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THE COURSE OF GLUCOSE INTOLERANCE IN CHILDREN WITH CYSTIC FIBROSIS: A RETROSPECTIVE STUDY – PRELIMINARY REPORT

PRZEBIEG NIETOLERANCJI GLUKOZY U DZIECI Z MUKOWISCYDOZĄ: BADANIE RETROSPEKTYWNE – DONIESIENIE WSTĘPNE

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Abstract

Diabetes is a common and severe complication of cystic fibrosis. If unrecognized, the condition not only causes deterioration of pulmonary function and failure to gain weight, but also a six-fold increase in mortality.

Aim: *1. To evaluate the course of abnormal glucose tolerance and cystic fibrosis-related diabetes (CFRD), as well as the effects of treating these conditions in children with cystic fibrosis. 2. To analyze the association between the classes of mutations in both alleles of the CFTR gene and glucose intolerance.*

Materials and methods: *Analysis was undertaken of the clinical records of 12 children (from the years 2002 to 2014), who were under the care of the Diabetes Outpatient Clinic at the Medical University of Warsaw and the Cystic Fibrosis Centre of the Institute of Mother and Child in Warsaw. The patients were divided into groups based on glucose tolerance categories in the Oral Glucose Tolerance Test (impaired glucose tolerance - IGT, cystic fibrosis related diabetes without fasting hyperglycemia – CFRD FH(-) or with fasting hyperglycemia – CFRD FH (+)). The mean age of the children who were referred to the Diabetes Outpatient Clinic was 12.09±3.57 years and the mean HbA1c at the baseline versus the end of the follow up was 6.16±1,77% versus 6.03±1.05%, respectively. We used the continuous glucose monitoring system (CGMS) for the diagnostics of 4 patients. The mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene were investigated in all the patients. All the children had mutations in at least one allele of the CFTR gene belonging to class I or II. Six (6/12) patients were homozygous, and 3 (3/12) patients heterozygous for the Phe508del (former F508del) mutation. Three children had other mutations (1717-1G>A/2183AA-G, R553X/3380delGAAG, G542X/2143delT).*

Results: *In our study group we recognized impaired glucose tolerance (IGT) in 7 (7/12) patients and cystic fibrosis-related diabetes (CFRD) in 5 (5/12) patients; there were 4 patients with CFRD FH(+) and 1 patient with CFRD FH(-). During follow up we observed IGT deterioration of glucose tolerance towards CFRD FH(-) in 4(4/7) patients. Eight (8/12) patients were on functional insulin therapy, five of them (5/8) used insulin pumps. The remaining patients (4 individuals - 4/12), who were in good condition and on a high-glycemic index product restricted diet, did not require insulin. In the group treated with insulin we observed improvement in BMI z-scores (from-1.14 to -0.70).*

Conclusions: *Glucose tolerance in children with cystic fibrosis deteriorates with age. Patients in a good condition and with good compliance to a low-glycemic index product diet, start insulin therapy later. Patients with a severe course of cystic fibrosis and diabetes require immediate insulin implementation. Insulin treatment improves their nutritional status. A continuous glucose monitoring system is a useful diagnostic tool which can be taken into account in therapeutic decisions. Prospective studies on the pediatric population with cystic fibrosis are needed in Poland for a better analysis of the associations between abnormal glucose tolerance, the class of mutation in the CFTR gene and the impact of glucose intolerance treatment on the clinical status of the patients.*

Key words: cystic fibrosis related diabetes, insulin, pump, glucose monitoring

Streszczenie

Cukrzyca jest częstym i ciężkim powikłaniem mukowiscydozy. Nierozpoznana nie tylko prowadzi do pogorszenia czynności płuc i słabszych przyrostów masy ciała, lecz również zwiększa 6-krotnie śmiertelność.

Cel: *1. Ocena przebiegu zaburzeń tolerancji glukozy i cukrzycy u dzieci z mukowiscydozą oraz efekty ich leczenia. 2. Ocena związku pomiędzy klasą mutacji w genie CFTR i nietolerancją glukozy.*

Materiały i metody: *Przeanalizowano retrospektywnie dokumentację medyczną 12 dzieci (z lat 2002--2014), będących pod opieką Poradni Diabetologicznej Kliniki Pediatrii Warszawskiego Uniwersytetu Medycznego i Zakładu Mukowiscydozy Instytutu Matki i Dziecka w Warszawie. Pacjentów podzielono według kategorii zaburzeń tolerancji glukozy w teście doustnego obciążenia glukozą (nieprawidłowa tolerancja glukozy, cukrzyca związana z mukowiscydozą bez hiperglikemii na czczo, cukrzyca związana z mukowiscydozą z hiperglikemią na czczo). Średni wiek dziecka w momencie skierowania do Poradni Diabetologicznej wynosił 12,09±3,57 lat, średnia wartość HbA1c na początku i na końcu obserwacji wynosiła 6,16±1,77% versus 6,03±1,05. U 4 pacjentów w trakcie diagnostyki zaburzeń przemiany węglowodanowej zastosowano ciągły monitoring glikemii. U wszystkich dzieci oznaczono klasy mutacji w genie CFTR. Wszyscy pacjenci mieli przynajmniej w jednym allelu genu CFTR mutacje należące do I lub II klasy. Sześcioro (6/12) pacjentów było homozygotami a troje (3/12) pacjentów heterozygotami mutacji Phe508del (dawniej F508del). Troje dzieci miało inne mutacje (1717-1G>A/2183AA-G, R553X/3380delGAAG, G542X/2143delT).*

Wyniki: *U 7 (7/12) pacjentów z badanej grupy rozpoznano nieprawidłową tolerancję glukozy, u 5 (5/12) pacjentów cukrzycę związaną z mukowiscydozą w tym u 4 pacjentów z hiperglikemią na czczo a u jednego bez hiperglikemii na czczo. W trakcie obserwacji stwierdziliśmy u 4 (4/7) pacjentów z nieprawidłową tolerancją glukozy pogorszenie jej przebiegu w kierunku cukrzycy bez hiperglikemii na czczo. U 8 (8/12) pacjentów zastosowano insulinoterapię, u większości (5/8) pacjentów przy pomocy pompy insulinowej. Pozostali pacjenci (4 osoby -4/12), którzy byli w dobrym stanie klinicznym i przestrzegali diety z ograniczeniem produktów o wysokim indeksie glikemicznym, nie wymagali insulinoterapii. U pacjentów leczonych insuliną obserwowano wzrost BMI z-scores (z -1,14 do -0,70).*

Wnioski: *Tolerancja glukozy u dzieci z mukowiscydozą pogarsza się z wiekiem. Pacjenci w dobrym stanie klinicznym i przestrzegający diety z ograniczeniem produktów o wysokim indeksie glikemicznym wymagają insulinoterapii w późniejszym okresie. Pacjenci z ciężkim przebiegiem mukowiscydozy i cukrzycą wymagają natychmiastowej insulinoterapii. Leczenie insuliną poprawia stan odżywienia. Ciągły monitoring glikemii jest przydatnym narzędziem diagnostycznym, który należy brać pod uwagę przy podejmowaniu decyzji terapeutycznych. Prospektywne badania większej populacji pediatrycznej chorych na mukowiscydozę w Polsce są potrzebne, celem lepszego poznania związku pomiędzy zaburzeniami tolerancji glukozy, klasą mutacji w genie CFTR, wpływu metody leczenia zaburzeń tolerancji glukozy na stan kliniczny pacjentów.*

Słowa kluczowe: cukrzyca związana z mukowiscydozą, insulina, pompa, monitoring glikemii

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INTRODUCTION

Cystic fibrosis-related diabetes (CFRD) is a common and serious co-morbidity. The pathophysiology of CFRD differs from both type 1 and type 2 diabetes and requires a unique clinical approach to diagnosis and management [1, 2]. Insulin deficiency is believed to be the primary cause of CFRD, but insulin resistance is also noted in cystic fibrosis patients [3].

The prevalence of this condition increases with age, from 9% in children aged 10 years or less to 43% in those beyond 30 years of age [4]. We predict an increase in the occurrence of CFRD due to the longer survival of patients. CFRD is not only known to cause a six-fold increase of the risk of death, but is also associated with pulmonary function decline and poor weight gain [5].

Given the insidious onset of this condition, deterioration in health status and diabetes-related complications, annual screening has been recommended in all children from the age of 10 years [1]. An oral glucose tolerance test is the recommended method of diagnosing cystic fibrosis-related diabetes, but it has some limitations. It cannot detect early abnormalities in glucose regulation. The beneficial role of a continuous glucose monitoring system (CGMS) in such cases was emphasized in previous studies [6].

Insulin replacement therapy is the treatment of choice for patients with CFRD [2]. Hardin reported in his study

that continuous subcutaneous insulin infusion (CSII) compared with basal-bolus insulin injection therapy, improves HbA1c, and increases BMI and body weight without causing hypoglycemia [7].

AIM

The aim of the study was:

1. To evaluate the course of abnormal glucose tolerance and cystic fibrosis-related diabetes (CFRD), as well as the effects of their treatment in children with cystic fibrosis.

2. To analyze the association between classes of mutations in both alleles of the CFTR gene and glucose intolerance.

MATERIAL AND METHODS

We retrospectively analyzed the clinical records of 12 children with cystic fibrosis who attended the Diabetes Outpatient Clinic at the Medical University of Warsaw and the Cystic Fibrosis Centre of the Institute of Mother and Child in Warsaw from 2002 to 2014. CFRD or IGT was diagnosed either in patients with clinical symptoms of hyperglycemia or in asymptomatic patients on the basis of an oral glucose tolerance test (OGTT) [2]. The reasons for referral to the Clinic were either impaired glucose tolerance or CFRD. Patients were under the control of the Diabetes Outpatient Clinic till their transfer to the Adults' Department at the age of 18 years. Most of the patients (10/12) were referred to the Diabetes Outpatient Clinic due to abnormal results in the screening test, 2 patients had symptoms of diabetes without ketoacidosis.

HbA1c assays were analyzed in order to assess the metabolic control of diabetes. Additionally, we evaluated other comorbidities in these patients, the treatment methods of abnormal glucose tolerance, the use of oral corticosteroids, their clinical status, BMI z-score, and mutations in the CFTR gene. We divided the children into groups based on the results of OGTT (IGT, CFRD FH(-), CFRD FH(+)) See Table I and Table II.

A statistical analysis was performed with Statistica 10 (StatSoft, Inc, Tulusa, USA) software. The assumption that the data were sampled from populations that follow Gaussian distributions was tested using the Kolmogorov and Smirnov methods. The BMI z-score was calculated using the World Health Organization AnthroPlus Calculator.

During the 12-year follow-up, data of 12 patients (8 girls and 4 boys) were analyzed. The mean age of the patients at baseline was 12.09±3.57 years and the mean HbA1c at baseline and at the end of the follow up was 6.16±1.77% and 6.03±1.05%, respectively. The mean age of the girls and the mean age of the boys at the time of diagnosis of abnormal glucose tolerance was 13.04±3.71 years and 10.19±2.74 years, respectively. The mean age of diagnosing cystic fibrosis was 3 months. We used a continuous glucose monitoring system at home for the diagnosis of four asymptomatic patients, which revealed post-prandial intermittent hyperglycemia (see an example in Figure 1). All the patients had exocrine pancreatic insufficiency. Four (4/12) children developed liver disease (see Table I and Table II).

RESULTS

Impaired glucose tolerance was recognized in 7 (7/12) patients, during follow-up 4 (4/7) patients developed cystic fibrosis related diabetes. Five (5/12) patients had CFRD: 4 patients had CFRD FH(+), 1 patient had CFRD FH(-).

2 patients had co-morbidities, which could have affected the onset of diabetes. One of them was treated with oral glucocorticosteroids due to juvenile idiopathic arthritis prior to the diagnosis of CFRD. The second girl developed diabetes one month after lung transplantation, being on immunosuppressive therapy. Three patients (only boys) had chronic respiratory failure and needed oxygen supplementation. Two of them underwent lung transplantation later on.

Three (3/12) patients underwent lung transplantation (LTx) due to chronic pulmonary failure in the course of the end stage of the broncho-pulmonary disease. One of them (1/3) had LTx prior to diagnosis of CFRD FH(+). Two patients (2/3) had LTx at the end of the follow up. Unfortunately, one of them died because of complications of a cytomegalovirus (CMV) chronic infection.

The mean HbA1c in the patients with IGT and CFRD at the time of diagnosis was 5.62±0.63% and 6.55±2.51%, respectively. The mean HbA1c in patients treated with insulin and being in good condition on a high-glycemic index product restricted diet during the follow up was 6.80±0.70 and 5.47±0.15 respectively. Changes in HbA1c in each individual treated with insulin can be seen in Figure 2. Changes in HbA1c in patients on a high-glycemic index product restricted diet can be seen in Figure 3. We recommended a high-glycemic index product restricted diet to 7 (7/12) patients - in 4 (4/7) cases in good clinical condition with good clinical effect, 3 (3/7) subjects started insulin therapy during the follow up, due to the deterioration of glucose tolerance. Eight (8/12) patients received insulin treatment. Five (5/8) of them were on insulin pump therapy (based on a basal/bolus regimen) with a mean daily insulin requirement of 0.64 units per kilogram of body weight. All the patients used insulin aspart in pumps. 3 patients used insulin pens. The insulin regimen was three daily injections of short-acting insulin in 2 patients; in 1 case three daily injections of short-acting insulin and intermediate-acting insulin (NPH) once.

The mean BMI z-scores in the group treated with insulin in the 5 years preceding the onset of the insulin therapy was -1.14. In this group, after insulin initiation, the mean BMI z-scores improved to -0.70. The BMI z-scores in patients treated with insulin is shown in Figure 4. In comparison with this group, the BMI z-scores in the group on the high-glycemic index product restricted diet deteriorated from 0.66 prior to referral to the Diabetes Outpatient Clinic to 0.35 during follow up. The BMI z-scores in patients on a high-glycemic index product restricted diet are shown in Figure 5.

We did not find any acute or chronic complication of diabetes in our patients during follow up.

Table I. Characteristics of patients with IGT.

Tabela I. Charakterystyka pacjentów z nieprawidłową tolerancją glukozy.

Initials ***Inicjały***	**Age at onset of CF (years)** ***Wiek w momencie rozpoznania mukowiscydozy (w latach)***	**Age of referral to the Diabetes Outpatient Clinic (years)** ***Wiek skierowania do Poradni Diabetologicznej (lata)***	**Abnormalities in OGTT** ***Nieprawidłowości w OGTT***	**Kind of treatment** ***Rodzja leczenia***	**CFTR gene mutations (Class)** ***Mutacje w genie CFTR (klasa)***
G.E.	1	11,38	IGT	Diet-insulintherapy (pump) *Dieta-insulinoterapia (pompa)*	*Phe508del G542x (II/I)*
O.P.	4/12	13,78	IGT	Insulintherapy (pens-pump) *Insulinoterapia (peny-pompa)*	*Phe508del Phe508del (II/II)*
K.M.	3/12	15,78	IGT	Diet-insulintherapy (pens) *Dieta-insulinoterapia (peny)*	*G542x 2143delT (I/I)*
J.K.	3/12	10,68	IGT	Diet-insulintherapy (pens) *Dieta-insulinoterapia (peny)*	*Phe508del Phe508del (II/II)*
D.M.	2/12	6,39	IGT	Diet *Dieta*	*Phe508del N1303K (II/II)*
U.M.	1/12	9,62	IGT	Diet *Dieta*	*Phe508del Phe508del (II/II)*
Z.M.	10	16,13	IGT	Diet / *Diet*	*1717-1 2183AA-G (I/I)*

Table I. Cont.
Tabela I. Cd.

Complications of CF and comorbidities ***Powikłania mukowiscydozy i choroby dodatkowe***	**Dosage of insulin at the beginnig /end of treatment (u/kg/day)** ***Dawka insuliny na początku /końcu terapii (u/kg/dobę)***	**Basal/bolus percentage at the beginning /end of treatment** ***Procent insuliny bazalnej /bolusowej na początku /końcu leczenia***	**Circumstances of diagnosis of glucose abnormalities (screening, symptoms, exacerbations)** ***Okoliczności rozpoznania zaburzeń gospodarki węglowodanowej (badania przesiewowe, objawy, zaostrzenia)***
Liver cirrhosis, exocrine pancreatic insufficiency *Marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki*	0,59/1,35	(19/81)/ (23/77)	Routine screening *Badania przesiewowe*
Lung transplantation due to chronic respiratory failure, liver cirrhosis, exocrine pancreatic insufficiency *Transplantacja płuc z powodu przewlekłej niewydolnosci oddechowej, marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki*	0,33/0,30	(0/100)/ (0/100)	Broncho-pulmonary exacerbations *Zaostrzenia choroby oskrzelowo-płucnej*
Juvenile idiopathic arthristis, exocrine pancreatic insufficiency *Młodzieńcze idiopatyczne zapalenie stawów, zewnątrzwydzielnicza niewydolność trzustki*	0,55/0,96	(0/100)/ (0/100)	Routine screening *Badania przesiewowe*
Chronic respiratory failure, hepatosplenomegaly, exocrine pancreatic insufficiency *Przewlekła niewydolność oddechowa, hepatosplenomegalia, zewnątrzwydzielnicza niewydolność trzustki*	0,12/0,15	(0/100)/ (0/100)	Broncho-pulmonary exacerbations *Zaostrzenia choroby oskrzelowo-płucnej*
Exocrine pancreatic insufficiency *Zewnątrzwydzielnicza niewydolność trzustki*	-	-	Routine screening *Badania przesiewowe*
Exocrine pancreatic insuficiency *Zewnątrzwydzielnicza niewydolność trzustki*	-	-	Routine screening *Badania przesiewowe*
Exocrine pancreatic insufficiency *Zewnątrzwydzielnicza niewydolność trzustki*	-	-	Routine screening *Badania przesiewowe*

Table II. Characteristics of patients with CFRD

Tabela II. Charakterystyka pacjentów z cukrzycą związaną z mukowiscydozą

Initials ***Inicjały***	**Age at onset of CF (years)** ***Wiek w momencie rozpoznania mukowiscydozy (w latach)***	**Age of referral to the Diabetes Outpatient Clinic (years)** ***Wiek skierowania do Poradni Diabetologicznej (lata)***	**Abnormalities in OGTT** ***Nieprawidłowości w OGTT***	**Kind of treatment** ***Rodzja leczenia***	**CFTR gene mutations (Class)** ***Mutacje w genie CFTR (klasa)***
Z.N.	3/12	17,3	CFRD FH(+)	Insulintherapy (pens-pump) *Insulinoterapia (peny-pompa)*	*R553X 3380G>A (I/I)*
R.K.	3/12	14,53	CFRD FH(+)	Insulintherapy (pump) *Insulinoterapia (pompa)*	*Phe508del G542x (II/I)*
M.D.	3/12	8,82	CFRD FH(+)	Insulintherapy (pens-pump) *Insulinoterapia (peny-pompa)*	*Phe508del Phe508del (II/II)*
P.S.	7	7,46	CFRD FH(+)	Insulintherapy (pens) *Insulinoterapia (peny)*	*Phe508del nieznana (II/unkown)*
U.D.	2/12	13,16	CFRD FH (-)	Diet *Dieta*	*Phe508del Phe508del (II/II)*

Table II. Cont.
Tabela II. Cd.

Complications of CF and comorbidities ***Powikłania mukowiscydozy i choroby dodatkowe***	**Dosage of insulin at the beginnig /end of treatment (u/kg/day)** ***Dawka insuliny na początku /końcu terapii (u/kg/dobę)***	**Basal/bolus percentage at the beginning /end of treatment** ***Procent insuliny bazalnej /bolusowej na początku /końcu leczenia***	**Circumstances of diagnosis of glucose abnormalities (screening, symptoms, exacerbations)** ***Okoliczności rozpoznania zaburzeń gospodarki węglowodanowej (badania przesiewowe, objawy, zaostrzenia)***
Lung transplantation due to chronic respiratory failure, exocrine pancreatic insufficiency *Transplantacja płuc z powodu przewlekłej niewydolności oddechowej, zewnątrzwydzielnicza niewydolność trzustki*	0,96/0,43	(27/73)/ (63/37)	Routine screening after lung transplantation *Badania przesiewowe po transplantacji płuc*
Exocrine pancreatic insufficiency *Zewnątrzwydzielnicza niewydolność trzustki*	1,04/1,50	(15/85)/ (21/79)	Polidypsia, poliuria *Polidypsja, wielomocz*
Lung transplantation due to chronic respiratory failure and recurrent pneumothorax, osteoporosis, liver cirrhosis, exocrine pancreatic insufficiency *Transplantacja płuc z powodu przewlekłej niewydolności oddechowej i nawracającej odmy opłucnowej, osteoporoza, marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki*	0,25/1,22	(9/91)/ (18/82	Broncho-pulmonary exacerbations *Zaostrzenia choroby oskrzelowo-płucnej*
Exocrine pancreatic insufficiency *Zewnątrzwydzielnicza niewydolność trzustki*	0,51/0,83	(7/93)/ (17/83)	Loss of weight, broncho-pulmonary exacerbations *Utrata masy, zaostrzenia choroby oskrzelowo-płucnej*
Exocrine pancreatic insufficiency *Zewnątrzwydzielnicza niewydolność trzustki*	-	-	Routine screening *Badania przesiewowe*

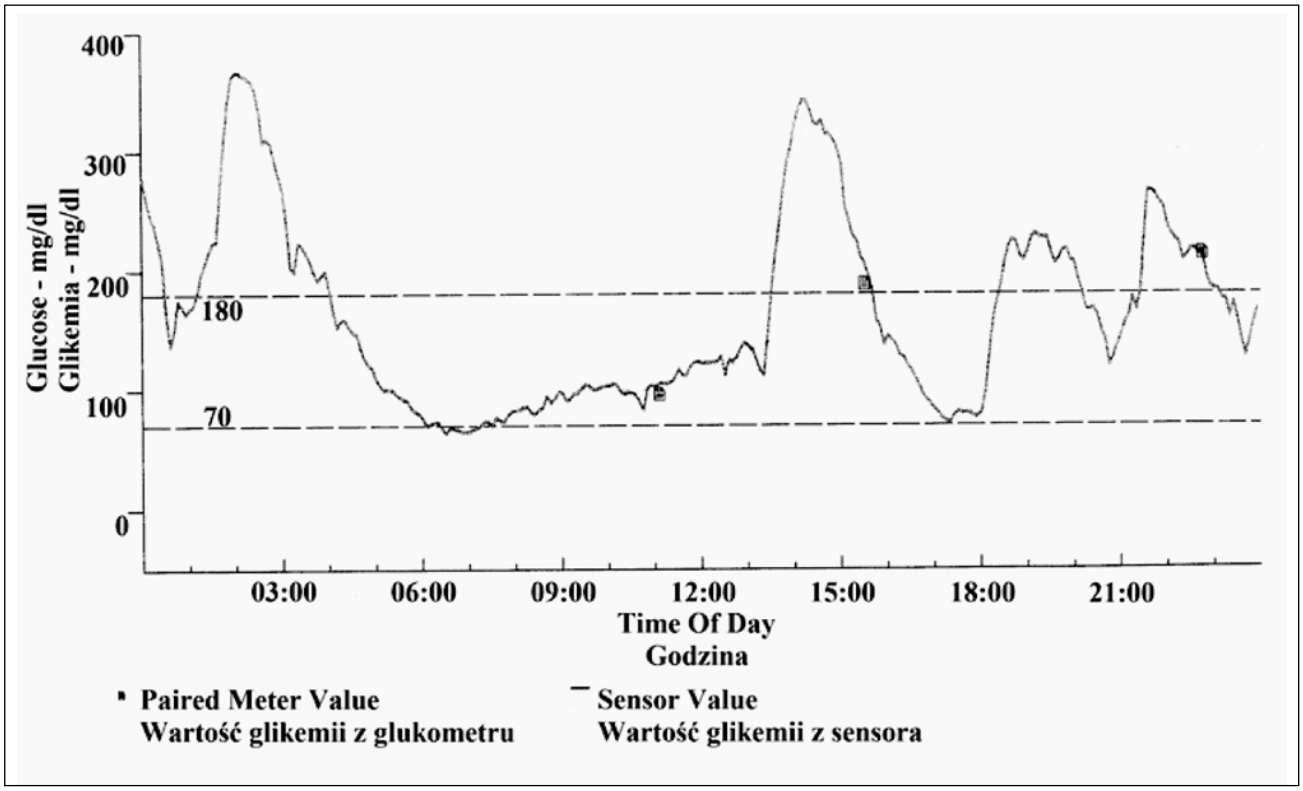

Fig. 1. Example of CGMS in a child with impaired glucose tolerance and cystic fibrosis. Postprandial hyperglycemia after high glycemic index meals.

Ryc. 1. Przykład zapisu monitoringu glikemii u dziecka z mukowiscydozą i nieprawidłową tolerancją glukozy. Poposiłkowe hiperglikemie po posiłkach o wysokim indeksie glikemicznym.

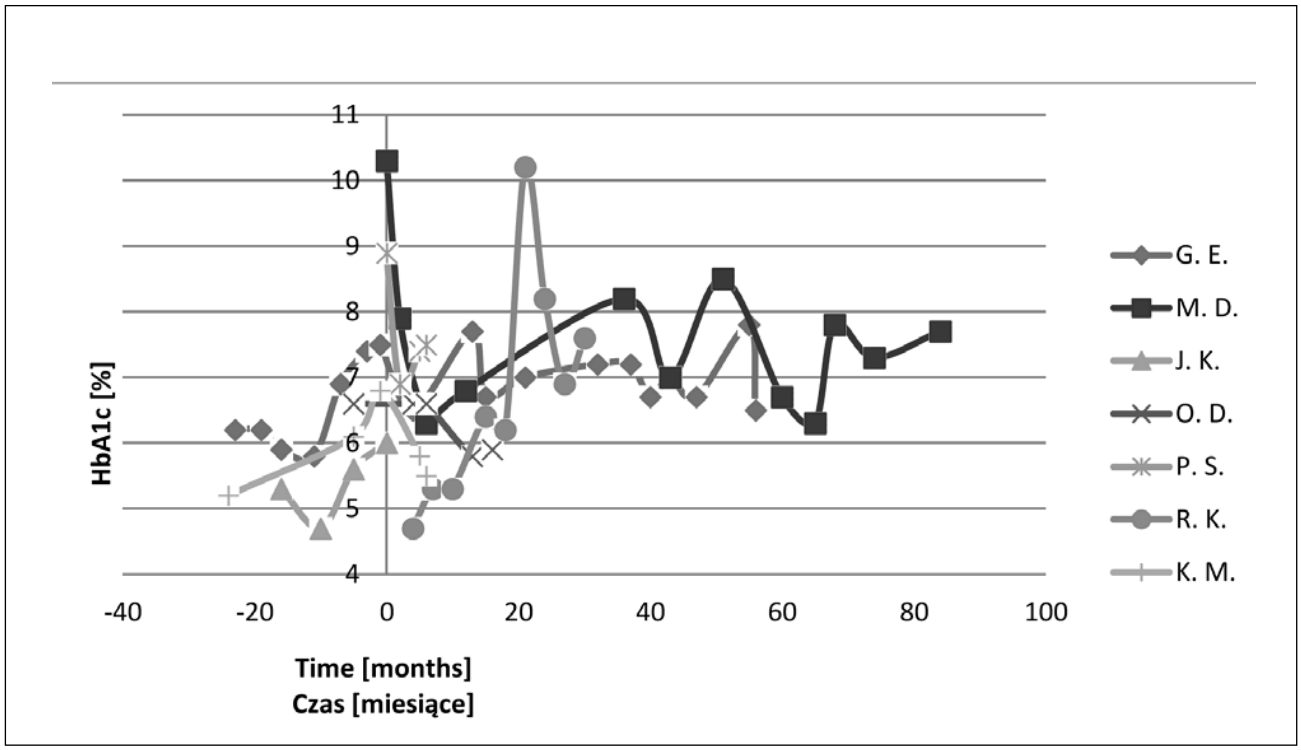

Fig. 2. The mean HbA1c in subject streated with insulin before and after beginning of treatment.

Ryc. 2. Średnie wartości HbA1c u pacjentów leczonych insuliną przed i po jej włączeniu.

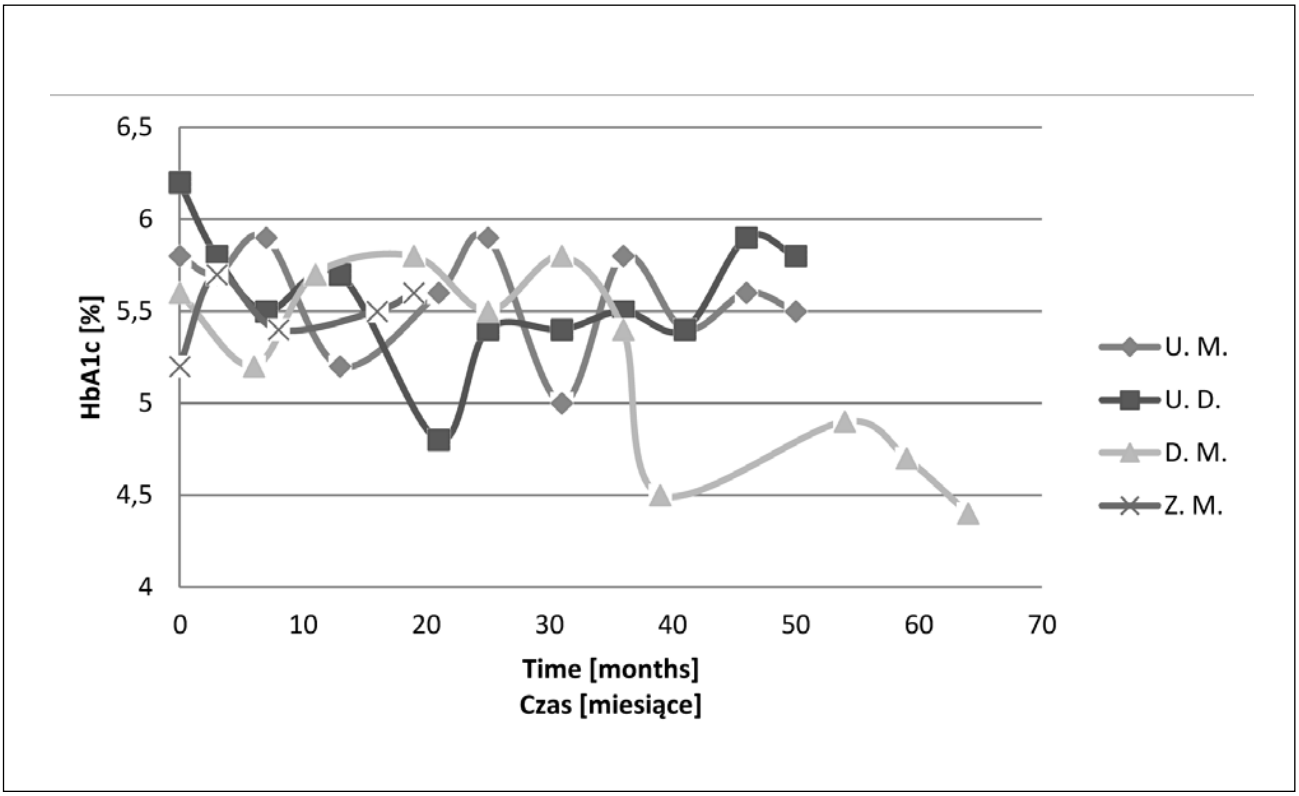

Fig. 3. The mean HbA1c in subjects on high glycemic index restricted diet.

Ryc. 3. Średnie wartości HbA1c u pacjentów na diecie z ograniczeniem produktów o wysokim indeksie glikemicznym.

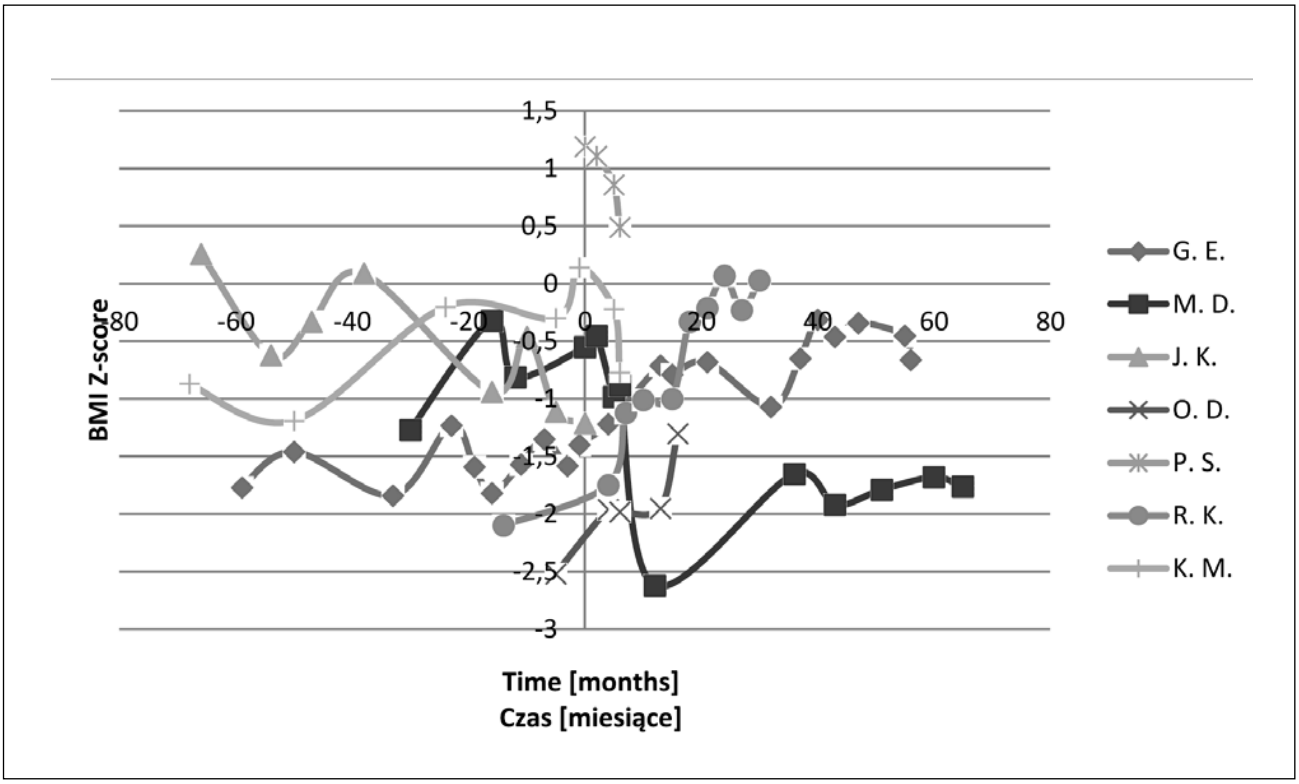

Fig. 4. BMI z-score in patients treated with insulin before and after initiation of insulin.

Ryc. 4. Wartości BMI z-score u pacjentów leczonych insuliną przed i po jej włączeniu.

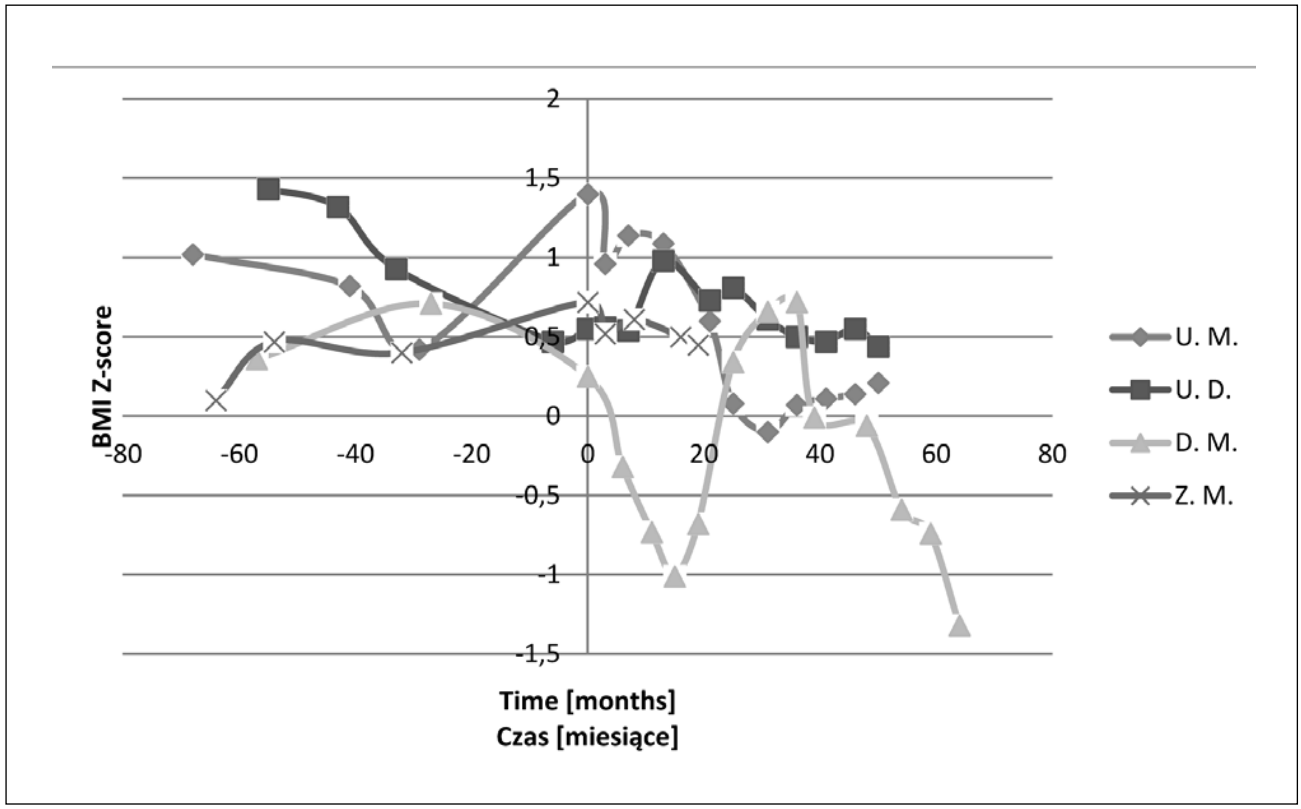

Fig. 5. BMI z-score in patients on high-glycaemic index restricted diet before and after referral to the Diabetes Outpatient Clinic.

Ryc. 5. Wartości BMI z-score u pacjentów na diecie z ograniczeniem produktów o wysokim indeksie glikemicznym przed i po skierowaniu do Poradni Diabetologicznej.

Mutations associated with cystic fibrosis were divided into classes reflecting CFTR functions: class I: G542X, R553X, 1717-1G>A, 3380delGAAG, 2183AA-G, 2143delT; class II: Phe508del (former F508del), N1303K. Genotype analysis of subjects revealed 5 (5/12) homozygous and 4 (4/12) heterozygous for Phe508del and other mutations (1717-1G>A/2183AA-G, R553X/3380delGAAG, G542X/2143delT) in 3 (3/12) patients. The classes of mutations in the CFTR gene are shown in Table I and Table II. We did not find class III, IV, V, VI mutations in our patients. Ten patients had severe mutations (class I through class II) in both alleles. One patient had a severe mutation in one allele, and had an unidentified mutation in the second allele.

DISCUSSION

The clinical presentation of abnormal glucose tolerance in children with cystic fibrosis is subtle [14]. In our study only 2 patients reported symptoms of hyperglycemia. Moreover, the HbA1c level did not distinguish between impaired glucose tolerance and CFRD. It is well known that CF patients often have an increased red blood cell turnover due to chronic hypoxia [15]. HbA1c can be falsely low and is not recommended as a reliable screening test in this population. Lang et al. found elevated HbA1c levels in only 16% patients with CFRD at the time of diagnosis [14].

There were 8 female patients included in our study. The association between female sex and CFRD is well described. Some researchers suggested earlier puberty as an explanation for these results and noted an increase of incidence in girls between the age of 5 and 10 years [10]. In our study, the mean age of girls on diagnosis of abnormal glucose tolerance was 13.04 ±3.71 years.

In 4 asymptomatic patients we used CGMS, which revealed postprandial hyperglycemia following high-glycemic index meals. We found CGMS useful especially for patients with impaired glucose tolerance and treated with a high-glycemic product restricted diet.

In our study we found 3 patients with poor pulmonary function who were treated with insulin. The study of Adler et al. confirmed the association of poor pulmonary function or corticosteroid use with CFRD [8]. Nevertheless, we did not analyze the association between glucose tolerance abnormalities and changes of FEV1 and FVC during the follow up in the study group. Other studies showed an accelerated decline in pulmonary function prior to the diagnosis of CFRD. It should be noted that pulmonary disease is more severe in patients with CFRD, with greater decline in lung function, more frequent pulmonary exacerbations

and an increased frequency of pathogens in the sputum culture [9]. However, two subjects were treated with oral glucocorticoids due to pulmonary exacerbation, which leads to hyperglycemia.

The association between the genotype and CFRD is controversial. Patients with the first and second class of mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene are at risk of developing cystic fibrosis-related diabetes. The development of diabetes in CF is related to pancreatic insufficiency, which correlates to mutations in the CFTR gene, especially for *Phe508del* mutation. Class I to III mutations are associated with exocrine pancreatic insufficiency, whereas class IV to VI mutations are not associated with pancreatic insufficiency[3]. Genotype analysis of our study revealed 5 patients with mutations of *Phe508del* in both alleles and 4 with *Phe508del* mutations in one allele. The most frequent mutation in our population is *Phe508del*. Cucinotta et al. demonstrated that *Phe508del* homozygosity may predispose to the risk of diabetes, which is consistent with the results of our study results. He also indicated that the *N1303K* mutation seems to play a protective role [10]. In contrast to this result, in our study one patient with the *Phe508del/N1303K* genotype was found. According to the data, most CF patients with diabetes are homozygous for *Phe508del*, probably due to the more severe pancreatic failure associated with this genotype. It should be stressed that the overall prevalence of the *Phe508del* mutation is very high (56%) in the Polish population [11].

The results of our study showed that the nutritional status deteriorated during the observation of the group following the high-glycemic product restricted diet in opposition to the increase in BMI z-scores in the group treated with insulin. The possible explanation was noted by Rana et al. in their review. They found that low glycemic index foods can lead to increased satiety, which results in less food being eaten throughout the day [12]. In making the treatment decision, more thought should be devoted to the anabolic effect of insulin rather than to looking at it as a hyperglycemia lowering drug. Perhaps the appropriate time of introducing the insulin therapy had been missed. It should be stressed that dietary therapy in a patient with an abnormal glucose tolerance test is hard to achieve. Dietary recommendations do not only combine the principles of the dietary management of both cystic fibrosis and diabetes mellitus, but most importantly also emphasize the need for a high energy diet in patients with cystic fibrosis related diabetes mellitus [8]. In our study it was demonstrated that non-compliance with diet is an important clinical problem in adolescents, which influences the kind of therapy. Rolon et al. stress the necessity of determining the optimal time for starting insulin therapy in patients with prediabetes in large, prospective randomized trials of low-dose insulin therapy [9].

In our study five out of the 8 patients treated with insulin were on an insulin pump. The study of Hardin et all. in patients with CFRD demonstrated the improvement in both body weight and lean body mass when insulin was delivered by continuous subcutaneous insulin infusion (CSII), rather than by multiple daily injections [7].

The patients with CFRD are at risk of diabetic microvascular complications, which on the one hand occur less frequently and might be less severe than in other types of diabetes, but on the other hand are similarly related to the duration of diabetes and the level of glycemic control. In our study we did not find any patient with diabetic complications. The possible explanation is the short-term of the follow up.

Our study has some limitations. The number of the children analyzed is very small. We did not evaluate the children in a prospective study.

CONCLUSIONS

Glucose tolerance in children with cystic fibrosis deteriorates with age. Patients in a good condition and with a good compliance to a low-glycemic index product diet start insulin therapy later. Patients with a severe course of cystic fibrosis and diabetes require immediate insulin implementation. Insulin treatment improves their nutritional status. A continuous glucose monitoring system is a useful diagnostic tool which can be taken into account in therapeutic decisions. Prospective studies on a pediatric population with cystic fibrosis are needed in Poland for better analysis of the associations between abnormal glucose tolerance in cystic fibrosis children, the class of CFTR mutation, and the impact of glucose intolerance treatment on the patients' clinical status.

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Conflicts of interest/Konflikt interesu
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