucose value	5.88±2.42	5.46±2.38	1.54	0.144
HbA1C	6.29±1.62	6.01±1.49	1.55	0.145

Values are shown as mean±standard deviation.

One year after the use of modulatory therapy, there was a statistically significant improvement in almost all parameters describing pulmonary and nutritional functions in the subjects. FEV1 and FVC increased, chlorides in sweat decreased, and body mass

and BMI increased, which was statistically significant. The values of blood glucose and HbA1C decreased after one year of using the therapy, but this difference was not statistically significant. It is clearly visible from the table that under the influence of



therapy there was a statistically significant average increase in lung functions, namely FEV1 by 17.94 ± 16.25 , and FVC by 17.38 ± 15.43 . A statistically significant increase was also shown by the BMI during the measurements, by an average of 1.34 ± 0.91 ,

and especially the body weight of our subjects increased by an average of 8.34 ± 10.35 .

We examined the microbiological characteristics of the subjects on the basis of non-parametric tests (McNeimar and Willcox test), and the results are shown in Table 3.

Table 3. Microbiological characteristics of the subjects.

Variable			Before therapy (n=16)		After therapy (n=16)		Wilcoxon signed rank test	
			n	%	n	%	Z	P
Chronic colonization	<i>Brukholderia capacia complex</i>							
No		16	100.0	16	100.0	Not applicable.		
Yes		0	0.0	0	0.0			
Chronic colonization	<i>Pseudomonas aeruginosa</i>							
No		5	31.3	12	75.0	-2.460 0.014		
Yes		6	37.5	4	25.0			
Intermittent		5	31.3	0	0.0			
Chronic colonization	<i>Staphylococcus aureus</i>							
No		0	0.0	8	50,0	-2.830 0.005		
Yes		16	100.0	8	50,0			
Bronhopulmonal compliaction	aspergylosis lung							
No		10	62.5	16	100.0	-2.449 0.014		
Yes		6	37.5	0	0.0			

The data from the table show that there was a statistically significant reduction in the colonization mentioned microorganisms after the introduction of therapy.

Although there was no statistically significant change in the laboratory measured values of the parameters related to glucoregulation, i.e. HbA1c measured in the laboratory and fasting blood glucose, insulin

was discontinued in one subject, i.e. one year after the introduction of modulatory therapy, he stopped using insulin. This decision was made based on AGP for this subject, where were notable no hyperglycemia episode, even a reactive one, but a lot of hypoglycemia episodes, after applying the insulin treatment. The subjects performed an ambulatory glucose profile on two occasions using a device for CGM, before and 12 months from the start of therapy, and the values are shown in table 4.

**Table 4.** Values of parameters from the ambulatory glucose profile, before and 12 months from the start of therapy, for the whole group and for subgroups of subjects who use any form of insulin, and subjects who do not use insulin.

Variable	Entire group		Subgroup on insulin		Subgroup without insulin	
	Before	After	Before	After	Before	After
N	13	13	4	3	9	10
TIR	92.69±8.41	94.00±6.15	87.75±12.84	95.67±5.77	94.89±5.16	93.50±6.47
TAR_I	3.54±7.51	1.92±2.33	7.50±13.67	3.33±4.04	1.78±1.79	1.50±1.65
TAR_II	0.15±0.55	0.23±0.60	0.50±1.00	0.67±1.15	0.00±0.00	0.10±0.31
TBR_I	3.31±4.87	3.15±5.19	3.75±4.99	0.33±0.58	3.11±5.11	4.00±5.70
TBR_II	0.48±0.95	0.69±1.18	0.50±0.58	0.00±0.00	0.44±1.62	0.90±1.29
No. hypo	5.92±7.94	6.54±11.41	8.25±10.21	1.67±2.08	7.18±1.50	8.00±12.74
No. hyper	6.00±10.96	4.30±6.21	11.75±19.12	7.67±12.42	4.39±1.46	3.30±3.50
CV	22.80±4.76	23.49±4.87	22.93±5.22	23.47±5.85	22.74±4.88	23.50±4.90
GMI	5.94±0.40	5.88±0.26	6.10±0.67	6.10±0.26	5.88±0.22	5.82±0.24
SG	6.11±0.89	5.98±0.60	6.48±1.56	6.50±0.70	5.94±0.43	5.82±0.50

Values are shown as mean ± standard deviation. TIR (Time In Range) – time spent in the range of glycemia from 3.9 to 10.0 mmol/L; TAR_I (Time Above Range_I) time spent in the glycemic range between 10.0 – 13.9 mmol/L; TAR_II (Time Above Range_II) – time spent in the glycemic range over 13.9 mmol/L; TBR_I (Time Below Range_I) - time spent in the glycemic range between 3.0 - 3.9 mmol/L; TBR_II (Time Below Range_II) - time spent in the glycemic range below 3.0 mmol/L; CV (Coefficient of Variation) – coefficient of variation expressed in percentages; GMI (Glucose management Indicator) – Glucose management indicator expressed in percentages; SG (sensor glucose value) – average value of glucose concentration in mmol/L measured by the sensor. A hypoglycemic or hyperglycemic episode is understood if the testee was below 3.9 mmol/L or 10.0 mmol/L for more than 15 minutes.

It is noticeable that for the entire group there was an improvement in TIR at the second measurement, a decrease in the time spent above 10.0 mmol/L, and therefore in

hyperglycemic episodes, while the time below 3.9 mmol/L increased slightly, and with it increased number of hypoglycemic episodes. Variability parameters such as CV, GMI, and SG are within recommended consensus limits, as are parameters of percent time spent in, above, or below the target range. Of the total number of respondents, 16 of them, three refused to use the device for CGM, of which one respondent is on insulin therapy. We divided the rest into two subgroups, with and without insulin. What is noticeable in the group using insulin is that on the second measurement there was a significant reduction in time spent below 3.9 mmol/L, where there was no time spent below 3.0 mmol/L at all. Accordingly, the number of hypoglycemic episodes, but also hyperglycemic episodes, decreased. TIR increased significantly due to the reduction of hypoglycemia, but also hyperglycemia, which significantly decreased. This was made due the reason that subjects who requires insulin are more often control their blood glucose and better in response decision made by this information.

In the subgroup without insulin, there was an increase in the percentage of time spent below 3.9 mmol/L, in both levels, which, even



after 12 months from the start of modulatory therapy, go beyond the values recommended by the consensus on the use of CGM in patients diagnosed with diabetes mellitus. Namely, the time below 3.9 mmol/l is more than 4.00% of the time, in accordance with which the number of hypoglycemic episodes also increased. TIR decreased at the expense of increasing the time in hyperglycemia,

because the time in hyperglycemia remained at approximately the same level.

In further analysis, we examined how parameters of glycemic variability correlate with variables describing lung functions (FEV1 and FVC). The values after 12 months were compared, because the analyzes were done at the same time.

Table 5. Correlation of lung function parameters with variables from ambulatory glucose profile. Correlation was calculated as Pearson's correlation coefficient with p value <0.05 as statistically significant.

Variable	FEV1						FVC					
	Entire group		Insulin		No-insulin		Entire group		Insulin		No-insulin	
	Coef f.	p	Coef f.	p	Coef f.	P	Coef f.	p	Coef f.	p	Coef f.	P
TIR	0.819	0.001	-0.064	0.959	0.893	0.001	0.657	0.015	-0.995	0.065	0.804	0.005
TAR_I	0.014	0.964	0.064	0.959	-0.034	0.925	0.157	0.609	0.995	0.065	-0.071	0.846
TAR_II	-0.051	0.870	0.064	0.959	-0.203	0.574	0.093	0.762	0.995	0.065	-0.299	0.401
TBR_I	- 0.825	<0.001	0.064	0.959	- 0.845	0.002	- 0.727	0.005	0.995	0.065	- 0.747	0.013
TBR_II	- 0.640	0.019	NA	NA	- 0.651	0.042	- 0.577	0.039	NA	NA	-0.574	0.083
No. hypo	- 0.879	<0.001	0.302	0.805	- 0.893	<0.001	- 0.781	0.002	0.941	0.219	- 0.808	0.005
No. hyper	-0.030	0.922	0.024	0.985	-0.123	0.735	0.163	0.595	0.998	0.039	-0.110	0.763
CV	-0.458	0.116	0.149	0.905	-0.535	0.111	-0.344	0.249	0.983	0.119	-0.523	0.121
GMI	0.441	0.132	0.251	0.838	0.502	0.140	0.463	0.111	0.958	0.186	0.405	0.245
SG	0.469	0.106	0.206	0.868	0.582	0.078	0.521	0.069	0.970	0.156	0.495	0.145

Values are shown as mean $\pm$ standard deviation. TIR (Time In Range) – time spent in the range of glycemia from 3.9 to 10.0 mmol/L; TAR_I (Time Above Range_I) time

spent in the glycemic range between 10.0 – 13.9 mmol/L; TAR_II (Time Above Range_II) – time spent in the glycemic range over 13.9 mmol/L; TBR_I (Time Below Range_I) -



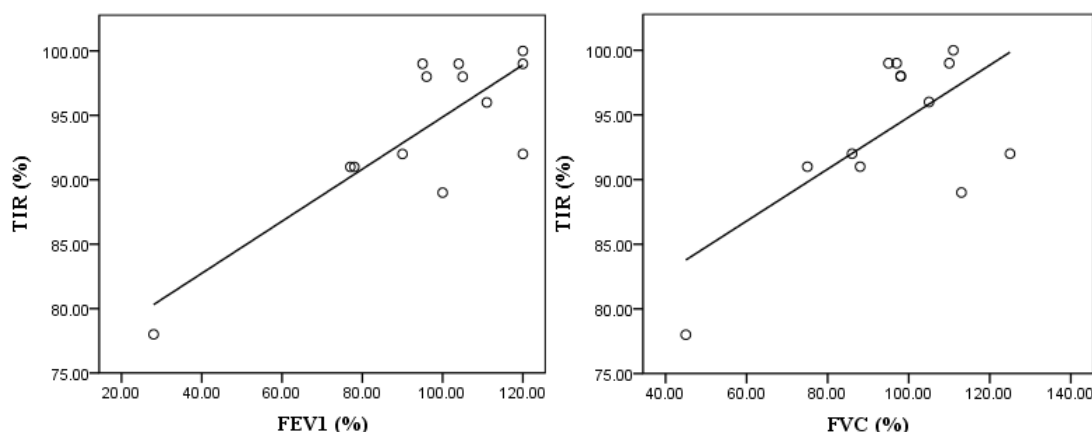
time spent in the glycemic range between 3.0 - 3.9 mmol/L; TBR_II (Time Below Range_II) - time spent in the glycemic range below 3.0 mmol/L; CV (Coefficient of Variation) – coefficient of variation expressed in percentages; GMI (Glucose management Indicator) – Glucose management indicator expressed in percentages; SG (sensor glucose value) – average value of glucose concentration in mmol/L measured by the sensor. A hypoglycemic or hyperglycemic episode is understood if the testee was below 3.9 mmol/L or 10.0 mmol/L for more than 15 minutes.

It is noticeable that there is a statistically significant positive correlation

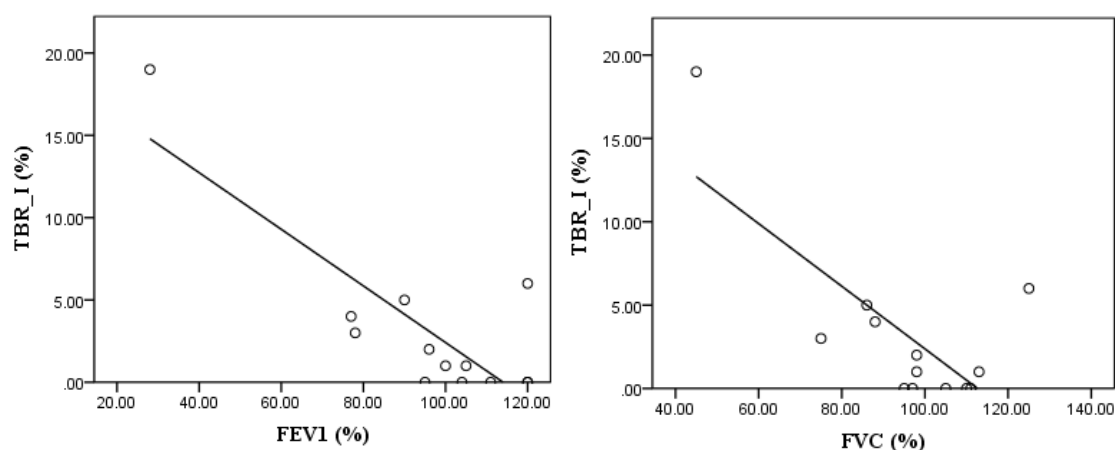
with TIR, while there is a negative correlation with the parameters describing hypoglycemia, observed in the group of all patients probably based by the values represented in the subgroup with ought insulin. This subgroup, consist of more participant than the subgroup with ought insulin, is mainly responsible for this statistical significance. A negative correlation with the number of hypoglycemic episodes was observed. This tells us that lung functions are lower if the number of hypoglycemic episodes is higher and if more time is spent in hypoglycemia, ie values below 3.9 mmol/L, regardless of whether the subject is on insulin or not. Hyperglycemia parameters have no statistically significant correlation with FEV1 and FVC.

Figure 1. Linear regression dependence of FEV1 and FVC with the parameter of glycemic variability from the ambulatory glucose profile:

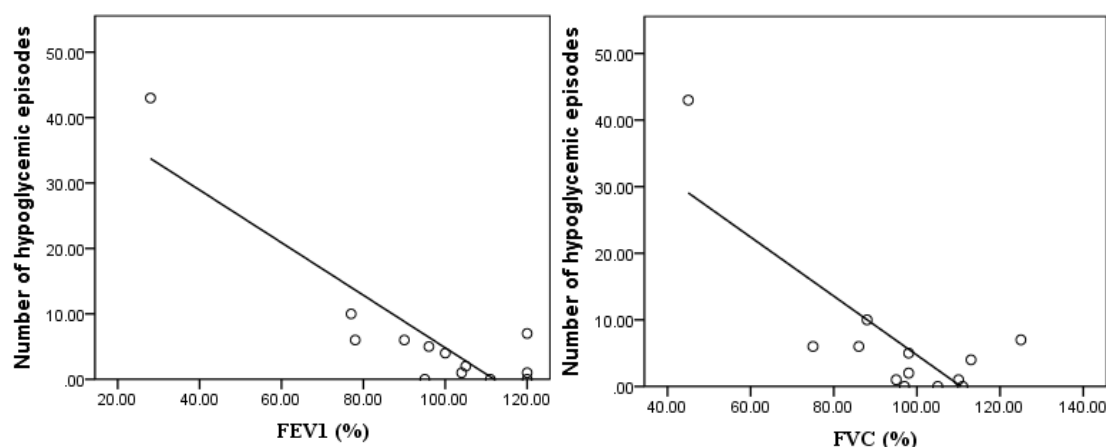
(A) Time in range - TIR (%) or time spent in glucose range from 3.9 mmol/L to 10.0 mmol/L, where it is notable direct correlation.



(B) Time below range – TBR_I (%) or time spent in glucose rang from 3.1 mmol/L to 3.9 mmol/L, where it is notable indirect correlation.



(C) Number of hypoglycemic episode where it is notable indirect correlation.



DISCUSSION

The main risk factor leading to increased morbidity and mortality among children and adolescents with CF is the degree of lung damage. The first abnormalities in lung function in CF patients are an elevated RV/TLC (residual volume/total lung capacity) ratio, which suggests disease of the small airways. With the gradual progression of the disease, reversible and irreversible changes in FEV1 are observed. The loss of elastic tissue in the inflammation affected lung parenchyma

contributes to the increase in the collapsibility of the larger airways, with a more pronounced dynamic compression of the airways during forced expiration, which is reflected in a decrease in FEV1 of 1 to 3% per year (20-21).

The introduction of CFTR-modulating therapy had an effect on the main pathophysiological driver in CF – impaired transport of chloride and bicarbonate. The drug affects the expression, function and stability of the altered CFTR protein, which is why we can consider it a functional drug. In our study, the



epidemiological characteristics of our patients are similar to the epidemiological characteristics of CF patients described in other studies.

By introducing modulatory therapy in our patients, we found clear evidence of a significant improvement in lung functions. FEV1 increased significantly from baseline ($80.12 \pm 26.26\%$) to 12 months of follow-up ($98.06 \pm 20.20\%$, $p < 0.001$). FVC values increased significantly from the initial value ($p = 0.001$). Our results are almost coherent with the conducted phase III study by Middleton et al. where an increase in FEV1 of 14.3% was recorded after 5.5 months of taking the drug (21). Similar results were reported by Nichols et al. in the PROMISE study, which was conducted on a rather large group of patients with CF in the USA (22). We found that mean BMI values were also significantly higher after 12 months of follow-up (18.94 ± 2.50 kg/m², $p < 0.001$) compared to values at the beginning of the study (16.98 ± 2.36 kg/m²). We assessed the status of colonization with PsA, we observed a transition from positive to negative detection in 25% ($p < 0.001$) of cases after one year of therapy. From the obtained results, we can see that the introduction of modeling therapy in a relatively short time had a great effect on the characteristics of the disease in our patients. This changed the paradigm of treating CF patients from exclusively symptomatic to pathophysiological and opened up a new horizon for patients. Our results are comparable with other conducted studies (23). Based on the results obtained from the ambulatory glucose profile obtained using a device for continuous glycemic monitoring, we can conclude that over time modulatory therapy has a positive effect on glycemic regulation in patients with CF and CFRD, and this has been shown in studies so far (24). In our study group, there was an increase in TIR from 92.69 ± 8.41 to 94.00 ± 6.15 after six months. In the study by Scully and colleagues, modulatory therapy was administered to 34 adults with CF, 9 of whom did not have

CFRD. The study showed an improvement in average sensor glucose, as well as an increase in the percentage of time spent in the target glycemic range of 3.9-10 mmol/L, and the improvement was greatest in patients with existing CFRD (25). Although there was a decrease in HbA1c, the t-test did not show statistical significance. We must know that the value of HbA1c is lower in people with CFRD in contrast to other forms of diabetes, but after six months of modulatory therapy in our study group there is a decrease in glycemia, an increase in TIR and a decrease in average glycemia, with the cessation of insulin therapy in one patient. The results obtained in the Peterson study in the CFRD patient group also did not result in a decrease in HbA1c. This study confirmed a significant reduction in HbA1c after initiation of modulatory therapy in 57 patients without CFRD of -0.16 ($p < 0.005$), in contrast to a decrease of -0.17 ($p = 0.25$) in 46 patients with CFRD, which was not statistically significant (26).

What is interesting in patients with CFRD is that the continuous monitoring of glycemia for 14 days made it possible for patients with CFRD to have no hypoglycemia after 12 months from introducing the therapy, which we consider a great success because during the control we advised the patients about eating meals properly and reducing the intake of high-carbohydrate products, which resulted in reducing the dose of insulin to the extent that it was completely discontinued in one patient. As can be seen in Table 4, there was a reduction in both the number of hypoglycemic and hyperglycemic episodes, so we can say that overall glycoregulation was better in our study group.

CF patients are at risk of spontaneous and iatrogenic hypoglycemia, which can occur in fasting or postprandial conditions. The pathophysiology of fasting hypoglycemia is related to malnutrition and increased energy expenditure during inflammation and acute infections. Postprandial, or reactive hypoglycemia, is the result of weakened insulin release in the first phase as the body's



response to glucose intake, and in the second phase there is prolonged and delayed insulin secretion. Additionally, an ineffective counterregulatory response to hypoglycemia may account for prolonged and additional hypoglycemia (27).

Children and adults with CF without diabetes are exposed to the risk of spontaneous hypoglycemia, which becomes more relevant with the introduction of modulatory therapy in the treatment of CF. In our patients without CFRD, between measurements the percentage of time spent in the range of glycemia below 3.0 mmol/L, i.e. the time in severe hypoglycemia (glycemia <3.1 mmol/L) increased from 0.44 ± 1.62 at the beginning of therapy to 0.90 ± 1.29 . At the same time, the percentage of time in the range of glycemia from 3.9 mmol/L to 3.1 mmol/L (TBR II) increased from 3.11 ± 5.11 to 4.00 ± 5.70 after 12 months. The total number of hypoglycemic events also increased from 7.18 ± 1.50 to 8.00 ± 12.74 . There is satisfaction that in the group of patients with CFRD there is a reduction of serious hypoglycemia <3.1 mmol/L from 0.50 ± 0.58 to 0.00 ± 0.00 after 12 months, which was contributed by the continuous monitoring of glycemia where we reduced insulin doses, but also corrected carbohydrate intake and thus achieved optimal glycemic control. Optimal glycemic control in CFRD with improvement after the introduction of modulatory therapy is becoming the standard, as there is even cessation of insulin intake, which was also the case in our study group in one patient (28).

It is noticeable that lung functions correlate positively with TIR, that is, the time spent in the target range of glycemia between 3.9 mmol/L and 10.0 mmol/L. The higher the percentage of this time, the better the lung functions are, that is, we are led to the conclusion that if glucoregulation is better, the lung functions are also better (10). What is interesting, however, is the correlation of hypoglycemia factors with lung functions, as well as the hypoglycemia parameters themselves, which increased in the entire

group under the influence of modulatory therapy, especially in subjects not on insulin therapy. The fact that hypoglycemic parameters negatively correlate with pulmonary functions in our study group is worrying, that is, the higher the percentage of time spent in hypoglycemia, or the greater the number of hypoglycemic episodes, the weaker the pulmonary functions.

For this reason, the use of continuous monitoring of glycemia, which can detect these hypoglycemic episodes, should be included in the standard practice of treating patients with cystic fibrosis. Namely, due to the negative correlation of hypoglycemia with lung functions, insulin, although necessary, must be carefully included in the therapy of people suffering from CF, because additional insulin can introduce a person to even greater hypoglycemia, which was determined by continuous monitoring of glycemia, and thus contribute reduction of lung functions. Furthermore, hypoglycemia additionally leads to energy deprivation of the body, which also weakens lung functions. The solution is an additional intake of carbohydrates, which is desirable for CF patients. However, this does not mean that it is necessary to constantly eat foods with artificial sweeteners, i.e. sweets, because such food can lead to postprandial hypoglycemia, but it is necessary to allocate additional carbohydrates to the already existing hypercaloric diet, and according to the recommendations, it is best to get UH from fruits and vegetables and fibers (29). This represents a future task for nutritionists to find the right ratios for this group of patients following continuous glycemic monitoring more often and earlier than before. The OGTT test, which is traditionally used in children >10 years of age to establish a diagnosis of diabetes, can potentially lead to hypoglycemia, but it is also misleading and the introduction of unnecessary insulin into the therapy, which can be harmful (30).

Namely, the test results should be interpreted with caution, and on the basis of them, react cautiously and make therapeutic



decisions. CGM showed in our study group that even people without diabetes, that is, insulin, can experience hypoglycemic episodes under the influence of this therapy, which lead to deterioration of lung functions. Therefore, an alternative to the OGTT test is CGM, much earlier and 10 years ago, whose results, in addition to being more graphic, can give a clear picture of hypoglycemic episodes, which are poorly or not at all detected by the OGTT test.

CONCLUSION

The initiation of CFTR modulator therapy leads to significant changes in glycemic regulation, which is reflected in more efficient insulin secretion and better utilization of glucose in the body. This has led to improved glycemic control, lower HbA1c values, and often reduced need for insulin therapy. However, these changes increase the risk of hypoglycemia, especially in the initial stages of treatment, which is why additional education of CF patients with and without diabetes about hypoglycemia and potential hypoglycemia, as well as adequate nutrition during modulator therapy is necessary. Also, CGM should be introduced before the start of this therapy to determine potentially harmful unrecognized hypoglycemia. In our study, the use of CGM proved to be a superior method compared to OGTT in disorders of glycoregulation in CF patients with and without diabetes on modulator therapy. This conclusion is very important, because the detection of hypoglycemia in patients requires timely dietary intervention and education of both the patient and the parent/guardian in order to suppress it.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data Availability Statement

The data presented in this study can be provided on request.

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Supplementary Material

Table 1. Socio-demographic, clinical and genetic characteristics of CF patients at baseline.

Variables	n	%
Sex		
Male	9	56.3
Female	7	43.8
Age, years (SV±SD)	15,68±5.46	
Initial symptoms age		
Up to 30 days	4	25.0
From 30 days to 1 year	8	50.0
More than 1 year	4	25.0
Age of diagnosis		
Up to 3 months	3	18.8
Up to 3 months to 1 year	7	43.8



From 1 to years	2	12.5
From 3 to 6 years	2	12.5
Over 6 years	2	12.5
Weight, kg (SV±SD)	42.69±17.20	
Hight, cm (SV±SD)	157.74±17.65	
BMI, kg/m² (SV±SD)	16.98±2.36	
Adequate for the age	6	37.5
Malnutrition	3	18.8
Border line	7	43.8
Initial symptoms of the disease		
Mekonial ileus	1	6.3
Sindrom of malnutrition	7	43.7
Recurrent bronchial obstructions	8	50.0
Gene mutation		
Homozygous delta F508	14	87.5
Heterozygous delta F508	2	12.5

Values are presented as mean±standard deviation for numerical variables; Categorical variables are presented as frequencies, that is, the number of individual cases with percentages of the total number of cases for each category.

Table 2. Characteristics of subjects before they started the therapy and 12 months after taking therapy for numerical variables.

Variable	Before the medicine	A year after	t-test	P
FEV1	80.13±26.27	98.06±25.21	-4.42	0.001
FVC	80.63±21.99	98.00±20.10	-4.51	<0.001
Chlorides in sweat	95.91±22.95	41.33±21.38	4.97	0.001
Body weight	42.69±17.20	51.03±12.68	-3.22	0.006
Body height	157.74±17.65	162.87±15.07	-4.20	0.001
BMI	16.98±2.36	18.94±2.50	-5.91	<0.001
Fasting blood glucose value	5.88±2.42	5.46±2.38	1.54	0.144
HbA1C	6.29±1.62	6.01±1.49	1.55	0.145

Values are shown as mean±standard deviation.

Table 3. Microbiological characteristics of the subjects.

Variable	Before therapy (n=16)	12 months after therapy (n=16)	Wilcoxon signed rank test
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			n	%			n	%	Z	P
Chronic colonization	<i>Brukholderia capacia complex</i>									
No			16	100.0			16	100.0	Not applicable.	
Yes			0	0.0			0	0.0		
Chronic colonization	<i>Pseudomonas aeruginosa</i>									
No			5	31.3			12	75.0		
Yes			6	37.5			4	25.0	-2.460	0.014
Intermittent			5	31.3			0	0.0		
Chronic colonization	<i>Staphylococcus aureus</i>									
No			0	0.0			8	50,0	-2.8282	0.005
Yes			16	100.0			8	50,0		
Bronhopulmonal compliaction	aspergylosis	lung								
No			10	62.5			16	100.0	-2.449	0.014
Yes			6	37.5			0	0.0		

Table 4. Values of parameters from the ambulatory glucose profile, 6 months and 12 months from the start of therapy, for the whole group and for subgroups of subjects who use any form of insulin, and subjects who do not use insulin.

Variable	Entire group		Subgroup on insulin		Subgruop without insulin	
	1 wearing	2 wearing	1 wearing	2 wearing	1 wearing	2 wearing
N	13	13	4	3	9	10
TIR	92.69±8.41	94.00±6.15	87.75±12.84	95.67±5.77	94.89±5.16	93.50±6.47
TAR_I	3.54±7.51	1.92±2.33	7.50±13.67	3.33±4.04	1.78±1.79	1.50±1.65
TAR_II	0.15±0.55	0.23±0.60	0.50±1.00	0.67±1.15	0.00±0.00	0.10±0.31
TBR_I	3.31±4.87	3.15±5.19	3.75±4.99	0.33±0.58	3.11±5.11	4.00±5.70
TBR_II	0.48±0.95	0.69±1.18	0.50±0.58	0.00±0.00	0.44±1.62	0.90±1.29
No. hypo	5.92±7.94	6.54±11.41	8.25±10.21	1.67±2.08	7.18±1.50	8.00±12.74
No. hyper	6.00±10.96	4.30±6.21	11.75±19.12	7.67±12.42	4.39±1.46	3.30±3.50
CV	22.80±4.76	23.49±4.87	22.93±5.22	23.47±5.85	22.74±4.88	23.50±4.90
GMI	5.94±0.40	5.88±0.26	6.10±0.67	6.10±0.26	5.88±0.22	5.82±0.24
SG	6.11±0.89	5.98±0.60	6.48±1.56	6.50±0.70	5.94±0.43	5.82±0.50



Values are shown as mean $\pm$ standard deviation. TIR (Time In Range) – time spent in the range of glycemia from 3.9 to 10.0 mmol/L; TAR_I (Time Above Range_I) time spent in the glycemic range between 10.0 – 13.9 mmol/L; TAR_II (Time Above Range_II) – time spent in the glycemic range over 13.9 mmol/L; TBR_I (Time Below Range_I) - time spent in the glycemic range between 3.0 - 3.9 mmol/L; TBR_II (Time Below Range_II) - time spent in the glycemic range below 3.0 mmol/L; CV (Coefficient of Variation) – coefficient of variation expressed in percentages; GMI (Glucose management Indicator) – Glucose management indicator expressed in percentages; SG (sensor glucose value) – average value of glucose concentration in mmol/L measured by the sensor. A hypoglycemic or hyperglycemic episode is understood if the testee was below 3.9 mmol/L or 10.0 mmol/L for more than 15 minutes.

Table 5. Correlation of lung function parameters with variables from ambulatory glucose profile. Correlation was calculated as Pearson's correlation coefficient with p value <0.05 as statistically significant.

Variable	FEV1						FVC					
	Entire group		Insulin		No-insulin		Entire group		Insulin		No-insulin	
	Coef f.	p	Coef f.	p	Coef f.	P	Coef f.	p	Coef f.	p	Coef f.	P
TIR	0.819	0.001	-0.064	0.959	0.893	0.001	0.657	0.015	-0.995	0.065	0.804	0.005
TAR_I	0.014	0.964	0.064	0.959	-0.034	0.925	0.157	0.609	0.995	0.065	-0.071	0.846
TAR_II	-0.051	0.870	0.064	0.959	-0.203	0.574	0.093	0.762	0.995	0.065	-0.299	0.401
TBR_I	- 0.825	<0.001	0.064	0.959	- 0.845	0.002	- 0.727	0.005	0.995	0.065	- 0.747	0.013
TBR_II	- 0.640	0.019	NA	NA	- 0.651	0.042	- 0.577	0.039	NA	NA	-0.574	0.083
No. hypo	- 0.879	<0.001	0.302	0.805	- 0.893	<0.001	- 0.781	0.002	0.941	0.219	- 0.808	0.005
No. hyper	-0.030	0.922	0.024	0.985	-0.123	0.735	0.163	0.595	0.998	0.039	-0.110	0.763
CV	-0.458	0.116	0.149	0.905	-0.535	0.111	-0.344	0.249	0.983	0.119	-0.523	0.121

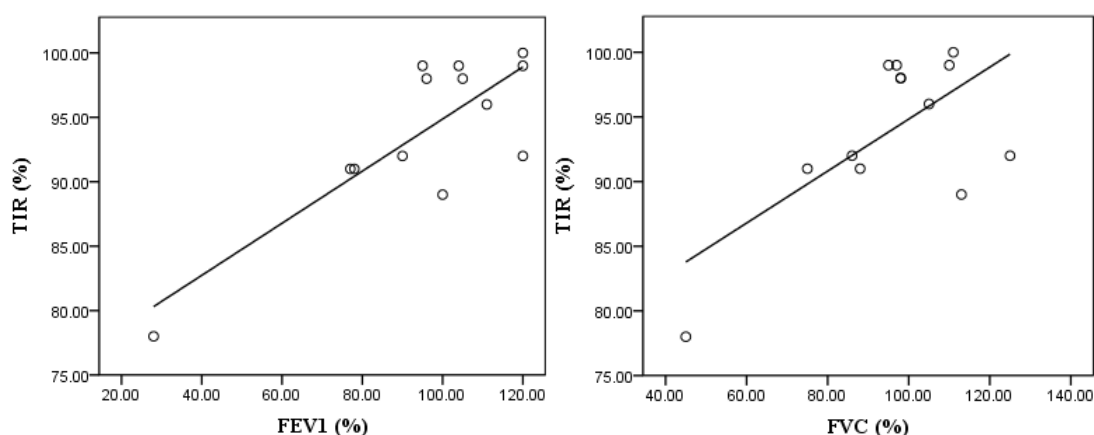


GMI	0.44 1	0.132	0.25 1	0.83 8	0.50 2	0.140	0.46 3	0.11 1	0.95 8	0.18 6	0.40 5	0.24 5
SG	0.46 9	0.106	0.20 6	0.86 8	0.58 2	0.078	0.52 1	0.06 9	0.97 0	0.15 6	0.49 5	0.14 5

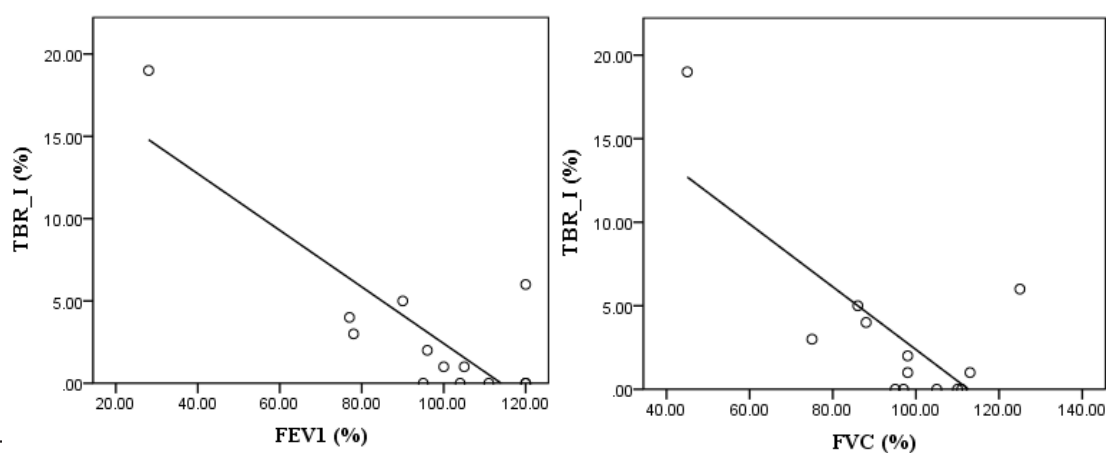
Values are shown as mean $\pm$ standard deviation. TIR (Time In Range) – time spent in the range of glycemia from 3.9 to 10.0 mmol/L; TAR_I (Time Above Range_I) time spent in the glycemic range between 10.0 – 13.9 mmol/L; TAR_II (Time Above Range_II) – time spent in the glycemic range over 13.9 mmol/L; TBR_I (Time Below Range_I) - time spent in the glycemic range between 3.0 - 3.9 mmol/L; TBR_II (Time Below Range_II) - time spent in the glycemic range below 3.0 mmol/L; CV (Coefficient of Variation) – coefficient of variation expressed in percentages; GMI (Glucose management Indicator) – Glucose management indicator expressed in percentages; SG (sensor glucose value) – average value of glucose concentration in mmol/L measured by the sensor. A hypoglycemic or hyperglycemic episode is understood if the testee was below 3.9 mmol/L or 10.0 mmol/L for more than 15 minutes.

Graph 1. Linear regression dependence of FEV1 and FVC with the parameter of glycemic variability from the ambulatory glucose profile:

(C) Time in range - TIR (%) or time spent in glucose range from 3.9 mmol/L to 10.0 mmol/L, where it is notable direct correlation.

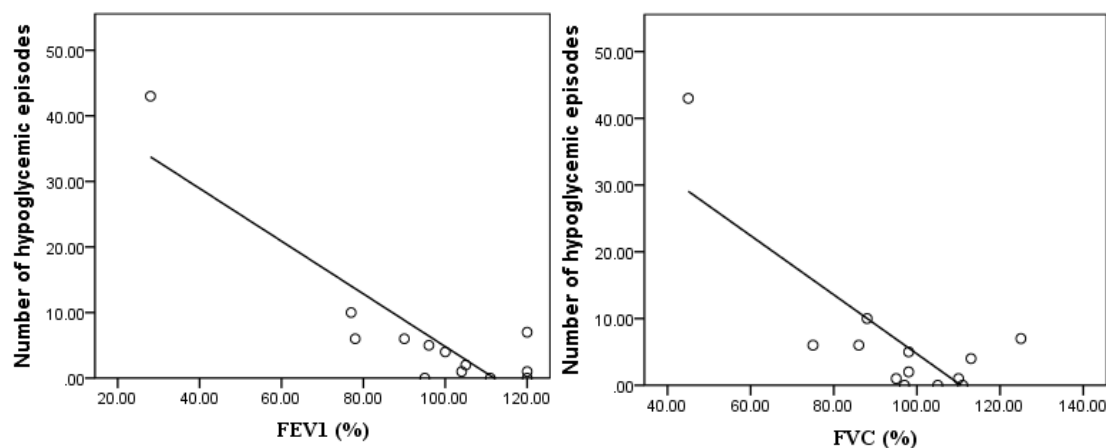


(B) Time below range – TBR_I (%) or time spent in glucose rang from 3.1 mmol/L to 3.9 mmol/L, where it is notable indirect correlation.





(C) Number of hypoglycemic episode where it is notable indirect correlation.



ABSTRACT *The aim: The discovery of so-called CFTR modulators has set a new milestone in the treatment of cysticfibrosis (CF) for patients with F508del mutations. Methods: The impact of modulatory therapy on glycoregulation in patients with CF before and one year after the introduction of therapy. Results: 16 patients were treated at the Clinic for Children's Diseases in Banja Luka, clinical, microbiological characteristics, as well as continuous glucose measurement by placing a glucometer were monitored during 12 months of therapy. Conclusion: The use of a glucose sensor proved to be a superior method compared to OGTT in the treatment of glycoregulation disorders in our patients.*

Keywords: cystic fibrosis, modulator therapy, lung function, glycoregulation, continuous glucose monitoring, hypoglycemia.

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